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Ruth E. Stevens for the degree of Doctor of Philosophy in Pharmacy presented on August 20, 1992.

Title: Pharmacokinetic Modeling of Theophylline and Dyphylline And Pharmacodynamics of Ibuprofen Input Rate on Antipyresis.

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Abstract approved: ______________________

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Pharmacokinetic parameters for theophylline and dyphylline were evaluated in horse cerebrospinal fluid (csf) and plasma. Pharmacokinetic parameters did not differ significantly ($p > 0.05$) at the same dose for either drug when administered alone or concomitantly. Theophylline and dyphylline penetrate horse csf to produce approximately 1/2 the concentrations found in plasma. Doubling the theophylline dose from 10 mg/Kg to 20 mg/Kg doubled both csf and plasma theophylline concentrations. However, doubling the dyphylline dose from 20 mg/Kg to 40 mg/Kg tripled both csf and plasma dyphylline concentrations. Simultaneous fitting between plasma and csf drug concentrations indicates that plasma is a good indicator for predicting csf concentrations for both theophylline and dyphylline.

The influence of ibuprofen input rate on antipyresis was studied in rats with yeast induced fever. In addition, a data analysis comparison was made between rat data collected from this present study and literature data from fevered children. Counterclockwise hysteresis curves (ibuprofen plasma concentration versus temperature decrement) were observed following ibuprofen oral suspension when administered to rats and children. When the collapsed hysteresis curves were plotted (mean predicted total ibuprofen effect compartment concentration versus mean predicted temperature decrement effect) the rat and children's curves were <u>not</u> superimposable. However, the collapsed hysteresis curves of mean predicted ibuprofen <u>unbound</u> effect concentration versus mean predicted temperature decrement effect were superimposable for data from the rats and children. Based on mean unbound ibuprofen effect compartment concentration versus mean predicted temperature decrement effect, the antipyretic response to ibuprofen appears to be comparable between rats and children. The apparent qualitative trend in temperature decrement, although not statistically significant, perhaps due to variability, appears to be different among ibuprofen input regimens in rats. Maximum temperature decrement appears to relate not just to the concentration of ibuprofen obtained at steady-state, but the rate at which it is obtained.

Pharmacokinetic Modeling of Theophylline and Dyphylline
And
Pharmacodynamics of Ibuprofen Input Rate on Antipyresis

by

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INTRODUCTION

Therapeutic effect of theophylline and dyphylline appears to be dependent upon their concentration in blood. Chapter I of this thesis deals with the determination of theophylline and dyphylline concentrations in horse cerebrospinal fluid (csf) and plasma when administered alone or concomitantly. In addition, simultaneous fitting of individual horse's plasma and csf concentrations were performed. Chapter II evaluates four ibuprofen input regimens in rats with yeast induced fever to ascertain concentration-temperature response profiles and the impact that ibuprofen input rate had on the magnitude of antipyresis. In addition, a data analysis comparison was made between rat data collected from this study and literature data from fevered children.

CHAPTER I

DETERMINATION OF THEOPHYLLINE AND DYPHYLLINE CONCENTRATIONS IN HORSE CEREBROSPINAL FLUID AND PLASMA

ABSTRACT

Pharmacokinetic parameters for theophylline and dyphylline were evaluated in horse plasma and cerebrospinal fluid (csf). Each horse was dosed in five ways: 1) Aminophylline, 10 mg/Kg intravenously (iv) infused, 2) Dyphylline, 20 mg/Kg iv bolus, 3) Aminophylline, 20 mg/Kg iv infusion, 4) Dyphylline, 40 mg/Kg iv bolus, and 5) Combination of aminophylline, 10 mg/Kg iv infusion first, followed by dyphylline, 20 mg/Kg iv bolus. Plasma and csf concentration time curves were fitted individually using PCNONLIN^R. Plasma and csf concentration time curves were fitted simultaneously using PCNONLIN^R or FUNFIT. Pharmacokinetic parameters did not differ significantly ($p > 0.05$) for either drug when administered alone or concomitantly. Theophylline and dyphylline penetrate horse csf to produce approximately 1/2 the concentrations found in plasma. Doubling the theophylline dose from 10 mg/Kg to 20 mg/Kg doubled both csf and plasma concentrations for theophylline. However, doubling the dyphylline dose from 20 mg/Kg to 40 mg/Kg tripled both csf and plasma concentrations. Simultaneous fitting of plasma and csf drug concentrations indicates that plasma is a good indicator for predicting csf drug concentration for both theophylline and dyphylline.

INTRODUCTION

Theophylline and dyphylline (methylxanthines) have been used as effective bronchodialators in humans, and theophylline is used in horses with chronic airway disease (heaves), (1-3). The therapeutic serum drug concentration range for theophylline in humans is between 10 and 20 μg/ml (4-6). Although the therapeutic range for serum dyphylline concentrations has not been determined unequivocally there is some evidence that at least 12 μg/ml may be required for bronchodilation (7,8).

Theophylline can be quite toxic to humans in slight overdoses. Literature has reported that plasma theophylline concentrations as low as 15 μg/ml can produce toxic symptoms (9). Dyphylline usually does not cause toxicity in humans even when administered at very high doses; unfortunately, some recent literature suggests it is also significantly less potent (only one tenth as potent as theophylline as a bronchodilator), (10). Most signs of methylxanthine toxicity are related to central nervous system stimulation. Toxic effects of theophylline (ie. convulsions and seizures) may be due to high concentrations of the drug in csf. Since dyphylline appears to be less toxic than theophylline, 40 times more water soluble and polar compared to theophylline (0.054

octanol/water relative to theophylline), (7,11) it might be predicted that dyphylline would not be sufficiently lipophilic to cross the blood brain barrier and penetrate the csf. Hence, a possible explanation for lower toxicity.

Dyphylline is predominately used for maintenance treatment of chronic asthma. If a patient is taking dyphylline, enters the hospital and is given aminophylline (salt of theophylline), the dose of aminophylline must be reduced according to the Food and Drug Administration and Physician's Desk Reference (12,13). Toxicity from the combination of these drugs could be synergistic if they displace one another from binding sites and increase the free fraction of drug available to penetrate the csf. However, if dyphylline does not penetrate csf or the combination is not toxic then a full dose of either drug could be administered to status asthmaticus (attack of severe acute asthma) subjects with an unknown dose of the other drug on board (14).

The pharmacokinetics parameters (half-life, volume of distribution and clearance) between humans and horses are quite similar for dyphylline and theophylline (2,7,15-17). Horses suffer from chronic obstructive pulmonary disease which is similar to asthma or chronic bronchitis in humans. For these reasons the horse was chosen as the animal model.

It was the purpose of this study to 1) determine relative extent to which dyphylline and theophylline penetrate csf, 2) compare pharmacokinetic parameters for theophylline and dyphylline in plasma and csf when administered alone and concomitantly and 3) determine for both drugs if plasma drug concentrations were a good indicator of csf drug concentrations by simultaneously fitting csf and plasma drug concentrations over time.

MATERIALS AND METHODS

Experimental Section

Six adult horses (4 stallions, 2 mares) weighing between 350 kg and 500 kg were used in this study. A cross-over study was conducted, with at least 7 days between experiments. Jugular catheters (14 gauge, 5 1/2 inch)[a] were inserted, connected to an extension set and stopcock,[b] and then taped in place and flushed with heparinized saline solution (25 U/ml) before collection of blood samples.

Blood samples were collected in tubes containing desiccated heparin[c] at 0, 10, 15, 20, 30, 40, 60, 90 minutes and 2, 3, 4, 5, 6, 8, 12, 24, and 30 hrs. Samples were centrifuged and the plasma removed and frozen within 2 hours for later analysis. For csf collection, a polyethylene catheter was placed in the subarachnoid space by passing it through a 17 gauge 8 inch Tuohy spinal needle placed in the lumbo-sacral

Footnotes

[a] Abacath^{R}, Abbott Laboratories, Chicago, Il.

[b] Add-A-Flo, McGaw Laboratories, Sabana Grande, Puerto Rico

[c] Venoject green stopper, Terumo Medical Corp, Elkton, Md.

intervertebral space, and left in place for a maximum of 32 hours. The procedure has been reported by Skarda without any ill effects to the horse (catheter left in place up to 120 hours) (18). Heart rate, respiration rate, and other signs of undesirable reactions were monitored at the times of sample collection at the College of Veterinary Medicine. Transpleural pressures were measured on any horse showing signs of respiratory distress. Csf was collected at the same times as blood collections and frozen within 2 hours for later analysis.

Theophylline was prepared as an aminophylline injection in 1L of commercially available 5% dextrose in water (D5W)[d]. Dyphylline was prepared by dissolving pure dyphylline powder in D5W to produce drug concentrations of 100 mg/ml. All solutions were prepared using sterile technique and autoclaved prior to dose administration. Each horse was dosed in the following five ways: 1) Aminophylline at 10 mg/Kg intravenously infused over 15 minutes, 2) Dyphylline at 20 mg/Kg as an intravenous bolus in 15 seconds or less, 3) Aminophylline at 20 mg/Kg intravenously infused over 15 minutes, 4) Dyphylline at 40 mg/Kg as an intravenous bolus in 15 seconds or less,

Footnote

[d] 5% Dextrose in water was from McGaw Laboratories, Irvine, Ca.

and 5) Combination of dyphylline at 20 mg/Kg and aminophylline at 10 mg/Kg with aminophylline intravenously infused over 15 minutes first, then dyphylline as an intravenous bolus within 15 seconds or less. Appendix A lists individual horse data (weight, dose, tau, and infusion rate) from aminophylline 10 mg/Kg or 20 mg/Kg infusion administered alone or concomitantly with dyphylline, or from dyphylline 20 mg/Kg or 40 mg/Kg administered alone or concomitantly with aminophylline.

Analytical Methods

All solvents other than deionized water were high-performance liquid chromatography grade and all chemicals were used as received: theophylline and B-hydroxy-ethyltheophylline (BHET) were from Sigma Chemical Company, St. Louis, MO. Dyphylline, 7-(2,3-dihydroxypropyl) theophylline, was a gift from the Lemmon Company, Sellersville, PA. Acetonitrile was purchased from Baker Chemical Company, Phillipsburg, NJ. Trichloroacetic acid (TCA) was purchased from Mallinckrodt, Inc., Paris, KY.

High pressure liquid chromatography (HPLC) was used to measure both theophylline and dyphylline in plasma and csf. Before sample analysis was undertaken, standard curves for each drug, separately and in combination, were generated. Calibration curve precision and accuracy were within 10%, except when 0.5-1 μg/ml concentration values were included in the standard curve which resulted in a coefficient of variation not higher than 16% (range 11% to 16%) for assay validation and sample analysis.

Sample preparation: Stock solutions for each drug were prepared in distilled water (5, 10, 20, 40, 80, 100, 140, 240, 300, 450, 600, 800 and 1000 μg/ml) using volumetric glassware for use in standard curve preparation. BHET in acetonitrile (7.5 ng/ml) was included as internal standard.

A theophylline/dyphylline standard curve was produced as follows: 90 ul of horse csf or plasma and 10 ul of each known stock drug solution (see paragraph above) were mixed together in a 0.5 ml polypropylene centrifuge tube (Cole-Palmer Instrument Company, Chicago, IL.). To the same centrifuge tube, 90 ul internal standard (BHET) and 10 ul of 10% TCA (v/v in distilled water) to precipitate protein were added, mixed and then centrifuged (Eppendorf 5414) for 6 minutes. Fifty (50) ul of supernatant was removed from corresponding theophylline or dyphylline mixtures, combined, and centrifuged for 3 minutes. Final drug amounts contained in these standard solutions were 0.25, 0.50, 1.0, 2.0, 4.0, 5.0, 7.0, 15.0 and 30 μg/ml for each drug.

Experimental samples for theophylline/dyphylline combination administration were prepared by mixing 100 ul of horse csf or plasma with 90 ul of internal standard, and 10 ul of 10% TCA. Samples were centrifuged 6 minutes and drug concentrations in supernatant determined by HPLC. Separate standard curves for theophylline and dyphylline were prepared the same as above without the 50/50 mix. Experimental samples were prepared the same as mentioned above. Isocratic conditions were maintained for HPLC using acetonitrile in distilled water (6.8% v/v) at a flow rate of 1.9 ml/min (Waters Associates M-6000). Automated injections (Waters Associates WISP, M-712) were made onto a C_{18}-reverse phase column (Zorbax 4.6mm * 25cm pro-10 ODS Bio Series). Ultraviolet absorbance (Waters Associates, M-440) was determined at 280 nm and drug concentrations were analyzed by peak area or peak height ratio (Shimadzu Corp., C-R3A integrator).

Data Analysis

Standard curves were analyzed using Platinum Works!^{R} (19). Initial estimates of pharmacokinetic parameters for individual horses and their means were determined by RSTRIP^R (20). Initial pharmacokinetic parameters were then programmed into PCNONLIN^R (21) to obtain final pharmacokinetic estimates for both drugs in an individual horse's plasma drug concentration versus (vs) time curve, or csf drug concentration vs time curve. Appendix B lists pharmacokinetic parameters for individual horses estimated using PCNONLIN^R. In addition, PCNONLIN^R simultaneously fit plasma and csf dyphylline concentration vs time curves for each individual horse. However, PCNONLIN^R was <u>not</u> used to simultaneously fit plasma and csf theophylline concentration vs time curves. The plasma theophylline concentration vs time curves were well estimated, but the csf theophylline vs time curves were poorly estimated by PCNONLIN^R. FUNFIT (22), an interactive curve fitting computer program, was used to simultaneously fit plasma and csf theophylline concentration versus time curves. Final fits for both the csf and plasma theophylline concentration vs time curves were excellent using FUNFIT. The overall goal of least squares fitting is to minimize the sum of the squares of the deviations between the observed values and the values predicted by the model. Plasma theophylline concentrations were one order of magnitude higher than the csf theophylline concentrations. The variance of the estimate (in this case the estimate is either the plasma or csf theophylline concentration) is proportional to the variance squared. It appears that the PCNONLIN^R internal optimization procedure ignores the csf theophylline concentrations to a lesser degree since the variance of the csf theophylline concentration estimates squared would be much smaller than the variance of the plasma theophylline concentration squared. However, FUNFIT's internal optimization procedure fitted each response system individually (ie., plasma and csf theophylline concentrations) in order to establish a variance estimate for the observations in that system and then fit the systems simultaneously where they were weighted proportional to their variance estimates. Appendix B lists pharmacokinetic parameters for individual horses estimated using FUNFIT.

A 2-compartment open pharmacokinetic model was adequate to describe pharmacokinetic parameters for both plasma theophylline and dyphylline concentrations in horses. Three compartments (central, tissue and csf) would have been the ideal model. However, the small fraction of dose which distributed into csf compared to drug distribution into other organs and tissues of the body was not sufficient to influence the plasma concentration-time profile, and/or the assay was not sensitive enough to detect the change. Therefore, the theoretical 3-compartment open pharmacokinetic model collapsed to a 2-compartment open pharmacokinetic model. RSTRIP^R confirmed the choice for a 2-compartment open model fit for both dyphylline and theophylline. Model Selection Criterion (MSC) parameter in RSTRIP[R] was used as the indicator of goodness of fit. The calculated MSC value obtained from the fit (the largest MSC designates the most appropriate model) showed the 2-compartment open model to be the most appropriate model.

Dyphylline Administrations: For each horse, PCNONLIN[R] was used to fit the individual plasma drug concentration vs time curve using a 2-compartment open pharmacokinetic model with bolus input. Csf drug concentration vs time curves for each horse were individually fitted by PCNONLIN[R] using a one-compartment open pharmacokinetic model with first-order input, first-order output and lag time. PCNONLIN[R] simultaneously fit an individual horse's plasma and csf drug concentration vs time data points using the following equations:

Plasma: Cp = A*exp(-alpha*(time)) + B*exp(-beta*(time))

CSF: Ccsf = M*exp(-alpha*(time)) + N*exp(-beta*(time))

where A, B, M and N are pre-exponential terms. Alpha and beta (shared parameters between plasma and csf dyphylline concentration vs time curves) are the absorption and elimination rate constants, respectively. Appendix C contains a computer program that was written in PCNONLIN[R] to fit plasma and csf dyphylline concentration versus time curves simultaneously.

Theophylline Administration: For each horse, PCNONLIN[R] fit the plasma or csf theophylline concentration vs time curves. The plasma theophylline concentration vs time curves were fitted to a two-compartment open pharmacokinetic model with constant iv input and first-order output. The csf theophylline concentration vs time curves were fitted to a one-compartment open pharmacokinetic model with first-order input, first-order output and lag time. FUNFIT simultaneously fit each horse's plasma and csf theophylline concentration vs time data points to a 2-compartment open pharmacokinetic model with infusion input for theophylline. Appendix C contains a computer program that was written in FUNFIT to fit theophylline's plasma and csf concentration versus time curves simultaneously. The equations used to describe the simultaneous fit for theophylline were:

```
Plasma:  Cp = A*(1-exp(alpha*Tau))*exp(-alpha*time)
            + B*(1-exp(beta*Tau))*exp(-beta*time)
```

$$\text{CSF: } Ccsf = M*(1-\exp(alpha*Tau))*\exp(-alpha*time) + N*(1-\exp(beta*Tau))*\exp(-beta*time)$$

where Tau is equal to 0.25 hours (the infusion time) when time was equal to or greater than 0.25 hours. Otherwise, Tau was equal to time when time was less than 0.25 hours. Appendix C contains a computer output of the pharmacokinetic parameters for theophylline plasma and csf concentrations fitted simultaneously for a horse.

Weighted and Statistical Data Analysis

In the nonlinear regression analysis (RSTRIP^R and PCNONLIN^R), residuals from calculated concentrations were weighted ($1/y^2$). Data are presented as means $\pm$ standard deviations.

Statistical analyses was done using the paired-sample t-test (parametric) and the Wilcoxon paired-sample test (nonparametric) to make statistical comparisons between experimental groups; p values $\leq$ 0.05 were considered to be significant (23,24).

RESULTS AND DISCUSSION

This research shows that dyphylline and theophylline penetrate csf to approximately 1/2 the concentration of plasma. Plasma and csf drug concentrations for dyphylline and theophylline are given in Appendix D for individual horses. Plasma and csf drug concentration versus time curves for both drugs are given in Appendix E. Figures I.1 and I.2 show that dyphylline concentrations of up to 8 μg/ml appear in csf following the 40 mg/Kg iv bolus dose. Csf dyphylline concentrations, while variable over time at the lower dose of 20 mg/Kg administered alone, averaged about 1/2 (Figure I.1) the plasma concentration with a mean ratio of 0.48 after equilibrium. Csf to plasma dyphylline concentration ratio at the 20 mg/Kg dose administered concomitantly with aminophylline (10 mg/Kg), or dyphylline (40 mg/Kg) administered alone, show no variability over time and have mean csf/plasma dyphylline concentration ratio's of 0.44 and 0.51, respectively (Figure I.2 and I.1, respectively). Appendix F lists the csf/plasma, csf/csf, and plasma/plasma dyphylline concentration ratio's for individual horses.

Figure I.1 shows that when the dyphylline dose was doubled, the plasma/plasma and csf/csf dyphylline

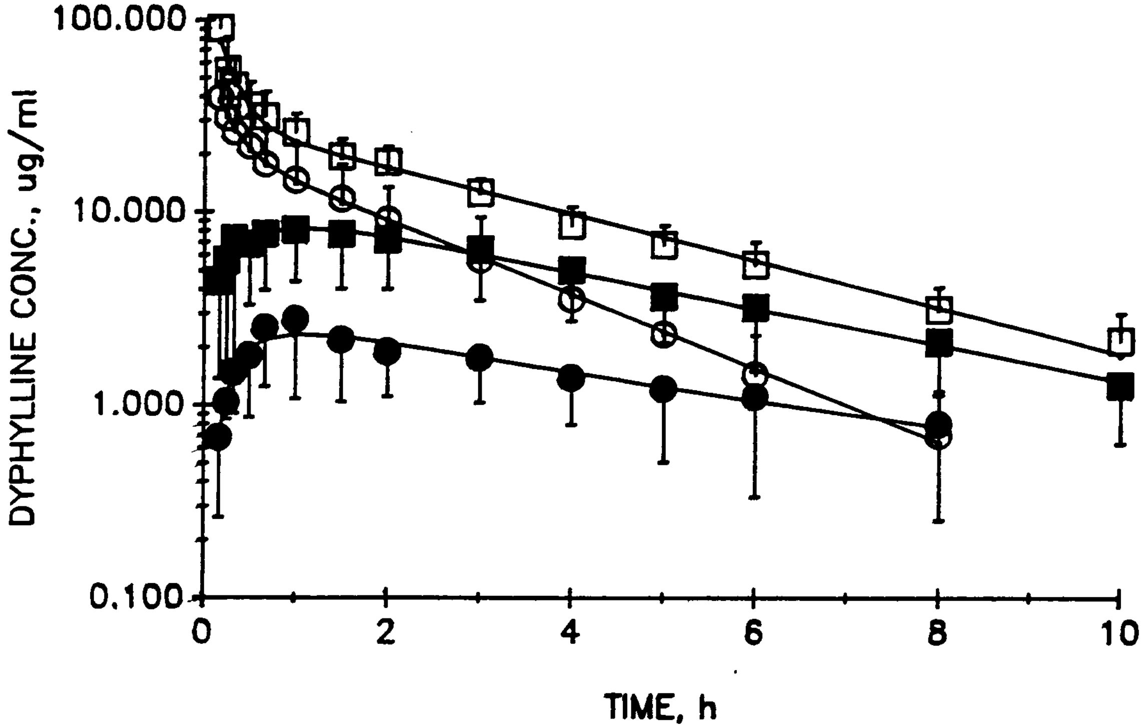

Figure I.1 Mean plasma or csf dyphylline concentration time curves fitted (PCNONLIN^{R}) by a two-compartment open pharmacokinetic model after an intravenous bolus, or a one-compartment open pharmacokinetic model with first-order input, first-order output and lag time, respectively, in 6 horses. O-O plasma (Dyphylline, 20 mg/Kg), ●-● csf (Dyphylline, 20 mg/Kg), □-□ plasma (Dyphylline, 40 mg/Kg) and ■-■ csf (Dyphylline, 40 mg/Kg). Mean dyphylline (20 mg/Kg) csf data consisted of 4 horses. Standard deviation error bars are shown except in those cases when they are smaller than the symbol.

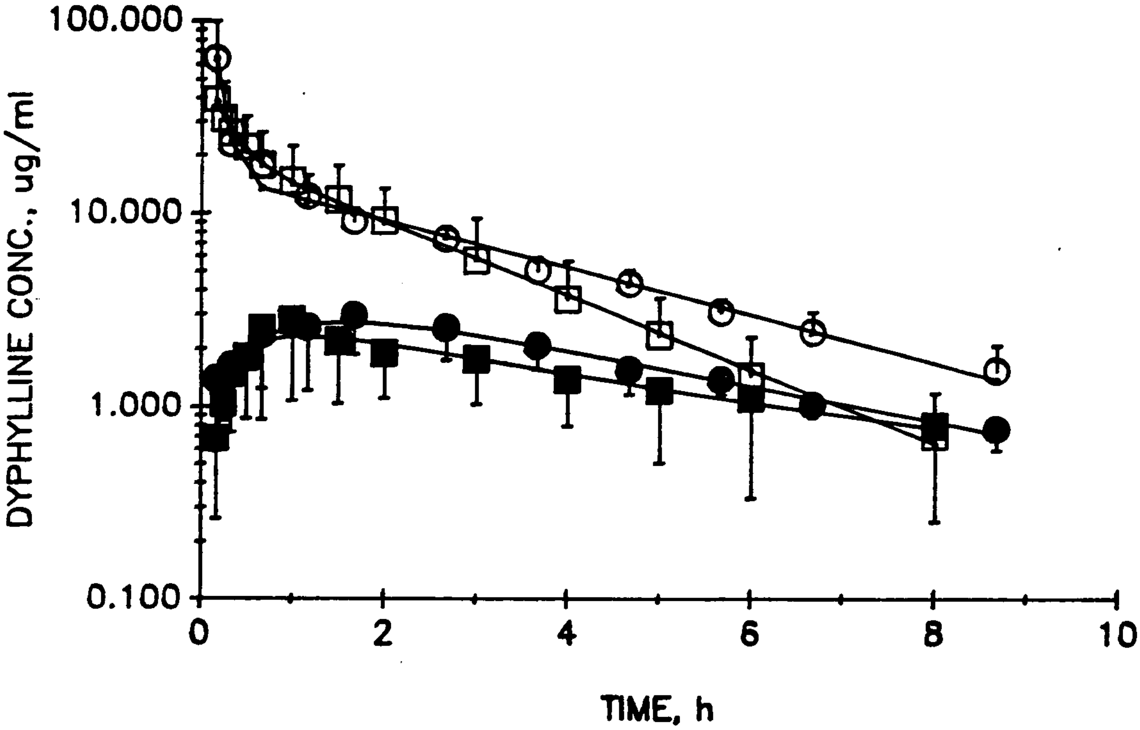

Figure I.2 Mean plasma or csf dyphylline concentration time curves fitted (PCNONLIN^R) by a two-compartment open pharmacokinetic model after (1) an intravenous bolus (plasma), (2) after aminophylline intravenously infused first followed by dyphylline as a intravenous bolus (plasma) or (3) a one-compartment open pharmacokinetic model with first-order input, first-order output and lag time (csf) in 6 horses. O-O plasma (Dyphylline, 20 mg/Kg, preceded by aminophylline, 10 mg/Kg), ●-● csf (Dyphylline, 20 mg/Kg, preceded by aminophylline, 10 mg/Kg), □-□ plasma (Dyphylline 20 mg/Kg, administered alone) and ■-■ csf (Dyphylline 20 mg/Kg, administered alone). Mean dyphylline (20 mg/Kg) csf data consisted of 4 horses. Standard deviation error bars are shown except in those cases when they are smaller than the symbol.

concentration ratio's were tripled (means were 2.86 and 2.94, respectively). In addition, volume of distribution at steady-state for dyphylline at 20 mg/Kg when administered alone or concomintantly was 327.40 L and 278.14 L respectively, however, when the dyphylline dose was doubled, the volume of distribution at steady-state was 452.01 L (Tables I.1 and I.2). Even though volume of distribution at steady-state was not statistically significant ($p > 0.05$) among the three dyphylline dose regimens, it appears that dyphylline may demonstrate nonlinear kinetics at higher doses in horses.

Visually, (Figures I.1 and I.2) the dyphylline 20 mg/Kg plasma elimination slope seems to be decreasing faster than for the 20 mg/Kg combination (dyphylline and aminophylline administered concomitantly) or the 40 mg/Kg dyphylline dose. Statistically, the half-lives or elimination rate constants (beta) do not differ significantly (Tables I.1 and I.2) from one another (half-lives: 1.99, 2.46 and 2.66 hrs respectively).

Figures I.3 and I.4 show that mean theophylline concentrations in horse csf were approximately 1/2 of concentrations found in horse plasma for all three administrations (aminophylline 10 mg/Kg, aminophylline 20 mg/Kg, and aminophylline 10 mg/Kg administered

Table I.1 Mean pharmacokinetic parameters from individually fitting (PCNONLIN^R) 6 horse's plasma or csf dyphylline concentrations, or by simultaneously fitting (PCNONLIN^R) plasma and csf dyphylline concentrations.

	MEAN PARAMETERS ESTIMATED FROM INDIVIDUAL FITTING		MEAN PARAMETERS ESTEMATED FROM SIMULTANEOUS FITTING	
	D20	D40	D20	D40
T1/2 (HRS)				
PLASMA	1.99 (1.36)	2.66 (0.41)	1.91 (0.55)	2.94 (0.27)
CSF	4.59 (2.40)	3.07 (0.59)	1.91 (0.55)	2.94 (0.27)
AUC (MG*HR/L) b				
PLASMA	57.61 (28.7)	129.20 (45.89)	62.18 (29.37)	128.72 (42.80)
CSF	11.73 (5.67)	42.73 (17.83)	8.80 (4.40)	45.50 (20.23)
PLASMA (HR-1)				
ALPHA	3.74 (3.41)	3.64 (2.87)	2.45 (1.14)	2.76 (2.93)
BETA	0.44 (0.17)	0.27 (0.05)	0.39 (0.11)	0.24 (0.02)
CSF (HR-1)				
ALPHA	3.17 (1.33)	2.18 (1.50)	2.45 (1.14)	2.76 (2.93)
BETA	0.19 (0.10)	0.23 (0.05)	0.39 (0.11)	0.24 (0.02)
Vd central (L)				
PLASMA	221 (153)	313 (225)	217.93 (128.94)	319.37 (263.18)
Vd area (L)				
PLASMA	407.33 (317.33)	536.94 (117.64)	402.88 (235.32)	604.70 (175.00)
Vss (L)				
PLASMA	327.40 (118.22)	452.01 (145.881)	327.40 (118.22)	452.01 (145.881)
Cl (L/HR)				
PLASMA	163.46 (75.16)	144.52 (45.35)	150.84 (92.05)	143.38 (41.47)
MRT (HRS)				
PLASMA	1.96 (0.484)	3.07 (0.764)	1.96 (0.484)	3.07 (0.764)
CSF	3.28 (0.41)	3.52 (0.44)	3.28 (0.41)	3.52 (0.44)

NOTES: ( ) = STANDARD DEVIATION Cl = DOSE/AUC Vss = Volume at Steady-state
b = TRAPAZOIDAL METHOD, (0-00) Vdarea = Cl/BETA
MRT CALCULATED FROM RSTRIP V central = DOSE/Cpo FOR SIMULTANEOUS FIT
D20 = DYPHYLLINE ADMINISTERED IV BOLUS AT 20 mg/kg
D40 = DYPHYLLINE ADMINISTERED IV BOLUS AT 40 mg/kg
Vss = (((KoT*AUMC)/(AUC)squared) - T(KoT)/(2*AUC))

Table I.2 Mean pharmacokinetic parameters from individually fitting (PCNONLIN[R]) 6 horse's plasma or csf drug concentrations, or by simultaneously fitting (PCNONLIN[R] for dyphylline and FUNFIT for theophylline) plasma and csf drug concentrations.

	MEAN PARAMETERS ESTIMATED FROM INDIVIDUAL FITTING		MEAN PARAMETERS ESTIMATED FROM SIMULTANEOUS FITTING	
	CD20	CT10	CD20	CT10
T1/2 (HRS)				
PLASMA	2.46 (0.20)	11.17 (2.46)	2.68 (0.34)	12.45 (3.01)
CSF	3.25 (1.57)	13.01 (3.09)	2.68 (0.34)	12.45 (3.01)
AUC (MG*HR/L) b				
PLASMA	83.12 (33.10)	155.3 (45.31)	80.17 (30.45)	155.3 (45.31)
CSF	14.50 (4.00)	96.39 (22.15)	12.25 (4.66)	96.39 (22.15)
PLASMA (HR-1)				
ALPHA	8.95 (3.31)	3.22 (2.20)	7.40 (3.97)	1.35 (1.02)
BETA	0.28 (0.02)	0.06 (0.01)	0.26 (0.03)	0.06 (0.01)
CSF (HR-1)				
ALPHA	0.93 (0.54)	1.06 (0.42)	7.40 (3.97)	1.35 (1.02)
BETA	0.25 (0.11)	0.056 (0.016)	0.26 (0.03)	0.06 (0.01)
Vd central (L)				
PLASMA	61.73 (51.87)	161.36 (82.85)	88.23 (77.93)	161.36 (82.85)
Vd area (L)				
PLASMA	399.40 (136.30)	365.26 (78.35)	452.13 (189.32)	422.85 (167.29)
Vss (L)				
PLASMA	278.14 (119.82)	387.78 (106.18)	278.14 (119.82)	387.78 (106.18)
Cl (L/HR)				
PLASMA	111.96 (40.72)	23.42 (5.90)	114.92 (40.03)	23.42 (5.90)
MRT (HRS)				
PLASMA	2.66 (0.67)	15.33 (3.27)	2.66 (0.67)	15.33 (3.27)
CSF	3.62 (0.48)	20.97 (3.38)	3.62 (0.48)	20.97 (3.38)

NOTES: ( ) = STANDARD DEVIATION b = TRAPAZOIDAL METHOD Cl = DOSE/AUC Vdarea = Cl/BETA
DOSE IN CLEARANCE CALCULATION IS BASED ON THEOPHYLLINE AMOUNT ADMINISTERED (80% OF AMINOPHYLLINE DOSE)

DYPHYLLINE'S MRT was calculated from RSTRIP (ver 2.0).

THEOPHYLLINE'S MRT was calculated by: MRT = MRT(infusion) - TAU/2

CD20: DYPHYLLINE 20 MG/KG ADMINISTERED CONCOMINANTLY WITH AMINOPHYLLINE 10 MG/KG.

CT10: AMINOPHYLLINE 10 MG/KG ADMINISTERED CONCOMINANTLY WITH DYPHYLLINE 20 MG/KG

Vss = Volume at Steady-state = (((KoT*AUMC)/(AUC)squared)) - (T(KoT)/2*AUC))

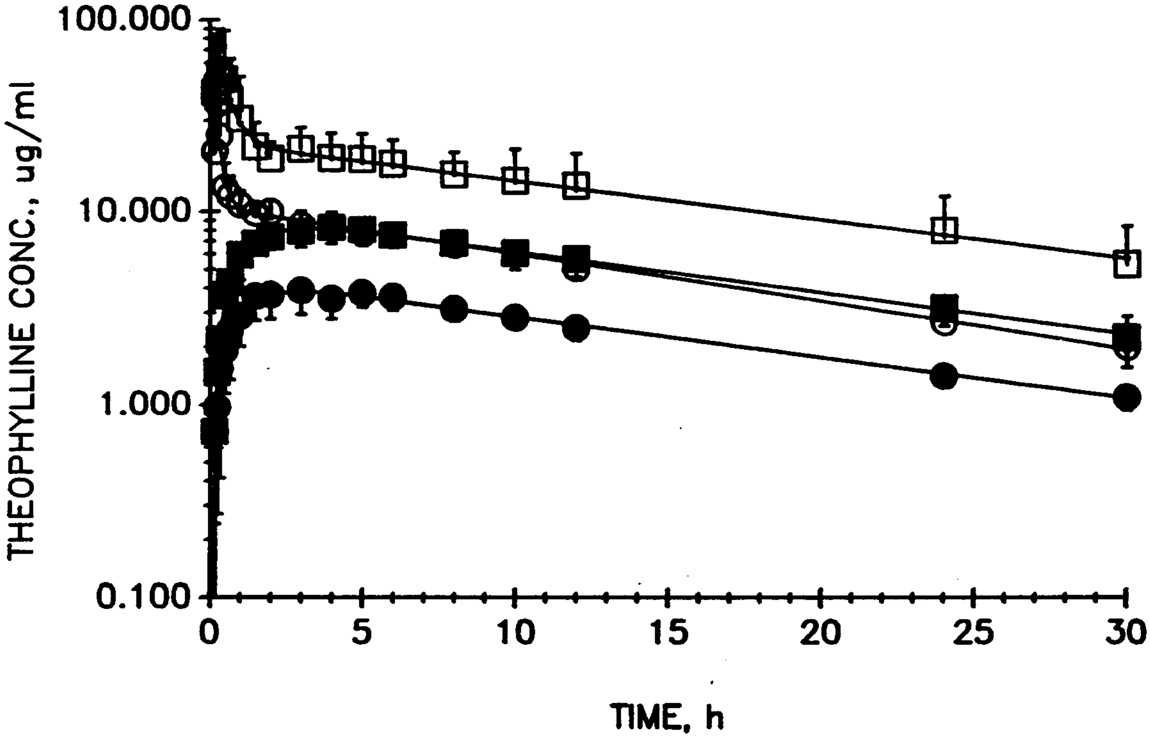

Figure I.3 Mean plasma or csf theophylline concentration time curves fitted (PCNONLIN^R) by a two-compartment open pharmacokinetic model after a dose of aminophylline intravenously infused over 15 minutes or a one-compartment open pharmacokinetic model with first-order input, first-order output and lag time in 6 horses. O-O plasma (Aminophylline, 10 mg/Kg), ●-● csf (Aminophylline 10 mg/Kg), □-□ plasma (Aminophylline, 20 mg/Kg) and ■-■ csf (Aminophylline, 20 mg/Kg). Standard deviation error bars are shown except in those cases when they are smaller than the symbol.

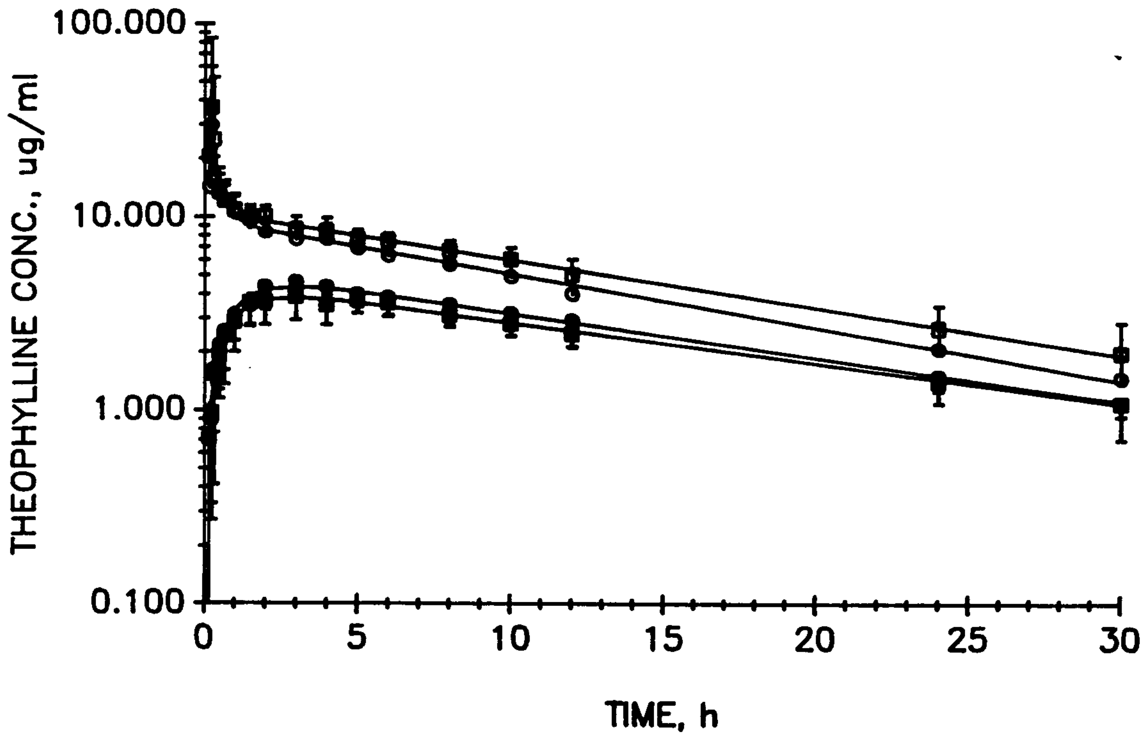

Figure I.4 Mean plasma or csf theophylline concentration time curves fitted (PCNONLIN[R]) by a two-compartment open pharmacokinetic model after a dose of (1) aminophylline at 10 mg/Kg intravenously infused over 15 minutes (plasma), or (2) aminophylline at 10 mg/Kg intravenously infused over 15 minutes followed by dyphylline, 20 mg/Kg, as an intravenous dose (plasma) or (3) a one-compartment open pharmacokinetic model with first-order input, first-order output and lag time (csf) in 6 horses. O-O plasma (Aminophylline, 10 mg/Kg, administered alone), ●-● csf (Aminophylline 10 mg/Kg, administered alone), □-□ plasma (Aminophylline followed by dyphylline, 20 mg/Kg) and ■-■ csf (Aminophylline followed by dyphylline, 20 mg/Kg). Standard deviation error bars are shown except in those cases when they are smaller than the symbol.

concomitantly with dyphylline (20 mg/Kg)). Mean csf/plasma theophylline concentration ratio's after equilibrium were 0.51, 0.46, and 0.59, respectively. Figure I.3 shows that plasma/plasma and csf/csf theophylline concentration ratio's were doubled (means after equilibrium were 2.22 and 2.22, respectively) when the dose was doubled. Appendix F lists the csf/plasma, csf/csf, and plasma/plasma theophylline concentration ratio's for individual horses. Mean plasma theophylline half-lives from the aminophylline 10 mg/Kg dose administered alone or concomitantly with dyphylline were 12.8 and 11.2 hours, respectively. Mean csf theophylline half-lives from the aminophylline 10 mg/Kg dose administered alone or concomitantly were 15.1 and 13.0 hours, respectively. The mean plasma and csf half-lives from the 20 mg/Kg theophylline dose were 14.63 and 13.92 hours, respectively.

Tables I.1, I.2 and I.3 list mean pharmacokinetic parameters for dyphylline and theophylline when administered alone or concomitantly in horses. Mean predicted pharmacokinetic values from the simultaneous fitting (pooled data) between plasma and csf drug concentration vs time curves are listed as well. Statistically, at the same drug dose, there were no significant differences for each drug among the

Table I.3 Mean pharmacokinetic parameters from individually fitting (PCNONLIN[R]) 6 horse's plasma or csf theophylline concentrations, or by simultaneously fitting (FUNFIT) plasma and csf theophylline concentrations.

	MEAN PARAMETERS ESTIMATED FROM INDIVIDUAL FITTING		MEAN PARAMETERS ESTIMATED FROM SIMULTANEOUS FITTING	
	T10	T20	T10	T20
T1/2 (HRS)				
PLASMA	12.76 (3.56)	14.63 (4.07)	14.39 (5.06)	15.40 (4.33)
CSF	15.05 (3.72)	13.92 (3.15)	14.39 (5.06)	15.40 (4.33)
AUC (MG*HR/L) b				
PLASMA	243.01 (157.49)	520.15 (283.01)	243.01 (157.49)	520.15 (283.01)
CSF	90.49 (9.97)	190.48 (40.55)	90.49 (9.97)	190.48 (40.55)
PLASMA (HR-1)				
ALPHA	7.68 (4.71)	3.27 (1.26)	2.68 (2.96)	1.95 (1.43)
BETA	0.058 (0.014)	0.050 (0.013)	0.05 (0.02)	0.05 (0.01)
CSF (HR-1)				
ALPHA	1.29 (0.51)	1.33 (1.19)	2.68 (2.96)	1.95 (1.43)
BETA	0.048 (0.011)	0.052 (0.010)	0.05 (0.02)	0.05 (0.01)
Vd central (L)				
PLASMA	124.99 (69.40)	131.03 (70.67)	124.99 (69.40)	131.03 (70.67)
Vd area (L)				
PLASMA	294.2 (76.77)	313.87 (97.25)	331.63 (66.90)	337.58 (120.60)
Vss (L)				
PLASMA	281.27 (135.90)	300.10 (99.15)	281.27 (135.90)	300.10 (99.15)
Cl (L/HR)				
PLASMA	17.53 (7.55)	16.75 (8.84)	17.53 (7.55)	16.75 (8.84)
MRT (HRS)				
PLASMA	15.74 (5.12)	19.56 (5.42)	15.74 (5.12)	19.56 (5.42)
CSF	22.79 (5.30)	21.02 (4.65)	22.79 (5.30)	21.02 (4.65)

NOTES: ( ) = STANDARD DEVIATION   Cl = DOSE/AUC

b= TRAPAZOIDAL METHOD, (0-00)   Vdarea = Cl/BETA

Vss = Volume at Steady-state = (((KoT*AUMC)/(AUC)squared)) - T(KoT)/(2*AUC))

MRT = MRT(infusion) - Tau/2 ((MRT(infusion) calculated from RSTRIP (ver. 2.0))

T10 = AMINOPHYLLINE AT 10 mg/kg INTRAVENOUSLY INFUSED OVER 15 MINUTES

T20 = AMINOPHYLLINE AT 20 mg/kg INTRAVENOUSLY INFUSED OVER 15 MINUTES

NOTE: DOSE IN CLEARANCE CALCULATION IS BASED ON THEOPHYLLINE AMOUNT ADMINISTERED (80% OF AMINOPHYLLINE DOSE) pharmacokinetic parameters when either drug was administered alone or concomitantly, except for one, volume of the central compartment (Vc) for dyphylline at the 20 mg/Kg dose (Vc was 61.73 L) when administered concomitantly with aminophylline was statistically less ($p < 0.05$) than when administered alone at the 20 mg/Kg and 40 mg/Kg dyphylline doses (Vc was 221 L and 313 L, respectively). However, the mean volume of distributions for area or steady-state were not significantly different for dyphylline or theophylline when administered alone or concomitantly (Table I.1, I.2 and I.3). Therefore, when dyphylline and aminophylline were administered concomitantly, they were not displacing one another from binding sites and not increasing the free fraction of drug available to penetrate csf. In addition, when aminophylline and dyphylline were administered concomitantly to each horse, there were no observable physiological effects (heart rate, respiration) or increase in side effects from the addition of dyphylline to the dosage regimen. This lack of side effects occurred in spite of the dyphylline dose at 40 mg/Kg being more than 2.5 times the recommended human dose, and being given as a rapid iv bolus in conjunction with a full dose of aminophylline. Although further studies with a larger horse population and a study in humans would be needed to confirm whether aminophylline and dyphylline administered concomitantly is clinically safe, these data suggest that a full dose of dyphylline can be administered to patients taking theophylline.

Assessment of csf drug profile is helpful in understanding observed clinical effects (nausea, vomiting, seizures) of theophylline in humans. If plasma drug concentrations are to be used as an alternative to csf analysis, a good correlation must exist between csf and plasma drug concentrations. To determine if plasma was a good predictor of csf drug concentrations, simultaneous fitting of plasma and csf drug concentration time curves was preformed. Appendix G contains simultaneous fitting of plasma and csf drug concentration versus time curves estimated from PCNONLIN^R and FUNFIT in individual horses. Simultaneous fitting between plasma and csf drug concentration versus time curves had an advantage over separate (individual) fitting of plasma and csf drug concentration versus time curves in each horse. This is to say that the data from plasma and csf drug concentration time points were pooled for a single fitting procedure in which the degrees of freedom were maximized and the error term was spread over more observations (25). The parameters alpha and beta were shared between the plasma and csf drug concentration

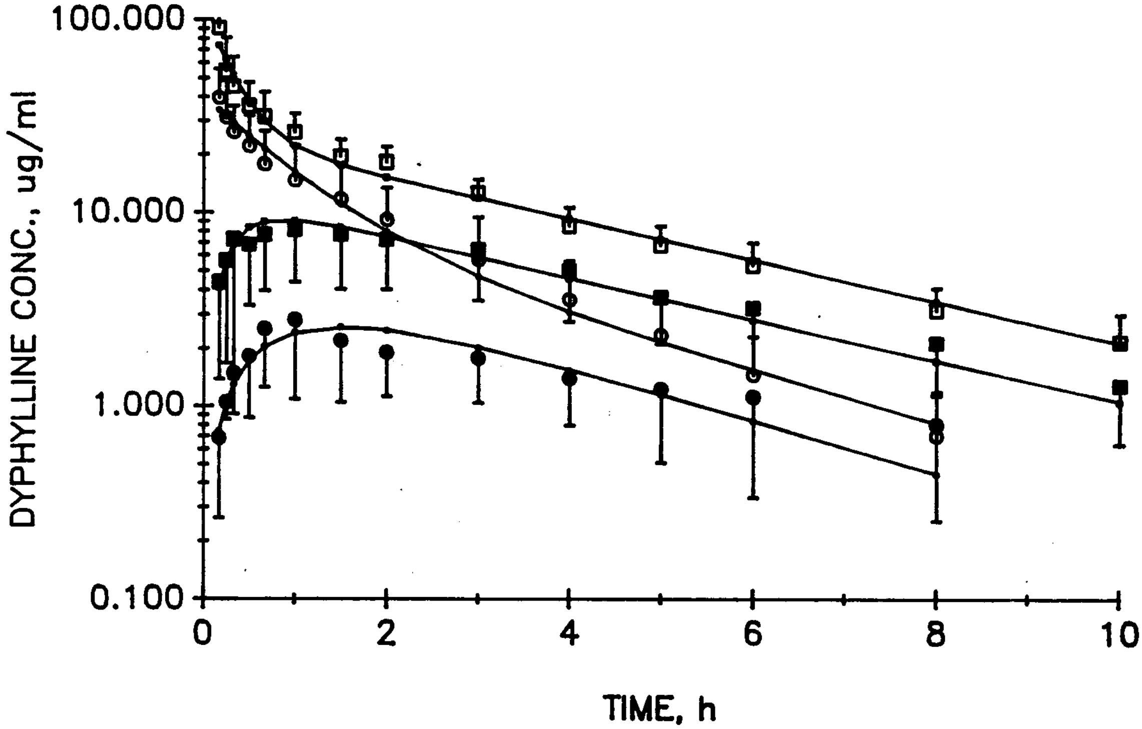

Figure I.5 Mean plasma or csf dyphylline concentration time curves fitted (PCNONLIN^R) simultaneously by a two-compartment open pharmacokinetic model with a intravenous bolus input in 6 horses. O-O plasma (Dyphylline, 20 mg/Kg, administered alone), ●-● csf (Dyphylline, 20 mg/Kg, administered alone), □-□ plasma (Dyphylline, 40 mg/Kg, administered alone) and ■-■ csf (Dyphylline, 40 mg/Kg, administered alone). Mean (20 mg/Kg) csf data consisted of 4 horses.

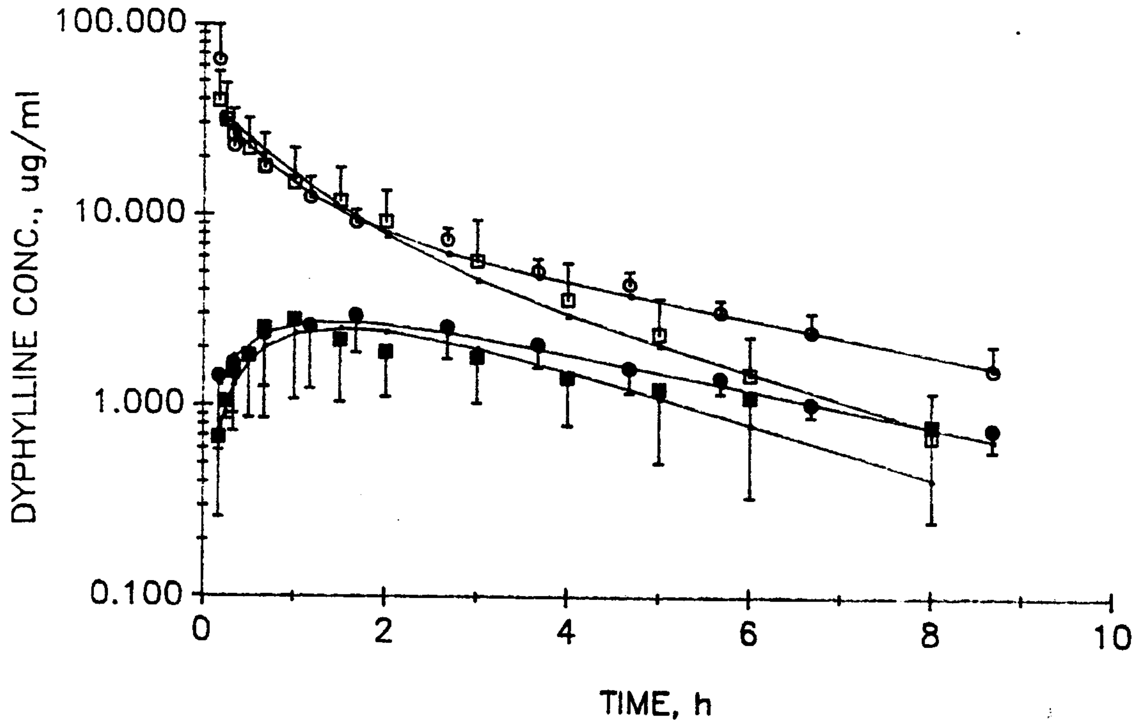

Figure I.6 Mean plasma or csf dyphylline concentration time curves fitted simultaneously (PCNONLIN[R]) by a two-compartment open pharmacokinetic model with intravenous bolus input in 6 horses. O-O plasma (Dyphylline, 20 mg/Kg, preceded by aminophylline, 10 mg/Kg), ●-● csf (Dyphylline, 20 mg/Kg, preceded by aminophylline, 10 mg/Kg), □-□ plasma (Dyphylline 20 mg/Kg, administered alone) and ■-■ csf (Dyphylline 20 mg/Kg, administered alone). Mean dyphylline (20 mg/Kg, administered alone) csf data consisted of 4 horses.

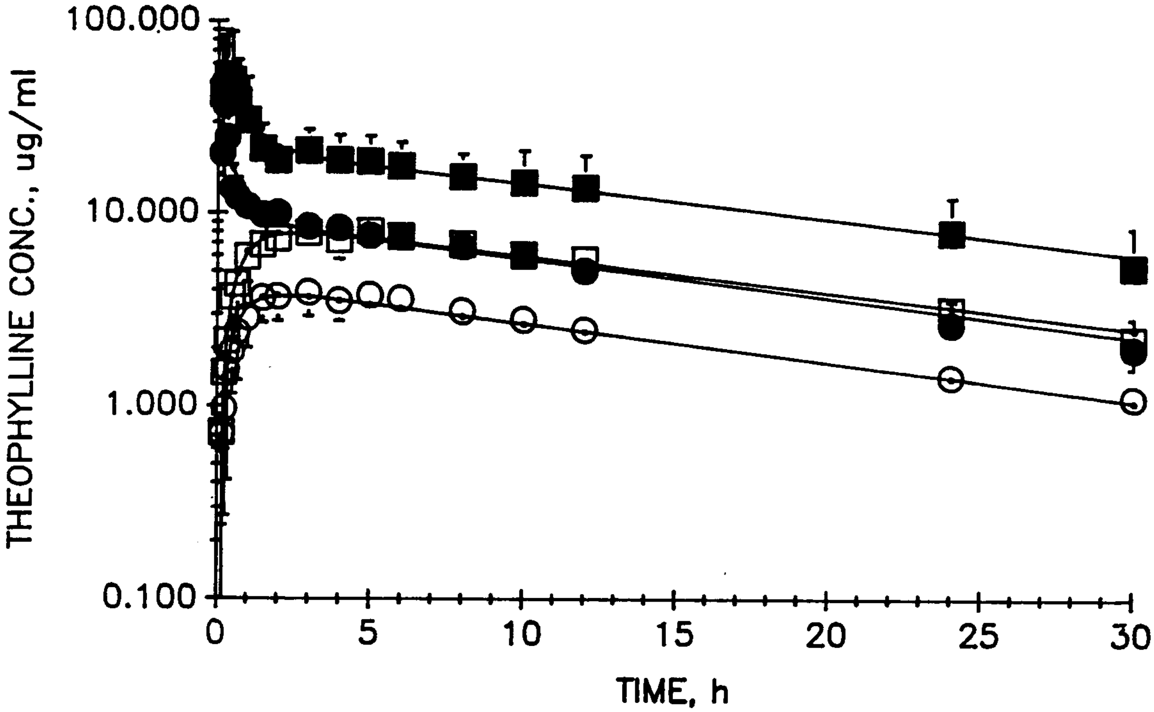

Figure I.7 Mean plasma or csf theophylline concentration time curves fitted (FUNFIT) simultaneously by a two-compartment open pharmacokinetic model with infusion input in 6 horses. ●-● plasma (Aminophylline, 10 mg/Kg), O-O csf (Aminophylline, 10 mg/Kg), ■-■ plasma (Aminophylline, 20 mg/Kg) and □-□ csf (Aminophylline, 20 mg/Kg). Standard deviation error bars are shown except in those cases when they are smaller than the symbol.

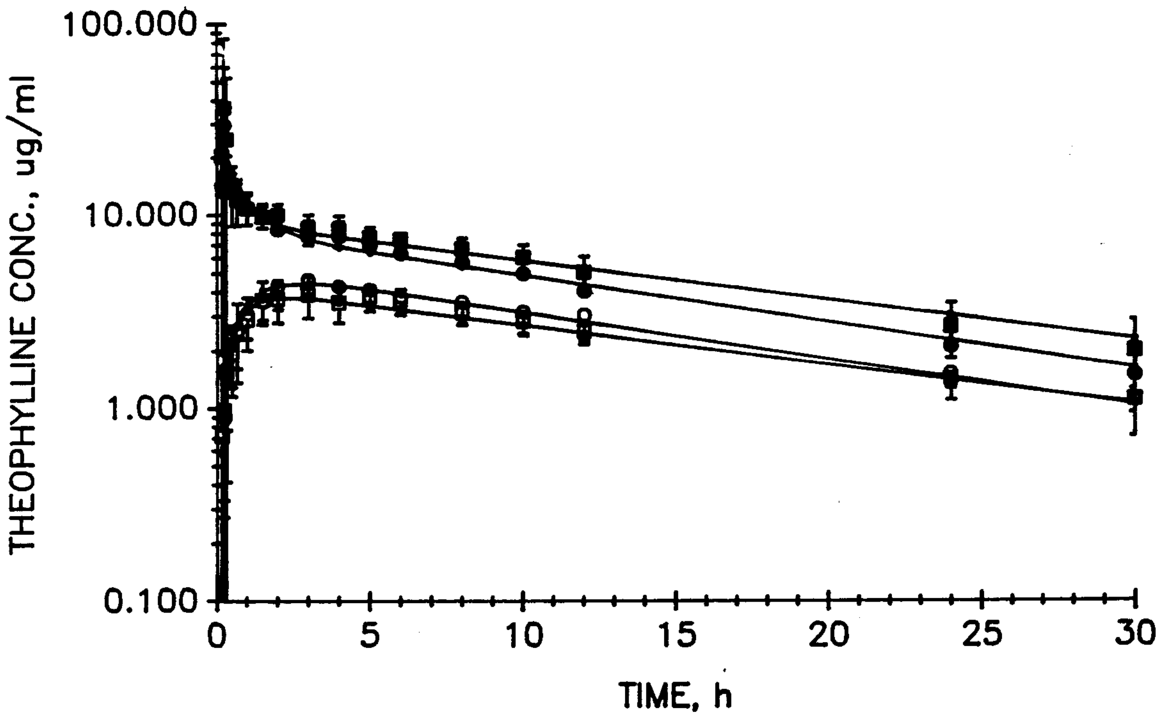

Figure I.8 Mean plasma or csf theophylline concentration time curves fitted (FUNFIT) simultaneously by a two-compartment open pharmacokinetic model with infusion input after a dose of (1) aminophylline at 10 mg/Kg intravenously infused over 15 minutes (plasma), (2) aminophylline at 10 mg/Kg intravenously infused over 15 minutes followed by dyphylline, 20 mg/Kg, as an intravenous dose (plasma) in 6 horses. O-O csf (Aminophylline, 10 mg/Kg, administered alone), ●-● plasma (Aminophylline, 10 mg/Kg, administered alone), □-□ csf (Aminophylline followed by dyphylline, 20 mg/Kg) and ■-■ plasma (Aminophylline followed by dyphylline, 20 mg/Kg). Standard deviation error bars are shown except in those cases when they are smaller than the symbol.

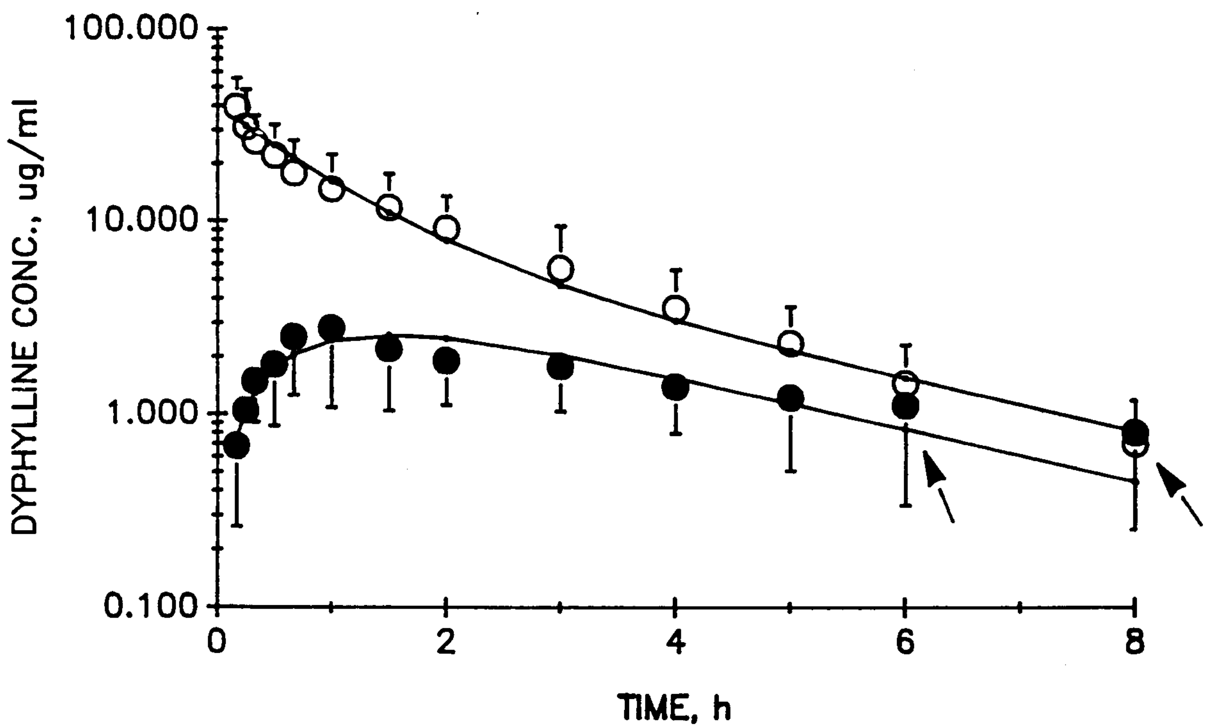

Figure I.9 Mean plasma or csf dyphylline concentration time curves for dyphylline, 20 mg/Kg, administered alone, fitted (PCNONLIN[R]) simultaneously by a two-compartment open pharmacokinetic model with intravenous bolus input in 6 horses. O-O plasma (Dyphylline, 20 mg/Kg, administered alone), ●-● csf (Dyphylline, 20 mg/Kg, administered alone). Mean dyphylline (20 mg/Kg, administered alone) csf data consisted of 4 horses.

versus time curves, thereby increasing the degrees of freedom by 2 for simultaneous fitting. If the simultaneous fitted parameter estimates were statistically different from the estimated pharmacokinetic parameters of the individual fits for both plasma and csf, plasma would not be a good predictor of csf concentrations. Figures I.5, I.6, I.7 and I.8 show mean observed data points with the predicted simultaneous fitted lines. There were no differences between individually fitted lines and simultaneous fitted lines for either plasma or csf drug data (Figures I.1-I.8). The only poor simultaneous fitted line was for the mean csf data points for the dyphylline 20 mg/Kg dose (Figure I.9, notice the mean observed points at time points 6 and 8 hours). At this particular dose, the plasma dyphylline concentration time curve had a faster mean elimination phase than for other dyphylline treatments. This observation was not unexpected since the plasma alpha and beta (shared parameters) for the dyphylline 20 mg/Kg dose were given as initial estimates for the simultaneous fitted equations. However, the csf dyphylline simultaneous fitted line fits through the standard error bars.

Figure I.10 shows the mean csf methylxanthine concentrations following dyphylline (20 and 40 mg/Kg

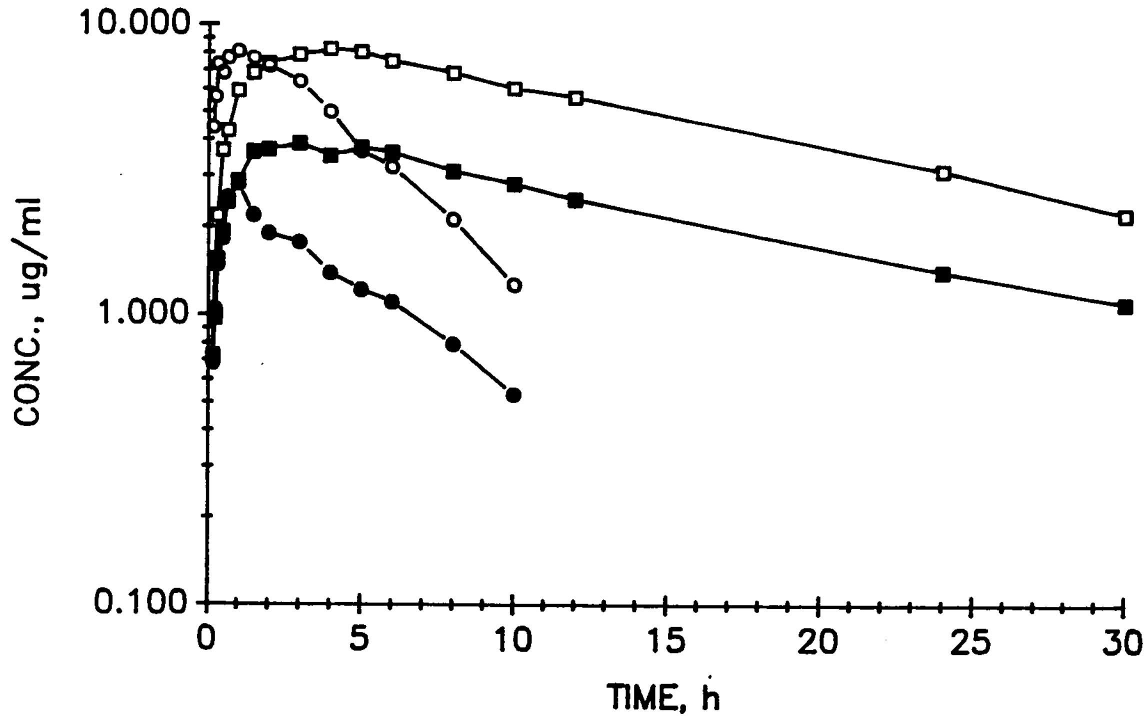

Figure I.10 Mean theophylline or dyphylline csf concentration time curves in 6 horses. O-O csf dyphylline 40 mg/Kg, ●-● csf dyphylline 20 mg/Kg (administered alone), □-□ csf theophylline 20 mg/Kg, ■-■ csf theophylline 10 mg/Kg (administered alone). Mean dyphylline (20 mg/Kg, administered alone) csf data consisted of 4 horses. No standard deviation bars given.

doses alone) and aminophylline (10 and 20 mg/Kg doses alone) administration. Both drugs appear to have approximately the same initial rate of absorption, but the elimination and duration after peak csf drug concentrations were very different. Theophylline plateaus and lingers in the csf for approximately 5 hours (3-8 hour), with the elimination predominately occurring after 8 hours. Detectable theophylline concentrations were still observed at 30 hours. Dyphylline reaches peak csf concentrations around 30-40 minutes, does not plateau, but the elimination of dyphylline occurs predominately after the peak dyphylline concentration, with detectable levels up to 10 hours. Csf theophylline concentration plateaus from 3 to 8 hours, therefore, the likelihood of maximum probability of toxicity would be from 3 to 8 hours following a theophylline dose, but for dyphylline, if no observed or measurable toxicity was seen by one hour after dose, central nervous system toxicity would be unlikely due to the decrease in csf dyphylline concentration.

CONCLUSIONS

The Physicians' Desk Reference (PDR) states for Dilor^{R} (dyphylline tablets), under contraindications: "Dyphylline should not be administered concurrently with other xanthine preparations" (13). This statement would lead one to believe that a combination of dyphylline and theophylline might produce a pharmacokinetic interaction or the drugs would be synergistic in toxicity. However, this research demonstrates that pharmacokinetic parameters for theophylline and dyphylline were not changed when administered concomitantly and no increase in toxicity occurred. Theophylline and dyphylline penetrate csf to approximately 1/2 plasma concentrations. Good simultaneous fitting between plasma and csf drug concentration for both dyphylline and theophylline indicates that plasma drug concentration is a good indicator to approximate csf drug concentration.

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CHAPTER II

PHARMACODYNAMICS OF IBUPROFEN INPUT RATE ON ANTIPYRESIS IN RATS

ABSTRACT

Influence of ibuprofen (Ib) input rate on antipyresis in rats with yeast induced fever was studied in four Ib input regimens: 1) oral suspension, 2) iv bolus followed by infusion, 3) slow iv infusion and 4) iv bolus. Mean maximum temperature decrement was achieved at 1 hr for regimen 4 (1°C), 2 hrs for regimen 1 and 2 (1.3°C and 1.2°C, respectively), and at 4 hours for regimen 3 (1.1°C). Literature data from fevered children were used to determine if rat data from the present study was dynamically (concentration (conc)-temperature decrement) similar to children. Collapsed counterclockwise hysteresis curves of mean predicted unbound Ib effect compartment conc vs mean predicted temperature decrement effect were superimposable between rats and children. Based on the mean unbound ibuprofen effect compartment conc in the range studied, the antipyretic response to Ib appears to be comparable between rats and children. The apparent qualitative trend in temperature decrement although not statistically significant, perhaps due to variability, appears to be different among Ib input regimens. Maximum temperature decrement appears to relate not just to the conc of Ib at steady-state, but the rate at which it is obtained.

INTRODUCTION

Although both rate and extent of drug absorption are required to define bioavailability, often the extent of absorption alone is utilized in determining bioequivalence among products. This may be due to experimental complexity and difficulty in obtaining an accurate rate of absorption and or clinical relevancy of the rate of absorption (1). Recent literature has shown that dosage regimen, or rate of drug administration can influence drug effect (2-9). Ibuprofen has similar pharmacologic actions to other nonsteroidal antipyretic agents such as aspirin, phenylbutazone, and indomethacin (10). Racemic ibuprofen, a known antipyretic agent (10), was used as a model drug as reported herein to investigate antipyretic intensity and duration among different ibuprofen input rates. Ibuprofen has the presence of a chiral carbon, alpha to the carboxylic acid group, and is a racemic mixture of enantiomers. The racemic mixture of ibuprofen was analyzed in this study instead of the active S(+) enantiomer in plasma because 1) ibuprofen is administered as a racemic mixture for analgesic, anti-inflammatory and antipyretic therapy, and

2) pharmacokinetic comparisons between results from this study and those previously reported require plasma concentration data on racemic ibuprofen.

Until now, rate of drug administration on drug effect has not been studied for antipyretic agents. A total of four ibuprofen input rates were employed to ascertain concentration-temperature response profiles and the rate of ibuprofen input effect on the magnitude of antipyresis. Two ibuprofen input rate regimens had an additional design goal, which was to determine and quantify the relative importance of two pharmacokinetic parameters on ibuprofen's antipyretic effect. Parameters were rate of increase in ibuprofen concentration and steady-state concentration of ibuprofen in plasma. In addition, a data analysis comparison was made between data generated in rats and literature data from fevered children (11).

Metabolism, protein binding and plasma half-live of ibuprofen appear similar between rats and humans (12-15). Core body temperature in rats compares well with humans (37.5°C), (16). Objectives of this research were to 1) evaluate the influence of ibuprofen input rate on antipyretic effect in rats with yeast induced fever and 2) to pharmacodynamically compare rat data from this present study with literature data from children.

MATERIALS AND METHODS

Analytical Methods

Chemicals and Solvents: All solvents other than deionized water were high-performance liquid chromatography grade and all chemicals were used as received from the company. Ibuprofen USP (United States Pharmacocapia) reference was from USP, Rockville, Md. Fenoprofen calcium (lot #B14-C42-021) was from Eli Lilly and Company, Indianapolis, In. Triethylamine (TEA) was from Sigma Chemical Company, St. Louis, Mo., isopropanol was from Alltech Associated, Inc., Deerfield, Il., isooctane was from Aldrich Chemical Company, Inc., Milwaukee, Wis., acetonitrile ((ACN) was from Baxter, Muskegon, Mi., sulfuric acid was from Mallinckrodt, Inc., St. Louis, Mo. and methanol and glacial acetic acid were from Baker, Phillipsburg, NJ.

Instrumentation

High pressure liquid chromatography (HPLC) was used to measure ibuprofen in rat plasma (17). The system consisted of a Hewlett Packard Series II, Model 1090 Liquid Chromatograph (Hewlett-Packard GmbH, Hewlett-Packard-Str, D0517 Waldbronn 2, Federal Republic of Germany) set at 0.3 ml/min., a spectrophotometer (HP with diode array) set at 232 and adjustable a.u.f.s. (absorbance units full scale) and a Beckman reversible phase column (ODS 5 micron, internal diameter 2.0 mm, 25 cm length, Part No. 244434, San Ramon, Ca.), protected with a Brownlee guard column (Spheri-10, RP-18, 10 micron, 30 * 4.6mm).

Preparation of Solutions

a. Mobile Phase: Sixty-forty (60/40, v/v) mixture of acetonitrile and 0.094% aqueous solution of TEA, adjusted to pH=3.6 (pH meter, Corning Scientific Co., Corning, NY) with glacial acetic acid. Ibuprofen eluted at 5.7 minutes and the internal standard, fenoprofen, eluted at 4.1 minutes.

b. Stock Solutions: Primary stock solutions of ibuprofen for standards (100 and 1000 μg/ml) were prepared by dissolving accurately weighed ibuprofen in methanol. Fenoprofen was used as internal standard (35 μg/ml) and was prepared by dissolving accurately weighed fenoprofen in methanol.

Standard and Sample Preparation

a. Standards: Rat plasma (100 ul) was collected by centrifuging blood samples for 5 mins. at 1800 RPM, and placed in 15 cm polypropylene centrifuge tubes (Elkay

Products, Inc., Shrewsbury, Ma.). The appropriate primary standard stock solution of ibuprofen was added to the rat plasma to provide concentrations of 1 - 40 μg/ml. Tubes were vortexed 15 seconds followed by addition of 10 ul of fenoprofen (35 mg/ml).

b. Samples: Samples were thawed at room temperature and vortexed for 15 seconds. Into 15 cm polypropylene centrifuge tubes, 100 ul of each sample was placed, followed by addition of 10 ul of fenoprofen and vortexed for 15 seconds.

c. Extraction Procedure for Standards and Samples (15): To both standard and sample tubes, 200 ul of 0.6 M sulfuric acid was added, followed by addition of 3 ml isooctane-isopropanol (95/5, v/v). Tubes were vortexed for 30 seconds and then centrifuged for 5 minutes at 1800 RPM. The upper organic layer was transferred by Pasteur pipet to clean, labelled 13*10 cm glass tubes and evaporated using the Speed Vac Sc2000 (model RH200-12, Savant Instruments Inc., Farmingdale, NY). Extraction residues were each reconstituted with 100 ul of mobile phase, vortexed for 15 seconds and transferred to a disposable 100 ul glass injection tube (Alltech, Deerfield, Il.) and 20 ul injected.

Experimental Section

Animal Model: Female Charles River retired breeders (CD-1, Charles River Laboratories, Wilmington, Mass.) weighing 300-500 grams were used in this study. Rats were allowed 6 days to adjust to the animal facilities and overcome possible stress incurred during transport. Rats were individually housed in metal cages in an environment of controlled temperature (23-25°C) and alternating 12 hour light (7 a.m.-7 p.m.) and dark cycles. Rats were allowed free access to rat chow (Rodent Chow^R, Purina Mills, Inc., St. Louis, Mo) and water, except during testing procedure (see Fever Induction Section).

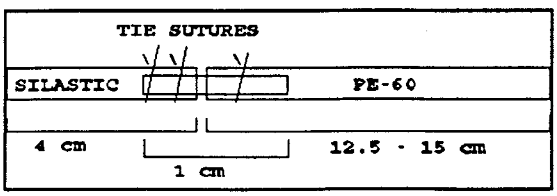
Supplies: Ibuprofen suspension (20 mg/ml) was a gift from Whitehall Laboratories, Inc., New York, NY. The ibuprofen suspension was diluted to 2 mg/ml in 0.5% methyl cellulose in distilled water (Sigma Chemical, St. Louis, MO) solution. Intravenous (iv) ibuprofen (50 mg/ml) was a gift (prepared formulation, proprietary) from Upjohn, Kalamazoo, MI. The iv ibuprofen stock concentration was diluted to 1 mg/ml with 0.9% saline solution (Kendall McGraw, Irvine, CA) and autoclaved for 15 minutes. Fever induction (see Experimental Procedures) required brewer's yeast (Brewers Bottom, Sigma Chemical, St. Louis, MO). Temperature monitoring instruments were from Yellow Springs Instruments (YSI) Company, Inc., Yellow Springs, Ohio (YSI Tele-thermometer, model 43TD, YSI 400 series probe, model 402, and YSI switch box, model 4002). Harvard Apparatus pumps (syringe infusion Pump 22, model 2400-001, Southnatick, Mass.) were used for infusion of drug or saline. Rat restrainers were from Braintree Scientific, Inc., Braintree, Ma. (model 800R).

Surgical Equipment: The anesthetic was sodium pentobarbital (Nebutal^R, 65 mg/ml) from A.J. Buck and Son, Hunt Valley, Maryland. Lidocaine HCL (2% Xylocaine^R (20 mg/ml) was from Astra Pharmaceutical Products, Inc., Westborough, Ma. Autoclip 9 mm stainless steel clips and remover were from Clay Adams, Division of Becton Dickinson and Company, Parsippany, New Jersey. The steel plug was made from electrical wire. Catheters (Angiocath^R, 24G, 3/4 inch, Deseret, Deseret Medical, Inc., Division of Becton, Dickinson and Company, Sandy, Utah) were used for rat tail vein injection of drug or saline.

Catheter Preparation: A 21 gauge stainless steel needle (1 cm) (Becton Dickinson and Company, Rutherford, New

Jersey) was cut and used as the metal connector to connect the polyethylene tubing with the silastic tubing. Polyethylene tubing (PE-60, 0.76 mm ID * 1.22 mm OD, Intramedic, non-radiopaque, Clay Adams, Division of Becton Dickinson and Company Parsippany, New Jersey) was cut 5-6 inches long. Silastic tubing (.025 in. ID * .047 in OD, Cat. # 602-155, Dow Corning Corporation, Medical Products, Midland, Michigan) was cut 4 cm long. Silastic and PE-60 tubing were tied to the metal connector using 4-0 silk suture (108-S, 100 yds, black braided silk, Surgical silk, non-sterile, Deknatel, Division of Howmedical, Inc., Queens Village, New York). At least three sutures were tied to the metal connector.

Diagram:



Polyvinylpyrrolidone (PVP) preparation: Nine (9) ml of filtered deionized water, 5 grams of PVP (Eastman Kodak Company, Rochester, New York) and 1 ml sodium heparin (0.9% Sodium Chloride Injection, USP, Kendall-McGaw Lab., Inc., Irvine, Ca., Heparin Sodium Injection, USP, SolPak

Laboratories, Franklin Park, Il., 1000 units/ml) were stirred by hand. Contents were chalky at first, but cleared after 5-10 minutes. The heparonized PVP preparation was used for maintenance of catheter lines. For example, the prevention of flap formation (clotting) at the end of the silastic tubing in contact with jugular vein was decreased dramatically.

Experimental Procedures

Rats were allowed a minimum acclimation period of 1 week before starting experiments. On the day before study, rats were subjected to external jugular vein cannulation under anesthesia (60 mg/Kg of sodium pentobarbital (Nebutal^{R})). With gentle rotation, approximately 3-4 cm of the silastic tubing section, with end beveled, was inserted toward the heart while the polyethylene tubing was tunneled under the skin above the shoulder, between the right eye and ear and out through an incision made between the middle of the rat's two ears. Into the catheter, 0.05 ml heparinized polyvinylpyrrolidone (PVP) was injected for maintenance of the catheter line. Once heparinized PVP had been injected through the catheter line, a 1/4 inch length steel plug was inserted at the end of the tubing. Both the steel plug and the PVP heparin solution were removed from the catheter line before blood collection. Both incisions (lower clavicle and between the ears) were closed using 9 mm autoclips. Lidocaine HCL (2% Xylocaine^{R}) was applied topically during the procedure to keep exposed tissue area moistened and act as a local anesthetic and vasodilator. Heparinized saline (10 units/ml) was used during the procedure to keep the tubing free of clot formation.

Fever Induction: For all ibuprofen input regimens the following procedure was followed: Thirty hours after catheter surgery, fever was induced with a 10 ml/kg of a 15% aqueous suspension of brewer's yeast injected all in one site subcutaneously below the nape of the rat's neck (18). The animals remained fasted for the duration of the experiment (approximately 24 hours). Water was available ad libitum. The temperature of each rat was obtained before induction of fever by inserting a marked lubricated thermistor rector probe exactly 4 cm into the rectum for 45 sec.

Blood Samples and Temperature Recording:

Regimen 1: Serial blood samples were collected from the cannula at time 0, 0.5, 1, 2, 3, 4, 5, and 6 hours post drug administration. Total rat blood withdrawn was 300 ul at each sampling time, which was replaced with 300 ul heparinized saline (10 units/ml). Blood samples were centrifuged immediately and plasma was stored at -20°C. Temperature readings were recorded at the following times: -10 minutes (predose), and 0, 0.5, 1, 2, 3, 4, 5, and 6 hours post drug administration. Temperature of each rat was recorded by insertion of a marked temperature probe into the rat's rectum 4 cm and waiting 45 seconds for thermometer equilibration prior to recording the temperature. Rats were <u>not</u> restrained any time during the pharmacokinetic study.

Regimen 2, 3 and 4: The same procedure was followed above for the next three ibuprofen input regimens except for the following deviations: Regimen 2: Another blood sample was collected from the cannula at 0.167 hours post drug administration with a corresponding temperature reading at the same time. Rats <u>were</u> restrained during the pharmacokinetic study. Regimen 3 and 4: Additional blood samples were collected from the cannula at 0.167 and 0.33 hours post drug administration with corresponding temperature readings at the same time. Rats were also restrained during the pharmacokinetic study.

Harvard 22 pump (infusion of saline or drug to maintain specified concentration): Rats were restrained for the duration of the drug infusion (no more than 6 hours). An angiocath[R] was inserted into the rat tail vein and connected to tubing on the Harvard 22 pump, and left in place for the duration of the experiment (4 hours).

Ibuprofen Input Regimens:

Regimen 1: Suspension Treatment: Shen (19) observed that a 6 mg/Kg ibuprofen oral administration in rats produced 1°C drop in fever reduction. Adams (13) showed that a 5 mg/Kg single ibuprofen oral dose in the rat reached similar plasma ibuprofen concentrations in man from a dose of 200 mg (3 mg/Kg). Based on literature (20,24) an oral ibuprofen suspension of 7.5 mg/Kg in 0.5% methyl cellulose saline base was chosen as the dose to administer to rats with yeast induced fever. Eighteen rats were cannulated and allowed to recover 30 hours before fever induction. Temperature was recorded prior to cannulation surgery (at least 4 temperature readings), 24 hours after surgery, and before yeast injection to make sure each rat had returned to normal baseline temperature. After surgical recovery, each rat was injected with brewer's yeast. Maximal fever occurred approximately 12 hours post injection. Rats that did not have a fever over 38.8°C were not used for the experiment. Nine rats were administered ibuprofen suspension (7.5 mg/Kg) through a metal oral gavage 12 hours after yeast injection. The other nine rats were controls and were administered a 0.5% methyl cellulose saline solution without drug, also 12 hours after yeast injection.

Regimen 2: Intravenous (iv) bolus followed by infusion to immediately obtain and maintain plasma ibuprofen concentration at about 4 μg/ml: Eighteen rats were cannulated and allowed to recover 30 hours before fever was induced. Fever was yeast-induced in eighteen rats 12 hours before iv administration of ibuprofen or saline. Nine rats were administered 0.83 mg/Kg of iv (1 mg/ml) ibuprofen injected through the rat tail vein followed by infusion (ibuprofen, 1 mg/ml) at 4.7 ul/min. The infusion pump was adjusted to 2.35 ul/min. at 30 minutes, 3.53 ul/min. at 60 minutes, 2.35 ul/min. again at 3 hours and left there until ending the experiment (4 hours) (see Preliminary Experiments Section). The other nine rats were controls. Controls were administered 0.83 ml/kg of 0.9% sodium saline through the rat tail vein followed by infusion of 0.9% sodium saline at 4.7 ul/min. The infusion pump was adjusted at the same settings and times as above for the nine experimental rats.

Regimen 3: Slow iv infusion to gradually produce about 4 μg/ml plasma ibuprofen concentration in 30 minutes and then maintain at approximately the same level. Eighteen rats were cannulated and allowed to recover 30 hours before fever was induced. Fever was yeast-induced in eighteen rats 12 hours before administration of ibuprofen or saline. Nine rats were infused (20 ul/min.) with ibuprofen (1 mg/ml) through the rat tail vein. The infusion pump was adjusted to 10 ul/min. at 30 minutes, 5 ul/min. at 3 hours and left there until the end of the experiment (4 hours) (see Preliminary Experiments Section). The other nine rats were controls. Control rats were infused (20 ul/min.) with 0.9% sodium saline through the rat tail vein. The infusion pump was adjusted at the same settings and times as above for the nine experimental rats.

Regimen 4: Ibuprofen iv bolus resulting in approximately 4 μg/ml peak ibuprofen concentration with no ibuprofen maintenance. Seven rats were cannulated and allowed to recover for 30 hours before fever was induced. This regimen was intended as a pilot study only and therefore, controls were not used. However, the plasma ibuprofen concentration versus temperature decrement response was interesting and therefore, included in the overall data analysis. Controls from regimen 1 were used as a reference for this regimen. Fever was yeast-induced in seven rats 12 hours before administration of ibuprofen. The seven rats were given 0.832 mg/Kg of iv (1 mg/ml) ibuprofen injected through the rat tail vein.

Preliminary Experiments

The iv bolus amount and infusion settings to achieve and maintain approximately 4 μg/ml plasma ibuprofen concentrations in rats were determined as follows based on preliminary experiments. Three rats were administered iv bolus ibuprofen (7.5 mg/Kg) through the right external jugular vein. Mean plasma ibuprofen concentration versus time profile (Figure II.1) was well fitted to a 2 compartmental model by SIMUSOLV^R (20), a computer software program. Initial parameter estimates were as follows:

0.176 l/kg,	volume of central compartment
0.0317/min.,	K10 (overall elimination rate constant from the central compartment)
0.0085/min.,	K12 (elimination rate constant from central compartment into the peripheral compartment)
0.0062/min.,	K21 (elimination rate constant from the peripheral compartment to the central compartment)

These initial parameters were then programmed into STANPUMP^R (STANPUMP^R is freely available from the author, Steven L. Shafer, M.D., Anesthesiology Service (112A),

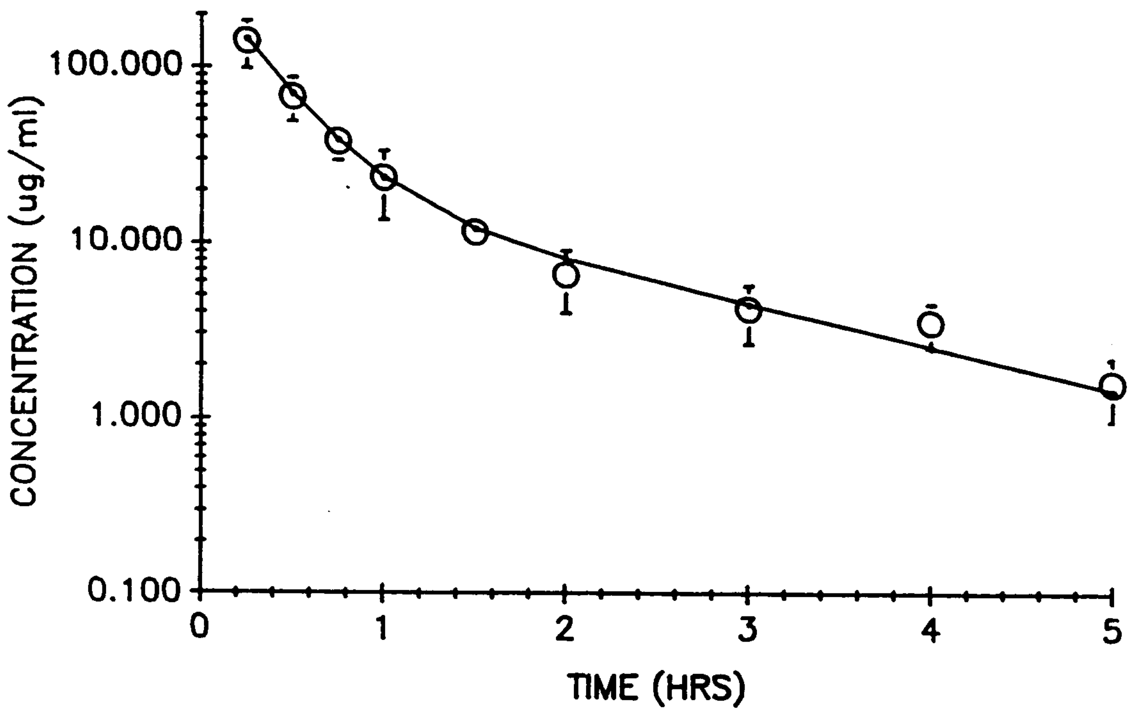


Figure II.1 Mean plasma ibuprofen concentrations after iv bolus administration (7.5 mg/Kg) to three rats. Data were best fitted to a two-compartment open pharmacokinetic model.

PAVAMC, 3801 Miranda Ave., Palo Alto, Ca. 94304). STANPUMP^R is a program which drives an infusion pump (in this case the Harvard 22 pump) to administer drugs according to a desired compartmental pharmacokinetic model and to maintain constant plasma concentrations of the drugs. The program is designed to deliver an iv bolus of drug followed by a predetermined infusion rate (based on the initial pharmacokinetic parameters programmed) to achieve and maintain the desired plasma concentration. In this case, STANPUMP^R calculated that 0.83 mg/Kg of an ibuprofen iv bolus (1 mg/ml) was needed to achieve 4 μg/ml plasma ibuprofen concentration immediately, followed by continuous ibuprofen infusion input rate to maintain about 4 μg/ml plasma ibuprofen concentrations. However, when ibuprofen concentrations were determined analytically, the plasma ibuprofen concentrations of two pilot rats showed the 5 minute sample to be approximately 4 μg/ml, while in the next time samples (15, 30, 60, 120, 180 and 240 minutes) plasma ibuprofen concentrations continued to increase over the 4 hour period (steady-state seemed to be observed graphically at 120 and 180 minutes), (Figure II.2). The reason is unknown for unexpected increasing plasma ibuprofen concentrations as the drug is not reported to follow non-linear pharmacokinetics.

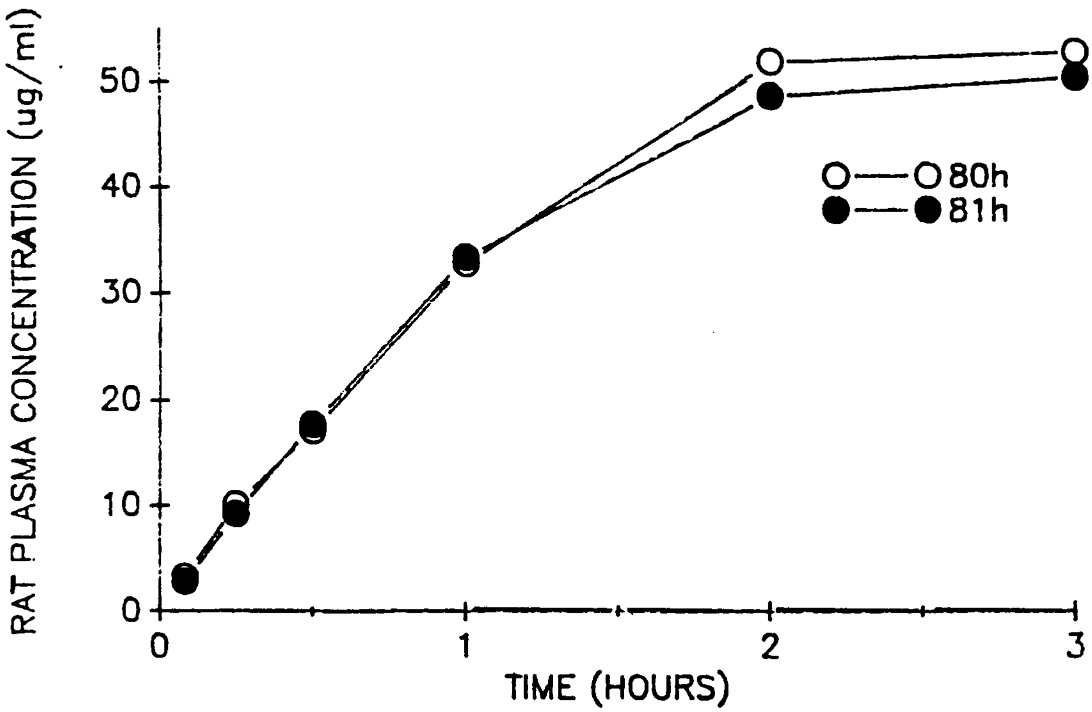


Figure II.2 Plasma ibuprofen concentrations in two rats. A Harvard 22 pump driven by STANPUMP[R], a computer software program, administered an iv ibuprofen solution to achieve 4 μg/ml immediately and then was expected to maintain this 4 μg/ml concentration according to programmed pharmacokinetic parameters.

A stable plasma drug concentration was desired, therefore, the Harvard 22 infusion pump was adjusted manually to produce a target concentration range of 3 μg/ml to 5 μg/ml. From analytical sampling over time, ibuprofen infusion regimen 2 above was determined empirically to sustain approximately 4 μg/ml plasma ibuprofen concentrations. Regimen 3 was also determined empirically, and was effective in gradually increasing the plasma ibuprofen concentration up to approximately 4 μg/ml and then maintaining about 4 μg/ml plasma ibuprofen concentration until the end of the experiment.

Data Analysis

Standard Curves were analyzed using Lotus^R (21). Pharmacokinetic analysis was done using SimuSolv^R and a nonparametric program written by Verotta and Sheiner (20,22). Statistical analysis was with SAS, with repeated measures and Tukey HSD test to make statistical comparisons among experimental dosing regimens and saline control groups; p values < 0.05 were considered to be significant (23). Appendix H contains the written SAS statistical computer programs.

RESULTS AND DISCUSSION

Oral ibuprofen reduced temperature in rats when compared to control rats (Figure II.3). Mean plasma ibuprofen concentrations achieved at 30 minutes in this study were much lower (3.8 μg/ml) than reported in Adams (13), (15 μg/ml), (Table II.1). Reasons for these differences are unknown, but not unexpected as the formulations differ and no attempt was made to duplicate drug particle size, suspension viscosity, or other formulation variables. Mean plasma ibuprofen concentrations from 1 to 4 hours were similar (Table II.1). A counterclockwise hysteresis loop was observed when plotting mean temperature decrement versus mean plasma ibuprofen concentrations (Figure II.4). A temperature decrement range existed from 0.5 hours (5 μg/ml) to 5 hours (2 μg/ml). This effect of only 2 μg/ml plasma ibuprofen concentration 5 hours post administration is clearly due to drug and not a loss of yeast induced fever as shown by comparison to control data (Figure II.3). To evaluate the full effect of ibuprofen on temperature decrement with different input rates, the middle of the temperature decrement window was chosen so there would be room for intensity change. Hence, 4 μg/ml plasma ibuprofen concentration was chosen

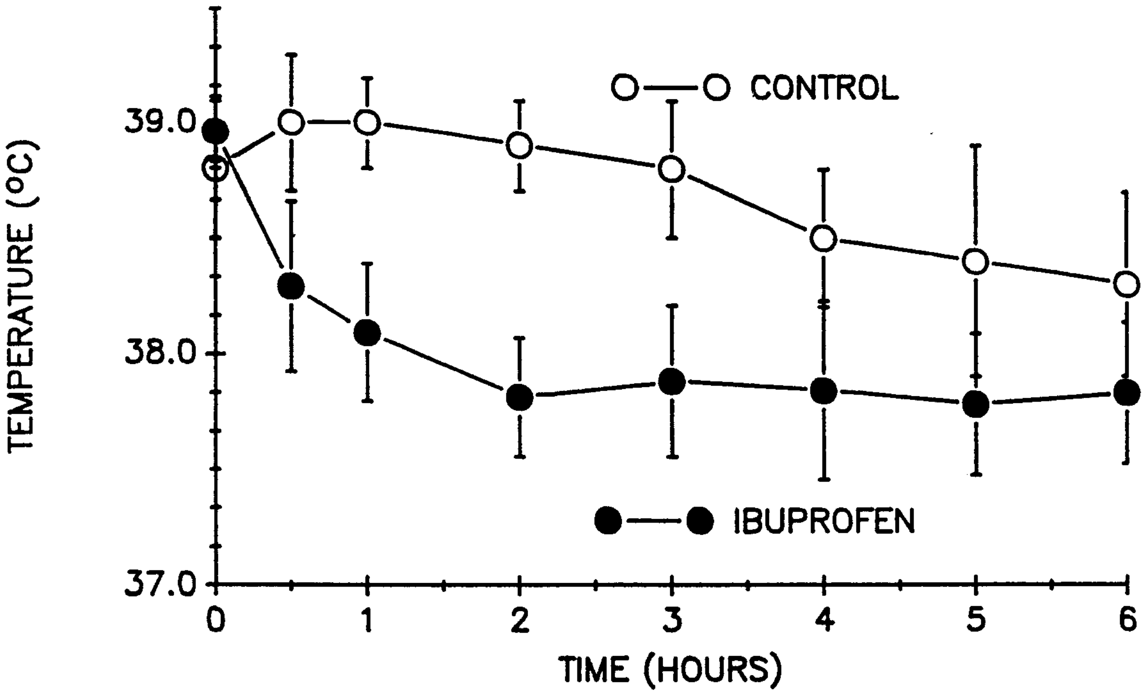


Figure II.3 Temperature reduction in rats with yeast induced fever after administrating (●-●) ibuprofen oral suspension, 7.5 mg/Kg, n=14, or (O-O) saline to controls, n=11.

Table II.1 Plasma ibuprofen concentrations after the administration of 5 mg/Kg oral suspension (Adams, et. al., Rheum. Physic. Med. Suppl: Symposuim on Ibuprofen, 9-22 (1970)) and ibuprofen oral suspension (7.5 mg/Kg) from this study in rats.

TIME (Hours)	Plasma Ibuprofen Concentration (μg/ml)	
	Dose of 5 mg/Kg	Dose of 7.5 mg/Kg
0.5	15.0	3.84
1	5.6	3.15
2	5.3	3.62
3		2.41
4	2.6	1.46

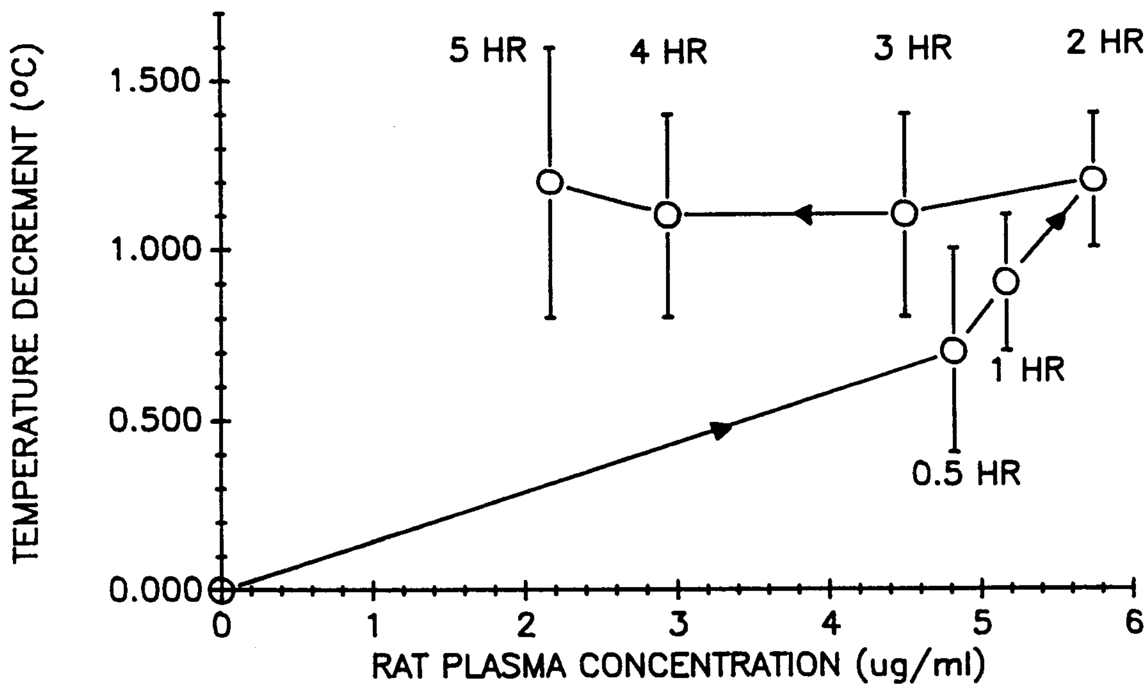


Figure II.4 Plasma ibuprofen concentration (μg/ml) versus temperature decrement (°C) profile after administering ibuprofen oral suspension (7.5 mg/Kg) to 14 rats with yeast induced fever. Counterclockwise hysteresis curve plotted in order of increasing time.

as the steady-state concentration to achieve and/or maintain for the next two ibuprofen input regimens. Individual temperature readings (°C) and temperature decrements for rats administered ibuprofen are listed in Appendix I. Individual temperature readings (°C) and temperature decrements for rats administered saline (controls) are listed in Appendix J.

Regimen 2 and Regimen 3: Administration of ibuprofen iv bolus followed by ibuprofen infusion (regimen 2) and ibuprofen infusion (regimen 3) reduced temperature (Figure II.5 and II.6) in rats with yeast induced fever. Regimen 2 (rapid drug rise) achieved maximum temperature decrement at 2 hours while regimen 3 (gradual drug rise) achieved maximum temperature decrement at 4 hours even though both ibuprofen input regimens had attained at least 4 μg/ml plasma ibuprofen concentration by 30 minutes post ibuprofen dose. Table II.2 lists the mean maximum temperature decrement and temperature decrement at 4 hours for each ibuprofen input regimen. These two input regimens were employed to separately quantify two pharmacokinetic variables as to their relative importance on antipyretic effect. They were the rate of increase in plasma ibuprofen concentration (gradual drug rise) and steady-state plasma ibuprofen concentration (rapid drug

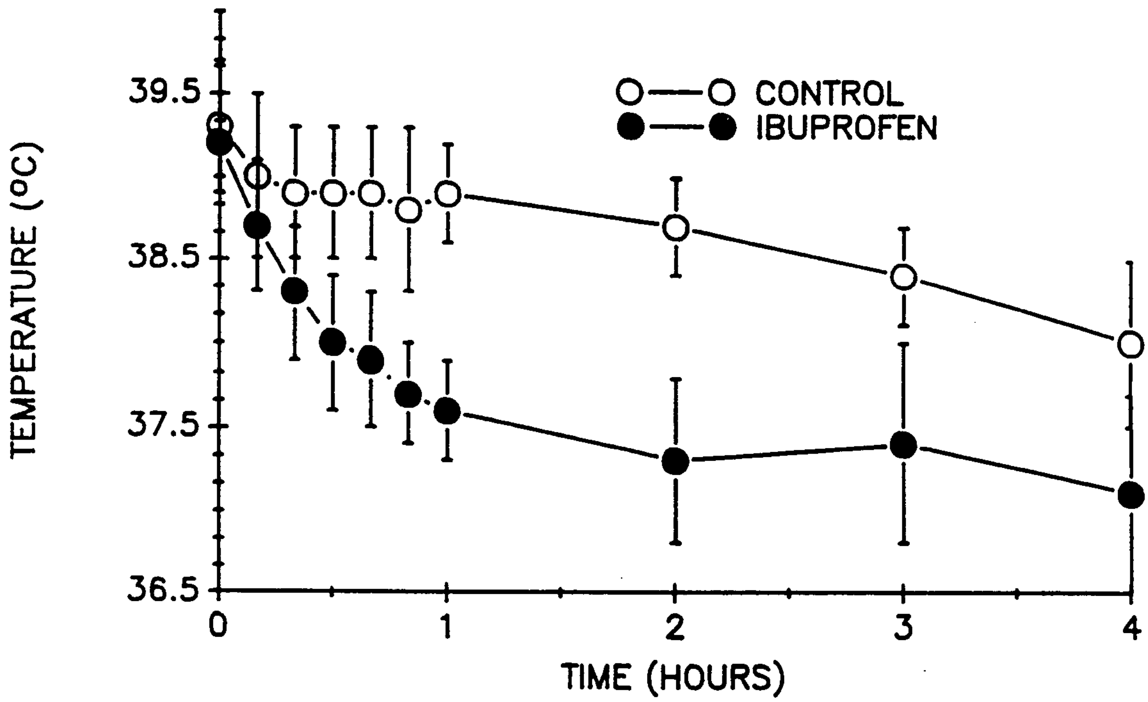


Figure II.5 Mean (± standard deviation) temperature (°C) readings after administration of ibuprofen iv bolus (0.83 mg/Kg) followed by ibuprofen infusion to obtain and maintain 4 μg/ml plasma ibuprofen concentrations, (●-●) regimen 2, n=9, or saline administered by iv bolus (0.83 mg/Kg) followed by saline infusion, (O-O) controls, regimen 2, n=9, into rats with yeast induced fever.

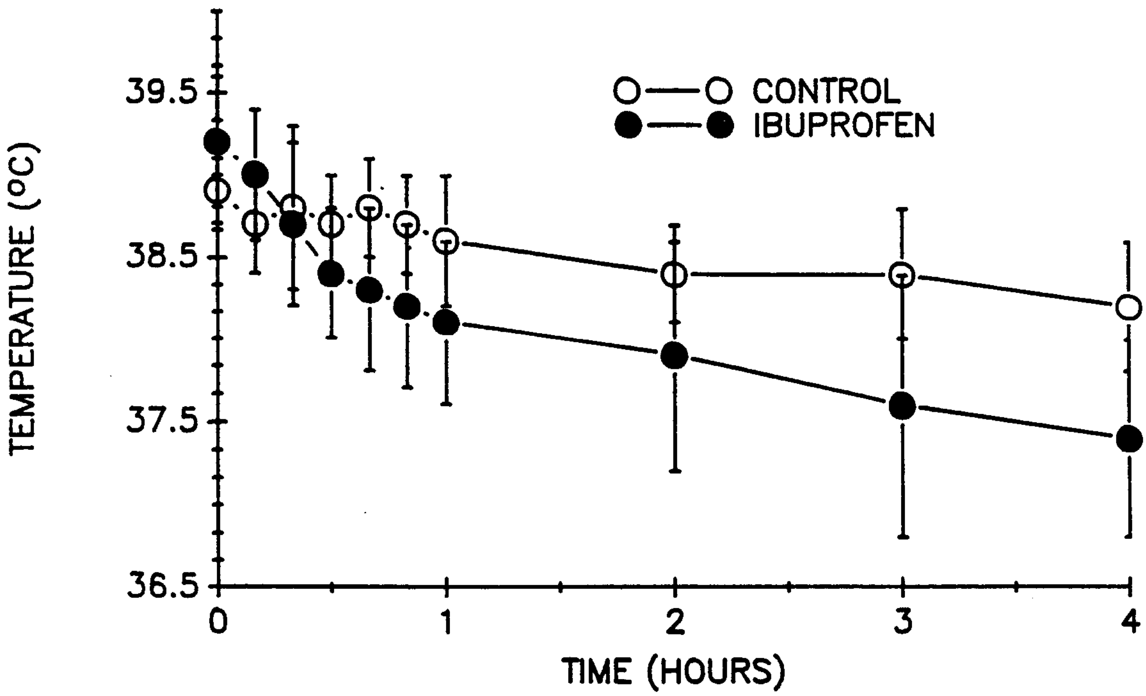


Figure II.6 Mean (± standard deviation) temperature (°C) readings after administration of ibuprofen slow infusion to obtain 4 μg/ml plasma ibuprofen concentration in 30 minutes and maintain approximately steady-state plasma ibuprofen concentrations over the next 3.5 hours, (●-●) regimen 3, n=9, or saline administered by slow infusion, (O-O) controls, regimen 3, n=9, into rats with yeast induced fever.

Table II.2 Mean temperature decrement readings (°C) from different ibuprofen dosing regimens.

DOSE REGIMEN	TIME TO MAXIMUM TEMPERATURE DECREMENT (HRS)	MEAN MAXIMUM TEMPERATURE DECREMENT (°C)	MEAN TEMPERATRURE DECREMENT AT 4 HOURS (°C)
1	2	1.3 (0.2)	0.9 (0.3)
2	2	1.2 (0.5)	0.7 (0.6)
3	4	1.1 (0.5)	1.1 (0.5)
4	1	1.0 (0.4)	0.3 (0.4)

(±) Standard deviation

rise). Regimen 2 was designed to immediately (rapid drug rise) produce steady-state concentrations of ibuprofen, while regimen 3 gradually (gradual rise) reached steady-state concentrations (Figure II.7). Plasma ibuprofen concentrations and temperature readings (°C) for individual rats are listed in Appendix K. The apparent qualitative trend in temperature decrement, although not statistically significant, perhaps due to variability, appears to be different between the two ibuprofen input regimens from 30 minutes until 4 hours (Figure II.8). It appears that maximum temperature decrement relates not just to the concentration of ibuprofen obtained at steady-state, but the rate at which it is obtained (Figures II.7 and II.8). Note that higher plasma ibuprofen concentrations from regimen 3 (gradual drug rise) gave a somewhat lesser effect than regimen 2 (rapid drug rise) as seen in Figures II.7 and II.8.

Regimen 4: Administration of ibuprofen iv bolus reduced temperature (Figure II.9) in rats with yeast induced fever. Mean maximum temperature reduction was achieved at 1 hour, however, by three hours post-dose, temperature reduction was not statistically different ($p = 0.17$) than control rats (Figure II.9). The iv bolus regimen was employed to ascertain if immediate obtainment of 4 $\mu g/ml$

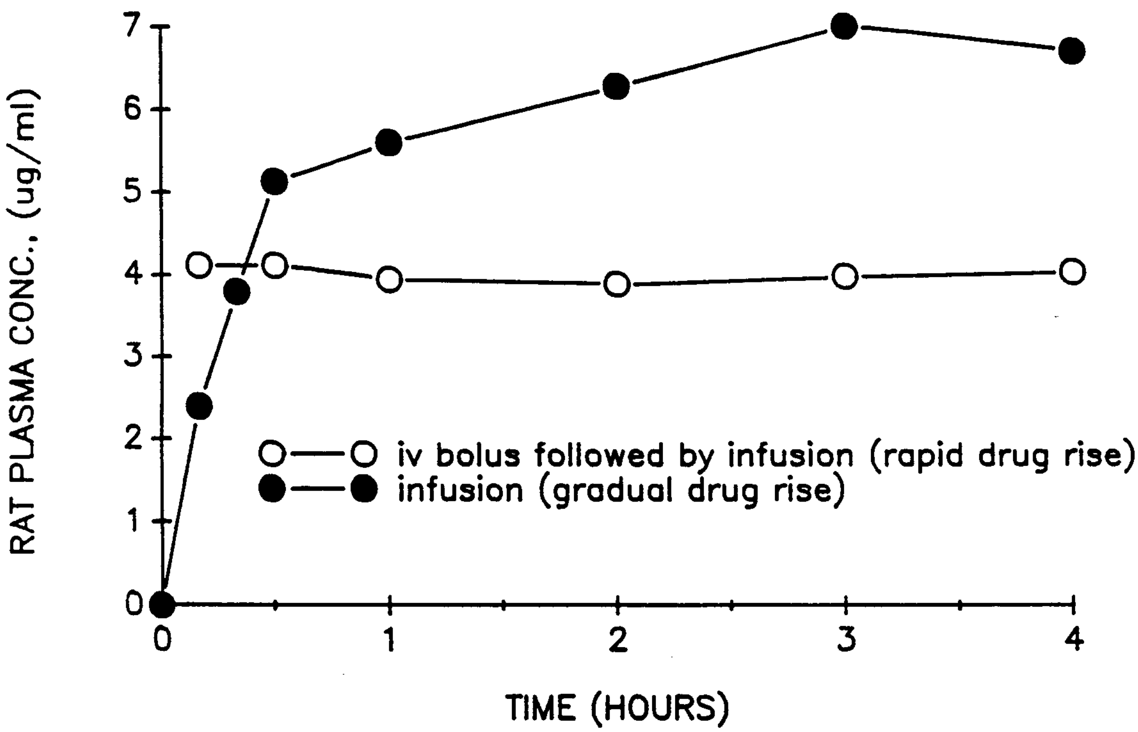


Figure II.7 Mean plasma ibuprofen concentrations from nine rats after administration of an iv bolus followed by ibuprofen infusion to immediately obtain and maintain 4 μg/ml plasma ibuprofen concentrations, regimen 2, (O-O). Mean plasma ibuprofen concentrations from nine rats after the administration of slow ibuprofen infusion to obtain 4 μg/ml in 30 minutes and then maintain approximately steady-state conditions over the next 3.5 hours, regimen 3, (●-●).

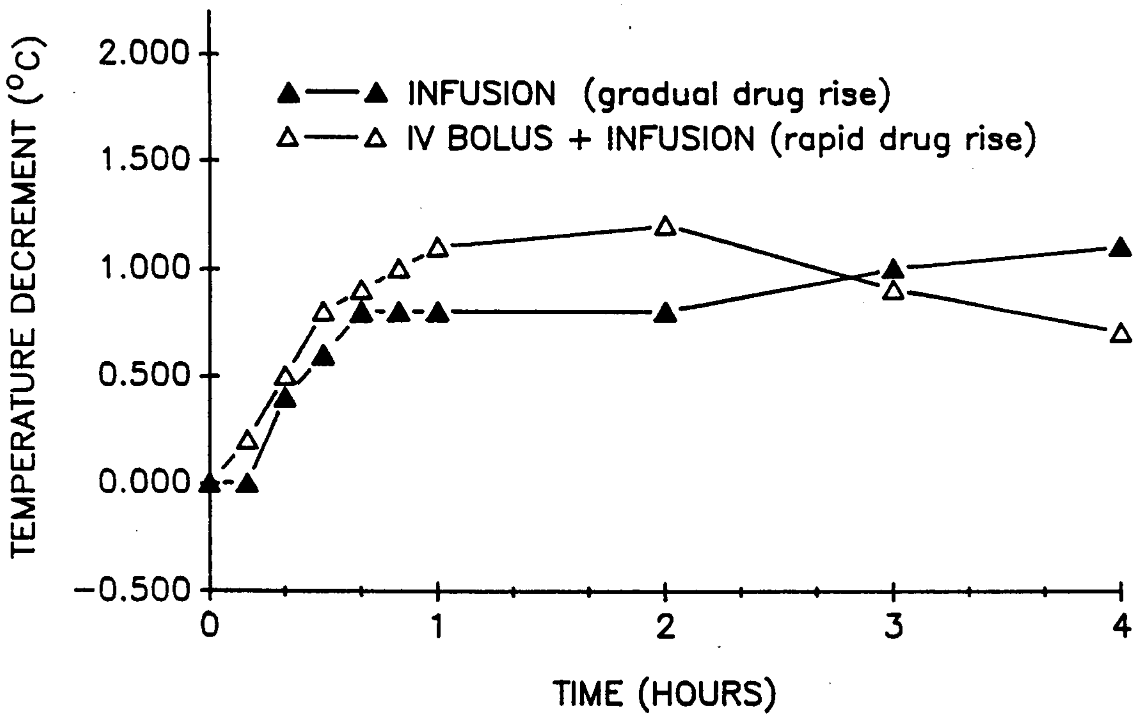


Figure II.8 Mean temperature decrement versus time profiles from two different ibuprofen input rates into rats with yeast induced fever. (△-△) regimen 2, n=9, Ibuprofen iv bolus followed by ibuprofen infusion to immediately obtain and maintain 4 μg/ml plasma ibuprofen concentrations until 4 hours post-dose. (▲-▲) regimen 3, n=9, slow ibuprofen infusion to obtain 4 μg/ml plasma ibuprofen concentrations in 30 minutes, then maintain approximately steady-state concentrations of 5-7 μg/ml over the next 3.5 hours.

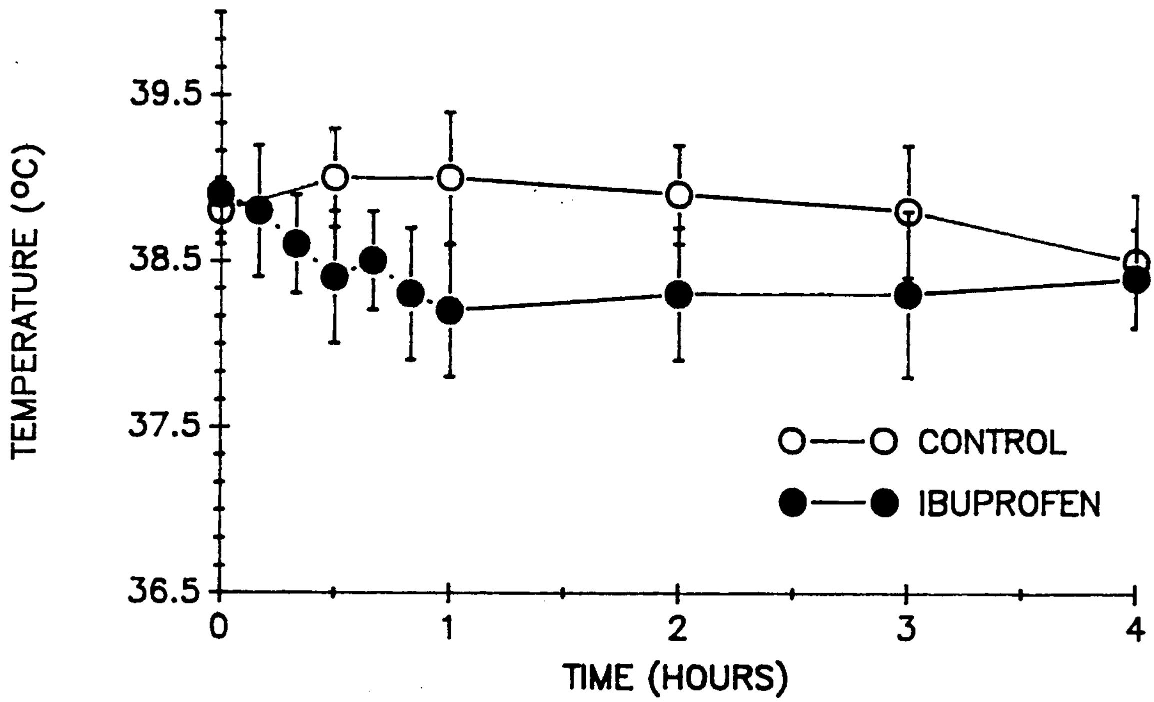


Figure II.9 Mean (± standard deviation) temperature (°C) readings after administration of ibuprofen iv bolus (0.83 mg/Kg), (●-●) regimen 4, n=7 or 0.5% methyl cellulose in saline administered by gavage, (O-O) controls from regimen 1, n=11, into rats with yeast induced fever.

peak plasma ibuprofen concentration was enough to reduce temperature and maintain temperature reduction over time. Plasma ibuprofen concentrations and temperature readings (°C) for individual rats are listed in Appendix k. Following 1 hour, as ibuprofen plasma concentrations were decreasing, temperature decrement was decreasing (Figure II.10). Therefore, there appears to be an ibuprofen plasma concentration-temperature decrement effect relationship.

Total saline volume administered to control rats over time varied for each input regimen (Table II.3). Extent of hydration over time appeared to influence temperature decrement as shown when comparing control rats among each input regimen (Figure II.11). Temperature decrement comparisons among experimental ibuprofen input regimens were made by subtracting respective mean control temperature values from each individual experimental rat's temperature values. Appendix I contains final temperature decrement readings when mean control temperature decrement was subtracted from each experimental rat for individual rats.

Figure II.12 shows that the mean maximum temperature decrement was achieved at 1 hr for regimen 4 (1°C), 2 hrs for regimen 1 and 2 (1.3°C and 1.2°C respectively) and at

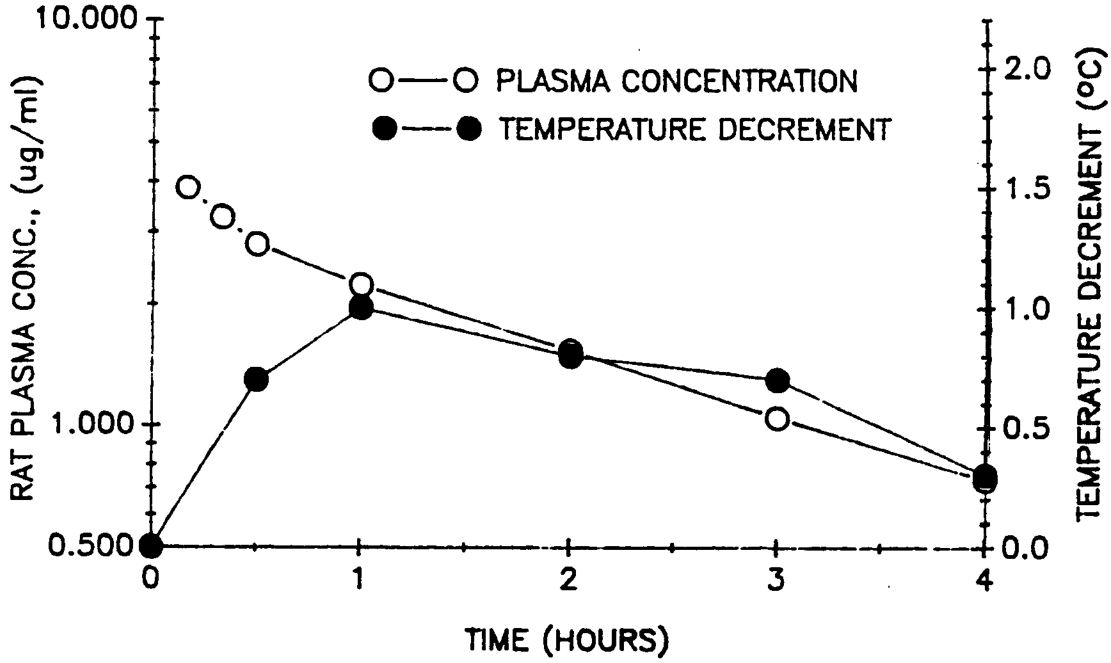


Figure II.10 Plasma ibuprofen concentration versus time curve and temperature decrement (°C) versus time curves for seven rats administered an ibuprofen iv bolus.

Table II.3 Mean total saline volumes administered to rats with yeast induced fever from different ibuprofen input regimens .

DOSING REGIMEN	MEAN TOTAL VOLUME (ML)
1	1.4
2	1.1
3	2.4
4	0.33

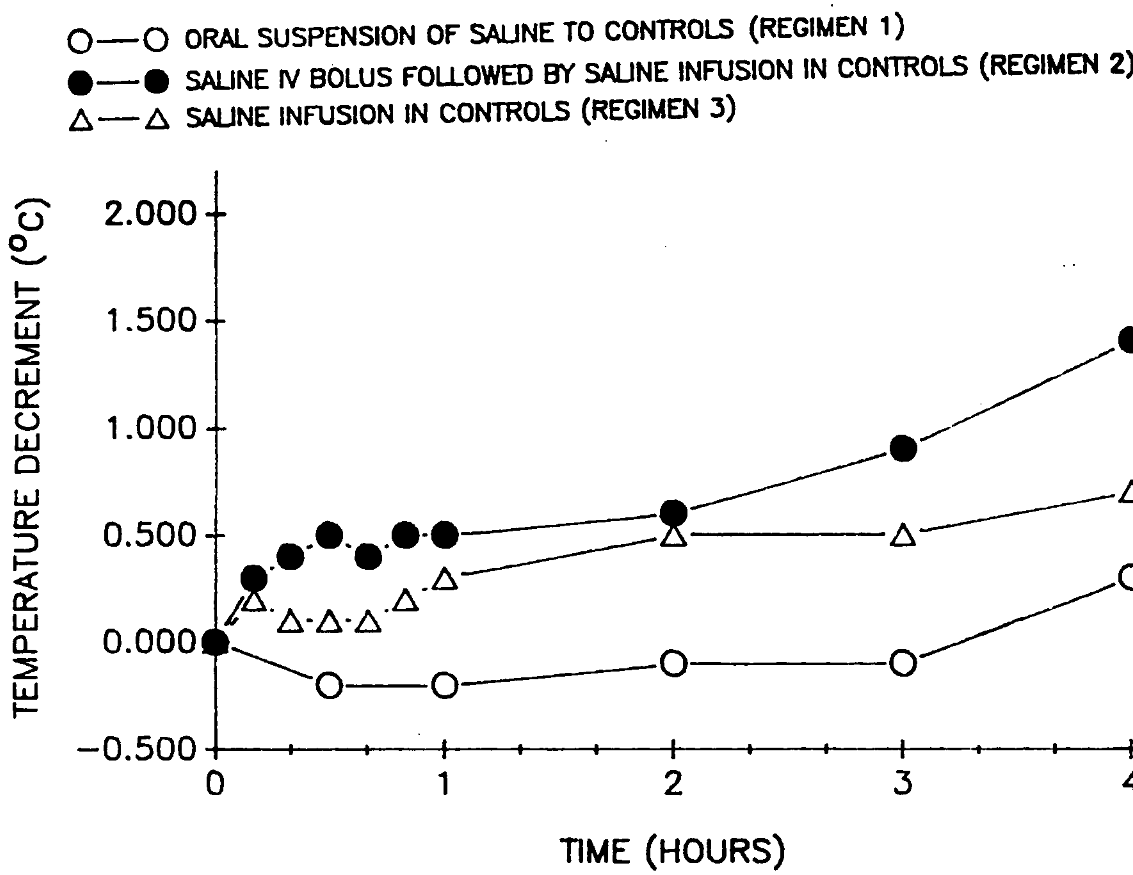


Figure II.11 Mean (± standard deviation) temperature (°C) readings versus time profiles from different saline input regimens into rats with yeast induced fever (Controls). (O-O) regimen 1, n=11, (●-●) regimen 2, n=9, (▲-▲) regimen 3, n=9.

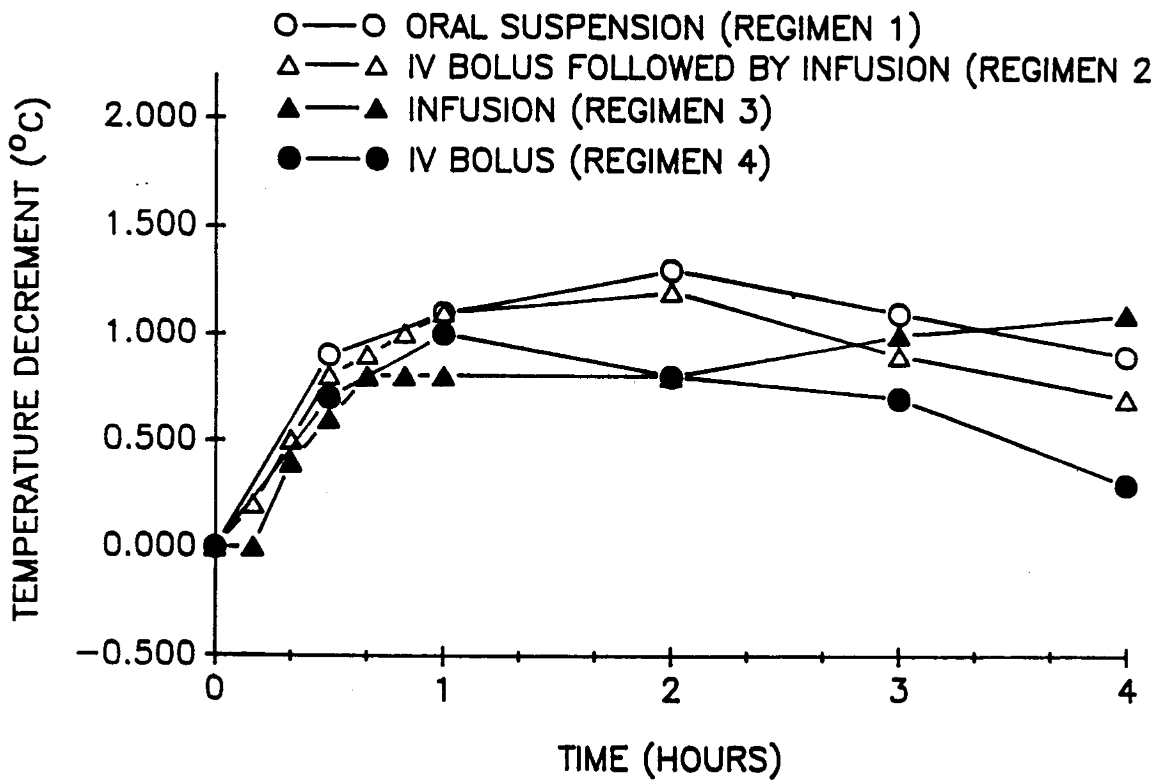


Figure II.12 Mean temperature decrement (°C) versus time profile from different ibuprofen input rates in rats with yeast induced fever. (O-O) regimen 1, n=11, (Δ-Δ) regimen 2, n=9, (▲-▲) regimen 3, n=9, (●-●) regimen 4, n=7.

4 hours for regimen 3 (1.1°C). Statisitical Analysis using SAS, with Repeated Measures showed that there was a statistically significant ($p=0.0045$) group*time interaction term whether time 0 was included in the analysis or not. The group*time interaction term is a statistical term that answers the question; does the difference between times (ie., mean temperature decrement recording at designated times) depend on the which group (ie., ibuprofen input rate regimen)? Further, when the ibuprofen input regimens were run two at a time to look at which input regimens actually exhibited group*time interaction, Repeated Measures showed that the suspension versus infusion regimen showed a statistically significant group*time interaction ($p = 0.0045$). The other ibuprofen input regimens comparisons showed no statistically significant group*time interaction term. Tukey HSD test showed that mean temperature decrement at 4 hours for the iv bolus regimen (0.3°C) was statistically significantly less ($p < 0.05$) than regimens 1 and 3 (0.9°C and 1.1°C, respectively). The other three regimens (1, 2 and 3) showed no statistical differences ($p > 0.05$) at 4 hours (Table II.2). Mean temperature decrement at 2 hours for the iv bolus regimen (0.5°C) was statistically significantly less ($p < 0.05$) than regimens 1 and 2 (1.3°C and 1.2°C, respectively), while mean

temperature decrement at 2 hours for the infusion regimen (0.8°C) was statistically significantly less ($p < 0.05$) than regimen 1 (1.3°C).

Regimen 1 (oral ibuprofen suspension) and regimen 2 (ibuprofen iv bolus followed by infusion) had similar plasma versus time and temperature decrement versus time profiles (Figures II.13 and II.14). This might indicate rapid ibuprofen absorption (within 5 to 10 minutes) into the systemic circulation post ibuprofen oral suspension administration. Adams (13) demonstrated that rat plasma ibuprofen levels after a single oral ibuprofen dose (5 mg/Kg), when graphed, had the appearance of an iv bolus administration. If there is rapid ibuprofen absorption, this might explain the similarity in temperature decrement profiles, since both rat regimens 1 and 2 in this study achieved approximately 4 μg/ml plasma ibuprofen concentrations immediately and maintained plasma ibuprofen concentrations around 4 μg/ml post ibuprofen administration.

Since data from fevered children were available from literature (11), it was possible to explore the relationship between the pharmacodynamics of ibuprofen in rats and children. Appendix L lists plasma ibuprofen concentrations and temperature decrement data from literature. Appendix L also lists individual rat's

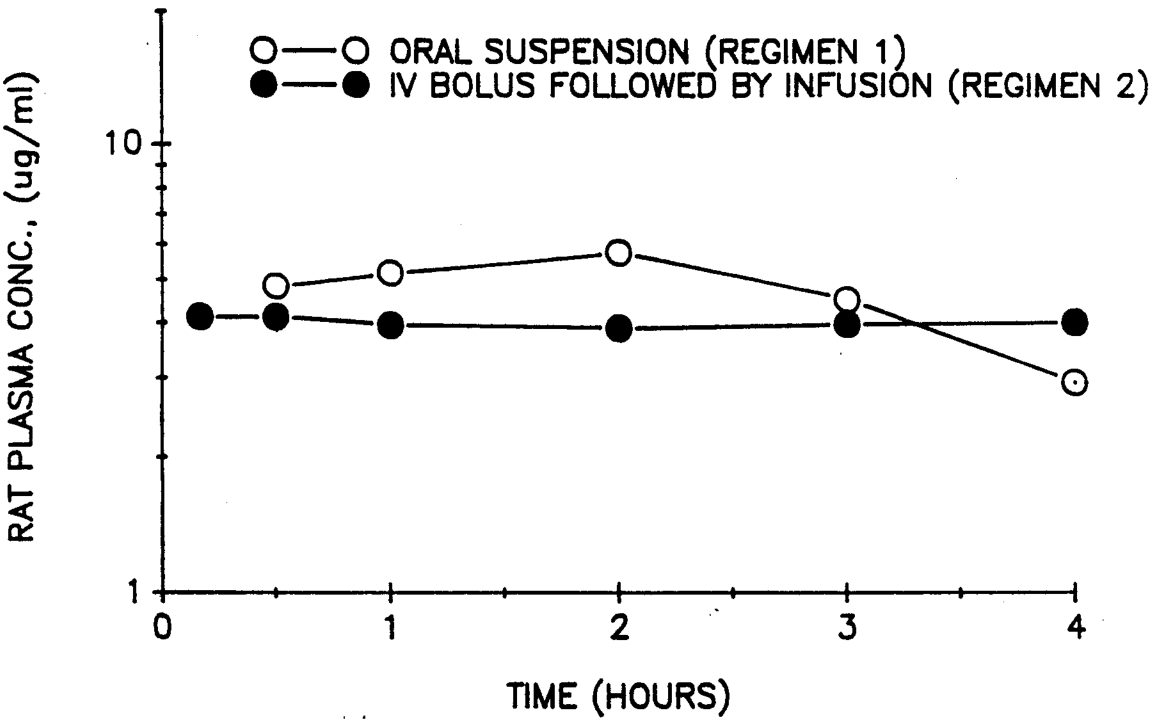


Figure II.13 Mean plasma ibuprofen concentration versus time profiles from administration of ibuprofen oral suspension (O-O) regimen 1, n=14, or from an ibuprofen iv bolus followed by infusion to obtain and maintain 4 μg/ml plasma concentration, (●-●) regimen 2, n=9, into rats with yeast induced fever.

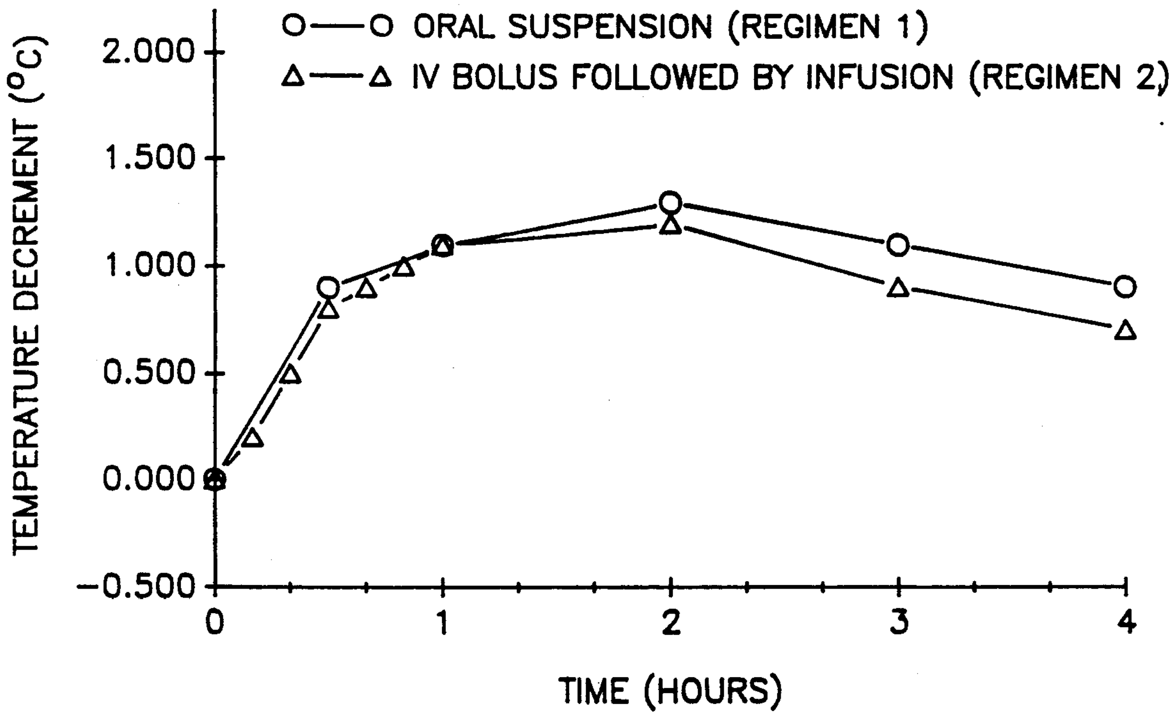


Figure II.14 Mean temperature decrement (°C) versus time profile from different ibuprofen input rates in rats with yeast induced fever. (O-O) regimen 1, n=11, (Δ-Δ) regimen 2, n=9.

weights used in all ibuprofen input regimens. Ibuprofen suspension used in this study was identical to the ibuprofen suspension used in Walson's (11) children's study (100 mg/5 ml suspension). When plasma ibuprofen concentrations were plotted against temperature decrement readings in order of increasing time, counterclockwise hysteresis curves were observed in rats and children (Figures II.4 and II.15). Counterclockwise hysteresis curves can represent a delay in equilibration between plasma drug concentration and the concentration of active substance at the effect site. In an attempt to describe the time course of ibuprofen antipyretic effect, K_{eo}, the rate constant for elimination of ibuprofen from the effect compartment (24,25) was estimated for rats from data of this study, and for children from data in Walson's (11) study. Nonparametric analysis (22) was done on both sets of data which resulted in mean t1/2-KEO, the half-life of the antipyretic effect in the effect compartment, values of 11.5 minutes for rats and 1.5 hours for children. Appendix M contains the nonparametric analysis for rats and children. These values are substantially different but upon conversion to biological time, to take into account each species' own internal clock (26,27), the rat t1/2-KEO value was 1.3 hours which compared favorably with 1.5 hours in

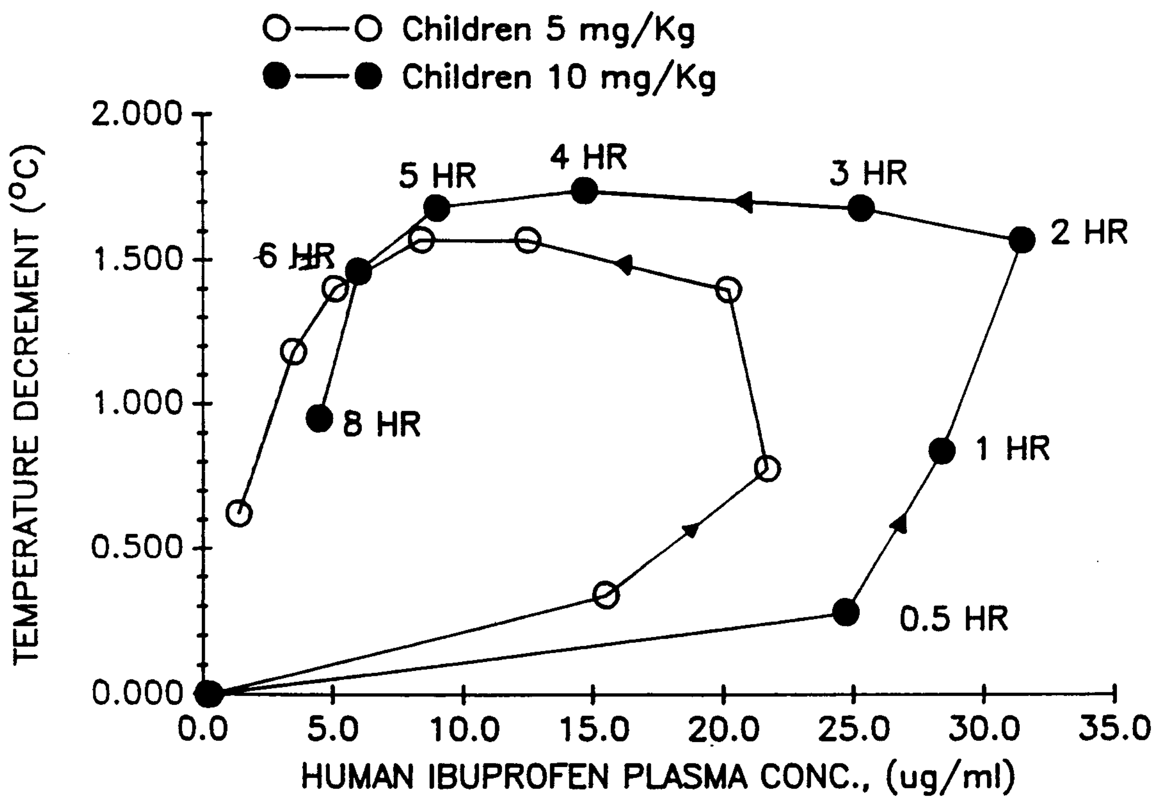


Figure II.15 Mean plasma ibuprofen concentrations (μg/ml) versus temperature decrement (°C) profile after administration of ibuprofen oral suspension, (O-O) 5 mg/Kg, n=29, or (●-●) 10 mg/Kg, n=25, to children. Counterclockwise hysteresis curves are plotted in order of increasing time. Data from Walson, P.D., et. al. Clin. Pharmacol. Ther. 46(1), 9-17 (1989).

children. Furthermore, the t1/2-KEO of 1.5 hours estimated in this work was in good agreement with the t1/2-KEO value from another study where the pharmacodynamics of ibuprofen induced antipyresis was evaluated in 51 children (28).

In addition, when predicted ibuprofen effect compartment concentration versus predicted temperature decrement effect (29,30) were plotted (collapsed hysteresis curves), the rat and children's curves were not superimposable (Figure II.16). Appendix M lists the predicted ibuprofen effect compartment concentration and predicted temperature decrement effect data. Since protein binding is different between rats and humans (96% bound in rats, 99% bound in humans (12,15)), the unbound fraction of ibuprofen concentration in the effect compartment was plotted. The collapsed hysteresis curves of mean predicted ibuprofen unbound effect concentration versus mean predicted temperature decrement effect were superimposable between rats and children (Figure II.17).

Further, the shape of the collapsed hysteresis curve for the children's 10 mg/Kg dose (Figure II.17) was representative of a sigmoidal (S-shaped) curve (30-33). Unbound ibuprofen effect compartment concentration data were fitted to a sigmoidal equation by PCNONLIN^{R} (34).

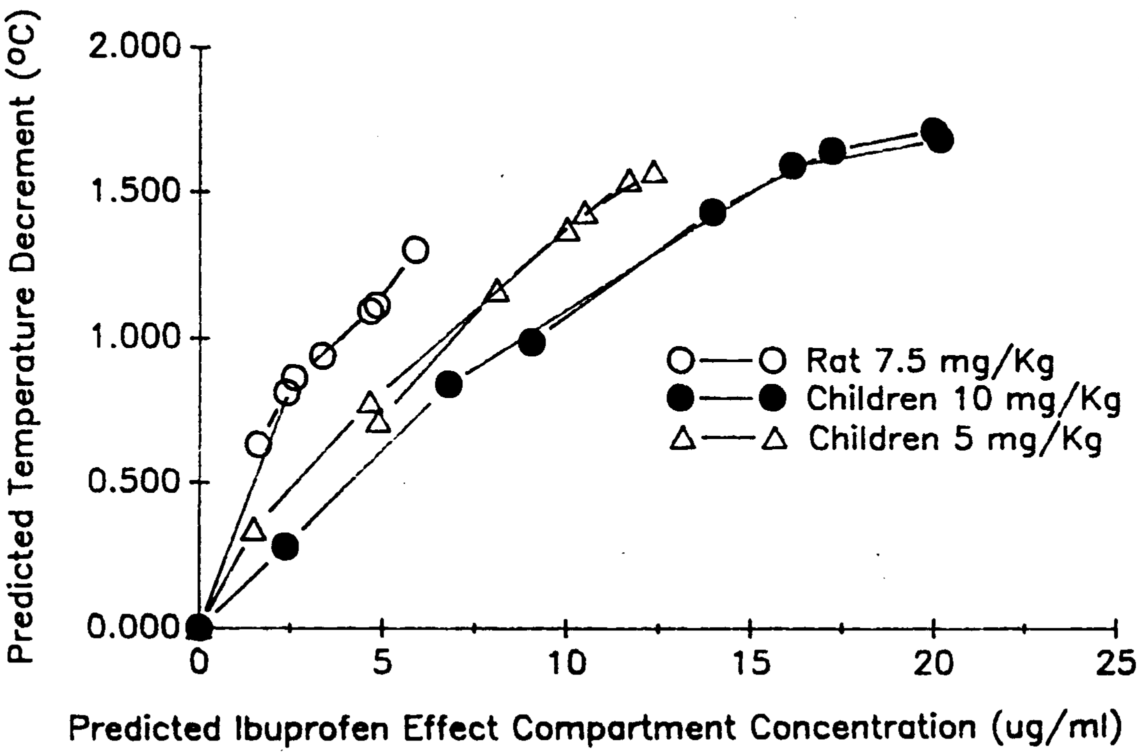


Figure II.16 Collapsed hysteresis curves of predicted total ibuprofen effect compartment concentration versus predicted temperature decrement readings in 1) (O-O) rats, 7.5 mg/Kg ibuprofen oral suspension, 2) (Δ-Δ) children, 5 mg/Kg ibuprofen oral suspension and 3) (●-●) children 10 mg/Kg ibuprofen oral suspension.

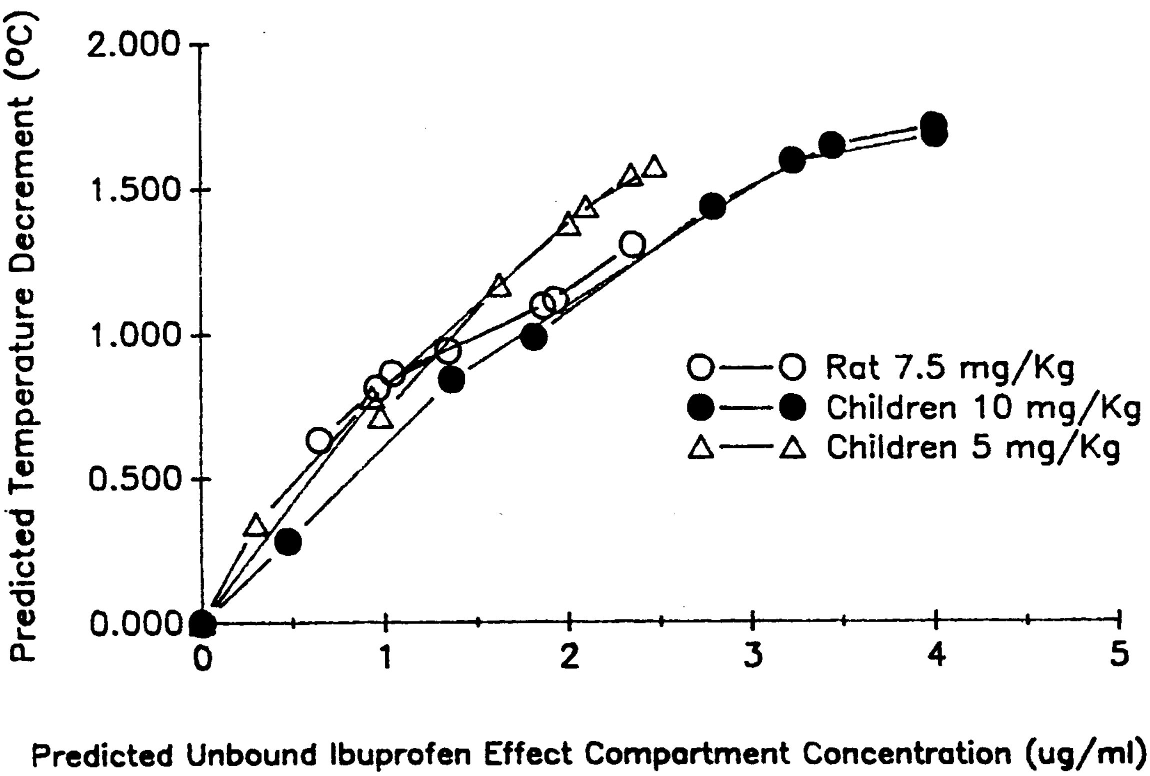


Figure II.17 Collapsed hysteresis curves of predicted <u>unbound</u> ibuprofen effect compartment concentration versus predicted temperature decrement readings in 1) (O-O) rats, 7.5 mg/Kg ibuprofen oral suspension, 2) (Δ-Δ) children, 5 mg/Kg ibuprofen oral suspension and 3) (●-●) children, 10 mg/Kg ibuprofen oral suspension.

Table II.4 Pharmacodynamic parameters for rats and children administered ibuprofen oral suspension.

	N	EC50 (μg/ml)	EMAX (°C)
Rat (7.5 mg/Kg)	0.75	3.67	3.0
Children (5 mg/Kg)	1.17	2.33	3.0
Children (10 mg/Kg)	1.39	2.28	2.5

N function of slope
EC50 drug concentration producing 50% of the maximal response (temperature decrement)
EMAX maximal effect shown by the drug

Appendix N lists the computer output results from the sigmoidal fit. Pharmacodynamic parameters estimated from the fit are listed in Table II.4. EC50 defined as minimum unbound ibuprofen effect compartment concentration giving 50% response (temperature decrement) was 2.28 μg/ml. N defined as a function of the slope was 1.39 and Emax defined as maximum effect (temperature decrement) shown by ibuprofen was 2.5 (°C). Although the shape of the collapsed hysteresis curves for rat's and children's 5 mg/Kg doses were representative of sigmoidal curves, maximum effect was not clearly defined by the observations. A pharmacodynamic analysis was done anyway using the sigmoidal equation by PCNONLIN^R. Results of the fit are comparable to the children's 10 mg/Kg dose (Table II.4). Emax for the rat 7.5 mg/Kg dose and children's 5 mg/Kg dose was the same, 3.0 (°C), N was 0.75 and 1.17, respectively, and the EC50 was 3.67 μg/ml and 2.33 μg/ml, respectively. It appears that the pharmacodynamic parameters among children and rats are comparable.

CONCLUSIONS

Ibuprofen administered to rats produced significant temperature reduction when compared to their respective control rats in all input rate regimens (Figures II.3, II.5, II.6 and II.9). The apparent qualitative trend in temperature decrement, although not statistically significant, perhaps due to variability, appears to be different among the ibuprofen input rates in rats. Maximum temperature decrement appears to relate not just to the concentration of ibuprofen obtained at steady-state, but the rate at which it is obtained. Thus, in designing dosage forms or determining bioequivalence of ibuprofen among various dosage forms, the importance of rate of absorption can not be overlooked. Based on mean unbound ibuprofen effect compartment concentration versus mean predicted temperature decrement effect, the antipyretic response to ibuprofen appears to be comparable between rats and children.

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APPENDICES

APPENDIX A

INDIVIDUAL HORSE DATA

(WEIGHT, DOSE, TAU, AND INFUSION RATE)

Table A.1 Individual horse data from aminophylline (10 mg/Kg, administered alone or concomitantly with dyphylline, 20 mg/Kg) intravenous infusion administration.

Horse Name	Weight (Kg)	Dose[a] (mg)	Tau[b] (min)	Infusion Rate[c] (mg/min)
Moon Mist	500	5000 (4000)	10	500 (400)
Taylor Lock	488	4800 (3840)	20	240 (192)
Picket Creek	350	3500 (2800)	15	233.3 (186.6)
Gypsy	373	3730 (2984)	15	248.7 (199)
Melodee	425.5	4255 (3404)	15	283.7 (227)
Linda	443	4430 (3544)	15	295.3 (236.2)
(Mean)	430	4286 (3428)	15	300.2 (240.2)

[a] Aminophylline contains approximately 80% theophylline. Dose (mg) without brackets is the amount of aminophylline (mg) injected. Dose (mg) in brackets is the amount of theophylline dose (80% of aminophylline dose) administered.

[b] Tau is the duration of aminophylline infusion.

[c] Infusion Rate = Dose (aminophylline)/ Tau
(Infusion Rate) = Dose (theophylline)/Tau

Table A.2 Individual horse data from aminophylline (20 mg/Kg, administered alone) intravenous infusion administration.

Horse Name	Weight (Kg)	Dose[a] (mg)	Tau[b] (min)	Infusion Rate[c] (mg/min)
Moon Mist	500	10,000 (8000)	10	1000 (800)
Taylor Lock	488	9760 (7808)	20	488 (390.4)
Picket Creek	350	7000 (5600)	20	350 (280)
Gypsy	373	7460 (5968)	20	373 (298.4)
Melodee	425.5	8510 (6808)	20	425.5 (340.4)
Linda	443	8860 (7088)	20	443 (354.4)
(Mean)	430	8598 (6878)	20	513 (410.4)

[a] Aminophylline contains approximately 80% theophylline. Dose (mg) without brackets is the amount of aminophylline (mg) injected. Dose (mg) in brackets is the amount of theophylline dose (80% of aminophylline dose) administered.

[b] Tau is the duration of aminophylline infusion.

[c] Infusion Rate = Dose (aminophylline)/ Tau
(Infusion Rate) = Dose (theophylline)/Tau

Table A.3 Individual horse data from dyphylline (20 mg/Kg (administered alone or concomitantly with aminophylline, 10 mg/Kg), or 40 mg/Kg administered alone)) intravenous administration.

Horse Name	Weight (Kg)	20 mg/Kg Dose (mg)	40 mg/Kg Dose (mg)
Moon Mist	500	10,000	20,000
Taylor Lock	488	9760	19,520
Picket Creek	350	7000	14,000
Gypsy	373	7460	14,920
Melodee	425.5	8510	17,020
Linda	443	8860	17,720
(Mean)	430	8598	17,197

APPENDIX B

INDIVIDUAL HORSE PHARMACOKINETIC PARAMETERS AFTER DYPHYLLINE AND THEOPHYLLINE ADMINISTRATION

Table B.1 Individual pharmacokinetic parameters for dyphylline iv bolus administration in horses (plasma concentrations).

DYPHYLLINE, 20 MG/KG IV BOLUS PRECEDED BY AMINOPHYLLINE INFUSION, 10 MG/KG (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	BETA (hr-1)	CL (L/hr)	Vdarea (L)	MRT (hrs)
MOON MIST	10000.000	12951.000	0.297	0.772	2.600	0.135
TAYLOR LOCK	9760.000	83.460	0.284	116.942	411.768	2.390
PICKET CREEK	7000.000	76.090	0.242	91.996	380.150	3.520
GYPSY	7460.000	138.940	0.293	53.692	183.250	1.740
MELODEE	8510.000	60.580	0.294	140.475	477.807	3.010
LINDA	8860.000	56.550	0.288	156.676	544.012	2.650
MEAN (WITHOUT MM)	8318.000	83.124	0.280	111.956	399.398	2.662
SD	1104.907	33.089	0.022	40.716	136.295	0.667

DYPHYLLINE, 20 MG/KG, IV BOLUS, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	BETA (hr-1)	CL (L/hr)	Vdarea (L)	MRT (hrs)
MOON MIST	10000.000	42.720	0.562	234.082	416.517	1.430
TAYLOR LOCK	9760.000	40.020	0.473	243.878	515.598	1.790
PICKET CREEK	7000.000	54.950	0.354	127.389	359.855	2.080
GYPSY	7460.000	113.440	0.484	65.762	135.871	1.860
MELODEE	8510.000	58.210	0.147	146.195	994.523	2.850
LINDA	8860.000	36.330	0.600	243.876	406.459	1.750
MEAN	8598.333	57.612	0.437	176.864	471.470	1.960
SD	1203.402	28.665	0.165	74.816	285.609	0.484

DYPHYLLINE, 40 MG/KG, IV BOLUS, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	BETA (hr-1)	CL (L/hr)	Vdarea (L)	MRT (hrs)
MOON MIST	20000.000	207.000	0.253	96.618	381.891	2.360
TAYLOR LOCK	19520.000	108.800	0.277	179.412	647.696	3.350
PICKET CREEK	14000.000	99.330	0.220	140.944	640.656	4.370
GYPSY	14920.000	160.800	0.230	92.786	403.418	3.060
MELODEE	17020.000	114.160	0.273	149.089	546.114	3.010
LINDA	17720.000	85.090	0.346	208.250	601.879	2.270
MEAN	17196.667	129.197	0.267	144.517	536.942	3.070
SD	2406.804	45.895	0.045	45.351	117.638	0.764

AUC and BETA calculated from PCNONLIN: 2-COMPARTMENT OPEN PHARMACOKINETIC MODEL WITH BOLUS INPUT (VER. 3.0)

Cl = DOSE/AUC   Vdarea = Cl/BETA   MRT calculated from RSTRIP (VER. 2.0)

Table B.2 Individual pharmacokinetic parameters for dyphylline iv bolus administration in horses (csf concentrations).

DYPHYLLINE, 20 MG/KG, IV BOLUS, PRECEDED BY AMINOPHYLLINE INFUSION, 10 MG/KG (CSF)

HORSE CODE	K12 (hr-1)	K21 (hr-1)	DOSE (mg)	AUC (0-00) (mg*hr/L)	ALPHA (hr-1)	BETA (hr-1)	DOSEt (mg)	MRT (hrs)
MOON MIST	--	--	10000.000	--	--	--	--	--
TAYLOR LOCK	1.840	0.338	9760.000	18.670	1.910	0.327	11344.536	3.530
PICKET CREEK	0.813	0.122	7000.000	13.240	0.802	0.123	8381.443	8.860
GYPSY	0.398	0.394	7460.000	18.440	0.635	0.319	9395.823	4.270
MELODEE	0.789	0.186	8510.000	9.290	0.924	0.145	8619.243	7.980
LINDA	0.808	0.228	8860.000	12.890	0.807	0.228	12364.214	5.450
MEAN (WITHOUT MM)	0.930	0.254	8318.000	14.506	1.016	0.228	10021.052	6.018
SD	0.538	0.111	1104.907	4.007	0.510	0.095	1752.592	2.318

DYPHYLLINE, 20 MG/KG, IV BOLUS, ADMINISTERED ALONE (CSF)

HORSE CODE	K12 (hr-1)	K21 (hr-1)	DOSE (mg)	AUC (0-00) (mg*hr/L)	ALPHA (hr-1)	BETA (hr-1)	DOSEt (mg)	MRT (hrs)
MOON MIST	--	--	10000.000	--	--	--	--	--
TAYLOR LOCK	--	--	9760.000	--	--	--	--	--
PICKET CREEK	3.750	0.248	7000.000	14.230	3.740	0.248	7517.182	4.300
GYPSY	2.260	0.110	7460.000	18.470	2.270	0.109	7801.758	9.600
MELODEE	1.900	0.306	8510.000	6.150	1.910	0.306	10080.424	3.800
LINDA	4.770	0.100	8860.000	8.060	4.800	0.100	8991.957	10.270
MEAN	3.170	0.191	7957.500	11.728	3.180	0.191	8597.830	6.993
SD	1.334	0.102	872.558	5.665	1.339	0.102	1176.853	3.415

DYPHYLLINE, 40 MG/KG, IV BOLUS, ADMINISTERED ALONE (CSF)

HORSE CODE	K12 (hr-1)	K21 (hr-1)	DOSE (mg)	AUC (0-00) (mg*hr/L)	ALPHA (hr-1)	BETA (hr-1)	DOSEt (mg)	MRT (hrs)
MOON MIST	2.630	0.234	20000.000	11.300	2.680	0.239	21548.546	4.550
TAYLOR LOCK	1.920	0.290	19520.000	48.650	2.050	0.288	21270.375	3.850
PICKET CREEK	1.320	0.277	14000.000	57.810	1.340	0.276	17368.421	4.370
GYPSY	5.000	0.229	14920.000	39.650	41.700	0.231	1798.934	4.340
MELODEE	1.140	0.181	17020.000	38.570	1.140	0.181	20232.325	6.400
LINDA	1.050	0.188	17720.000	60.400	1.040	0.189	21863.690	5.790
MEAN	2.177	0.233	17196.667	42.730	8.325	0.234	17347.048	4.883
SD	1.505	0.045	2406.804	17.829	16.362	0.044	7791.203	0.986

NOTE: "t" refers to perpherial compartment (CSF)

Dt = K12*Do (EXP(-BETA*TIME)) - EXP(-ALPHA*TIME))/ (ALPHA - BETA)

K12, K21, and AUC were calculated from PCNONLIN (VER. 3.0)

MRT, ALPHA and BETA were calculated from RSTRIP (VER. 2.0)

Table B.3 Individual pharmacokinetic parameters for theophylline after aminophylline infusion in horses (plasma concentrations).

AMINOPHYLLINE, 10 MG/KG, INFUSION FOLLOWED BY DYPHYLLINE, 20 MG/KG IV BOLUS (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	BETA (hr-1)	CL (L/hr)	Vdarea (L)	MRTpi (hrs)	TAU (hr)	MRTinf (hrs)
MOON MIST	4000.000	135.570	0.078	29.505	378.270	12.350	0.250	12.475
TAYLOR LOCK	3840.000	176.340	0.067	21.776	325.017	14.750	0.250	14.875
PICKET CREEK	2800.000	101.270	0.054	27.649	512.016	15.890	0.250	16.015
GYPSY	2984.000	233.030	0.045	12.805	284.560	21.340	0.330	21.505
MELODEE	3404.000	133.910	0.072	25.420	353.056	13.170	0.330	13.335
LINDA	3544.000	151.680	0.069	23.365	338.623	13.670	0.250	13.795
MEAN	3428.667	155.300	0.064	23.420	365.257	15.195	0.277	15.333
SD	469.569	45.307	0.012	5.904	78.354	3.255	0.041	3.265

AMINOPHYLLINE, 10 MG/KG, INFUSION, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	BETA (hr-1)	CL (L/hr)	Vdarea (L)	MRTpi (hrs)	TAU (hr)	MRTinf (hrs)
MOON MIST	4000.000	549.180	0.044	7.284	165.536	9.610	0.250	9.735
TAYLOR LOCK	3840.000	142.940	0.072	26.864	373.117	13.280	0.500	13.530
PICKET CREEK	2800.000	173.520	0.057	16.136	283.096	17.090	0.250	17.215
GYPSY	2984.000	273.170	0.038	10.924	287.463	24.730	0.250	24.855
MELODEE	3404.000	142.220	0.064	23.935	373.980	15.440	0.170	15.525
LINDA	3544.000	177.000	0.071	20.023	282.008	13.440	0.250	13.565
MEAN	3428.667	243.005	0.058	17.528	294.200	15.598	0.278	15.738
SD	469.569	157.486	0.014	7.549	76.765	5.129	0.113	5.118

AMINOPHYLLINE, 20 MG/KG, INFUSION, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	BETA (hr-1)	CL (L/hr)	Vdarea (L)	MRTpi (hrs)	TAU (hr)	MRTinf (hrs)
MOON MIST	8000.000	805.380	0.036	9.933	275.922	25.610	0.170	25.695
TAYLOR LOCK	7808.000	256.450	0.064	30.446	475.726	15.440	0.330	15.605
PICKET CREEK	5600.000	414.430	0.047	13.513	287.501	21.590	0.330	21.755
GYPSY	5968.000	939.930	0.035	6.349	181.412	25.310	0.330	25.475
MELODEE	6808.000	298.100	0.065	22.838	351.353	15.090	0.330	15.255
LINDA	7088.000	406.620	0.056	17.432	311.277	13.440	0.330	13.605
MEAN	6878.667	520.152	0.051	16.752	313.865	19.413	0.303	19.565
SD	962.722	283.013	0.013	8.835	97.252	5.442	0.065	5.424

AUC and BETA calculated from RSTRIP (VER. 2.0)
DOSE LISTED IS THE AMOUNT OF THEOPHYLLINE INJECTED (80% OF AMINOPHYLLINE DOSE)
Cl = DOSE/AUC (DOSE = THEOPHYLLINE DOSE INJECTED)
Vdarea = Cl/BETA
MRTpi (pi = post-infusion) calculated from RSTRIP (VER. 2.0)
MRTinf = MRTpi + Tau/2

Table B.4 Individual pharmacokinetic parameters for theophylline after aminophylline infusion in horses (csf concentrations).

AMINOPHYLLINE, 10 MG/KG, INFUSION FOLLOWED BY DYPHYLLINE, 20 MG/KG, (CSF)

HORSE CODE	K12 (hr-1)	K21 (hr-1)	DOSE (mg)	AUC (0-00) (mg*hr/L)	ALPHA (hr-1)	BETA (hr-1)	MRT (hrs)
MOON MIST	0.901	0.045	4000.000	87.970	0.905	0.045	23.340
TAYLOR LOCK	1.420	0.050	3840.000	92.320	1.440	0.050	20.880
PICKET CREEK	0.490	0.041	2800.000	139.390	0.371	0.043	25.740
GYPSY	1.400	0.053	2984.000	95.800	1.410	0.052	19.770
MELODEE	1.450	0.066	3404.000	75.550	1.460	0.066	15.830
LINDA	0.700	0.083	3544.000	87.320	0.720	0.054	20.000
MEAN	1.060	0.056	3428.667	96.392	1.051	0.052	20.927
SD	0.419	0.016	469.569	22.151	0.456	0.008	3.381

AMINOPHYLLINE, 10 MG/KG, INFUSION, ADMINISTERED ALONE (CSF)

HORSE CODE	K12 (hr-1)	K21 (hr-1)	DOSE (mg)	AUC (0-00) (mg*hr/L)	ALPHA (hr-1)	BETA (hr-1)	MRT (hrs)
MOON MIST	1.730	0.036	4000.000	87.060	1.740	0.036	28.190
TAYLOR LOCK	1.420	0.061	3840.000	82.690	1.420	0.061	17.030
PICKET CREEK	2.000	0.054	2800.000	89.500	3.350	0.051	19.910
GYPSY	0.934	0.034	2984.000	105.910	0.933	0.034	30.490
MELODEE	0.915	0.050	3404.000	79.400	0.914	0.050	21.120
LINDA	0.720	0.054	3544.000	98.380	0.720	0.054	20.000
MEAN	1.287	0.048	3428.667	90.490	1.513	0.048	22.790
SD	0.511	0.011	469.569	9.966	0.976	0.011	5.301

AMINOPHYLLINE, 20 MG/KG, INFUSION, ADMINISTERED ALONE (CSF)

HORSE CODE	K12 (hr-1)	K21 (hr-1)	DOSE (mg)	AUC (0-00) (mg*hr/L)	ALPHA (hr-1)	BETA (hr-1)	MRT (hrs)
MOON MIST	0.820	0.035	8000.000	252.470	0.822	0.035	30.160
TAYLOR LOCK	1.090	0.051	7808.000	162.330	1.100	0.051	20.380
PICKET CREEK	3.730	0.060	5600.000	144.780	3.850	0.059	17.190
GYPSY	0.965	0.051	5968.000	222.210	0.961	0.051	20.630
MELODEE	0.470	0.061	6808.000	168.470	0.475	0.061	18.600
LINDA	0.900	0.051	7088.000	192.590	0.783	0.056	19.190
MEAN	1.329	0.052	6878.667	190.475	1.332	0.052	21.025
SD	1.195	0.009	962.722	40.545	1.251	0.009	4.647

K12 and K21 calculated from PCNONLIN (VER. 3.0)

MRT, ALPHA, BETA and AUC calculated from RSTRIP (VER. 2.0)

Table B.5 Pharmacokinetic parameters for dyphylline after an iv bolus administration in horses. Plasma and csf dyphylline concentrations fitted simultaneously by PCNONLIN[R]. (Plasma parameters)

DYPHYLLINE, 20 MG/KG, IV BOLUS, PRECEDED BY AMINOPHYLLINE, 10 MG/KG (PLASMA)

HORSE CODE	DOSE (mg)	AUC (mg*hr/L)	BETA (hr-1)	CL (L/hr)	Vdarea (L)
MOON MIST	10000.000	--	--	--	--
TAYLOR LOCK	9760.000	81.150	0.276	120.271	435.765
PICKET CREEK	7000.000	73.100	0.242	95.759	395.699
GYPSY	7460.000	131.500	0.289	56.730	196.298
MELODEE	8510.000	57.950	0.285	146.851	515.266
LINDA	8860.000	57.160	0.216	155.003	717.609
MEAN (WITHOUT MM)	8318.000	80.172	0.262	114.923	452.127
SD	1104.907	30.450	0.032	40.025	189.320

DYPHYLLINE, 20 MG/KG, IV BOLUS, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	AUC (mg*hr/L)	BETA (hr-1)	CL (L/hr)	Vdarea (L)
MOON MIST	--	--	--	--	--
TAYLOR LOCK	--	--	--	--	--
PICKET CREEK	7000.000	54.380	0.330	128.724	389.718
GYPSY	7460.000	104.370	0.417	71.476	171.406
MELODEE	8510.000	53.770	0.269	158.267	588.352
LINDA	8860.000	36.180	0.530	244.887	462.050
MEAN	7957.500	62.175	0.387	150.838	402.882
SD	872.558	29.369	0.113	72.313	174.790

DYPHYLLINE, 40 MG/KG, IV BOLUS, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	AUC (mg*hr/L)	BETA (hr-1)	CL (L/hr)	Vdarea (L)
MOON MIST	20000.000	200.300	0.250	99.850	399.401
TAYLOR LOCK	19520.000	108.430	0.274	180.024	657.022
PICKET CREEK	14000.000	99.460	0.243	140.760	579.260
GYPSY	14920.000	161.200	0.220	92.556	420.708
MELODEE	17020.000	112.200	0.210	151.693	722.350
LINDA	17720.000	90.700	0.230	195.369	849.432
MEAN	17196.667	128.715	0.238	143.375	604.695
SD	2406.804	42.813	0.023	41.472	174.997

AUC and BETA calculated from PCNONLIN (VER. 3.0)

Cl = DOSE/AUC   Vdarea = Cl/BETA

MRT calculated from RSTRIP (VER. 2.0)

Table B.6 Pharmacokinetic parameters for dyphylline after an iv bolus administration in horses. Plasma and csf dyphylline concentrations fitted simultaneously by PCNONLIN[R]. (Plasma parameters)

DYPHYLLINE, 20 MG/KG, IV BOLUS, PRECEDED BY AMINOPHYLLINE, 10 MG/KG (PLASMA)

HORSE CODE	DOSE (mg)	C1 (mg/L)	C2 (mg/L)	Cpo (mg/L)	V central (L)
MOON MIST	10000.000	--	--	--	--
TAYLOR LOCK	9760.000	15.080	244.000	259.080	37.672
PICKET CREEK	7000.000	15.260	90.010	105.270	66.496
GYPSY	7460.000	18.700	800.600	819.300	9.105
MELODEE	8510.000	13.260	56.570	69.830	121.867
LINDA	8860.000	8.400	34.610	43.010	205.999
MEAN (WITHOUT MM)	8318.000	14.140	245.158	259.298	88.228
SD	1104.907	3.763	321.125	324.039	77.926

DYPHYLLINE, 20 MG/KG, IV BOLUS, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	C1 (mg/L)	C2 (mg/L)	Cpo (mg/L)	V central (L)
MOON MIST	10000.000	--	--	--	--
TAYLOR LOCK	9760.000	--	--	--	--
PICKET CREEK	7000.000	12.380	47.740	60.120	116.434
GYPSY	7460.000	35.220	41.470	76.690	97.275
MELODEE	8510.000	11.140	13.740	24.880	342.042
LINDA	8860.000	17.740	10.300	28.040	315.977
MEAN	8598.333	19.120	28.313	47.433	217.932
SD	1203.402	11.109	19.038	25.177	128.939
MEAN (WITHOUT LINDA)	7656.667	19.580	34.317	53.897	185.250
SD	773.972	13.559	18.094	26.460	136.123

DYPHYLLINE, 40 MG/KG, IV BOLUS, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	C1 (mg/L)	C2 (mg/L)	Cpo (mg/L)	V central (L)
MOON MIST	20000.000	32.650	600.000	632.650	31.613
TAYLOR LOCK	19520.000	26.710	28.950	55.660	350.701
PICKET CREEK	14000.000	25.330	-7.840	17.490	800.457
GYPSY	14920.000	22.300	74.200	96.500	154.611
MELODEE	17020.000	16.320	50.000	66.320	256.634
LINDA	17720.000	10.000	45.000	55.000	322.182
MEAN	17196.667	22.218	131.718	153.937	319.366
SD	2406.804	8.034	231.012	235.884	263.180
MEAN (WITHOUT MM)	16636.000	20.132	38.062	58.194	376.917
SD	2209.814	6.931	30.359	28.314	248.474

C1 and C2 calculated from PCNONLIN (VER. 3.0)

Cpo = C1 + C2 V central = DOSE/Cpo

Table B.7 Pharmacokinetic parameters for theophylline after an aminophylline infusion administration in horses. Plasma and csf theophylline concentrations fitted simultaneously by FUNFIT. (Plasma and csf parameters)

AMINOPHYLLINE, 10 MG/KG, INFUSION, ADMINISTERED ALONE

HORSE DATA FILE	A	ALPHA	T1/2 ALPH	B	BETA	T1/2 BETA	M	N
WPCT10MM	99.92	8.21	0.08	1080.06	0.03	20.19	-2.36	333.04
WPCT10TL	0.01	1.06	0.65	569.68	0.08	9.19	-21.61	321.97
WPCT10PC	19.34	3.93	0.18	676.04	0.05	12.86	-3.09	352.12
WPCT10G	62.89	1.07	0.65	1100.54	0.03	21.24	-13.15	440.04
WPCT10M	7.65	1.18	0.59	579.47	0.06	11.87	-15.20	294.34
WPCT10L	14.18	0.60	1.16	700.95	0.06	10.96	-37.00	397.34
MEAN	34.00	2.68	0.55	784.46	0.05	14.39	-15.40	356.48
SD	39.08	2.96	0.39	242.56	0.02	5.06	12.90	53.43
CV	114.96	110.82	70.01	30.92	33.49	35.18	-83.74	14.99

AMINOPHYLLINE, 20 MG/KG, INFUSION, ADMINISTERED ALONE

HORSE DATA FILE	A	ALPHA	T1/2 ALPH	B	BETA	T1/2 BETA	M	N
WPCT20MM	159.79	3.28	0.21	3752.84	0.03	22.64	-17.56	1041.42
WPCT20TL	55.34	1.00	0.69	1003.07	0.06	11.95	-33.76	634.34
WPCT20PC	9.58	4.19	0.17	1497.13	0.05	13.09	-10.10	638.27
WPCT20G	263.13	1.18	0.59	3200.91	0.04	18.59	-32.90	1131.21
WPCT20M	34.43	0.72	0.96	1194.88	0.06	11.87	-60.53	722.08
WPCT20L	45.81	1.32	0.52	1703.28	0.05	14.24	-30.34	819.16
MEAN	94.68	1.95	0.52	2058.69	0.05	15.40	-30.87	831.08
SD	97.39	1.43	0.30	1138.15	0.01	4.33	17.33	210.82
CV	102.86	73.28	57.33	55.29	24.33	28.11	-56.14	25.37

AMINOPHYLLINE, 10 MG/KG, FOLLOWED BY DYPHYLLINE, 20 MG/KG, IV BOLUS

HORSE DATA FILE	A	ALPHA	T1/2 ALPH	B	BETA	T1/2 BETA	M	N
WCT10MM	65.56	0.84	0.82	491.16	0.05	13.18	-20.66	328.03
WCT10TL	16.08	1.45	0.48	725.08	0.06	11.88	-14.58	344.33
WCT10PC	48.66	0.43	1.62	420.99	0.04	17.17	-50.50	619.79
WCT10G	24.25	3.30	0.21	845.27	0.05	13.91	-6.80	400.07
WCT10M	19.13	1.17	0.59	506.58	0.08	9.23	-20.06	307.17
WCT10L	35.08	0.88	0.79	529.13	0.07	9.33	-24.47	377.76
MEAN	34.79	1.35	0.75	586.37	0.06	12.45	-22.85	396.19
SD	19.21	1.02	0.48	162.68	0.01	3.01	14.87	114.55
CV	55.22	75.60	63.89	27.74	23.90	24.20	-65.09	28.91

AVERAGES FITTED

HORSE DATA FILE	A	ALPHA	T1/2 ALPH	B	BETA	T1/2 BETA	M	N
WPCT20AV	96.07	1.21	0.57	1835.66	0.05	14.24	-31.30	793.10
WCT10AV	36.09	1.29	0.54	597.69	0.06	12.56	-15.71	384.51
WPCT10AV	35.67	1.87	0.37	774.19	0.04	14.91	-8.23	360.34

Table B.8 Pharmacokinetic parameters for theophylline after an aminophylline infusion administration in horses. Plasma and csf theophylline concentrations fitted simultaneously by FUNFIT. (Plasma parameters)

AMINOPHYLLINE, 10 MG/KG, INFUSION, ADMINISTERED ALONE

HORSE DATA FILE	A (ug/ml)	B (ug/ml)	A+B (ug/ml)	CL (L/hr)	BETA (hr-1)	T1/2 BETA (hr)	VD AREA (L)	AMOUNT (mg)
WPCT10MM	99.92	1080.06	1179.98	7.28	0.03	20.19	214.24	4000.00
WPCT10TL	0.01	569.68	569.69	26.86	0.08	9.19	358.19	3840.00
WPCT10PC	19.34	676.04	695.38	16.14	0.05	12.86	322.72	2800.00
WPCT10G	62.89	1100.54	1163.43	10.92	0.03	21.24	364.13	2984.00
WPCT10M	7.65	579.47	587.12	23.94	0.06	11.87	412.67	3404.00
WPCT10L	14.18	700.95	715.13	20.02	0.06	10.96	317.83	3544.00
MEAN	34.00	784.46	818.45	17.53	0.05	14.39	331.63	3428.67
SD	39.08	242.56	279.62	7.55	0.02	5.06	66.90	469.57
CV	114.96	30.92	34.16	43.07	33.49	35.18	20.17	13.70

AMINOPHYLLINE, 20 MG/KG, INFUSION, ADMINISTERED ALONE

WPCT20MM	159.79	3752.84	3912.63	9.93	0.03	22.64	331.10	8000.00
WPCT20TL	55.34	1003.07	1058.41	30.45	0.06	11.95	524.93	7808.00
WPCT20PC	9.58	1497.13	1506.71	13.51	0.05	13.09	255.44	5600.00
WPCT20G	263.13	3200.91	3464.04	6.35	0.04	18.59	171.59	5968.00
WPCT20M	34.43	1194.88	1229.31	22.84	0.06	11.87	393.76	6808.00
WPCT20L	45.81	1703.28	1749.09	17.43	0.05	14.24	348.64	7088.00
MEAN	94.68	2058.69	2153.37	16.75	0.05	15.40	337.58	6878.67
SD	97.39	1138.15	1220.43	8.83	0.01	4.33	120.60	962.72
CV	102.86	55.29	56.68	52.74	24.33	28.11	35.72	14.00

AMINOPHYLLINE, 10 MG/KG, FOLLOWED BY DYPHYLLINE, 20 MG/KG, IV BOLUS

WCT10MM	65.56	491.16	556.72	29.51	0.05	13.18	560.93	4000.00
WCT10TL	16.08	725.08	741.16	21.78	0.06	11.88	375.45	3840.00
WCT10PC	48.66	420.99	469.65	27.65	0.04	17.17	691.23	2800.00
WCT10G	24.25	845.27	869.52	12.81	0.05	13.91	256.10	2984.00
WCT10M	19.13	506.58	525.71	25.42	0.08	9.23	338.93	3404.00
WCT10L	35.08	529.13	564.21	23.37	0.07	9.33	314.47	3544.00
MEAN	34.79	586.37	621.16	23.42	0.06	12.45	422.85	3428.67
SD	19.21	162.68	152.02	5.90	0.01	3.01	167.29	469.57
CV	55.22	27.74	24.47	25.21	23.90	24.20	39.56	13.70

AVERAGES FITTED

WPCT20AV	96.07	1835.66	1931.73		0.05	14.24
WCT10AV	36.09	597.69	633.78		0.06	12.56
WPCT10AV	35.67	774.19	809.86		0.04	14.91

Cl = DOSE/AUC (DOSE IS BASED ON THEOPHYLLINE DOSE AMOUNT GIVEN (80% OF AMINOPHYLLINE INJECTED))

Vd area = Cl/beta

Table B.9 Pharmacokinetic parameters for dyphylline after an iv bolus administration in horses. Plasma and csf dyphylline concentrations fitted simultaneously by PCNONLIN[R]. (Csf parameters)

DYPHYLLINE, 20 MG/KG, IV BOLUS, PRECEDED BY AMINOPHYLLINE, 10 MG/KG (CSF)

HORSE CODE	AUC (mg*hr/L)	BETA (hr-1)	C1 (mg/L)	C2 (mg/L)
MOON MIST	--	--	--	--
TAYLOR LOCK	16.800	0.276	5.020	-12.890
PICKET CREEK	10.060	0.242	2.570	-5.000
GYPSY	14.530	0.289	4.560	-15.000
MELODEE	5.170	0.285	1.640	-2.940
LINDA	14.710	0.216	3.620	-3.800
MEAN (WITHOUT MM)	12.254	0.262	3.482	-7.926
SD	4.660	0.032	1.394	5.593

DYPHYLLINE, 20 MG/KG, IV BOLUS, ADMINISTERED ALONE (CSF)

HORSE CODE	AUC (mg*hr/L)	BETA (hr-1)	C1 (mg/L)	C2 (mg/L)
MOON MIST	--	--	--	--
TAYLOR LOCK	--	--	--	--
PICKET CREEK	14.580	0.330	5.750	-7.950
GYPSY	9.570	0.417	5.000	-5.000
MELODEE	6.740	0.269	2.310	-2.020
LINDA	4.310	0.530	2.860	-4.130
MEAN	8.800	0.387	3.980	-4.775
SD	4.412	0.113	1.655	2.459

DYPHYLLINE, 40 MG/KG, IV BOLUS, ADMINISTERED ALONE (CSF)

HORSE CODE	AUC (mg*hr/L)	BETA (hr-1)	C1 (mg/L)	C2 (mg/L)
MOON MIST	8.960	0.250	2.380	-5.000
TAYLOR LOCK	50.500	0.274	15.080	-12.580
PICKET CREEK	60.170	0.243	17.330	-18.380
GYPSY	44.300	0.220	9.770	0.560
MELODEE	42.100	0.210	10.680	-11.900
LINDA	66.900	0.230	17.860	-11.970
MEAN	45.488	0.238	12.183	-9.878
SD	20.230	0.023	5.853	6.645

AUC and BETA calculated from PCNONLIN (VER. 3.0), BETA IS FROM PLASMA DYPHYLLLINE CONCENTRATION CURVE FITTING

Cpo = C1 + C2

Table B.10 Volume of the central compartment calculated for theophylline and dyphylline by PCNONLIN[R] for individual horses. (Individual fitting of plasma drug concentrations.)

HORSE CODE	DOSE (mg)	PLASMA CT10 V central (L)	PLASMA T10 V central (L)	DOSE (mg)	PLASMA T20 V central (L)
MOON MIST	4000.000	61.696	17.920	8000.000	57.640
TAYLOR LOCK	3840.000	201.496	175.040	7808.000	214.624
PICKET CREEK	2800.000	289.344	82.248	5600.000	144.000
GYPSY	2984.000	104.960	103.544	5968.000	44.136
MELODEE	3404.000	194.992	170.120	6808.000	200.616
LINDA	3544.000	115.680	201.088	7088.000	125.152
MEAN	3428.667	161.361	124.993	6878.667	131.028
SD	469.569	82.852	69.402	962.722	70.668

HORSE CODE	DOSE (mg)	PLASMA CD20 V central (L)	PLASMA D20 V central (L)	DOSE (mg)	PLASMA D40 V central (L)
MOON MIST	10000.000	0.091	113.680	20000.000	27.290
TAYLOR LOCK	9760.000	31.840	268.880	19520.000	324.000
PICKET CREEK	7000.000	48.600	104.550	14000.000	695.500
GYPSY	7460.000	7.720	51.500	14920.000	153.080
MELODEE	8510.000	78.070	368.540	17020.000	161.850
LINDA	8860.000	142.440	419.840	17720.000	230.100
MEAN	8598.333	51.460	221.165	17196.667	265.303
SD	1203.402	52.784	153.236	2406.804	232.250
MEAN	WITHOUT MM	61.730			
SD		51.870			

PLASMA CT10: AMINOPHYLLINE, 10 MG/KG, FOLLOWED BY DYPHYLLINE, 20 MG/KG
PLASMA T10: AMINOPHYLLINE, 10 MG/KG, INFUSED OVER 15 MINUTES
PLASMA T20: AMINOPHYLLINE, 20 MG/KG, INFUSED OVER 15 MINUTES
PLASMA CD20: AMINOPHYLLINE, 10 MG/KG, FOLLOWED BY DYPHYLLINE, 20 MG/KG
PLASMA D20: DYPHYLLINE, 20 MG/KG, IV BOLUS
PLASMA D40: DYPHYLLINE, 40 MG/KG, IV BOLUS

NOTE: VOLUME OF CENTRAL COMPARTMENT FOR THEOPHYLLINE IS BASED ON THEOPHYLLINE DOSE AMOUNT GIVEN (80% OF AMINOPHYLLINE INJECTED)

Table B.11 Volume of the distribution at Steady-state for theophylline for individual horses.

AMINOPHYLLINE, 10 MG/KG, INFUSION FOLLOWED BY DYPHYLLINE, 20 MG/KG IV BOLUS (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	AUMC(0-00) (mg*hr/L)	Ko (mg/hr)	TAU (hr)	Vss (L)
MOON MIST	4000.000	135.570	1674.600	24000.000	0.250	541.150
TAYLOR LOCK	3840.000	176.340	2600.500	11520.000	0.250	238.809
PICKET CREEK	2800.000	101.270	1609.200	11196.000	0.250	435.734
GYPSY	2984.000	233.030	4971.900	11940.000	0.330	357.969
MELODEE	3404.000	133.910	1763.800	13620.000	0.330	436.556
LINDA	3544.000	151.680	2073.800	14172.000	0.250	316.441
MEAN	3428.667	155.300	2448.967	14408.000	0.277	387.776
SD	469.569	45.307	1288.659	4846.269	0.041	106.180

AMINOPHYLLINE, 10 MG/KG, INFUSION, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	AUMC(0-00) (mg*hr/L)	Ko (mg/hr)	TAU (hr)	Vss (L)
MOON MIST	4000.000	549.180	5276.200	24000.000	0.250	103.599
TAYLOR LOCK	3840.000	142.940	1897.800	11520.000	0.500	524.940
PICKET CREEK	2800.000	173.520	2965.700	11196.000	0.250	273.680
GYPSY	2984.000	273.170	6755.300	11940.000	0.250	268.858
MELODEE	3404.000	142.220	2195.900	13620.000	0.170	249.988
LINDA	3544.000	177.000	2379.000	14172.000	0.250	266.539
MEAN	3428.667	243.005	3578.317	14408.000	0.278	281.267
SD	469.569	157.486	1976.102	4846.269	0.113	135.904

AMINOPHYLLINE, 20 MG/KG, INFUSION, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	AUMC(0-00) (mg*hr/L)	Ko (mg/hr)	TAU (hr)	Vss (L)
MOON MIST	8000.000	805.380	20624.000	48000.000	0.170	258.593
TAYLOR LOCK	7808.000	256.450	3958.800	23424.000	0.330	460.327
PICKET CREEK	5600.000	414.430	8946.900	16800.000	0.330	286.590
GYPSY	5968.000	939.930	23787.000	17904.000	0.330	158.042
MELODEE	6808.000	298.100	4498.000	20424.000	0.330	337.423
LINDA	7088.000	406.620	7127.300	21264.000	0.330	299.639
MEAN	6878.667	520.152	11490.333	24636.000	0.303	300.102
SD	962.722	283.013	8552.821	11689.136	0.065	99.148

DOSE LISTED IS THE AMOUNT OF THEOPHYLLINE INJECTED (80% OF AMINOPHYLLINE DOSE)

AUC (0-00) and AUMC (0-00) calculated by RSTRIP (Ver. 2.0)

Vss = Volume at Steady-State = (KoT*AUMC/(AUC)^2 - T(KoT)/2*AUC)

Table B.12 Volume of the distribution at Steady-state for dyphylline for individual horses.

DYPHYLLINE, 20 MG/KG IV BOLUS PRECEDED BY AMINOPHYLLINE INFUSION, 10 MG/KG (P

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	AUMC (0-00) (mg*hr/L)	Vss (L)
MOON MIST	10000.000	12951.000	1718.900	0.102
TAYLOR LOCK	9760.000	83.460	196.700	275.612
PICKET CREEK	7000.000	76.090	267.590	323.529
GYPSY	7460.000	138.940	232.040	89.670
MELODEE	8510.000	60.580	122.130	283.200
LINDA	8860.000	56.550	151.200	418.910
MEAN (WITHOUT MM)	8318.000	83.124	193.932	278.184
SD	1104.907	33.089	58.879	119.822

DYPHYLLINE, 20 MG/KG, IV BOLUS, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	AUMC (0-00) (mg*hr/L)	Vss (L)
MOON MIST	10000.000	42.720	60.980	334.137
TAYLOR LOCK	9760.000	40.020	71.280	434.374
PICKET CREEK	7000.000	54.950	114.860	266.276
GYPSY	7460.000	113.440	211.660	122.700
MELODEE	8510.000	58.210	150.940	379.087
LINDA	8860.000	36.330	63.730	427.806
MEAN	8598.333	57.612	112.242	327.397
SD	1203.402	28.665	60.079	118.220

DYPHYLLINE, 40 MG/KG, IV BOLUS, ADMINISTERED ALONE (PLASMA)

HORSE CODE	DOSE (mg)	AUC (0-00) (mg*hr/L)	AUMC (0-00) (mg*hr/L)	Vss (L)
MOON MIST	20000.000	207.000	597.700	278.980
TAYLOR LOCK	19520.000	108.800	362.280	597.402
PICKET CREEK	14000.000	99.330	436.070	618.762
GYPSY	14920.000	160.800	498.190	287.469
MELODEE	17020.000	114.160	349.800	456.827
LINDA	17720.000	85.090	193.120	472.644
MEAN	17196.667	129.197	406.193	452.014
SD	2406.804	45.895	138.953	145.881

AUC calculated from PCNONLIN: 2-COMPARTMENT OPEN PHARMACOKINETIC MODEL WITH BOLUS INPUT (VER. 3.0)

AUMC calculated from RSTRIP (Ver. 2.0)

Vss = Volume at Steady-state = (Dose * AUMC)/(AUC)^2

APPENDIX C

TYPICAL COMPUTER PROGRAMS AND OUTPUTS FOR SIMULTANEOUS AND INDIVIDUAL FITTINGS FOR HORSE PLASMA AND CSF DRUG CONCENTRATIONS BY PCNONLIN^{R} OR FUNFIT

Text C.1 PCNONLIN[R] nonlinear estimation program for simultaneously fitting plasma and csf dyphylline concentrations.

```
TITLE
FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS
(MEAN)
MODEL
COMM
NPAR 6
NCON 4
NSECO 2
PNAMES 'A','B','ALPHA','BETA','M','N'
SNAMES 'AUC-1','AUC-2'
END
TEMP
A=P(1)
B=P(2)
ALPHA=P(3)
BETA=P(4)
M=P(5)
N=P(6)
END
FUNC 1
T=X
F = A*EXP(-ALPHA*T) + B*EXP(-BETA*T)
END
FUNC 2
T=X
F = M*EXP(-ALPHA*T) + N*EXP(-BETA*T)
END
SECO
S(1)= A/ALPHA + B/BETA
S(2)= M/ALPHA + N/BETA
END
EOM
CONS 17197 1 17197 0
INIT 27.99 114.97 .278 5.21 11.19 -9.28
LOWER 15 90 0 3 8 -15
UPPER 40 150 5 10 20 0
WEIGHT -2
NFUNC 2
NOBS 14,14
DATA 'A:WPCD40AV'
OUTPUT PLOT DATA SECO PARM
BEGIN
FINISH
```

Text C.2a Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

```
FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION WEIGHTED SS      A           B             ALPHA        BETA
                           M           N
    0        19.5037        27.99       115.0          .2780        5.210
                            11.19      -9.280
                 RANK =   6 COND = 139.4
    1        9.71450        25.01       111.4          .2453        4.290
                            10.91      -12.73
                 RANK =   6 COND = 112.8
    2        8.54126        24.70       97.43          .2489        3.816
                            12.19      -13.87
                 RANK =   6 COND = 163.3
    3        8.06012        24.58       91.30          .2468        3.527
                            12.03      -13.55
                 RANK =   6 COND = 510.7
    4        7.99452        24.34       90.17          .2459        3.475
                            12.05      -13.40
                 RANK =   6 COND = 2957.
    5        7.98845        24.28       90.09          .2454        3.493
                            12.03      -13.42
                 RANK =   6 COND = 5070.
    6        7.98447        24.31       90.01          .2456        3.485
                            12.04      -13.41
                 RANK =   6 COND = .2881E+05

CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN    .000100
    6        7.98382        24.30       90.00          .2456        3.486
                            12.04      -13.41
```

Text C.2b Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

PARAMETER	ESTIMATE	STANDARD ERROR	95% CONFIDENCE LIMITS		
A	24.304103	1.636665	20.909893	27.698312	UNIVARIATE
			17.890748	30.717458	PLANAR
B	90.001203	17.068903	54.602746	125.399659	UNIVARIATE
			23.115856	156.886549	PLANAR
ALPHA	.245576	.011028	.222706	.268447	UNIVARIATE
			.202362	.288791	PLANAR
BETA	3.485933	.569934	2.303971	4.667895	UNIVARIATE
			1.252617	5.719249	PLANAR
M	12.035184	.807491	10.360564	13.709804	UNIVARIATE
			8.870992	15.199376	PLANAR
N	-13.413679	2.458290	-18.511820	-8.315539	UNIVARIATE
			-23.046611	-3.780748	PLANAR

Text C.2c Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

*** CORRELATION MATRIX OF THE ESTIMATES ***

	A	B	ALPHA	BETA	M	N
A	1.00000					
B	.02831	1.00000				
ALPHA	.83709	-.02868	1.00000			
BETA	.34034	.85005	.22272	1.00000		
M	.36050	-.22613	.47627	-.12971	1.00000	
N	-.45105	-.40981	-.44809	-.56882	-.58998	1.00000

*** EIGENVALUES OF (Var - Cov) MATRIX ***

NUMBER	EIGENVALUE
1	.1132E+05
2	9.247
3	1.450
4	.2055
5	.5724E-01
6	.1240E-02

Condition number = 3021.

Text C.2d Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN^{R}.

FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

*** SUMMARY OF NONLINEAR ESTIMATION ***

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1700	90.04	73.07	16.97	.4163E-02	.3713	35.77
.2500	53.60	60.51	-6.907	.1175E-01	.3760	-14.68
.3300	44.79	50.90	-6.110	.1682E-01	.3160	-11.91
.5000	35.27	37.25	-1.976	.2713E-01	.3361	-3.953
.6700	31.14	29.32	1.815	.3481E-01	.3369	3.635
1.000	25.67	21.77	3.902	.5122E-01	.2674	7.228
1.500	19.17	17.30	1.872	.9184E-01	.2512	3.420
2.000	17.93	14.96	2.973	.1050	.2331	5.353
3.000	12.40	11.64	.7636	.2195	.2369	1.379
4.000	8.380	9.101	-.7207	.4806	.2450	-1.309
5.000	6.650	7.119	-.4690	.7632	.2293	-.8418
6.000	5.260	5.569	-.3088	1.220	.2344	-.5565
8.000	3.090	3.408	-.3177	3.535	.3117	-.6162
10.00	2.130	2.085	.4477E-01	7.439	.3707	.9428E-01

CORRECTED SUM OF SQUARED OBSERVATIONS = 7829.68
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 266.029
SUM OF SQUARED RESIDUALS = 409.292
SUM OF WEIGHTED SQUARED RESIDUALS = 5.67133
S = .841972 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .975

Text C.2e Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

*** SUMMARY OF NONLINEAR ESTIMATION ***

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1700	4.380	4.127	.2531	.5666	.5160	.8143
.2500	5.600	5.707	-.1072	.3466	.2974	-.2046
.3300	7.260	6.853	.4074	.2062	.2222	.7276
.5000	6.790	8.297	-1.507	.2358	.2646	-2.785
.6700	7.650	8.911	-1.261	.1857	.2410	-2.285
1.000	8.060	9.004	-.9438	.1673	.2200	-1.683
1.500	7.640	8.255	-.6148	.1862	.2119	-1.090
2.000	7.170	7.352	-.1820	.2114	.2006	-.3204
3.000	6.340	5.761	.5794	.2704	.1767	1.006
4.000	4.960	4.507	.4535	.4419	.1804	.7890
5.000	3.630	3.525	.1047	.8249	.2029	.1847
6.000	3.190	2.758	.4324	1.068	.1943	.7582
8.000	2.110	1.687	.4225	2.442	.2148	.7508
10.00	1.260	1.033	.2274	6.847	.2647	.4202

CORRECTED SUM OF SQUARED OBSERVATIONS = 63.8048
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 52.7159
SUM OF SQUARED RESIDUALS = 6.37561
SUM OF WEIGHTED SQUARED RESIDUALS = 2.31249
S = .537644 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .978

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 415.667
SUM OF WEIGHTED SQUARED RESIDUALS = 7.98382
S = .602412 WITH 22 DEGREES OF FREEDOM

Text C.2f Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

SUMMARY OF ESTIMATED SECONDARY PARAMETERS

PARAMETER	ESTIMATE	STANDARD ERROR
AUC-1	124.785973	3.680851
AUC-2	45.159952	2.578657

Text C.2g Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

```
FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

   100.0000|
    93.7500|    O
    87.5000|
    81.2500|
    75.0000|    *
    68.7500|
    62.5000|    *
    56.2500|    O
    50.0000|    O*
    43.7500|     *
    37.5000|     O*
    31.2500|      *+O
    25.0000|        ***O
    18.7500|           ***+****
    12.5000|                   *+*****+*****+***
     6.2500|                                    **+***********+***********+
      .0000|
            -+-----------+-----------+-----------+-----------+-----------+-
             .000       2.000       4.000       6.000       8.000      10.000
                                      X
```

Text C.2h Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

```
FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

10.0000|
 9.3750|      ****
 8.7500|      *   ***
 8.1250|     * OO  O***
 7.5000|    O*        +**
 6.8750|     O          *** O
 6.2500|    *              ***
 5.6250|    O                ****
 5.0000|    O                   **+*
 4.3750|    *                       ****
 3.7500|                               *+***  O
 3.1250|                                    ******
 2.5000|                                         ******** O
 1.8750|                                                ***********    O
 1.2500|                                                          *****
  .6250|
  .0000|
         -+-----------+-----------+-----------+-----------+-----------+-
          .000       2.000       4.000       6.000       8.000      10.000
                                    X
```

Text C.2i Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

```
FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  1
PLOT OF OBSERVED Y VS. WEIGHTED CALCULATED Y


WEIGHTED CALCULATED Y
      7.0000|
      6.8438|
      6.6875|                               *      *
      6.5313|    *
      6.3750|      *  *
      6.2188|      *                   *
      6.0625|
      5.9063|
      5.7500|    *
      5.5938|           *           *
      5.4375|
      5.2813|               *
      5.1250|
      4.9688|              *     *
      4.8125|                                                              *
      4.6563|
      4.5000|
              -+------------+------------+------------+------------+------------+-
               .000       20.000       40.000       60.000       80.000      100.000
                                           OBSERVED Y
```

Text C.2j Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

```
FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  1
PLOT OF WEIGHTED CALCULATED Y VS. WEIGHTED RESIDUAL

WEIGHTED RESIDUAL
     1.5000|
     1.3438|
     1.1875|        *
     1.0313|           * *
      .8750|
      .7188|                    *
      .5625|
      .4063|                         **
      .2500|                               *
      .0938|  -------------------------------------------------------------
     -.0625|
     -.2188|                                          *
     -.3750|                                            * *
     -.5313|                                                *
     -.6875|                                                    **
     -.8438|
    -1.0000|
             -+-----------+-----------+-----------+-----------+-----------+-
             4.500       5.000       5.500       6.000       6.500       7.000
                                        WEIGHTED CALCULATED Y
```

Text C.2k Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

```
FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  1
PLOT OF X VS WEIGHTED RESIDUAL Y

WEIGHTED RESIDUAL
     2.0000|
     1.8125|
     1.6250|
     1.4375|
     1.2500|    *
     1.0625|        *     *
      .8750|
      .6875|           *
      .5000|       *            *
      .3125|
      .1250|  ------------------------------------------------------------*
     -.0625|
     -.2500|     *                          *     *
     -.4375|                          *                       *
     -.6250|    *
     -.8125|
    -1.0000|
             -+-----------+-----------+-----------+-----------+-----------+-
              .000       2.000       4.000       6.000       8.000      10.000
                                             X
```

Text C.21 Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

```
FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  2
PLOT OF OBSERVED Y VS. WEIGHTED CALCULATED Y

WEIGHTED CALCULATED Y
     4.5000|
     4.3750|
     4.2500|
     4.1250|                                           *
     4.0000|
     3.8750|                                                *
     3.7500|                                                   *
     3.6250|                                                *
     3.5000|                                              *
     3.3750|                                    *
     3.2500|                        *
     3.1250|                             *                *
     3.0000|                                *        *
     2.8750|                      *
     2.7500|          *    *
     2.6250|
     2.5000|
             -+-----------+-----------+-----------+-----------+-----------+-
              .000       2.000       4.000       6.000       8.000      10.000
                                        OBSERVED Y
```

Text C.2m Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

```
FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  2
PLOT OF WEIGHTED CALCULATED Y VS. WEIGHTED RESIDUAL

WEIGHTED RESIDUAL
     1.0000|
      .8750|
      .7500|       *
      .6250|         *
      .5000|             *
      .3750|                 *
      .2500|                     *
      .1250|                         *
      .0000|  ---------------------------**-----------------------------------
     -.1250|
     -.2500|                                   *
     -.3750|                                       *
     -.5000|                                             *
     -.6250|                                                  *
     -.7500|
     -.8750|
    -1.0000|

            -+---------------+---------------+---------------+---------------+-
            2.500           3.000           3.500           4.000           4.500
                                         WEIGHTED CALCULATED Y
```

Text C.2n Typical computer output from a simultaneous fit between horse plasma and csf dyphylline concentrations by PCNONLIN[R].

```
FITTING DYPHYLLINE IV BOLUS AT 40 mg/kg IN 2 COMPARTMENTS (MEAN)
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  2
PLOT OF X VS WEIGHTED RESIDUAL Y

WEIGHTED RESIDUAL
     1.0000|
      .8750|
      .7500|                                                      *
      .6250|                                                              *
      .5000|                                               *
      .3750|                      *          *
      .2500|   *
      .1250|                                       *
      .0000|  --*-------*-------------------------------------------------
     -.1250|
     -.2500|           *
     -.3750|       *
     -.5000|      *
     -.6250|    *
     -.7500|
     -.8750|
    -1.0000|
           -+-----------+-----------+-----------+-----------+-----------+-
           .000       2.000       4.000       6.000       8.000      10.000
                                        X
```

Text C.3a FUNFIT computer program to simultaneously fit plasma and csf theophylline concentrations.

```
      SUBROUTINE MODEL(T,C,P,NP,IFUN)

      PARAMETER (N=2)
      REAL P(NP)
      CHARACTER*79 SUBJ
      CHARACTER*1 RESP
      LOGICAL SHOWIT
      DATA ZERO,ONE,TWO/0.0,1.0,2.0/
      ENTRY DOOR(T,C,P,NP,IFUN)

      B = P(1)
      BETA = P(2)
      A = P(3)
      ALPHA = BETA+P(4)
      AM = P(5)
      AN = P(6)

      TAU = 0.25
      IF (T .LT. TAU) THEN
        T2 = T
      ELSEIF (T .GE. TAU) THEN
        T2 = TAU
      ENDIF
      IF (IFUN .EQ. 1) THEN
        C=A*(EXP(ALPHA*T2)-ONE)*EXP(-ALPHA*T)+
     *    B*(EXP(BETA*T2)-ONE)*EXP(-BETA*T)
      ELSEIF (IFUN .EQ. 2) THEN
          C=AM*(EXP(ALPHA*T2)-ONE)*EXP(-ALPHA*T)+
     *      AN*(EXP(BETA*T2)-ONE)*EXP(-BETA*T)
      ENDIF
      IF (IFUN .NE. 0) RETURN

      CALL PROMT(SHOWIT)
      CALL GETDLA(SUBJ,NL)
      IF (SHOWIT) THEN
      CALL MRGOFF
      CALL MNAME('THEOPHYLLINE')
      CALL TITLE(SUBJ(1:NL))
      CALL BGINO
      CALL LABLX('HOURS')
      CALL LABLYL('CONC., UG/ML')
      CALL ADDOBS(1,1)
      CALL ADDFUN(1)
      CALL ADDOBS(2,2)
      CALL ADDFUN(2)
      CALL SHOWPL
      CALL PAUSE
```

Text C.3b FUNFIT computer program to simultaneously fit plasma and csf theophylline concentrations.

```
      WRITE (3,61) SUBJ
      FORMAT(1X,A79)
      WRITE (3,*) '    A       = ',A
      WRITE (3,*) '   ALPHA    = ',ALPHA
      WRITE (3,*) ' T1/2 ALPHA = ',ALOG(TWO)/ALPHA
      WRITE (3,*) '    B       = ',B
      WRITE (3,*) '   BETA     = ',BETA
      WRITE (3,*) ' T1/2 BETA  = ',ALOG(TWO)/BETA

PRINT AM

       WRITE (3,*) '    AM       = ',AM
       WRITE (3,*) '    AN       = ',AN

     ENDIF
     END
```

Text C.4a Typical computer output from a simultaneous fit between horse plasma and csf theophylline concentrations by FUNFIT.

```
****************************
*   RUN BY: Ruth Stevens   *
*   19-AUG-90   18:32:52   *
****************************
```

DATA SET NUMBER: 12 -FUNFIT- CALL NUMBER: 2
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	1703.28	0.000000E+00	NONE	1.578E-03
2	4.868488E-02	0.000000E+00	NONE	100.
3	45.8087	0.000000E+00	NONE	4.874E-03
4	1.27195	0.000000E+00	NONE	0.779
5	-30.3420	UNCONSTRAINED		5.171E-02
6	819.163	0.000000E+00	NONE	4.309E-03

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	22.3427	80.6973	0.966721
2	17	5.70971	5.42407	0.977787
TOTAL	34	28.0524	86.1211	0.985998

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	23.2	22.9	0.321	1.39
2	0.250	33.6	33.5	0.134	0.398
3	0.333	36.5	32.1	4.46	12.2
4	0.500	29.4	29.6	-0.195	-0.663
5	0.667	27.1	27.6	-0.508	-1.87
6	1.00	20.7	24.7	-3.99	-19.3
7	1.50	18.4	21.9	-3.45	-18.7
8	2.00	19.2	20.2	-0.980	-5.10
9	3.00	20.2	18.4	1.85	9.13
10	4.00	18.1	17.3	0.832	4.60
11	5.00	18.1	16.4	1.70	9.43
12	6.00	19.6	15.6	4.06	20.7
13	8.00	16.4	14.1	2.26	13.8
14	10.0	12.0	12.8	-0.858	-7.18
15	12.0	10.6	11.6	-1.07	-10.1
16	24.0	6.84	6.48	0.356	5.21
17	30.0	3.86	4.84	-0.981	-25.4

Text C.4b Typical computer output from a simultaneous fit between horse plasma and csf theophylline concentrations by FUNFIT.

```
------------------------- FUNCTION  2 -------------------------
  1   0.167      1.00      0.628      0.372      37.2
  2   0.250      1.39      1.38       1.211E-02  0.871
  3   0.333      2.21      2.22      -1.369E-02 -0.619
  4   0.500      3.30      3.66      -0.357     -10.8
  5   0.667      4.07      4.79      -0.722     -17.7
  6    1.00      5.39      6.39      -0.996     -18.5
  7    1.50      7.16      7.69      -0.527     -7.37
  8    2.00      8.02      8.25      -0.234     -2.92
  9    3.00      8.79      8.44       0.348      3.96
 10    4.00      8.53      8.20       0.334      3.92
 11    5.00      8.50      7.85       0.652      7.67
 12    6.00      7.40      7.49      -8.578E-02 -1.16
 13    8.00      7.63      6.79       0.835      10.9
 14    10.0      6.46      6.16       0.295      4.57
 15    12.0      6.92      5.59       1.33       19.2
 16    24.0      3.25      3.12       0.132      4.06
 17    30.0      2.04      2.33      -0.288     -14.1

WGHT. EXP. =  -1

FUNCTION EVALUATIONS:  455

-------------------------------------------------------------------

MODL ID: THEOPHYLLINE
PLOT ID: F 2 D12 P 1 X 3179 19-AUG-90 18:34 RS
THEOPHYLLINE 20 MG/KG, LINDA
    A        =    45.80872
   ALPHA     =    1.320631
 T1/2 ALPHA  =   0.5248608
    B        =    1703.278
   BETA      =   4.8684884E-02
 T1/2 BETA   =    14.23742
    AM       =   -30.34198
    AN       =    819.1628
```

Text C.5 Typical PCNONLIN^{R} nonlinear estimation program for individual fitting for plasma dyphylline concentrations in horses.

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

LISTING OF INPUT COMMANDS

MODEL 8
TITLE
TWO COMPARTMENT IV BOLUS INPUT AND FIRST-ORDER OUTPUT
DYPHYLLINE PLASMA 40 MG/KG
THE FOLLOW..NG COMMAND WAS NOT RECOGNIZED
DYPH

NCON 4
CONS 20000 1 20000 0
INIT 31.6 492.4 0.243 7.70
LOWER 15 300 0 0
UPPER 100 700 5 15
NOBS 14
WEIGHT -2
DATA 'A:RPD40MM.DAT'
OUTPUT PLOT DATA SECO PARM
BEGIN
```

BATCH FILE:

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

LISTING OF INPUT COMMANDS

NEWP 0,1
CONS 17020 1 17020 0
INIT 24.62 76.4 0.27 3.23
LOWER 0 50 0 0
UPPER 50 100 10 10
NOBS 14
WEIGHT -2
DATA 'A:RPD40M.DAT'
OUTPUT PLOT DATA SECO PARM
BEGIN
```

Text C.6 Typical computer output from an individual fit for plasma dyphylline concentrations in a horse by PCNONLIN[R].

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

LISTING OF INPUT COMMANDS

MODEL 4
TITLE
ONE COMPARTMENT FIRST-ORDER INPUT WITH FIRST-ORDER OUTPUT
DYPHYLLINE CSF 40 MG/KG
THE FOLLOWING COMMAND WAS NOT RECOGNIZED
DYPH

NCON 3
CONS 1 20000 0
INIT 6895 3.24 0.22 0.05
LOWER 4000 0 0 0
UPPER 8000 5 5 0.167
NOBS 15
WEIGHT -2
DATA 'A:PCD40MM.DAT'
OUTPUT PLOT DATA SECO PARM
BEGIN

*** NOTE ***  A WEIGHT COULD NOT BE COMPUTED FOR A DATA OBSERVATION
WEIGHT SET EQUAL TO ZERO
```

BATCH FILE:

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

LISTING OF INPUT COMMANDS

NEWP 0,1
CONS 1 17020 0
INIT 1685 1.14 0.179 0
LOWER 1000 0 0 -1
UPPER 2500 5 15 0.167
NOBS 15
WEIGHT -2
DATA 'A:PCD40M.DAT'
OUTPUT PLOT DATA SECO PARM
BEGIN

*** NOTE ***  A WEIGHT COULD NOT BE COMPUTED FOR A DATA OBSERVATION
WEIGHT SET EQUAL TO ZERO
```

Text C.7 Typical PCNONLIN[R] nonlinear estimation program for individual fitting of plasma theophylline concentrations in horses.

```
              PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

 LISTING OF INPUT COMMANDS

 MODEL 10
 TITLE
 TWO COMPARTMENT ZERO-ORDER INPUT WITH FIRST-ORDER OUTPUT
 THEOPHYLLINE PLASMA 20 MG/KG
 THE FOLLOWING COMMAND WAS NOT RECOGNIZED
 THEO

 NCON 5
 CONS 10000 1 10000 0 .167
 INIT 27.9 123.7 0.04 2.17
 LOWER 0 0 0 0
 UPPER 95 500 5 15
 NOBS 18
 WEIGHT -2
 DATA 'A:PPT20MM.DAT'
 OUTPUT PLOT DATA SECO PARM
 BEGIN

 *** NOTE ***  A WEIGHT COULD NOT BE COMPUTED FOR A DATA OBSERVATION
 WEIGHT SET EQUAL TO ZERO
```

BATCH FILE:

```
              PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

 LISTING OF INPUT COMMANDS

 NEWP 0,1
 CONS 7000 1 7000 0 .333
 INIT 18.5 15.6 0.045 2.01
 LOWER 0 0 0 0
 UPPER 55 90 5 15
 NOBS 18
 WEIGHT -2
 DATA 'A:PPT20PC.DAT'
 OUTPUT PLOT DATA SECO PARM
 BEGIN

 *** NOTE ***  A WEIGHT COULD NOT BE COMPUTED FOR A DATA OBSERVATION
 WEIGHT SET EQUAL TO ZERO
```

Text C.8 Typical PCNONLIN[R] nonlinear estimation program for individual fitting of csf theophylline concentrations in horses.

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

LISTING OF INPUT COMMANDS

MODEL 4
TITLE
ONE COMPARTMENT FIRST-ORDER INPUT WITH FIRST-ORDER OUTPUT
THEOPHYLLINE CSF 20 MG/KG
THE FOLLOWING COMMAND WAS NOT RECOGNIZED
THEO

NCON 3
CONS 1 10000 0
INIT 1137 0.860 0.033 0.125
LOWER 1000 0 0 0
UPPER 2000 5 5 0.167
NOBS 18
WEIGHT -2
DATA 'A:PCT20MM.DAT'
OUTPUT PLOT DATA SECO PARM
BEGIN

*** NOTE ***  A WEIGHT COULD NOT BE COMPUTED FOR A DATA OBSERVATION
WEIGHT SET EQUAL TO ZERO
```

BATCH FILE:

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

LISTING OF INPUT COMMANDS

NEWP 0,1
CONS 1 7000 0
INIT 779 2.971 0.061 0.153
LOWER 1000 0 0 -1
UPPER 2500 5 15 0.250
NOBS 18
WEIGHT -2
DATA 'A:PCT20PC.DAT'
OUTPUT PLOT DATA SECO PARM
BEGIN
*** ERROR 35 ***  AN INITIAL PARAMETER ESTIMATE
IS OUTSIDE OF THE SPECIFIED UPPER AND LOWER LIMITS.
PARAMETER LIMITS IGNORED - EXECUTION CONTINUING.

*** NOTE ***  A WEIGHT COULD NOT BE COMPUTED FOR A DATA OBSERVATION
WEIGHT SET EQUAL TO ZERO
```

APPENDIX D

PLASMA AND CSF DRUG CONCENTRATION DATA FOR INDIVIDUAL HORSES

Table D.1 Csf theophylline concentrations for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes.

DRUG: Theophylline
DOSE (mg/kg): 10
SAMPLED FLUID (ug/ml): CSF

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17	0.30	0.40	2.36	0.25	0.23	0.74	0.71	0.83	116.10
0.25	0.65	1.13	2.26	0.45	0.37	0.98	0.97	0.70	71.51
0.33	1.35	1.44	3.73	0.78	0.60	1.32	1.54	1.13	73.35
0.50	1.69	2.11	3.36	1.19	1.37	1.79	1.92	0.78	40.48
0.67	2.09	2.67	4.42	1.40	1.73	2.19	2.42	1.07	44.34
1.00	2.34	2.97	4.51	2.03	2.50	2.80	2.86	0.87	30.61
1.50	2.84	4.49	4.97	2.76	3.14	3.47	3.61	0.91	25.29
2.00	2.68	4.56	5.00	3.54	3.07	3.14	3.67	0.92	25.00
3.00	2.96	4.97	4.60	2.62	3.63	4.30	3.85	0.94	24.31
4.00	2.93	3.33	4.14	2.53	3.50	4.50	3.49	0.74	21.08
5.00	2.99	4.59	3.74	3.47	3.42	4.18	3.73	0.58	15.41
6.00	3.22	4.15	3.30	3.67	2.91	4.25	3.58	0.54	14.97
8.00	2.90	3.48	3.02	3.02	2.49	3.62	3.09	0.41	13.26
10.00	2.52	2.74	2.70	2.99	2.38	3.43	2.79	0.37	13.41
12.00	2.24	2.55	2.28	2.55	2.11	3.09	2.47	0.35	14.21
24.00	1.45	1.23	1.33	1.65	1.28	1.44	1.40	0.15	10.85
30.00	1.10	0.84	1.11	1.30	1.00	1.21	1.09	0.16	14.76

Table D.2 Plasma theophylline concentrations for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes.

DRUG: Theophylline
DOSE (mg/kg): 10
SAMPLED FLUID (ug/ml): PLASMA

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17	57.01	8.14	20.67	16.50	10.51	9.73	20.43	18.53	90.73
0.25	132.21	8.82	20.67	32.00	10.22	15.04	36.49	47.64	130.55
0.33	80.80	10.07	15.29	20.56	9.33	12.81	24.81	27.73	111.77
0.50	12.30	11.84	12.39	22.21	8.66	12.21	13.27	4.61	34.71
0.67	10.53	10.30	12.19	18.47	9.61	10.95	12.01	3.28	27.31
1.00	11.54	10.59	10.17	13.15	7.30	11.86	10.77	1.99	18.52
1.50	10.20	11.84	8.31	10.30	9.03	8.77	9.74	1.30	13.33
2.00	9.56	10.78	8.35	11.69	8.32	10.85	9.93	1.41	14.17
3.00	8.94	7.18	7.81	10.84	6.63	9.30	8.45	1.55	18.34
4.00	8.01	7.27	6.73	9.93	7.29	10.56	8.30	1.57	18.97
5.00	8.32	7.18	7.50	7.28	6.88	8.27	7.57	0.59	7.86
6.00	7.95	8.37	6.74	6.67	6.71	8.05	7.42	0.79	10.63
8.00	7.95	5.51	6.16	6.80	6.02	7.31	6.62	0.90	13.65
10.00	6.82	4.93	5.72	7.22	4.96	6.30	5.99	0.95	15.93
12.00	5.69	3.71	5.06	6.48	3.84	5.08	4.98	1.07	21.42
24.00	3.38	1.65	2.35	3.90	2.11	2.39	2.63	0.84	32.00
30.00	2.90	1.42	1.72	3.24	1.26	1.30	1.97	0.87	44.15

Table D.3 Csf theophylline concentrations for individual horses after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes.

DRUG: Theophylline
DOSE (mg/kg): 20
SAMPLED FLUID (ug/ml): CSF

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17	0.30	1.05	0.35	1.38	0.25	1.00	0.72	0.48	66.66
0.25	0.85	1.44	2.99	1.83	0.40	1.39	1.48	0.89	60.11
0.33	1.49	2.07	3.82	2.63	0.82	2.21	2.17	1.02	47.06
0.50	2.29	3.86	5.90	4.42	2.13	3.30	3.65	1.41	38.71
0.67	2.92	3.64	6.88	5.66	2.40	4.07	4.26	1.70	39.96
1.00	5.56	5.32	8.28	6.91	3.80	5.39	5.88	1.54	26.14
1.50	6.13	6.60	7.63	7.15	6.06	7.16	6.79	0.63	9.26
2.00	5.95	6.64	7.32	8.90	7.01	8.02	7.31	1.04	14.25
3.00	5.73	7.08	7.56	9.75	7.98	8.79	7.82	1.39	17.80
4.00	7.98	6.99	7.06	11.00	7.64	8.53	8.20	1.49	18.15
5.00	7.71	6.75	7.35	10.58	7.03	8.50	7.99	1.41	17.63
6.00	8.03	6.00	7.30	8.65	7.33	7.40	7.45	0.89	11.88
8.00	7.67	5.97	5.28	7.30	6.87	7.63	6.79	0.97	14.29
10.00	6.82	5.52	4.18	7.20	5.83	6.46	6.00	1.09	18.09
12.00	6.36	4.78	4.01	6.18	5.21	6.92	5.58	1.10	19.65
24.00	4.08	2.74	2.24	3.22	3.12	3.25	3.11	0.61	19.66
30.00	3.06	1.79	1.47	2.95	1.86	2.04	2.20	0.65	29.83

Table D.4 Plasma theophylline concentrations for individual horses after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes.

SAMPLE DRUG: Theophylline
DOSE (mg/kg): 20
D FLUID (ug/ml): PLASMA

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17	119.47	17.28	22.82	53.40	15.94	23.18	42.02	40.36	96.06
0.25	89.10	25.85	20.32	76.27	20.68	33.62	44.31	30.39	68.58
0.33	77.95	28.33	26.77	116.45	26.67	36.53	52.12	37.16	71.30
0.50	86.27	22.69	23.30	109.02	22.34	29.42	48.84	38.57	78.97
0.67	53.84	25.22	21.56	81.09	21.81	27.11	38.44	24.17	62.88
1.00	35.32	18.31	19.99	69.88	17.97	20.66	30.36	20.43	67.30
1.50	22.54	16.02	17.95	36.39	18.46	18.41	21.63	7.54	34.85
2.00	23.66	13.29	17.53	23.36	15.48	19.22	18.76	4.19	22.31
3.00	24.36	17.89	16.33	32.16	15.58	20.21	21.09	6.28	29.79
4.00	24.39	12.86	15.62	29.18	12.58	18.09	18.79	6.69	35.59
5.00	22.45	11.99	14.08	29.96	14.74	18.08	18.55	6.68	36.01
6.00	23.40	9.24	13.01	24.04	15.82	19.64	17.53	5.89	33.60
8.00	21.20	8.56	14.13	20.23	11.94	16.39	15.41	4.86	31.57
10.00	24.47	8.14	11.12	20.91	9.18	11.96	14.30	6.74	47.12
12.00	20.75	6.76	11.98	22.12	8.49	10.56	13.44	6.45	48.02
24.00	11.64	4.03	6.07	13.84	4.48	6.84	7.82	4.01	51.29
30.00	8.34	2.18	4.73	9.56	2.52	3.86	5.20	3.07	59.10

Table D.5 Csf dyphylline concentrations for individual horses after the administration of dyphylline, 20 mg/Kg, iv bolus.

DRUG: Dyphylline
DOSE (mg/kg): 20
SAMPLED FLUID (ug/ml): CSF

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17		28.98	0.50	1.30	0.40	0.50	0.68	0.42	62.12
0.25		21.69	1.15	1.26	0.91	0.84	1.04	0.20	18.93
0.33		14.30	2.23	1.62	0.92	1.13	1.48	0.58	39.47
0.50		11.81	2.82	2.43	0.96	1.05	1.81	0.95	52.36
0.67		12.42	4.00	3.19	1.42	1.47	2.52	1.28	50.95
1.00		12.54	4.98	3.32	1.33	1.51	2.79	1.72	61.66
1.50		9.62	2.63	3.60	1.21	1.29	2.18	1.15	52.59
2.00		7.85	2.60	2.54	1.23	1.17	1.89	0.79	41.94
3.00		4.83	2.27	2.52	1.17	1.08	1.76	0.74	42.11
4.00		2.85	1.36	2.21	0.84	1.09	1.38	0.60	43.33
5.00		2.10	1.07	2.20	0.53	1.05	1.21	0.71	58.23
6.00		1.69	1.06	2.17	0.38	0.78	1.10	0.77	69.83
8.00		1.12	0.74	1.52	0.20	0.70	0.79	0.54	68.86
10.00		0.58	0.57	0.89	0.11	0.57	0.53	0.32	60.35
12.00		0.33	0.45	0.80	0.06	0.46	0.44	0.30	68.96

Table D.6 Plasma dyphylline concentrations for individual horses after the administration of dyphylline, 20 mg/Kg, iv bolus.

DRUG: Dyphylline
DOSE (mg/kg): 20
SAMPLED FLUID (ug/ml): Plasma

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17	40.00	35.77	43.96	68.21	23.54	23.29	39.13	16.58	42.38
0.25	23.31	21.46	37.42	63.75	21.36	17.83	30.86	17.49	56.70
0.33	23.37	19.46	28.59	44.15	21.52	18.40	25.92	9.63	37.16
0.50	16.49	19.50	21.43	41.68	17.04	15.23	21.90	9.95	45.43
0.67	14.43	13.52	14.61	35.45	13.22	14.53	17.63	8.75	49.64
1.00	9.53	11.51	14.62	29.73	12.40	9.47	14.54	7.69	52.84
1.50	7.74	9.06	9.63	23.26	12.35	7.69	11.62	5.95	51.20
2.00	7.04	6.61	6.85	17.72	8.69	7.32	9.04	4.32	47.75
3.00	3.65	3.02	4.18	12.95	5.85	4.11	5.63	3.71	65.91
4.00	1.93	2.25	3.52	7.43	3.73	2.27	3.52	2.05	58.24
5.00	1.17	1.70	2.19	4.70	2.66	1.50	2.32	1.28	55.12
6.00	0.63	0.91	1.75	2.56	2.19	0.55	1.43	0.85	59.66
8.00	0.21	0.34	0.85	0.99	1.43	0.31	0.69	0.48	69.84

Table D.7 Csf dyphylline concentrations for individual horses after the administration of dyphylline, 40 mg/Kg, iv bolus.

DRUG: Dyphylline
DOSE (mg/kg): 40
SAMPLED FLUID (ug/ml): CSF

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17	0.83	6.82	3.53	7.41	1.00	6.68	4.38	3.01	68.63
0.25	1.32	7.83	3.70	11.37	1.87	7.49	5.60	3.94	70.43
0.33	1.62	7.85	4.11	17.20	2.44	10.33	7.26	5.89	81.17
0.50	1.86	8.90	8.14	10.02	2.89	8.92	6.79	3.49	51.35
0.67	1.90	10.20	10.68	10.35	4.08	8.68	7.65	3.74	48.87
1.00	2.16	11.73	12.00	7.79	5.89	8.76	8.06	3.72	46.14
1.50	2.16	11.15	11.88	6.45	5.59	8.60	7.64	3.66	47.88
2.00	1.91	8.84	10.97	6.18	5.99	9.13	7.17	3.20	44.59
3.00	1.93	7.83	7.94	4.52	5.82	9.98	6.34	2.87	45.22
4.00	1.43	4.59	7.84	3.92	5.14	6.86	4.96	2.26	45.60
5.00	0.94	3.58	5.45	3.21	3.87	4.72	3.63	1.55	42.60
6.00	0.59	3.18	3.19	2.70	3.63	5.88	3.19	1.70	53.21
8.00	0.57	1.66	3.00	1.73	2.38	3.32	2.11	1.00	47.55
10.00	0.32	0.94	1.34	1.10	1.71	2.18	1.26	0.64	50.92

Table D.8 Plasma dyphylline concentrations for individual horses after the administration of dyphylline, 40 mg/Kg, iv bolus.

DRUG: Dyphylline
DOSE (mg/kg): 40
SAMPLED FLUID (ug/ml): Plasma

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17	230.00	46.98	20.16	92.39	75.47	75.25	90.04	73.16	81.25
0.25	94.84	39.02	18.52	73.04	54.74	41.44	53.60	27.10	50.55
0.33	57.47	35.71	16.44	73.35	43.93	41.84	44.79	19.35	43.20
0.50	37.04	29.61	19.66	56.32	34.81	34.18	35.27	12.03	34.10
0.67	34.42	25.84	18.89	50.88	28.65	28.17	31.14	10.90	34.99
1.00	27.07	24.13	21.34	38.41	23.88	19.17	25.67	6.79	26.47
1.50	21.50	17.63	16.22	27.51	17.18	15.00	19.17	4.63	24.17
2.00	22.93	17.11	18.15	21.73	15.26	12.41	17.93	3.94	21.99
3.00	15.00	13.68	11.60	14.31	10.37	9.45	12.40	2.26	18.21
4.00	10.29	7.89	9.60	10.03	7.80	4.69	8.38	2.10	25.05
5.00	9.05	7.21	6.20	7.23	6.53	3.66	6.65	1.76	26.55
6.00	7.60	4.79	5.94	5.75	4.85	2.64	5.26	1.64	31.15
8.00	4.03	2.65	3.94	3.67	2.65	1.61	3.09	0.95	30.75
10.00	3.17	2.18	2.46	2.46	1.79	0.70	2.13	0.83	39.17
12.00	2.18	1.40	1.44	1.28	1.03	0.35	1.28	0.60	46.70

Table D.9 Csf theophylline concentrations for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

DRUG: Theophylline (Given concomitantly with dyphylline)
DOSE (mg/kg): 10
SAMPLED FLUID (ug/ml): CSF

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17									
0.25	0.40	0.50	0.80	1.27	0.55	1.83	0.89	0.56	62.30
0.33	0.50	1.50	1.29	2.53	1.12	2.70	1.61	0.85	53.02
0.50	1.27	1.74	1.75	2.57	1.84	3.74	2.15	0.88	41.06
0.67	1.45	1.91	2.13	3.29	2.44	3.99	2.54	0.94	37.12
1.00	2.02	3.19	2.38	3.30	3.24	4.32	3.08	0.80	26.17
1.50	2.55	3.93	2.75	3.32	4.21	4.12	3.48	0.72	20.60
2.00	3.02	4.60	3.23	5.77	4.66	4.70	4.33	1.03	23.82
3.00	3.97	4.20	3.90	5.70	4.66	5.12	4.59	0.71	15.48
4.00	3.85	4.23	4.20	4.15	4.40	5.10	4.32	0.42	9.75
5.00	3.21	3.27	4.41	4.49	4.06	4.36	3.97	0.58	14.66
6.00	2.99	3.45	4.39	3.85	3.25	4.90	3.81	0.73	19.10
8.00	2.59	3.26	4.13	3.56	2.83	4.64	3.50	0.78	22.25
10.00	2.56	2.69	4.32	2.93	2.57	3.91	3.16	0.76	24.03
12.00	2.29	2.97	4.37	2.36	2.27	3.12	2.90	0.81	27.94
24.00	1.39	1.36	2.32	1.49	1.18	1.24	1.50	0.42	27.94
30.00	1.12	1.15	1.69	1.16	0.73	0.60	1.08	0.38	35.73

Table D.10 Plasma theophylline concentrations for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg.

DRUG: Theophylline (Given concomitantly with dyphylline)
DOSE (mg/kg): 10
SAMPLED FLUID (ug/ml): Plasma

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17	26.79	11.62	0.73	16.02	10.67	18.73	14.09	8.75	62.09
0.25	90.00	15.64	12.28	26.09	12.16	21.40	29.60	30.09	101.67
0.33	19.60	15.34	9.89	19.62	13.37	19.77	16.27	4.11	25.28
0.50	15.00	12.16	8.48	16.16	12.25	16.51	13.43	3.06	22.81
0.67	11.83	12.93	8.98	12.62	15.86	11.27	12.25	2.26	18.42
1.00	10.38	11.03	7.07	12.93	12.74	11.40	10.93	2.13	19.51
1.50	11.94	10.21	6.99	10.65	9.64	9.06	9.75	1.67	17.12
2.00	8.39	10.24	6.06	9.28	7.42	8.59	8.33	1.46	17.48
3.00	7.24	9.43	4.65	8.68	7.44	8.34	7.63	1.67	21.86
4.00	7.95	8.44	4.74	8.87	8.39	7.55	7.66	1.50	19.57
5.00	7.21	7.83	3.99	8.87	6.08	7.32	6.88	1.68	24.45
6.00	5.84	7.71	3.93	7.00	6.50	6.82	6.30	1.31	20.84
8.00	5.50	7.24	3.79	7.07	5.13	5.21	5.66	1.30	23.04
10.00	4.61	6.47	3.09	6.40	4.27	4.64	4.91	1.31	26.60
12.00	2.41	5.44	2.75	5.08	3.92	4.36	3.99	1.22	30.60
24.00	1.69	2.20	1.36	3.60	1.63	1.94	2.07	0.80	38.75
30.00	1.30	1.58	0.95	2.68	1.05	1.25	1.47	0.63	42.99

Table D.11 Csf dyphylline concentrations for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

DRUG: Dyphylline (Given concomitantly with Theophylline)
DOSE (mg/kg): 20
SAMPLED FLUID (ug/ml): CSF

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17		2.24	1.32	2.19	0.37	0.89	1.40	0.82	58.29
0.33		2.46	1.39	2.69	0.52	1.14	1.64	0.91	55.66
0.67		4.72	1.67	2.82	1.00	1.50	2.34	1.49	63.49
1.17		4.94	1.80	2.55	1.62	1.97	2.58	1.37	53.04
1.67		4.27	1.89	3.94	2.20	2.42	2.94	1.08	36.78
2.67		3.39	1.97	3.45	1.68	2.25	2.55	0.82	32.24
3.67		2.50	1.80	2.69	1.50	1.82	2.06	0.51	24.60
4.67		1.18	1.54	2.22	1.30	1.53	1.55	0.40	25.90
5.67		1.15	1.48	1.73	1.20	1.32	1.38	0.24	17.17
6.67		0.83	1.22	1.04	1.07	0.93	1.02	0.15	14.41
8.67		0.56	1.03	0.66	0.86	0.71	0.76	0.18	24.24

NOTE: MOON MIST'S CONCENTRATIONS WERE BELOW 1ug/ml.

Table D.12 Plasma dyphylline concentrations for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg.

DRUG: Dyphylline (Given concomitantly with Theophylline)
DOSE (mg/kg): 20
SAMPLED FLUID (ug/ml): Plasma

TIME	Moon Mist	Taylor Lock	Picket Creek	Gypsy	Melodee	Linda	MEAN	STD DEV	CV(%)
0.17	20000.00	68.12	35.51	123.42	45.00	48.38	3386.74	8138.86	240.32
0.33	6408.00	23.24	17.40	30.27	18.81	23.67	1086.90	2606.80	239.84
0.67	382.16	15.97	16.31	22.89	18.33	14.63	78.38	148.85	189.90
1.17	18.68	10.67	12.42	17.96	8.90	11.15	13.30	4.06	30.52
1.67	12.69	8.53	10.47	10.80	7.94	7.57	9.67	1.99	20.55
2.67	9.18	7.47	7.67	8.18	7.96	5.34	7.63	1.27	16.66
3.67	6.73	5.68	5.59	5.54	4.30	3.93	5.30	1.02	19.27
4.67	4.17	4.77	4.97	4.68	3.56	3.37	4.25	0.67	15.70
5.67	3.46	2.95	3.62	3.47	2.75	2.45	3.12	0.47	15.07
6.67	2.50	2.40	3.20	2.86	1.85	1.73	2.42	0.57	23.41
8.67	1.76	1.30	2.24	1.92	1.15	1.03	1.57	0.48	30.59

NOTE: MEAN 2, STD DEV 2, AND CV% 2 DO NOT INCLUDE MOON MIST.

TIME	MEAN 2	STD DEV 2	CV% 2
0.17	64.09	35.23	54.97
0.33	22.68	5.04	22.24
0.67	17.63	3.23	18.31
1.17	12.22	3.45	28.22
1.67	9.06	1.48	16.34
2.67	7.32	1.14	15.59
3.67	5.01	0.83	16.52
4.67	4.27	0.75	17.46
5.67	3.05	0.49	16.08
6.67	2.41	0.63	26.29
8.67	1.53	0.53	34.37

APPENDIX E

PLASMA AND CSF DRUG CONCENTRATION-TIME CURVES FOR INDIVIDUAL HORSES

Figure E.1 Csf dyphylline concentration versus time curves for individual horses after the administration of dyphylline, 20 mg/Kg, iv bolus (n=5).

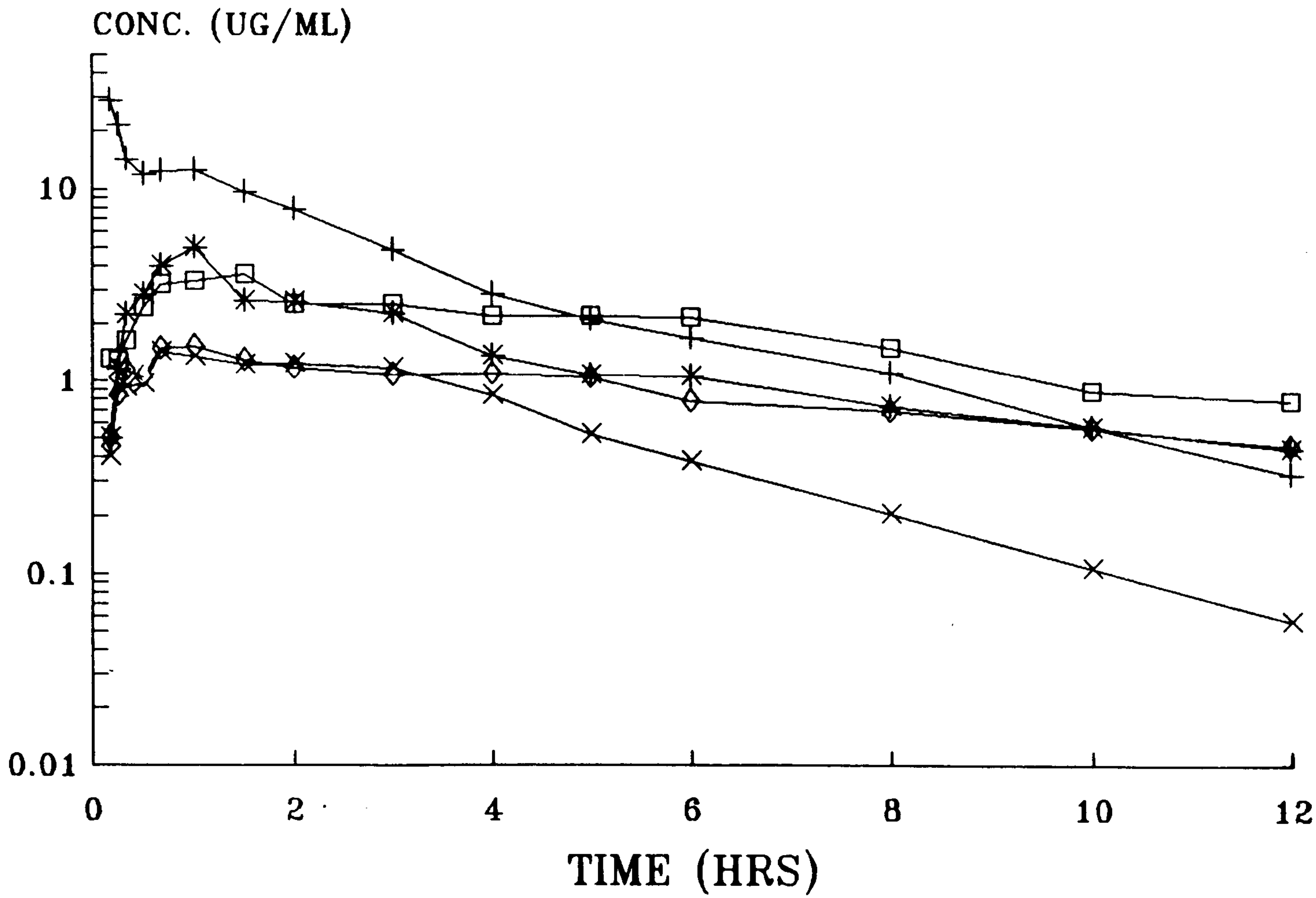


Figure E.2 Plasma dyphylline concentration versus time curves for individual horses after the administration of dyphylline, 20 mg/Kg, iv bolus (n=6).

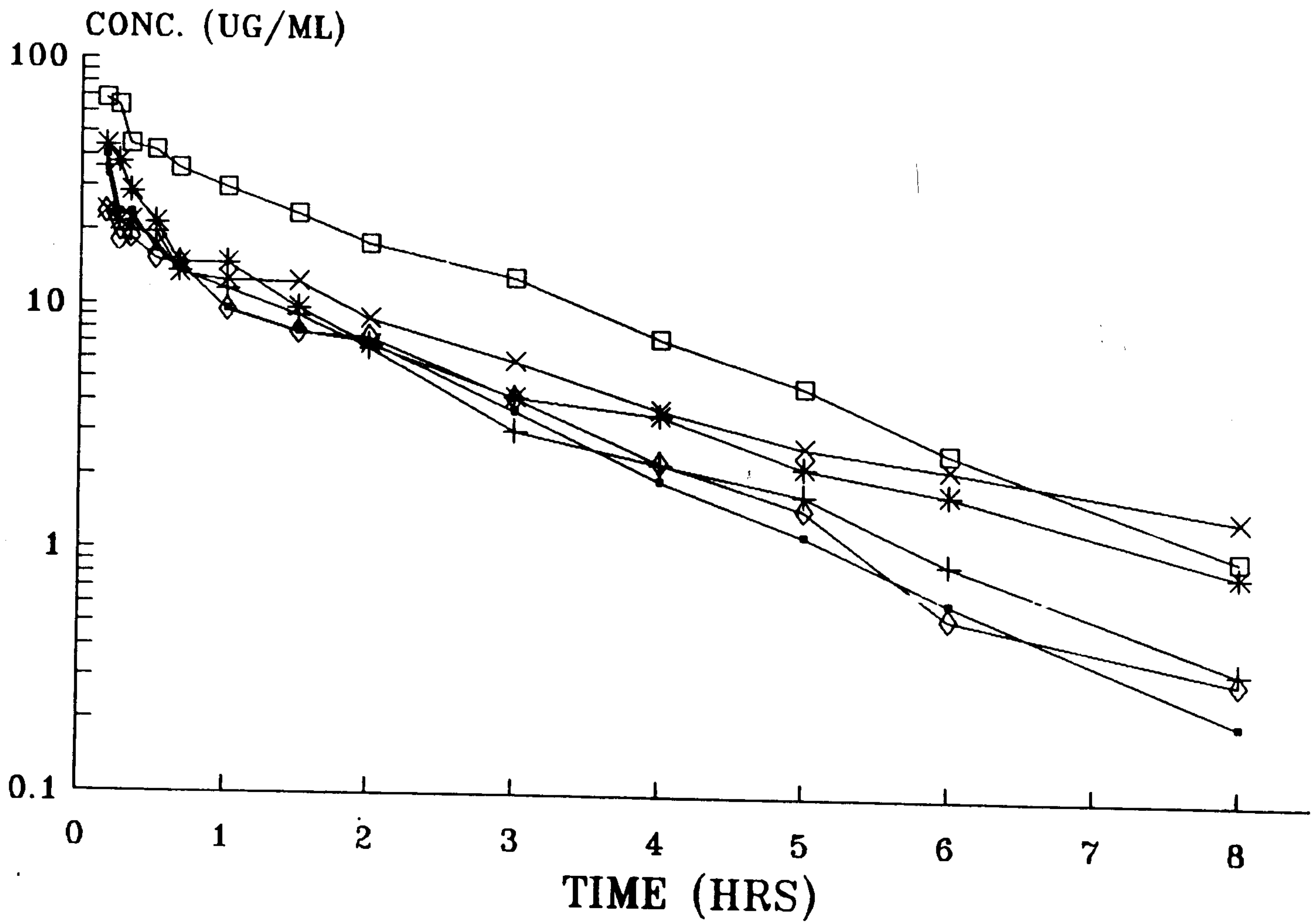


Figure E.3 Csf dyphylline concentration versus time curves for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus (n=6).

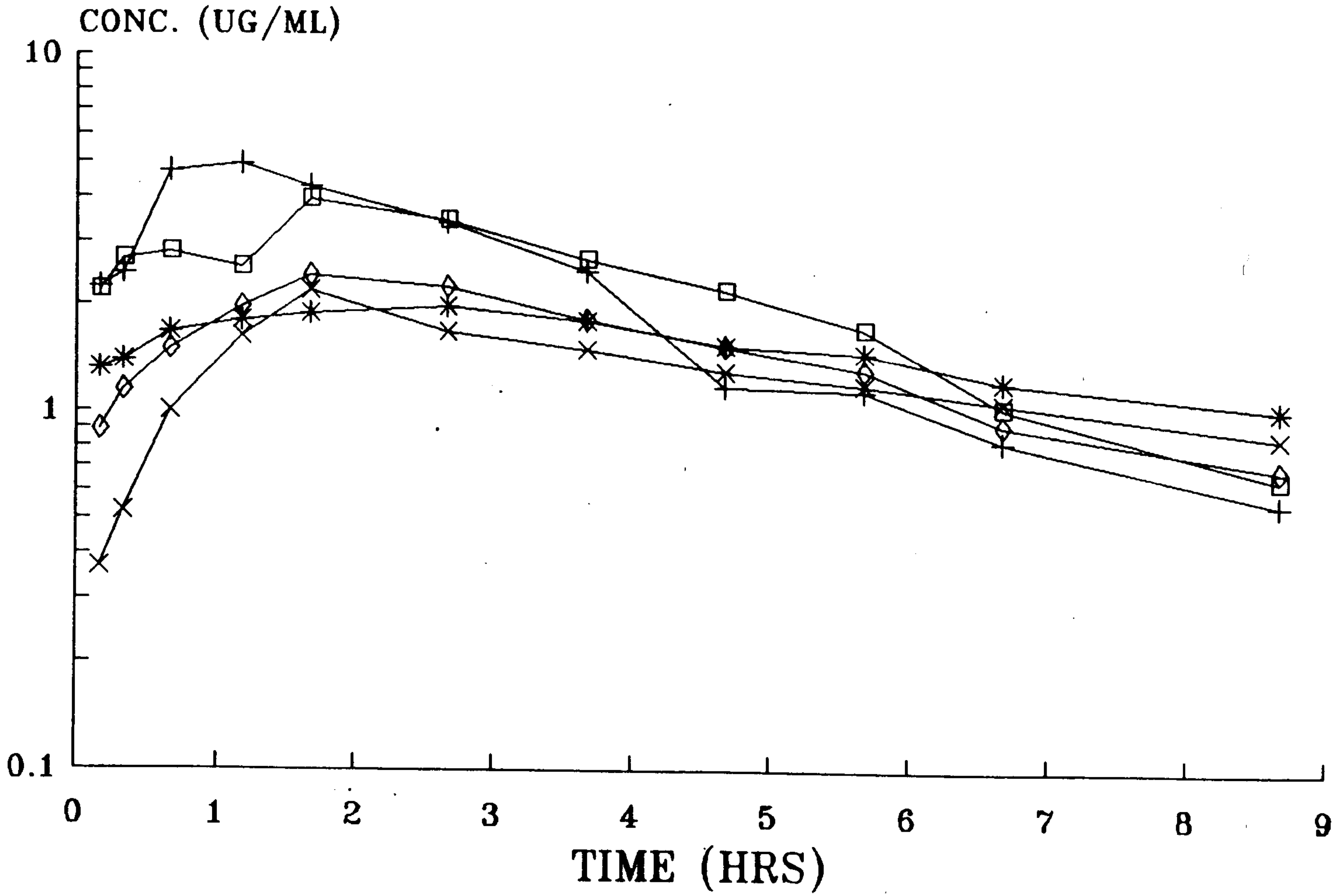


Figure E.4 Plasma dyphylline concentration versus time curves for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus (n=6).

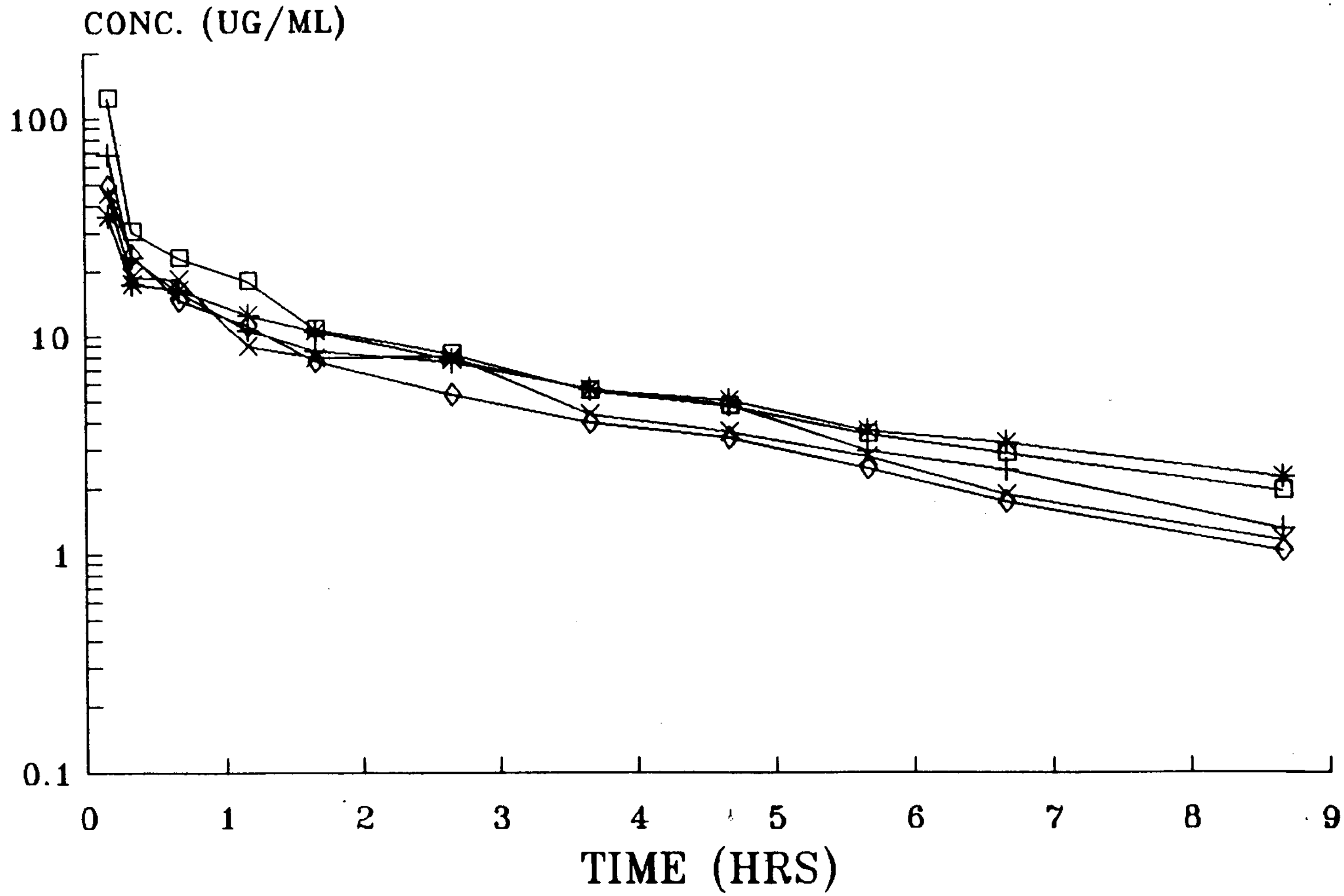


Figure E.5 Csf dyphylline concentration versus time curves for individual horses after the administration of dyphylline, 40 mg/Kg, iv bolus (n=6).

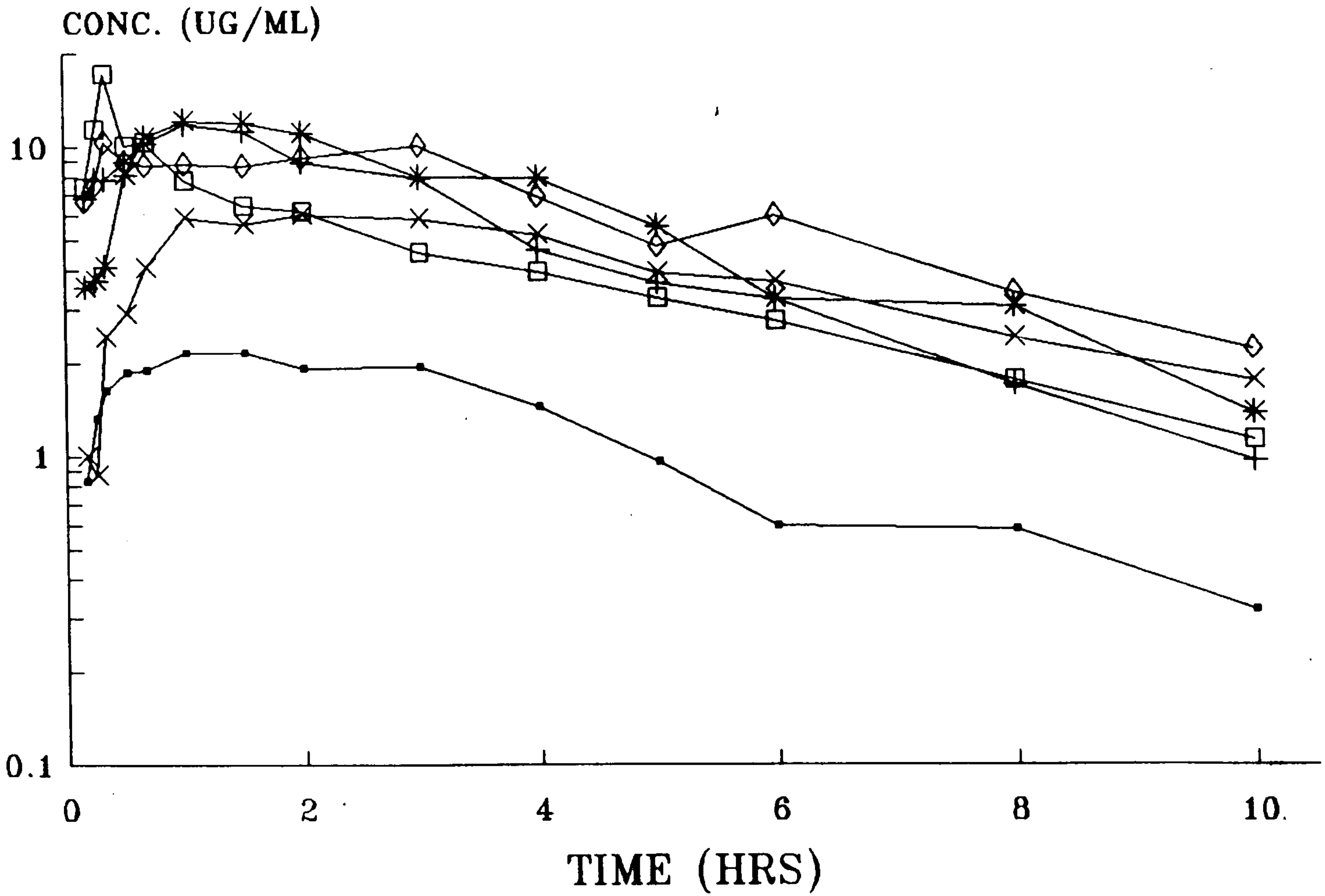


Figure E.6 Plasma dyphylline concentration versus time curves for individual horses after the administration of dyphylline, 40 mg/Kg, iv bolus (n=6).

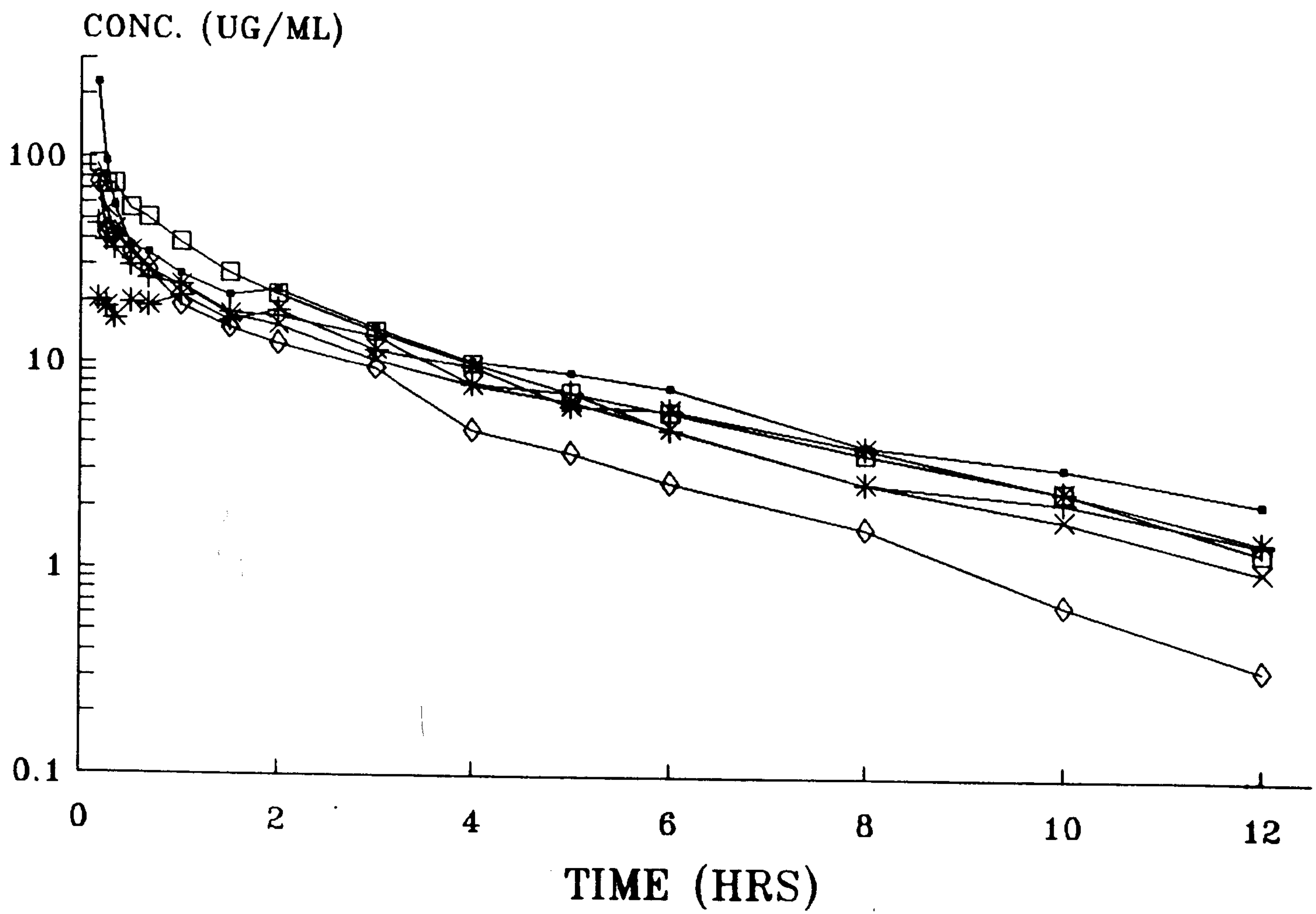


Figure E.7 Csf theophylline concentration versus time curves for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes (n=6).

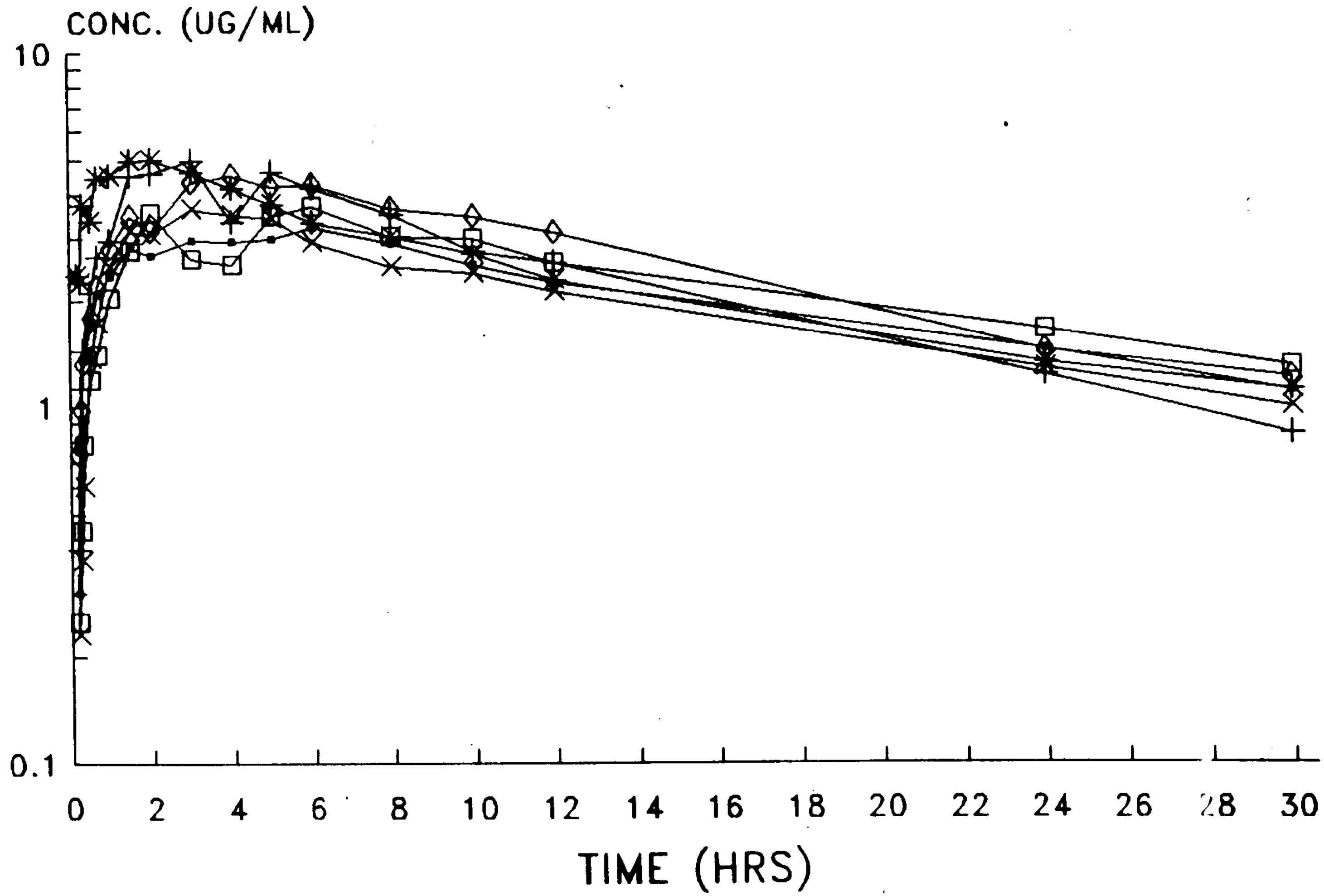


Figure E.8 Plasma theophylline concentration versus time curves for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes (n=6).

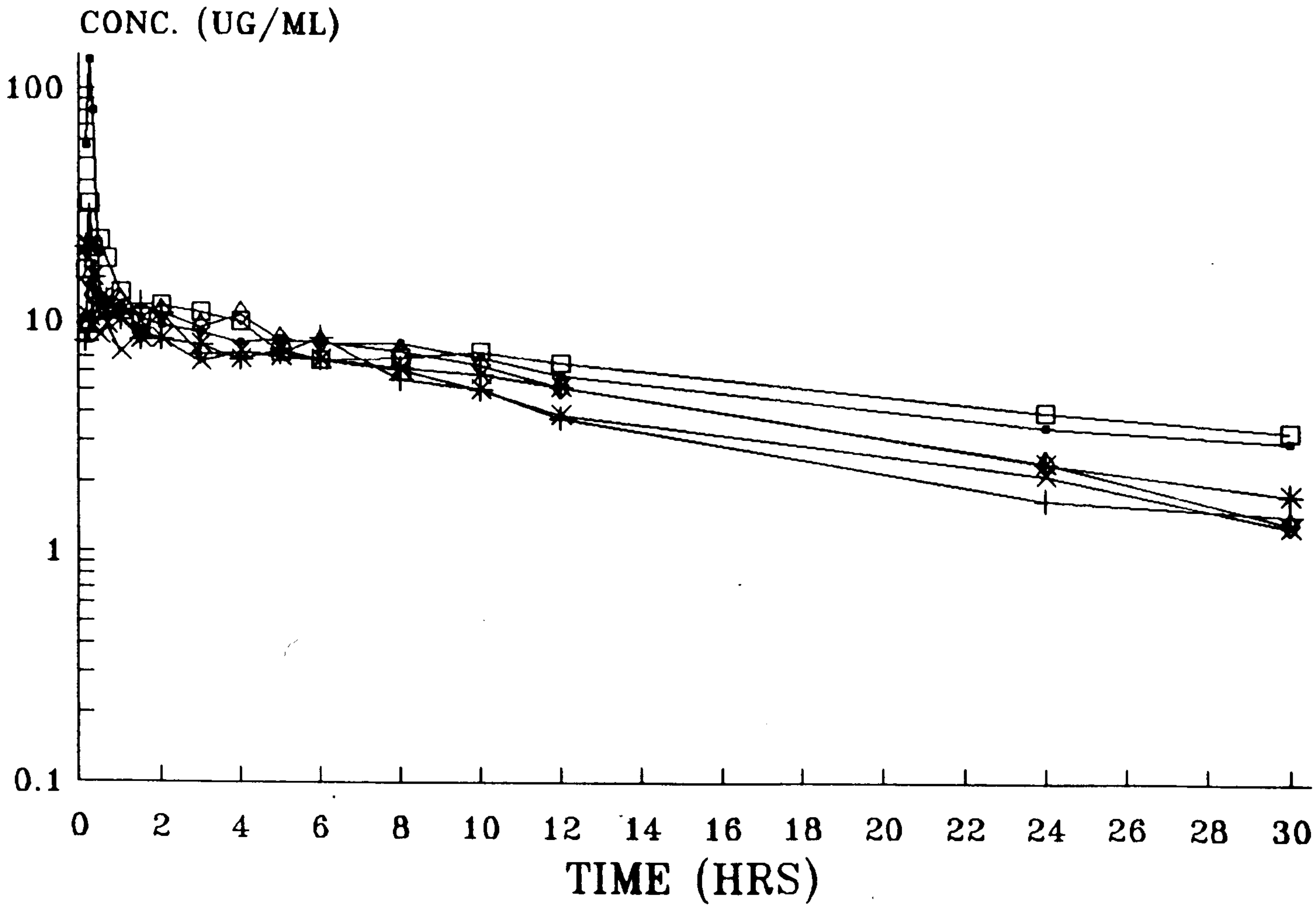


Figure E.9 Csf theophylline concentration versus time curves for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus (n=6).

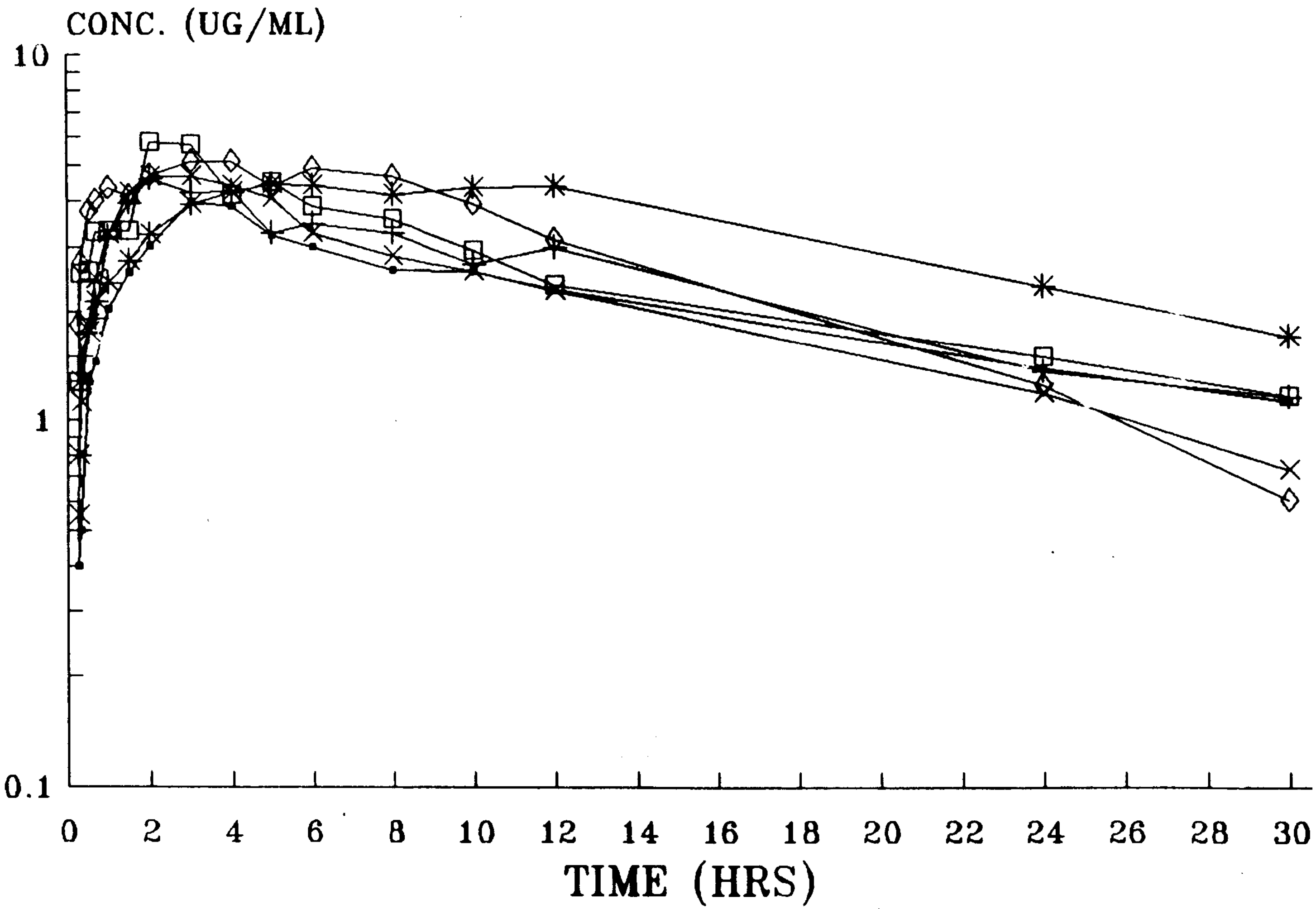


Figure E.10 Plasma theophylline concentration versus time curves for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus (n=6).

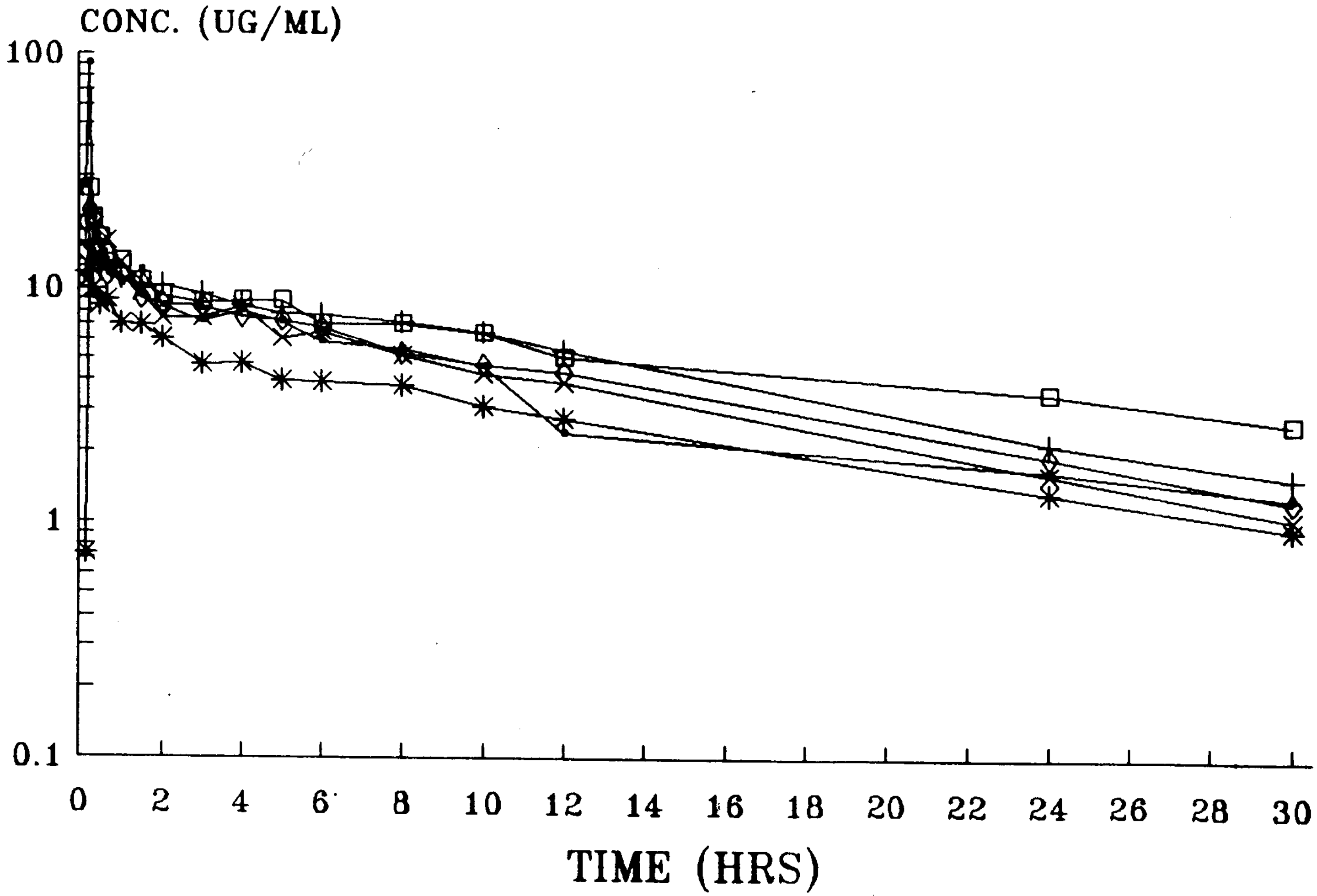


Figure E.11 Csf theophylline concentration versus time curves for individual horses after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes (n=6).

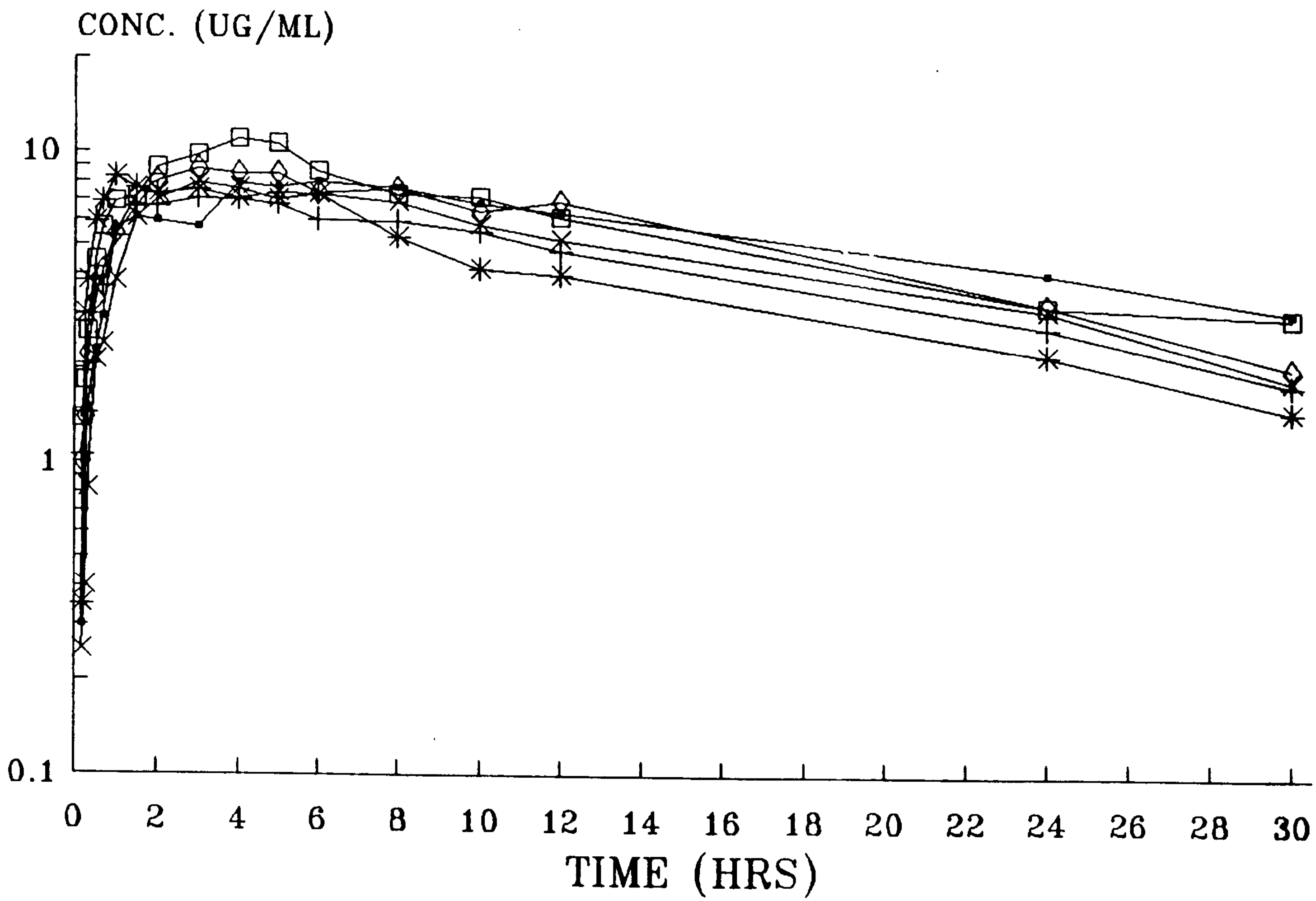
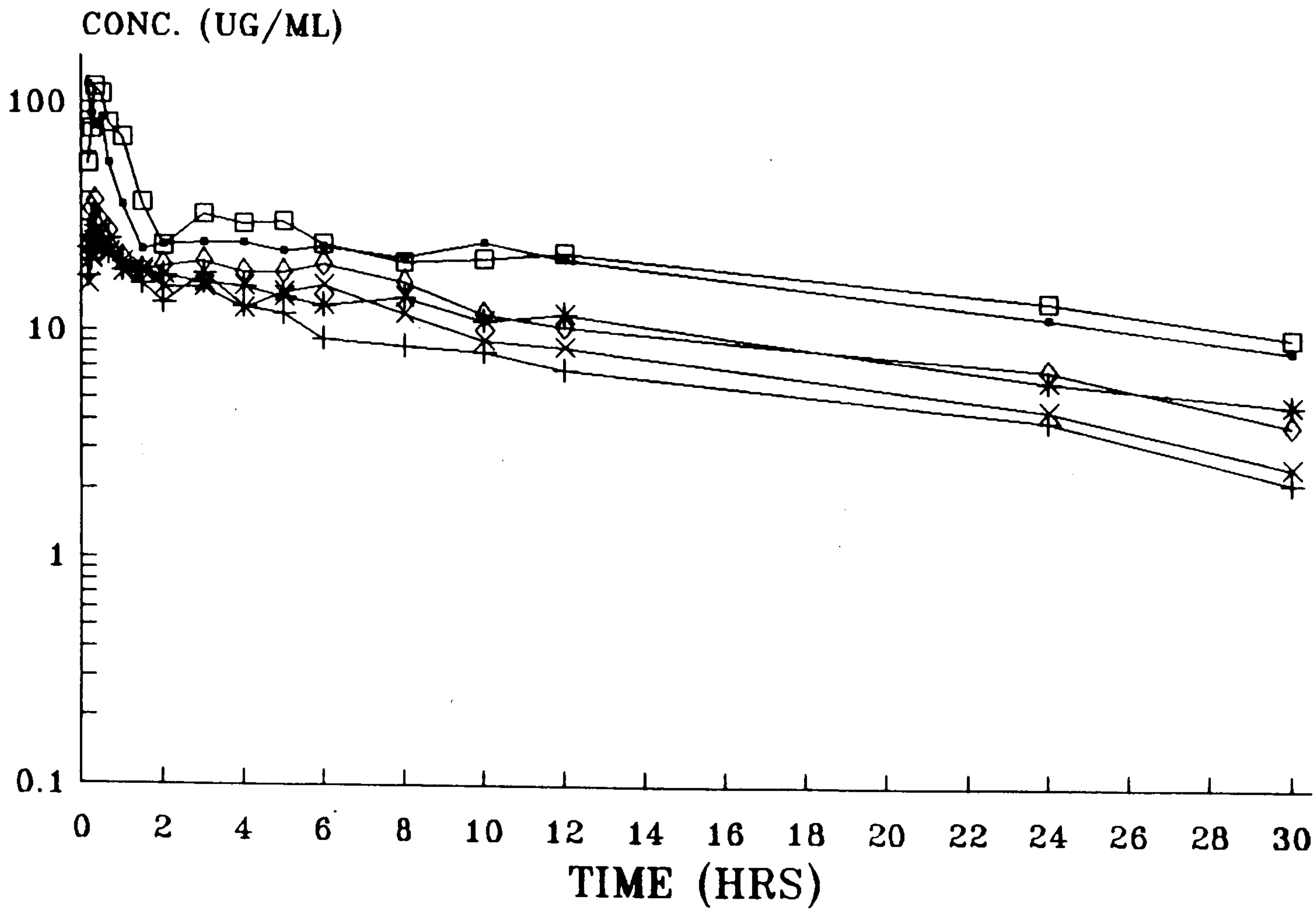


Figure E.12 Plasma theophylline concentration versus time curves for individual horses after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes (n=6).



APPENDIX F

CSF/PLASMA, CSF/CSF AND PLASMA/PLASMA DRUG CONCENTRATION RATIO'S FOR INDIVIDUAL HORSES

Table F.1 Csf/plasma theophylline concentration ratio's for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes.

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.00	2.96	8.94	0.33	4.97	7.18	0.69	4.60	7.81	0.59
4.00	2.93	8.01	0.37	3.33	7.27	0.46	4.14	6.73	0.62
5.00	2.99	8.32	0.36	4.59	7.18	0.64	3.74	7.50	0.50
6.00	3.22	7.95	0.41	4.15	8.37	0.50	3.30	6.74	0.49
8.00	2.90	7.95	0.36	3.48	5.51	0.63	3.02	6.16	0.49
10.00	2.52	6.82	0.37	2.74	4.93	0.56	2.70	5.72	0.47
12.00	2.24	5.69	0.39	2.55	3.71	0.69	2.28	5.06	0.45
24.00	1.45	3.38	0.43	1.23	1.65	0.75	1.33	2.35	0.57
30.00	1.10	2.90	0.38	0.84	1.42	0.59	1.11	1.72	0.65
MEAN			0.38			0.61			0.54
SD			0.03			0.09			0.07

	GYPSY			MELODEE			LINDA		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.00	2.62	10.84	0.24	3.63	6.63	0.55	4.30	9.30	0.46
4.00	2.53	9.93	0.25	3.50	7.29	0.48	4.50	10.56	0.43
5.00	3.47	7.28	0.48	3.42	6.88	0.50	4.18	8.27	0.51
6.00	3.67	6.67	0.55	2.91	6.71	0.43	4.25	8.05	0.53
8.00	3.02	6.80	0.44	2.49	6.02	0.41	3.62	7.31	0.50
10.00	2.99	7.22	0.41	2.38	4.96	0.48	3.43	6.30	0.54
12.00	2.55	6.48	0.39	2.11	3.84	0.55	3.09	5.08	0.61
24.00	1.65	3.90	0.42	1.28	2.11	0.61	1.44	2.39	0.60
30.00	1.30	3.24	0.40	1.00	1.26	0.79	1.21	1.30	0.93
MEAN			0.40			0.53			0.57
SD			0.10			0.11			0.15

OVERALL MEAN = 0.51 STANDARD DEVIATION = 0.09

Table F.2 Csf/plasma theophylline concentration ratio's for individual horses after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes.

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.00	5.73	24.36	0.24	7.08	17.89	0.40	7.56	16.33	0.46
4.00	7.98	24.39	0.33	6.99	12.86	0.54	7.06	15.62	0.45
5.00	7.71	22.45	0.34	6.75	11.99	0.56	7.35	14.08	0.52
6.00	8.03	23.40	0.34	6.00	9.24	0.65	7.30	13.01	0.56
8.00	7.67	21.20	0.36	5.97	8.56	0.70	5.28	14.13	0.37
10.00	6.82	24.47	0.28	5.52	8.14	0.68	4.18	11.12	0.38
12.00	6.36	20.75	0.31	4.78	6.76	0.71	4.01	11.98	0.33
24.00	4.08	11.64	0.35	2.74	4.03	0.68	2.24	6.07	0.37
30.00	3.06	8.34	0.37	1.79	2.18	0.82	1.47	4.73	0.31
MEAN			0.32			0.64			0.42
SD			0.04			0.12			0.09

	GYPSY			MELODEE			LINDA		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.00	9.75	32.16	0.30	7.98	15.58	0.51	8.79	20.21	0.43
4.00	11.00	29.18	0.38	7.64	12.58	0.61	8.53	18.09	0.47
5.00	10.58	29.96	0.35	7.03	14.74	0.48	8.50	18.08	0.47
6.00	8.65	24.04	0.36	7.33	15.82	0.46	7.40	19.64	0.38
8.00	7.30	20.23	0.36	6.87	11.94	0.58	7.63	16.39	0.47
10.00	7.20	20.91	0.34	5.83	9.18	0.64	6.46	11.96	0.54
12.00	6.18	22.12	0.28	5.21	8.49	0.61	6.92	10.56	0.66
24.00	3.22	13.84	0.23	3.12	4.48	0.70	3.25	6.84	0.48
30.00	2.95	9.56	0.31	1.86	2.52	0.74	2.04	3.86	0.53
MEAN			0.32			0.59			0.49
SD			0.05			0.09			0.08

OVERALL MEAN = 0.46 STANDARD DEVIATION = 0.13

Table F.3 Csf/plasma theophylline concentration ratio's for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.00	3.97	7.24	0.55	4.20	9.43	0.45	3.90	4.65	0.84
4.00	3.85	7.95	0.48	4.23	8.44	0.50	4.20	4.74	0.89
5.00	3.21	7.21	0.45	3.27	7.83	0.42	4.41	3.99	1.11
6.00	2.99	5.84	0.51	3.45	7.71	0.45	4.39	3.93	1.12
8.00	2.59	5.50	0.47	3.26	7.24	0.45	4.13	3.79	1.09
10.00	2.56	4.61	0.56	2.69	6.47	0.42	4.32	3.09	1.40
12.00	2.29	2.41	0.95	2.97	5.44	0.55	4.37	2.75	1.59
24.00	1.39	1.69	0.82	1.36	2.20	0.62	2.32	1.36	1.71
30.00	1.12	1.30	0.86	1.15	1.58	0.73	1.69	0.95	1.78
MEAN			0.63			0.51			1.28
SD			0.19			0.11			0.35

	GYPSY			MELODEE			LINDA		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.00	5.70	8.68	0.66	4.66	7.44	0.63	5.12	8.34	0.61
4.00	4.15	8.87	0.47	4.40	8.39	0.52	5.10	7.55	0.68
5.00	4.49	8.87	0.51	4.06	6.08	0.67	4.36	7.32	0.60
6.00	3.85	7.00	0.55	3.25	6.50	0.50	4.90	6.82	0.72
8.00	3.56	7.07	0.50	2.83	5.13	0.55	4.64	5.21	0.89
10.00	2.93	6.40	0.46	2.57	4.27	0.60	3.91	4.64	0.84
12.00	2.36	5.08	0.46	2.27	3.92	0.58	3.12	4.36	0.72
24.00	1.49	3.60	0.41	1.18	1.63	0.72	1.24	1.94	0.64
30.00	1.16	2.68	0.43	0.73	1.05	0.69	0.60	1.25	0.48
MEAN			0.49			0.61			0.69
SD			0.07			0.08			0.13

OVERALL MEAN = 0.70 STANDARD DEVIATION = 0.29

OVERALL MEAN WITHOUT PICKET CREEK = 0.586 STANDARD DEVIATION = 0.084

Table F.4 Csf/plasma dyphylline concentration ratio's for individual horses after the administration of dyphylline, 20 mg/Kg, iv bolus.

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.00	NOTHING	3.65	0.00	4.83	3.02	1.60	2.27	4.18	0.54
4.00		1.93	0.00	2.85	2.25	1.27	1.36	3.52	0.39
5.00		1.17	0.00	2.10	1.70	1.24	1.07	2.19	0.49
6.00		0.63	0.00	1.69	0.91	1.86	1.06	1.75	0.61
8.00		0.21	0.00	1.12	0.34	3.26	0.74	0.85	0.87
10.00			0.00			0.00			0.00
MEAN			0.00			1.84			0.58
SD			0.00			0.83			0.18

NOT INCLUDED IN AVERAGE
(UNREALISTIC CSF CURVE)

	GYPSY			MELODEE			LINDA		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.00	2.52	12.95	0.19	1.17	5.85	0.20	1.08	4.11	0.26
4.00	2.21	7.43	0.30	0.84	3.73	0.23	1.09	2.27	0.48
5.00	2.20	4.70	0.47	0.53	2.66	0.20	1.05	1.50	0.70
6.00	2.17	2.56	0.85	0.38	2.19	0.17	0.78	0.55	1.42
8.00	1.52	0.99	1.53	0.20	1.43	0.14	0.70	0.31	2.25
10.00			0.00			0.00			0.00
MEAN			0.67			0.19			1.02
SD			0.54			0.03			0.81

OVERALL MEAN = 0.62 STANDARD DEVIATION = 0.34

Table F.5 Csf/plasma dyphylline concentration ratio's for individual horses after the administration of dyphylline, 40 mg/Kg, infused over 15 minutes.

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.00	1.93	15.00	0.13	7.83	13.68	0.57	7.94	11.60	0.68
4.00	1.43	10.29	0.14	4.59	7.89	0.58	7.84	9.60	0.82
5.00	0.94	9.05	0.10	3.58	7.21	0.50	5.45	6.20	0.88
6.00	0.59	7.60	0.08	3.18	4.79	0.66	3.19	5.94	0.54
8.00	0.57	4.03	0.14	1.66	2.65	0.63	3.00	3.94	0.76
10.00	0.32	3.17	0.10	0.94	2.18	0.43	1.34	2.46	0.54
MEAN			0.12			0.56			0.70
SD			0.03			0.08			0.14

	GYPSY			MELODEE			LINDA		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.00	4.52	14.31	0.32	5.82	10.37	0.56	9.98	9.45	1.06
4.00	3.92	10.03	0.39	5.14	7.80	0.66	6.86	4.69	1.46
5.00	3.21	7.23	0.44	3.87	6.53	0.59	4.72	3.66	1.29
6.00	2.70	5.75	0.47	3.63	4.85	0.75	5.88	2.64	2.23
8.00	1.73	3.67	0.47	2.38	2.65	0.90	3.32	1.61	2.06
10.00	1.10	2.46	0.45	1.71	1.79	0.96	2.18	0.70	3.12
MEAN			0.42			0.74			1.87
SD			0.06			0.16			0.76

OVERALL MEAN = 0.74 STANDARD DEVIATION = 0.60

Table F.6 Csf/plasma dyphylline concentration ratio's for individual horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.67	NOTHING	6.73	0.00	2.50	5.68	0.44	1.80	5.59	0.32
4.67		4.17	0.00	1.18	4.77	0.25	1.54	4.97	0.31
5.67		3.46	0.00	1.15	2.95	0.39	1.48	3.62	0.41
6.67		2.50	0.00	0.83	2.40	0.35	1.22	3.20	0.38
8.67		1.76	0.00	0.56	1.30	0.43	1.03	2.24	0.46
MEAN			0.00			0.37			0.38
SD			0.00			0.08			0.06

	GYPSY			MELODEE			LINDA		
TIME	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO	CSF	PLASMA	RATIO
3.67	2.69	5.54	0.49	1.50	4.30	0.35	1.82	3.93	0.46
4.67	2.22	4.68	0.47	1.30	3.56	0.37	1.53	3.37	0.45
5.67	1.73	3.47	0.50	1.20	2.75	0.44	1.32	2.45	0.54
6.67	1.04	2.86	0.36	1.07	1.85	0.58	0.93	1.73	0.54
8.67	0.66	1.92	0.34	0.86	1.15	0.75	0.71	1.03	0.68
MEAN			0.43			0.50			0.54
SD			0.07			0.17			0.09

OVERALL MEAN = 0.44 STANDARD DEVIATION = 0.07

Table F.7 Csf/csf theophylline concentration ratio's for individual horses. (Csf theophylline concentrations after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes/ csf theophylline concentrations after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes).

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	CSF 10	CSF 20	RATIO	CSF 10	CSF 20	RATIO	CSF 10	CSF 20	RATIO
3.00	2.96	5.73	0.52	4.97	7.08	0.42	4.60	7.56	0.61
4.00	2.93	7.98	0.37	3.33	6.99	0.42	4.14	7.06	0.59
5.00	2.99	7.71	0.39	4.59	6.75	0.44	3.74	7.35	0.51
6.00	3.22	8.03	0.40	4.15	6.00	0.54	3.30	7.30	0.45
8.00	2.90	7.67	0.38	3.48	5.97	0.49	3.02	5.28	0.57
10.00	2.52	6.82	0.37	2.74	5.52	0.46	2.70	4.18	0.65
12.00	2.24	6.36	0.35	2.55	4.78	0.47	2.28	4.01	0.57
24.00	1.45	4.08	0.36	1.23	2.74	0.53	1.33	2.24	0.59
30.00	1.10	3.06	0.36	0.84	1.79	0.61	1.11	1.47	0.76
MEAN			0.39			0.49			0.59
SD			0.05			0.06			0.08

	GYPSY			MELODEE			LINDA		
TIME	CSF 10	CSF 20	RATIO	CSF 10	CSF 20	RATIO	CSF 10	CSF 20	RATIO
3.00	2.62	9.75	0.47	3.63	7.98	0.45	4.30	8.79	0.41
4.00	2.53	11.00	0.38	3.50	7.64	0.46	4.50	8.53	0.41
5.00	3.47	10.58	0.35	3.42	7.03	0.49	4.18	8.50	0.40
6.00	3.67	8.65	0.38	2.91	7.33	0.40	4.25	7.40	0.39
8.00	3.02	7.30	0.41	2.49	6.87	0.36	3.62	7.63	0.33
10.00	2.99	7.20	0.38	2.38	5.83	0.41	3.43	6.46	0.37
12.00	2.55	6.18	0.37	2.11	5.21	0.40	3.09	6.92	0.30
24.00	1.65	3.22	0.41	1.28	3.12	0.41	1.44	3.25	0.39
30.00	1.30	2.95	0.38	1.00	1.86	0.54	1.21	2.04	0.49
MEAN			0.39			0.44			0.39
SD			0.04			0.05			0.05

OVERALL MEAN = 0.45 STANDARD DEVIATION = 0.08

Table F.8 Csf/csf theophylline concentration ratio's for individual horses. (Csf theophylline concentrations after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes/ csf theophylline concentrations after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus).

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	CSF 10	CSF C10	RATIO	CSF 10	CSF C10	RATIO	CSF 10	CSF C10	RATIO
3.00	2.96	3.97	0.75	4.97	4.20	0.70	4.60	3.90	1.18
4.00	2.93	3.85	0.76	3.33	4.23	0.69	4.14	4.20	0.99
5.00	2.99	3.21	0.93	4.59	3.27	0.91	3.74	4.41	0.85
6.00	3.22	2.99	1.08	4.15	3.45	0.93	3.30	4.39	0.75
8.00	2.90	2.59	1.12	3.48	3.26	0.89	3.02	4.13	0.73
10.00	2.52	2.56	0.98	2.74	2.69	0.94	2.70	4.32	0.63
12.00	2.24	2.29	0.98	2.55	2.97	0.75	2.28	4.37	0.52
24.00	1.45	1.39	1.04	1.23	1.36	1.07	1.33	2.32	0.57
30.00	1.10	1.12	0.98	0.84	1.15	0.96	1.11	1.69	0.66
MEAN			0.96			0.87			0.76
SD			0.13			0.13			0.21

	GYPSY			MELODEE			LINDA		
TIME	CSF 10	CSF C10	RATIO	CSF 10	CSF C10	RATIO	CSF 10	CSF C10	RATIO
3.00	2.62	5.70	0.81	3.63	4.66	0.78	4.30	5.12	0.71
4.00	2.53	4.15	1.00	3.50	4.40	0.80	4.50	5.10	0.69
5.00	3.47	4.49	0.83	3.42	4.06	0.84	4.18	4.36	0.78
6.00	3.67	3.85	0.86	2.91	3.25	0.90	4.25	4.90	0.59
8.00	3.02	3.56	0.85	2.49	2.83	0.88	3.62	4.64	0.54
10.00	2.99	2.93	0.92	2.38	2.57	0.93	3.43	3.91	0.61
12.00	2.55	2.36	0.97	2.11	2.27	0.93	3.09	3.12	0.68
24.00	1.65	1.49	0.89	1.28	1.18	1.08	1.44	1.24	1.03
30.00	1.30	1.16	0.96	1.00	0.73	1.37	1.21	0.60	1.66
MEAN			0.90			0.94			0.81
SD			0.07			0.18			0.35

OVERALL MEAN = 0.87 STANDARD DEVIATION = 0.08

Table F.9 Csf/csf dyphylline concentration ratio's for individual horses. (Csf dyphylline concentrations after the administration of dyphylline, 20 mg/Kg, iv bolus/ csf dyphylline concentrations after the administration of dyphylline, 40 mg/Kg, iv bolus).

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	CSF 20	CSF 40	RATIO	CSF 20	CSF 40	RATIO	CSF 20	CSF 40	RATIO
3.00	NOTHING		--	4.83	7.83	0.62	2.27	7.94	0.29
4.00			--	2.85	4.59	0.62	1.36	7.84	0.17
5.00			--	2.10	3.58	0.59	1.07	5.45	0.20
6.00			--	1.69	3.18	0.53	1.06	3.19	0.33
8.00			--	1.12	1.66	0.67	0.74	3.00	0.25
10.00			--		0.94	--			--
MEAN			--			0.61			0.25
SD			--			0.05			0.06

NOT INCLUDED IN AVERAGE
(UNREALISTIC CSF CURVE)

	GYPSY			MELODEE			LINDA		
TIME	CSF 20	CSF 40	RATIO	CSF 20	CSF 40	RATIO	CSF 20	CSF 40	RATIO
3.00	2.52	4.52	0.56	1.17	5.82	0.20	1.08	9.98	0.11
4.00	2.21	3.92	0.56	0.84	5.14	0.16	1.09	6.86	0.16
5.00	2.20	3.21	0.69	0.53	3.87	0.14	1.05	4.72	0.22
6.00	2.17	2.70	0.80	0.38	3.63	0.11	0.78	5.88	0.13
8.00	1.52	1.73	0.88	0.20	2.38	0.09	0.70	3.32	0.21
10.00			--			--			--
MEAN			0.70			0.14			0.17
SD			0.14			0.05			0.05

OVERALL MEAN = 0.34 STANDARD DEVIATION = 0.32

Table F.10 Csf/csf dyphylline concentration ratio's for individual horses. (Csf dyphylline concentrations after the administration of dyphylline, 20 mg/Kg, iv bolus/ csf dyphylline concentrations after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus).

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	CSF 20	CSF C20	RATIO	CSF 20	CSF C20	RATIO	CSF 20	CSF C20	RATIO
3.00	NOTHING		--	4.83	2.50	1.93	2.27	1.80	1.26
4.00			--	2.85	1.18	2.42	1.36	1.54	0.88
5.00			--	2.10	1.15	1.83	1.07	1.48	0.72
6.00			--	1.69	0.83	2.03	1.06	1.22	0.87
8.00			--	1.12	0.56	2.00	0.74	1.03	0.72
10.00			--			--			--
MEAN			--			2.04			0.89
SD			--			0.22			0.22

NOT INCLUDED IN AVERAGE
(UNREALISTIC CSF CURVE)

	GYPSY			MELODEE			LINDA		
TIME	CSF 20	CSF C20	RATIO	CSF 20	CSF C20	RATIO	CSF 20	CSF C20	RATIO
3.00	2.52	2.69	0.94	1.17	1.50	0.78	1.08	1.82	0.59
4.00	2.21	2.22	1.00	0.84	1.30	0.65	1.09	1.53	0.71
5.00	2.20	1.73	1.27	0.53	1.20	0.44	1.05	1.32	0.80
6.00	2.17	1.04	2.09	0.38	1.07	0.36	0.78	0.93	0.84
8.00	1.52	0.66	2.32	0.20	0.86	0.24	0.70	0.71	0.99
10.00			--			--			--
MEAN			1.52			0.49			0.79
SD			0.64			0.22			0.15

OVERALL MEAN = 1.15 STANDARD DEVIATION = 0.62

Table F.11 Plasma/plasma theophylline concentration ratio's for individual horses. (Csf theophylline concentrations after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes/ csf theophylline concentrations after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes).

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	P 10	P 20	RATIO	P 10	P 20	RATIO	P 10	P 20	RATIO
3.00	8.94	24.36	0.37	7.18	17.89	0.50	7.81	16.33	0.48
4.00	8.01	24.39	0.33	7.27	12.86	0.62	6.73	15.62	0.43
5.00	8.32	22.45	0.37	7.18	11.99	0.69	7.50	14.08	0.53
6.00	7.95	23.40	0.34	8.37	9.24	0.86	6.74	13.01	0.52
8.00	7.95	21.20	0.38	5.51	8.56	0.93	6.16	14.13	0.44
10.00	6.82	24.47	0.28	4.93	8.14	0.84	5.72	11.12	0.51
12.00	5.69	20.75	0.27	3.71	6.76	0.84	5.06	11.98	0.42
24.00	3.38	11.64	0.29	1.65	4.03	0.84	2.35	6.07	0.39
30.00	2.90	8.34	0.35	1.42	2.18	1.33	1.72	4.73	0.36
MEAN			0.33			0.83			0.45
SD			0.04			0.23			0.06

	GYPSY			MELODEE			LINDA		
TIME	P 10	P 20	RATIO	P 10	P 20	RATIO	P 10	P 20	RATIO
3.00	10.84	32.16	0.24	6.63	15.58	0.43	9.30	20.21	0.33
4.00	9.93	29.18	0.23	7.29	12.58	0.58	10.56	18.09	0.40
5.00	7.28	29.96	0.25	6.88	14.74	0.47	8.27	18.08	0.38
6.00	6.67	24.04	0.28	6.71	15.82	0.42	8.05	19.64	0.34
8.00	6.80	20.23	0.30	6.02	11.94	0.50	7.31	16.39	0.37
10.00	7.22	20.91	0.27	4.96	9.18	0.54	6.30	11.96	0.41
12.00	6.48	22.12	0.23	3.84	8.49	0.45	5.08	10.56	0.36
24.00	3.90	13.84	0.17	2.11	4.48	0.47	2.39	6.84	0.31
30.00	3.24	9.56	0.18	1.26	2.52	0.50	1.30	3.86	0.33
MEAN			0.24			0.48			0.36
SD			0.04			0.05			0.04

OVERALL MEAN = 0.45 STANDARD DEVIATION = 0.21

Table F.12 Plasma/plasma theophylline concentration ratio's for individual horses. (Csf theophylline concentrations after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes/ csf theophylline concentrations after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus).

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	P 10	P C10	RATIO	P 10	P C10	RATIO	P 10	P C10	RATIO
3.00	8.94	7.24	1.23	7.18	9.43	0.95	7.81	4.65	1.68
4.00	8.01	7.95	1.01	7.27	8.44	0.95	6.73	4.74	1.42
5.00	8.32	7.21	1.15	7.18	7.83	1.06	7.50	3.99	1.88
6.00	7.95	5.84	1.36	8.37	7.71	1.03	6.74	3.93	1.72
8.00	7.95	5.50	1.45	5.51	7.24	1.10	6.16	3.79	1.63
10.00	6.82	4.61	1.48	4.93	6.47	1.05	5.72	3.09	1.85
12.00	5.69	2.41	2.36	3.71	5.44	1.05	5.06	2.75	1.84
24.00	3.38	1.69	2.00	1.65	2.20	1.54	2.35	1.36	1.73
30.00	2.90	1.30	2.23	1.42	1.58	1.84	1.72	0.95	1.81
MEAN			1.59			1.17			1.73
SD			0.49			0.30			0.14

	GYPSY			MELODEE			LINDA		
TIME	P 10	P C10	RATIO	P 10	P C10	RATIO	P 10	P C10	RATIO
3.00	10.84	8.68	0.90	6.63	7.44	0.89	9.30	8.34	0.79
4.00	9.93	8.87	0.76	7.29	8.39	0.87	10.56	7.55	0.97
5.00	7.28	8.87	0.85	6.88	6.08	1.13	8.27	7.32	0.94
6.00	6.67	7.00	0.96	6.71	6.50	1.03	8.05	6.82	0.98
8.00	6.80	7.07	0.87	6.02	5.13	1.17	7.31	5.21	1.16
10.00	7.22	6.40	0.89	4.96	4.27	1.16	6.30	4.64	1.07
12.00	6.48	5.08	1.00	3.84	3.92	0.98	5.08	4.36	0.88
24.00	3.90	3.60	0.65	2.11	1.63	1.29	2.39	1.94	1.09
30.00	3.24	2.68	0.64	1.26	1.05	1.20	1.30	1.25	1.01
MEAN			0.84			1.08			0.99
SD			0.13			0.15			0.11

OVERALL MEAN = 1.23 STANDARD DEVIATION = 0.35

Table F.13 Plasma/plasma dyphylline concentration ratio's for individual horses. (Csf dyphylline concentrations after the administration of dyphylline, 20 mg/Kg, iv bolus/ csf dyphylline concentrations after the administration of dyphylline, 40 mg/Kg, iv bolus).

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	P 20	P 40	RATIO	P 20	P 40	RATIO	P 20	P 40	RATIO
3.00	3.65	15.00	0.24	3.02	13.68	0.22	4.18	11.60	0.36
4.00	1.93	10.29	0.19	2.25	7.89	0.29	3.52	9.60	0.37
5.00	1.17	9.05	0.13	1.70	7.21	0.24	2.19	6.20	0.35
6.00	0.63	7.60	0.08	0.91	4.79	0.19	1.75	5.94	0.29
8.00	0.21	4.03	0.05	0.34	2.65	0.13	0.85	3.94	0.22
10.00			--			--			--
MEAN			0.14			0.21			0.32
SD			0.08			0.06			0.06

	GYPSY			MELODEE			LINDA		
TIME	P 20	P 40	RATIO	P 20	P 40	RATIO	P 20	P 40	RATIO
3.00	12.95	14.31	0.90	5.85	10.37	0.56	4.11	9.45	0.43
4.00	7.43	10.03	0.74	3.73	7.80	0.48	2.27	4.69	0.48
5.00	4.70	7.23	0.65	2.66	6.53	0.41	1.50	3.66	0.41
6.00	2.56	5.75	0.45	2.19	4.85	0.45	0.55	2.64	0.21
8.00	0.99	3.67	0.27	1.43	2.65	0.54	0.31	1.61	0.19
10.00			--			--			--
MEAN			0.60			0.49			0.35
SD			0.25			0.06			0.14

OVERALL MEAN = 0.35 STANDARD DEVIATION = 0.17

Table F.14 Plasma/plasma dyphylline concentration ratio's for individual horses. (Csf dyphylline concentrations after the administration of dyphylline, 20 mg/Kg, iv bolus/ csf dyphylline concentrations after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus).

	MOON MIST			TAYLOR LOCK			PICKET CREEK		
TIME	P 20	P C20	RATIO	P 20	P C20	RATIO	P 20	P C20	RATIO
3.00	3.65	6.73	0.54	3.02	5.68	0.53	4.18	5.59	0.75
4.00	1.93	4.17	0.46	2.25	4.77	0.47	3.52	4.97	0.71
5.00	1.17	3.46	0.34	1.70	2.95	0.58	2.19	3.62	0.60
6.00	0.63	2.50	0.25	0.91	2.40	0.38	1.75	3.20	0.55
8.00	0.21	1.76	0.12	0.34	1.30	0.26	0.85	2.24	0.38
10.00			--			--			--
MEAN			0.34			0.44			0.60
SD			0.17			0.12			0.15

	GYPSY			MELODEE			LINDA		
TIME	P 20	P C20	RATIO	P 20	P C20	RATIO	P 20	P 40	RATIO
3.00	12.95	5.54	2.34	5.85	4.30	1.36	4.11	3.93	1.05
4.00	7.43	4.68	1.59	3.73	3.56	1.05	2.27	3.37	0.67
5.00	4.70	3.47	1.35	2.66	2.75	0.97	1.50	2.45	0.61
6.00	2.56	2.86	0.90	2.19	1.85	1.18	0.55	1.73	0.32
8.00	0.99	1.92	0.52	1.43	1.15	1.24	0.31	1.03	0.30
10.00			--			--			--
MEAN			1.34			1.16			0.59
SD			0.69			0.16			0.31

OVERALL MEAN = 0.75 STANDARD DEVIATION = 0.41

APPENDIX G

PLASMA AND CSF DRUG CONCENTRATION-TIME CURVES SIMULTANEOUSLY FITTED BY FUNFIT OR PCNONLIN^{R} AND THE CORRESPONDING COMPUTER DATA OUTPUT FOR INDIVIDUAL HORSES

Text G.1a Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Moon Mist, combo 10 mg/Kg)

[redacted] -FUNFIT- CALL NUMBER: 23

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	491.164	0.000000E+00	NONE	5.111E-04
2	5.258282E-02	0.000000E+00	NONE	100.
3	65.5619	0.000000E+00	NONE	9.677E-04
4	0.790418	0.000000E+00	NONE	3.42
5	-20.6617	UNCONSTRAINED		0.208
6	328.030	0.000000E+00	NONE	1.808E-02

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	3.25771	5288.21	0.658928
2	16	0.778694	2.19217	0.939673
TOTAL	33	4.03640	5290.40	0.709844

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	26.8	12.9	13.9	51.8
2	0.250	90.0	18.9	71.1	79.0
3	0.333	19.6	18.0	1.60	8.15
4	0.500	15.0	16.4	-1.42	-9.48
5	0.667	11.8	15.0	-3.21	-27.1
6	1.00	10.4	12.8	-2.41	-23.2
7	1.50	11.9	10.3	1.59	13.3
8	2.00	8.39	8.70	-0.310	-3.69
9	3.00	7.24	6.78	0.463	6.39
10	4.00	7.95	5.79	2.16	27.1
11	5.00	7.21	5.22	1.99	27.5
12	6.00	5.84	4.84	1.00	17.1
13	8.00	5.50	4.29	1.21	22.1
14	10.0	4.61	3.84	0.765	16.6
15	12.0	2.41	3.46	-1.05	-43.5
16	24.0	1.69	1.84	-0.150	-8.87
17	30.0	1.30	1.34	-4.207E-02	-3.24
			FUNCTION 2		
1	0.250	0.400	0.358	4.225E-02	10.6
2	0.333	0.500	0.604	-0.104	-20.9
3	0.500	1.27	1.05	0.222	17.5
4	0.667	1.45	1.43	2.147E-02	1.48
5	1.00	2.02	2.03	-1.193E-02	-0.591
6	1.50	3.02	2.64	0.377	12.5
7	2.00	2.55	3.01	-0.459	-18.0
8	3.00	3.97	3.32	0.649	16.4
9	4.00	3.21	3.35	-0.141	-4.39
10	5.00	3.85	3.27	0.584	15.2

Text G.1b Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Linda, combo 10 mg/Kg)

11	6.00	2.59	3.14	-0.545	-21.1
12	8.00	2.56	2.84	-0.284	-11.1
13	10.0	2.29	2.56	-0.275	-12.0
14	12.0	2.99	2.31	0.681	22.8
15	24.0	1.39	1.23	0.161	11.6
16	30.0	1.12	0.896	0.224	20.0

WGHT. EXP. = -2

FUNCTION EVALUATIONS: 504

MODL ID: THEOPHYLLINE
PLOT ID: F23 D13 P11 X 3178 19-AUG-90 16:48 RS
THEOPHYLLINE COMBO 10 MG/KG, MOON MIST

A	=	65.56187
ALPHA	=	0.8430008
T1/2 ALPHA	=	0.8222379
B	=	491.1639
BETA	=	5.2582815E-02
T1/2 BETA	=	13.18201
AM	=	-20.66173
AN	=	328.0303

[redacted] -FUNFIT- CALL NUMBER: 17
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	529.133	0.000000E+00	NONE	4.408E-03
2	7.427780E-02	0.000000E+00	NONE	100.
3	35.0821	0.000000E+00	NONE	1.762E-02
4	0.804130	0.000000E+00	NONE	0.772
5	-24.4741	UNCONSTRAINED		8.212E-02
6	377.762	0.000000E+00	NONE	2.047E-02

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	2.72323	110.924	0.915722
2	16	1.59496	2.99188	0.952331
TOTAL	33	4.31818	113.915	0.943978

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	18.7	11.3	7.42	39.6
2	0.250	21.4	16.7	4.75	22.2
3	0.333	19.8	16.1	3.66	18.5
4	0.500	16.5	15.1	1.40	8.49
5	0.667	11.3	14.2	-2.96	-26.3
6	1.00	11.4	12.8	-1.39	-12.2
7	1.50	9.06	11.2	-2.12	-23.4

Text G.1c Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Average, 20 mg/Kg)

8	2.00	8.59	10.0	-1.45	-16.8
9	3.00	8.34	8.55	-0.214	-2.57
10	4.[illegible]	7.55	7.62	-7.495E-02	-0.993
11	5.00	7.32	6.95	0.373	5.09
12	6.00	6.82	6.40	0.425	6.23
13	8.00	5.21	5.48	-0.272	-5.22
14	10.0	4.64	4.72	-7.997E-02	-1.72
15	12.0	4.36	4.07	0.293	6.71
16	24.0	1.94	1.67	0.272	14.0
17	30.0	1.25	1.07	0.182	14.5
			FUNCTION 2		
1	0.250	1.83	2.12	-0.295	-16.1
2	0.333	2.70	2.42	0.279	10.3
3	0.500	3.74	2.95	0.792	21.2
4	0.667	3.99	3.39	0.597	15.0
5	1.00	4.32	4.08	0.243	5.64
6	1.50	4.12	4.72	-0.604	-14.7
7	2.00	4.70	5.07	-0.366	-7.78
8	3.00	5.12	5.24	-0.115	-2.25
9	4.00	5.10	5.08	1.861E-02	0.365
10	5.00	4.36	4.81	-0.449	-10.3
11	6.00	4.90	4.50	0.397	8.10
12	8.00	4.64	3.90	0.737	15.9
13	10.0	3.91	3.37	0.542	13.9
14	12.0	3.12	2.90	0.216	6.94
15	24.0	1.24	1.19	4.916E-02	3.96
16	30.0	0.601	0.763	-0.162	-26.9

```
WGHT. EXP. =  -2

FUNCTION EVALUATIONS:  658

MODL ID: THEOPHYLLINE
PLOT ID: F17 D18 P 8 X 3178 19-AUG-90 16:40 RS
THEOPHYLLINE COMBO 10 MG/KG, LINDA
      A        =    35.08208
    ALPHA      =   0.8784083
  T1/2 ALPHA   =   0.7890946
      B        =    529.1326
    BETA       =   7.4277803E-02
  T1/2 BETA    =    9.331821
     AM        =   -24.47406
     AN        =    377.7616
[redacted]   -FUNFIT- CALL NUMBER:   18
C<<   3
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MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	1835.65	0.000000E+00	NONE	1.954E-04
2	4.867788E-02	0.000000E+00	NONE	100.
3	96.0662	0.000000E+00	NONE	-1.849E-04
4	1.15978	0.000000E+00	NONE	1.97
5	-31.2993	UNCONSTRAINED		0.106

Text G.1d Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Average, 20 mg/Kg)

6 793.102 0.000000E+00 NONE 6.414E-03

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	2.40000	265.865	0.966734
2	17	0.264029	1.02014	0.994898
TOTAL	34	2.66403	266.885	0.983469

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.170	42.0	33.0	9.05	21.5
2	0.250	44.3	47.3	-2.94	-6.64
3	0.330	52.1	44.9	7.26	13.9
4	0.500	48.8	40.5	8.39	17.2
5	0.670	38.4	36.8	1.61	4.18
6	1.00	30.4	31.5	-1.17	-3.85
7	1.50	21.6	26.4	-4.79	-22.2
8	2.00	18.8	23.4	-4.65	-24.8
9	3.00	21.1	20.3	0.766	3.63
10	4.00	18.8	18.8	2.146E-02	0.114
11	5.00	18.5	17.7	0.849	4.58
12	6.00	17.5	16.8	0.723	4.12
13	8.00	15.4	15.2	0.182	1.18
14	10.0	14.3	13.8	0.486	3.40
15	12.0	13.4	12.5	0.908	6.76
16	24.0	7.82	6.99	0.832	10.6
17	30.0	5.20	5.22	-1.787E-02	-0.344
			FUNCTION 2		
1	0.170	0.720	0.723	-3.454E-03	-0.480
2	0.250	1.48	1.43	4.804E-02	3.25
3	0.330	2.17	2.15	2.326E-02	1.07
4	0.500	3.65	3.44	0.206	5.65
5	0.670	4.26	4.49	-0.226	-5.31
6	1.00	5.88	5.95	-7.215E-02	-1.23
7	1.50	6.79	7.23	-0.435	-6.41
8	2.00	7.31	7.83	-0.515	-7.05
9	3.00	7.82	8.10	-0.277	-3.54
10	4.00	8.20	7.90	0.295	3.60
11	5.00	7.99	7.59	0.403	5.05
12	6.00	7.45	7.24	0.207	2.77
13	8.00	6.79	6.58	0.212	3.13
14	10.0	5.97	5.97	1.877E-03	3.145E-02
15	12.0	5.61	5.41	0.195	3.48
16	24.0	3.11	3.02	9.092E-02	2.92
17	30.0	2.20	2.25	-5.440E-02	-2.47

WGHT. EXP. = -2

FUNCTION EVALUATIONS: 702

MODL ID: THEOPHYLLINE
PLOT ID: F18 019 P 9 X 3178 19-AUG-90 16:42 RS
THEOPHYLLINE AVERAGE 20 MG/KG (AVERAGE OF 6 HORSES)
A = 96.06619
ALPHA = 1.208462
T1/2 ALPHA = 0.5735778

Text G.1e Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Melodee, combo 10 mg/Kg)

```
     B      =   1835.655
   BETA     =  4.8677877E-02
T1/2 BETA   =   14.23947
    AM      =  -31.29933
    AN      =   793.1019
```

[redacted] -FUNFIT- CALL NUMBER: 6

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	506.584	0.000000E+00	NONE	7.415E-03
2	7.506169E-02	0.000000E+00	NONE	100.
3	19.1280	0.000000E+00	NONE	1.364E-02
4	1.09931	0.000000E+00	NONE	1.62
5	-20.0632	UNCONSTRAINED		0.156
6	307.172	0.000000E+00	NONE	2.108E-02

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	5.95144	27.6726	0.952031
2	16	0.649994	0.656830	0.988919
TOTAL	33	6.60143	28.3296	0.974728

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	10.7	9.72	0.953	8.93
2	0.250	12.2	14.3	-2.12	-17.5
3	0.333	13.4	13.8	-0.404	-3.02
4	0.500	12.3	12.9	-0.621	-5.07
5	0.667	15.9	12.1	3.75	23.6
6	1.00	12.7	10.9	1.82	14.3
7	1.50	9.64	9.70	-5.540E-02	-0.575
8	2.00	7.42	8.88	-1.46	-19.7
9	3.00	7.44	7.85	-0.414	-5.56
10	4.00	8.39	7.17	1.22	14.6
11	5.00	6.08	6.61	-0.532	-8.74
12	6.00	6.50	6.12	0.378	5.81
13	8.00	5.13	5.26	-0.134	-2.62
14	10.0	4.27	4.53	-0.260	-6.09
15	12.0	3.92	3.90	2.144E-02	0.547
16	24.0	1.63	1.58	4.614E-02	2.83
17	30.0	1.05	1.01	4.446E-02	4.22
			FUNCTION 2		
1	0.250	0.550	0.606	-5.600E-02	-10.2
2	0.333	1.12	1.04	7.540E-02	6.73
3	0.500	1.84	1.80	4.148E-02	2.25
4	0.667	2.44	2.41	3.354E-02	1.37
5	1.00	3.24	3.28	-4.227E-02	-1.30
6	1.50	4.21	4.02	0.187	4.44
7	2.00	4.66	4.35	0.306	6.57
8	3.00	4.66	4.44	0.217	4.65

Text G.1f Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Picket Creek, combo 10 mg/Kg)

9	4.00	4.40	4.25	0.153	3.48
10	5.00	4.06	3.98	8.144E-02	2.01
11	6.00	3.25	3.70	-0.453	-13.9
12	8.00	2.83	3.19	-0.361	-12.8
13	10.0	2.57	2.75	-0.177	-6.88
14	12.0	2.27	2.36	-9.393E-02	-4.14
15	24.0	1.18	0.960	0.220	18.6
16	30.0	0.730	0.612	0.118	16.1

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 407

MODL ID: THEOPHYLLINE
PLOT ID: F 6 D17 P 3 X 3178 19-AUG-90 16:28 RS
THEOPHYLLINE COMBO 10 MG/KG, MELODEE

A	=	19.12803
ALPHA	=	1.174372
T1/2 ALPHA	=	0.5902281
B	=	506.5836
BETA	=	7.5061686E-02
T1/2 BETA	=	9.234367
AM	=	-20.06315
AN	=	307.1721

DATA SET NUMBER: 15 -FUNFIT- CALL NUMBER: 2
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	420.986	0.000000E+00	NONE	4.008E-03
2	4.036153E-02	0.000000E+00	NONE	100.
3	48.6567	0.000000E+00	NONE	2.080E-02
4	0.388787	0.000000E+00	NONE	2.63
5	-50.4963	UNCONSTRAINED		1.995E-02
6	619.786	0.000000E+00	NONE	5.820E-03

FUNCTION	OBSERVATIONS	SUM OF SQUARES	CORRELATION(R)
1	17	42.1774	0.874350
2	16	0.722226	0.984780
TOTAL	33	42.8996	0.907428

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	0.730	6.19	-5.46	-748.
2	0.250	12.3	9.18	3.10	25.3
3	0.333	9.89	8.99	0.901	9.11
4	0.500	8.48	8.63	-0.151	-1.77

Text G.1g Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Gypsy, combo 10 mg/Kg)

5	0.667	8.98	8.29	0.685	7.63
6	1.00	7.07	7.69	-0.618	-8.74
7	1.50	6.99	6.91	7.651E-02	1.09
8	2.00	6.06	6.27	-0.214	-3.53
9	3.00	4.65	5.30	-0.653	-14.0
10	4.00	4.74	4.62	0.117	2.47
11	5.00	3.99	4.13	-0.144	-3.60
12	6.00	3.93	3.77	0.159	4.05
13	8.00	3.79	3.27	0.521	13.7
14	10.0	3.09	2.93	0.163	5.28
15	12.0	2.75	2.66	8.762E-02	3.19
16	24.0	1.36	1.62	-0.261	-19.2
17	30.0	0.952	1.27	-0.320	-33.6
			FUNCTION 2		
1	0.250	0.801	1.09	-0.284	-35.5
2	0.333	1.28	1.24	4.071E-02	3.17
3	0.500	1.75	1.55	0.205	11.7
4	0.667	2.13	1.82	0.307	14.4
5	1.00	2.38	2.31	6.645E-02	2.79
6	1.50	2.75	2.91	-0.162	-5.89
7	2.00	3.23	3.37	-0.144	-4.46
8	3.00	3.90	3.99	-8.747E-02	-2.24
9	4.00	4.20	4.32	-0.121	-2.88
10	5.00	4.41	4.47	-5.788E-02	-1.31
11	6.00	4.39	4.50	-0.108	-2.46
12	8.00	4.13	4.37	-0.236	-5.72
13	10.0	4.32	4.12	0.200	4.63
14	12.0	4.37	3.84	0.531	12.1
15	24.0	2.32	2.39	-6.571E-02	-2.83
16	30.0	1.69	1.87	-0.183	-10.8

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FUNCTION EVALUATIONS:  453

MODL ID: THEOPHYLLINE
PLOT ID: F 2 015 P 1 X 3178 19-AUG-90 16:23 RS
THEOPHYLLINE COMBO 10 MG/KG, PICKET CREEK
    A         =    48.65668
  ALPHA       =   0.4291487
 T1/2 ALPHA   =    1.615168
    B         =    420.9859
  BETA        =   4.0361535E-02
 T1/2 BETA    =    17.17346
    AM        =   -50.49630
    AN        =    619.7863
 DATA SET NUMBER:   16     -FUNFIT- CALL NUMBER:     3
C<<   3
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MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	845.275	0.000000E+00	NONE	6.286E-03
2	4.981539E-02	0.000000E+00	NONE	100.
3	24.2522	0.000000E+00	NONE	8.331E-02
4	3.25333	0.000000E+00	NONE	0.204

Text G.1h Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Gypsy, combo 10 mg/Kg)

5	-6.80456	UNCONSTRAINED		1.848E-02
6	400.067	0.000000E+00	NONE	2.975E-03

FUNCTION	OBSERVATIONS	SUM OF SQUARES	CORRELATION(R)
1	17	13.6380	0.988349
2	16	8.01081	0.847796
TOTAL	33	21.6488	0.989867

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	16.0	17.3	-1.27	-7.90
2	0.250	26.1	24.1	2.00	7.65
3	0.333	19.6	20.8	-1.16	-5.92
4	0.500	16.2	16.3	-0.142	-0.877
5	0.667	12.6	13.7	-1.07	-8.44
6	1.00	12.9	11.2	1.71	13.2
7	1.50	10.6	10.0	0.600	5.64
8	2.00	9.28	9.63	-0.350	-3.78
9	3.00	8.68	9.12	-0.444	-5.11
10	4.00	8.87	8.68	0.191	2.15
11	5.00	8.87	8.26	0.613	6.91
12	6.00	7.00	7.86	-0.856	-12.2
13	8.00	7.07	7.11	-4.105E-02	-0.581
14	10.0	6.40	6.44	-3.672E-02	-0.574
15	12.0	5.08	5.83	-0.746	-14.7
16	24.0	3.60	3.20	0.395	11.0
17	30.0	2.68	2.38	0.303	11.3
			FUNCTION 2		
1	0.250	1.27	1.13	0.143	11.3
2	0.333	2.53	2.02	0.507	20.0
3	0.500	2.57	3.22	-0.645	-25.1
4	0.667	3.29	3.88	-0.595	-18.1
5	1.00	3.30	4.45	-1.15	-34.8
6	1.50	3.32	4.59	-1.27	-38.3
7	2.00	5.77	4.53	1.24	21.6
8	3.00	5.70	4.32	1.38	24.3
9	4.00	4.15	4.11	4.224E-02	1.02
10	5.00	4.49	3.91	0.582	13.0
11	6.00	3.85	3.72	0.132	3.42
12	8.00	3.56	3.37	0.194	5.46
13	10.0	2.93	3.05	-0.116	-3.98
14	12.0	2.36	2.76	-0.398	-16.8
15	24.0	1.49	1.52	-2.676E-02	-1.80
16	30.0	1.16	1.12	3.511E-02	3.03

FUNCTION EVALUATIONS: 459

MODL ID: THEOPHYLLINE
PLOT ID: F 3 D16 P 2 X 3178 19-AUG-90 16:25 RS
THEOPHYLLINE COMBO 10 MG/KG, GYPSY

A	=	24.25219
ALPHA	=	3.303146
T1/2 ALPHA	=	0.2098446
B	=	845.2749
BETA	=	4.9815370E-02

Text G.1i Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Melodee, 20 mg/Kg)

T1/2 BETA = 13.91432
AM = -6.804564
AN = 400.0669

[redacted] -FUNFIT- CALL NUMBER: 45
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	1194.88	0.000000E+00	NONE	1.189E-03
2	5.837237E-02	0.000000E+00	NONE	100.
3	34.4309	0.000000E+00	NONE	1.411E-03
4	0.665042	0.000000E+00	NONE	4.46
5	-60.5321	UNCONSTRAINED		7.483E-02
6	722.083	0.000000E+00	NONE	8.191E-03

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	7.10098	47.5527	0.963049
2	17	1.18578	1.55963	0.993591
TOTAL	34	8.28675	49.1123	0.985682

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	15.9	15.5	0.430	2.70
2	0.250	20.7	23.0	-2.33	-11.3
3	0.333	26.7	22.6	4.08	15.3
4	0.500	22.3	21.8	0.527	2.36
5	0.667	21.8	21.1	0.703	3.22
6	1.00	18.0	19.9	-1.91	-10.6
7	1.50	18.5	18.4	6.163E-02	0.334
8	2.00	15.5	17.2	-1.76	-11.3
9	3.00	15.6	15.5	5.768E-02	0.370
10	4.00	12.6	14.3	-1.71	-13.6
11	5.00	14.7	13.3	1.44	9.76
12	6.00	15.8	12.5	3.36	21.2
13	8.00	11.9	11.0	0.908	7.60
14	10.0	9.18	9.80	-0.623	-6.79
15	12.0	8.49	8.72	-0.230	-2.70
16	24.0	4.48	4.33	0.153	3.41
17	30.0	2.52	3.05	-0.529	-21.0
FUNCTION 2					
1	0.167	0.250	0.116	0.134	53.4
2	0.250	0.400	0.446	-4.629E-02	-11.6
3	0.333	0.820	0.979	-0.159	-19.4
4	0.500	2.13	1.95	0.178	8.38
5	0.667	2.40	2.80	-0.403	-16.8
6	1.00	3.80	4.19	-0.392	-10.3
7	1.50	6.06	5.67	0.390	6.43
8	2.00	7.01	6.62	0.389	5.54
9	3.00	7.98	7.54	0.440	5.52
10	4.00	7.64	7.74	-9.785E-02	-1.31

Text G.1j Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Gypsy, 20 mg/Kg)

11	5.00	7.03	7.61	-0.575	-8.19
12	6.00	7.33	7.32	8.088E-03	0.110
13	8.00	6.87	6.62	0.253	3.68
14	10.0	5.83	5.91	-8.238E-02	-1.41
15	12.0	5.21	5.27	-5.658E-02	-1.09
16	24.0	3.12	2.62	0.505	16.2
17	30.0	1.86	1.84	1.761E-02	0.947

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 455

MODL ID: THEOPHYLLINE
PLOT ID: F45 D11 P12 X 3176 19-AUG-90 15:24 RS
THEOPHYLLINE 20 MG/KG, MELODEE

A	=	34.43090
ALPHA	=	0.7234144
T1/2 ALPHA	=	0.9581606
B	=	1194.881
BETA	=	5.8372367E-02
T1/2 BETA	=	11.87458
AM	=	-60.53214
AN	=	722.0829

[redacted] -FUNFIT- CALL NUMBER: 42

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	3200.91	0.000000E+00	NONE	7.793E-04
2	3.727790E-02	0.000000E+00	NONE	100.
3	263.131	0.000000E+00	NONE	6.543E-03
4	1.14428	0.000000E+00	NONE	1.37
5	-32.8966	UNCONSTRAINED		2.684E-02
6	1131.21	0.000000E+00	NONE	2.197E-03

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	279.964	2718.74	0.926040
2	17	11.7009	11.1923	0.967382
TOTAL	34	291.665	2729.94	0.957784

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	53.4	67.0	-13.6	-25.4
2	0.250	76.3	97.0	-20.7	-27.2
3	0.333	116.	90.6	25.8	22.2
4	0.500	109.	79.5	29.5	27.1
5	0.667	81.1	70.4	10.7	13.2

Text G.1k Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Picket Creek, 20 mg/Kg)

6	1.00	69.9	56.6	13.3	19.0
7	1.50	36.4	43.7	-7.32	-20.1
8	2.00	23.4	36.3	-13.0	-55.5
9	3.00	32.2	29.4	2.75	8.55
10	4.00	29.2	26.6	2.56	8.77
11	5.00	30.0	25.1	4.84	16.2
12	6.00	24.0	24.0	8.907E-04	3.705E-03
13	8.00	20.2	22.2	-2.02	-9.98
14	10.0	20.9	20.6	0.265	1.27
15	12.0	22.1	19.2	2.96	13.4
16	24.0	13.8	12.3	1.59	11.5
17	30.0	9.56	9.79	-0.235	-2.46
			FUNCTION 2		
1	0.167	1.38	1.13	0.251	18.2
2	0.250	1.83	2.08	-0.250	-13.7
3	0.333	2.63	2.83	-0.203	-7.73
4	0.500	4.42	4.13	0.286	6.46
5	0.667	5.66	5.19	0.469	8.28
6	1.00	6.91	6.74	0.174	2.52
7	1.50	7.15	8.09	-0.945	-13.2
8	2.00	8.90	8.77	0.133	1.50
9	3.00	9.75	9.14	0.606	6.21
10	4.00	11.0	9.02	1.98	18.0
11	5.00	10.6	8.76	1.82	17.2
12	6.00	8.65	8.46	0.191	2.20
13	8.00	7.30	7.86	-0.560	-7.66
14	10.0	7.20	7.30	-9.560E-02	-1.33
15	12.0	6.18	6.77	-0.592	-9.57
16	24.0	3.22	4.33	-1.11	-34.4
17	30.0	2.95	3.46	-0.512	-17.3

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 370

MODL ID: THEOPHYLLINE
PLOT ID: F42 010 P10 X 3176 19-AUG-90 15:15 RS
THEOPHYLLINE 20 MG/KG, GYPSY

A	=	263.1310
ALPHA	=	1.181554
T1/2 ALPHA	=	0.5866401
B	=	3200.912
BETA	=	3.7277900E-02
T1/2 BETA	=	18.59405
AM	=	-32.89656
AN	=	1131.213

DATA SET NUMBER: 9 -FUNFIT- CALL NUMBER: 32
C<< 3

Text G.11 Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Picket Creek, 20 mg/Kg)

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	1497.13	0.000000E+00	NONE	2.381E-03
2	5.293465E-02	0.000000E+00	NONE	100.
3	9.58445	0.000000E+00	NONE	3.067E-02
4	4.13908	0.000000E+00	NONE	0.136
5	-10.1043	UNCONSTRAINED		0.141
6	638.270	0.000000E+00	NONE	5.254E-03

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	16.7222	76.2910	0.932484
2	17	5.35998	5.13586	0.973584
TOTAL	34	22.0822	81.4268	0.976014

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	22.8	18.C	4.82	21.1
2	0.250	20.3	25.9	-5.59	-27.5
3	0.333	26.8	24.0	2.78	10.4
4	0.500	23.3	21.6	1.69	7.27
5	0.667	21.6	20.3	1.22	5.68
6	1.00	20.0	19.2	0.806	4.03
7	1.50	18.0	18.5	-0.505	-2.81
8	2.00	17.5	17.9	-0.415	-2.37
9	3.00	16.3	17.0	-0.686	-4.20
10	4.00	15.6	16.1	-0.518	-3.32
11	5.00	14.1	15.3	-1.23	-8.71
12	6.00	13.0	14.5	-1.51	-11.6
13	8.00	14.1	13.1	1.07	7.58
14	10.0	11.1	11.7	-0.627	-5.64
15	12.0	12.0	10.6	1.41	11.8
16	24.0	6.07	5.60	0.471	7.77
17	30.0	4.73	4.08	0.655	13.8
			FUNCTION 2		
1	0.167	0.350	0.531	-0.131	-51.6
2	0.250	2.99	1.83	1.16	38.8
3	0.333	3.82	3.72	9.901E-02	2.59
4	0.500	5.90	5.98	-8.006E-02	-1.36
5	0.667	6.88	7.07	-0.185	-2.70
6	1.00	8.28	7.78	0.493	6.02
7	1.50	7.63	7.82	-0.189	-2.48
8	2.00	7.32	7.64	-0.324	-4.43
9	3.00	7.56	7.25	0.306	4.04
10	4.00	7.06	6.88	0.180	2.55
11	5.00	7.35	6.53	0.824	11.2
12	6.00	7.30	6.19	1.11	15.2
13	8.00	5.28	5.57	-0.287	-5.44
14	10.0	4.01	5.01	-0.998	-24.9
15	12.0	4.18	4.50	-0.325	-7.77
16	24.0	2.24	2.39	-0.147	-6.55
17	30.0	1.47	1.74	-0.267	-18.2

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 852

Text G.1m Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Moon Mist, 20 mg/Kg)

MODL ID: THEOPHYLLINE
PLOT ID: F32 D 9 P 8 X 3176 19-AUG-90 15:03 RS
THEOPHYLLINE 20 MG/KG, PICKET CREEK

A	=	9.584447
ALPHA	=	4.192014
T1/2 ALPHA	=	0.1653494
B	=	1497.128
BETA	=	5.2934654E-02
T1/2 BETA	=	13.09439
AM.	=	-10.10426
AN	=	638.2698

[redacted] -FUNFIT- CALL NUMBER: 30

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	3752.84	0.000000E+00	NONE	9.143E-04
2	3.061871E-02	0.000000E+00	NONE	100.
3	159.792	0.000000E+00	NONE	8.377E-02
4	3.25274	0.000000E+00	NONE	1.36
5	-17.5634	NONE	0.000000E+00	-5.479E-04
6	1041.42	0.000000E+00	NONE	1.354E-04

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	11596.5	2717.23	0.918286
2	17	5.85706	37.3774	0.877836
TOTAL	34	11602.3	2754.60	0.950396

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	119.	86.6	32.9	27.5
2	0.250	89.1	118.	-29.0	-32.5
3	0.333	77.9	96.7	-18.7	-24.0
4	0.500	86.3	67.8	18.5	21.4
5	0.667	53.8	51.0	2.83	5.26
6	1.00	35.3	35.6	-0.272	-0.770
7	1.50	22.5	29.0	-6.48	-28.7
8	2.00	23.7	27.4	-3.75	-15.8
9	3.00	24.4	26.3	-1.96	-8.03
10	4.00	24.4	25.5	-1.12	-4.60
11	5.00	22.5	24.7	-2.29	-10.2
12	6.00	23.4	24.0	-0.597	-2.55
13	8.00	21.2	22.6	-1.37	-6.47
14	10.0	24.5	21.2	3.24	13.2
15	12.0	20.8	20.0	0.780	3.76
16	24.0	11.6	13.8	-2.19	-18.8
17	30.0	8.34	11.5	-3.17	-38.0

FUNCTION 2

Text G.1n Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Linda, 10 mg/Kg)

1	0.167	0.300	-2.10	2.40	-801.
2	0.250	0.850	-1.89	2.74	323.
3	0.333	1.49	0.433	1.06	71.0
4	0.500	2.29	3.55	-1.26	-55.1
5	0.667	2.92	5.34	-2.42	-82.9
6	1.00	5.56	6.92	-1.36	-24.5
7	1.50	6.13	7.48	-1.35	-22.0
8	2.00	5.95	7.50	-1.55	-26.0
9	3.00	5.73	7.30	-1.57	-27.4
10	4.00	7.98	7.08	0.900	11.3
11	5.00	7.71	6.87	0.844	10.9
12	6.00	8.03	6.66	1.37	17.1
13	8.00	7.67	6.26	1.41	18.3
14	10.0	6.82	5.89	0.928	13.6
15	12.0	6.36	5.54	0.818	12.9
16	24.0	4.08	3.84	0.242	5.94
17	30.0	3.06	3.19	-0.134	-4.37

WGHT. EXP. = 1

FUNCTION EVALUATIONS: 346
MODL ID: THEOPHYLLINE
PLOT ID: F30 D 7 P 7 X 3176 19-AUG-90 14:59 RS
THEOPHYLLINE 20 MG/KG, MOON MIST

A	=	159.7915
ALPHA	=	3.283358
T1/2 ALPHA	=	0.2111092
B	=	3752.836
BETA	=	3.0618712E-02
T1/2 BETA	=	22.63803
AM	=	-17.56338
AN	=	1041.419

DATA SET NUMBER: [illegible] -FUNFIT- CALL NUMBER: 17
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	700.749	0.000000E+00	NONE	4.849E-03
2	6.326643E-02	0.000000E+00	NONE	100.
3	14.1827	0.000000E+00	NONE	1.393E-02
4	0.533525	0.000000E+00	NONE	2.48
5	-37.0046	UNCONSTRAINED		6.293E-02
6	397.345	0.000000E+00	NONE	1.319E-02

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	4.96372	16.2600	0.960786
2	17	0.769924	0.643494	0.988600

Text G.1o Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Linda, 10 mg/Kg)

TOTAL 34 5.73355 16.9036 0.984784

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	9.73	8.71	1.02	10.5
2	0.250	15.0	13.0	2.07	13.8
3	0.333	12.8	12.8	-2.542E-03	-1.984E-02
4	0.500	12.2	12.5	-0.310	-2.54
5	0.667	10.9	12.2	-1.30	-11.8
6	1.00	11.9	11.7	0.114	0.960
7	1.50	8.77	11.1	-2.33	-26.5
8	2.00	10.9	10.5	0.312	2.87
9	3.00	9.30	9.62	-0.324	-3.48
10	4.00	10.6	8.89	1.67	15.9
11	5.00	8.27	8.26	1.019E-02	0.123
12	6.00	8.05	7.71	0.341	4.24
13	8.00	7.31	6.76	0.554	7.58
14	10.0	6.30	5.94	0.358	5.69
15	12.0	5.08	5.23	-0.152	-2.99
16	24.0	2.39	2.45	-5.798E-02	-2.43
17	30.0	1.30	1.67	-0.375	-28.8
			FUNCTION 2		
1	0.167	0.740	0.666	7.414E-02	10.0
2	0.250	0.980	1.11	-0.126	-12.9
3	0.333	1.32	1.32	-1.526E-03	-0.116
4	0.500	1.79	1.72	7.065E-02	3.95
5	0.667	2.19	2.07	0.116	5.30
6	1.00	2.80	2.67	0.132	4.71
7	1.50	3.47	3.33	0.141	4.07
8	2.00	3.14	3.78	-0.637	-20.3
9	3.00	4.30	4.25	5.422E-02	1.26
10	4.00	4.50	4.37	0.129	2.86
11	5.00	4.18	4.32	-0.136	-3.24
12	6.00	4.25	4.17	8.212E-02	1.93
13	8.00	3.62	3.77	-0.148	-4.10
14	10.0	3.43	3.35	8.046E-02	2.35
15	12.0	3.09	2.96	0.130	4.20
16	24.0	1.44	1.39	5.232E-02	3.63
17	30.0	1.21	0.949	0.261	21.5

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 401
MODL ID: THEOPHYLLINE
PLOT ID: F17 D 6 P 6 X 3176 19-AUG-90 14:42 RS
THEOPHYLLINE 10 MG/KG, LINDA

A = 14.18268
ALPHA = 0.5967912
T1/2 ALPHA = 1.161457
B = 700.9490
BETA = 6.3266426E-02
T1/2 BETA = 10.95600
AM = -37.00455
AN = 397.3447

Text G.1p Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Melodee, 10 mg/Kg)

[redacted] -FUNFIT- CALL NUMBER: 15
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	579.472	0.000000E+00	NONE	4.546E-03
2	5.837619E-02	0.000000E+00	NONE	100.
3	7.64735	0.000000E+00	NONE	2.459E-02
4	1.11779	0.000000E+00	NONE	1.52
5	-15.1976	UNCONSTRAINED		0.186
6	294.345	0.000000E+00	NONE	1.626E-02

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	4.07600	19.1903	0.918322
2	17	0.421098	0.371201	0.991225
TOTAL	34	4.49710	19.5615	0.971017

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.170	10.5	7.11	3.40	32.4
2	0.250	10.2	10.3	-0.124	-1.21
3	0.330	9.33	10.1	-0.800	-8.57
4	0.500	8.66	9.73	-1.07	-12.3
5	0.670	9.61	9.38	0.229	2.38
6	1.00	7.30	8.84	-1.54	-21.1
7	1.50	9.03	8.25	0.778	8.61
8	2.00	8.32	7.83	0.491	5.90
9	3.00	6.63	7.23	-0.597	-9.00
10	4.00	7.29	6.77	0.522	7.15
11	5.00	6.80	6.37	0.430	6.33
12	6.00	6.71	6.00	0.706	10.5
13	8.00	6.02	5.34	0.680	11.3
14	10.0	4.96	4.75	0.208	4.20
15	12.0	3.40	4.23	-0.828	-24.4
16	24.0	2.11	2.10	1.144E-02	0.542
17	30.0	1.26	1.48	-0.218	-17.3
		FUNCTION 2			
1	0.170	0.230	0.152	7.758E-02	33.7
2	0.250	0.370	0.393	-2.282E-02	-6.17
3	0.330	0.600	0.721	-0.121	-20.1
4	0.500	1.37	1.32	5.264E-02	3.84
5	0.670	1.73	1.80	-6.875E-02	-3.97
6	1.00	2.50	2.48	2.070E-02	0.828
7	1.50	3.14	3.07	6.564E-02	2.09
8	2.00	3.07	3.36	-0.286	-9.32
9	3.00	3.63	3.48	0.150	4.15
10	4.00	3.50	3.38	0.121	3.46
11	5.00	3.42	3.22	0.203	5.93
12	6.00	2.91	3.04	-0.134	-4.61
13	8.00	2.49	2.71	-0.222	-8.92
14	10.0	2.38	2.41	-3.363E-02	-1.41

Text G.1q Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Gypsy, 10 mg/Kg)

15	12.0	2.11	2.15	-3.770E-02	-1.79
16	24.0	1.28	1.07	0.214	16.7
17	30.0	1.00	0.751	0.249	24.9

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 454

MODL ID: THEOPHYLLINE
PLOT ID: F15 D 5 P 5 X 3176 19-AUG-90 14:40 RS
THEOPHYLLINE 10 MG/KG, MELODEE

```
     A        =   7.647349
   ALPHA      =   1.176165
 T1/2 ALPHA   =   0.5893284
     B        =   579.4721
   BETA       =   5.8376189E-02
 T1/2 BETA    =   11.87380
    AM        =   -15.19759
    AN        =   294.3445
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[redacted] -FUNFIT- CALL NUMBER: 12

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	1100.54	0.000000E+00	NONE	1.814E-04
2	3.262678E-02	0.000000E+00	NONE	100.
3	62.8869	0.000000E+00	NONE	5.864E-04
4	1.03928	0.000000E+00	NONE	1.60
5	-13.1460	UNCONSTRAINED		0.179
6	440.037	0.000000E+00	NONE	7.759E-03

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	0.336177	94.8853	0.954967
2	17	0.291648	1.94490	0.953019
TOTAL	34	0.627825	96.8301	0.976124

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	16.5	16.3	0.213	1.29
2	0.250	32.0	23.7	8.28	25.9
3	0.333	20.6	22.4	-1.88	-9.15
4	0.500	22.2	20.2	2.03	9.16
5	0.667	18.5	18.3	0.196	1.06
6	1.00	13.1	15.3	-2.19	-16.7
7	1.50	10.3	12.5	-2.15	-20.9
8	2.00	11.7	10.7	0.981	8.39
9	3.00	10.8	8.95	1.87	17.4

Text G.1r Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Picket Creek, 10 mg/Kg)

10	4.00	9.93	8.18	1.75	[illegible]
11	5.00	7.28	7.75	-0.468	-6.42
12	6.00	6.67	7.44	-0.772	[illegible]
13	8.00	6.80	6.95	-0.146	-2.15
14	10.0	7.22	6.50	0.715	9.91
15	12.0	6.48	6.09	0.387	5.97
16	24.0	3.90	4.12	-0.219	-5.62
17	30.0	3.24	3.39	-0.147	-4.53
			FUNCTION 2		
1	0.167	0.250	0.236	1.351E-02	5.40
2	0.250	0.450	0.484	-3.437E-02	-7.64
3	0.333	0.780	0.738	4.224E-02	5.42
4	0.500	1.19	1.18	8.227E-03	0.691
5	0.667	1.40	1.55	-0.150	-10.7
6	1.00	2.03	2.11	-7.513E-02	-3.70
7	1.50	2.76	2.62	0.137	4.98
8	2.00	3.54	2.90	0.637	18.0
9	3.00	2.62	3.11	-0.486	-18.5
10	4.00	2.53	3.11	-0.577	-22.8
11	5.00	3.47	3.04	0.428	12.3
12	6.00	3.67	2.96	0.713	19.4
13	8.00	3.02	2.78	0.245	8.11
14	10.0	2.99	2.60	0.389	13.0
15	12.0	2.55	2.44	0.114	4.46
16	24.0	1.65	1.65	2.961E-03	0.179
17	30.0	1.30	1.35	-5.421E-02	-4.17

WGHT. EXP. = -2

FUNCTION EVALUATIONS: 452
MODL ID: THEOPHYLLINE
PLOT ID: F12 D 4 P 4 X 3175 19-AUG-90 14:37 RS
THEOPHYLLINE 10 MG/KG, GYPSY
A = 62.88694
ALPHA = 1.071905
T1/2 ALPHA = 0.6466497
B = 1100.541
BETA = 3.2626782E-02
T1/2 BETA = 21.24473
AM = -13.14596
AN = 440.0370

DATA SET NUMBER: 3 -FUNFIT- CALL NUMBER: 10
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	676.045	0.000000E+00	NONE	4.668E-03
2	5.387769E-02	0.000000E+00	NONE	100.

Text G.1s Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Picket Creek, 10 mg/Kg)

3	19.3400	0.000000E+00	NONE	1.262E-02
4	3.67461	0.000000E+00	NONE	3.959E-02
5	-3.08809	UNCONSTRAINED		0.100
6	352.118	0.000000E+00	NONE	1.479E-02

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	1.37435	38.2827	0.960119
2	17	3.81882	7.92029	0.868487
TOTAL	34	5.19317	46.2026	0.971721

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	20.7	15.4	5.31	25.7
2	0.250	20.7	21.1	-0.472	-2.28
3	0.333	15.3	17.7	-2.45	-16.0
4	0.500	12.4	13.5	-1.06	-8.59
5	0.667	12.2	11.2	0.995	8.16
6	1.00	10.2	9.32	0.848	8.33
7	1.50	8.31	8.55	-0.235	-2.83
8	2.00	8.35	8.24	0.106	1.27
9	3.00	7.81	7.80	1.022E-02	0.131
10	4.00	6.73	7.39	-0.660	-9.81
11	5.00	7.50	7.00	0.497	6.63
12	6.00	6.74	6.64	0.105	1.55
13	8.00	6.16	5.96	0.202	3.29
14	10.0	5.72	5.35	0.371	6.49
15	12.0	5.06	4.80	0.257	5.09
16	24.0	2.35	2.52	-0.166	-7.06
17	30.0	1.72	1.82	-0.101	-5.86
			FUNCTION 2		
1	0.167	2.36	1.67	0.692	29.3
2	0.250	2.26	2.78	-0.520	-23.0
3	0.333	3.73	3.30	0.434	11.6
4	0.500	3.36	3.92	-0.565	-16.8
5	0.667	4.42	4.23	0.189	4.27
6	1.00	4.51	4.42	8.686E-02	1.93
7	1.50	4.97	4.39	0.580	11.7
8	2.00	6.66	4.29	2.37	35.7
9	3.00	3.40	4.06	-0.662	-19.5
10	4.00	4.14	3.85	0.291	7.02
11	5.00	3.74	3.65	9.261E-02	2.48
12	6.00	3.30	3.46	-0.156	-4.73
13	8.00	3.02	3.10	-8.301E-02	-2.75
14	10.0	2.70	2.79	-8.602E-02	-3.19
15	12.0	2.28	2.50	-0.221	-9.71
16	24.0	1.33	1.31	1.965E-02	1.48
17	30.0	1.11	0.948	0.162	14.6

WGHT. EXP. = -2

FUNCTION EVALUATIONS: 453
MODL ID: THEOPHYLLINE
PLOT ID: F10 D 3 P 3 X 3175 19-AUG-90 14:34 RS
THEOPHYLLINE 10 MG/KG, PICKET CREEK

Text G.1t Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Taylor Lock, 10 mg/Kg)

```
      A        =     19.34001
    ALPHA      =     3.923493
  T1/2 ALPHA   =     0.176441
      B        =     676.0447
    BETA       =    5.3879693E-02
  T1/2 BETA    =     12.86472
     AM        =    -3.088089
     AN        =     352.1180
```

[redacted] -FUNFIT- CALL NUMBER: 7

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	569.679	0.000000E+00	NONE	7.488E-03
2	7.536191E-02	0.000000E+00	NONE	100.
3	7.106768E-03	0.000000E+00	NONE	-9.447E-04
4	0.986797	0.000000E+00	NONE	1.58
5	-21.6109	UNCONSTRAINED		0.126
6	321.970	0.000000E+00	NONE	1.855E-02

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	5.71280	19.3450	0.943176
2	17	1.86286	2.11572	0.969006
TOTAL	34	7.57566	21.4607	0.973469

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	8.14	7.13	1.01	12.5
2	0.250	8.82	10.6	-1.81	-20.6
3	0.333	10.1	10.6	-0.498	-4.94
4	0.500	11.8	10.4	1.40	11.9
5	0.667	10.3	10.3	-4.704E-03	-4.567E-02
6	1.00	10.6	10.0	0.541	5.11
7	1.50	11.8	9.68	2.16	18.3
8	2.00	10.8	9.32	1.46	13.6
9	3.00	7.18	8.64	-1.46	-20.4
10	4.00	7.27	8.02	-0.745	-10.2
11	5.00	7.18	7.43	-0.253	-3.53
12	6.00	8.37	6.89	1.48	17.6
13	8.00	5.51	5.93	-0.419	-7.61
14	10.0	4.93	5.10	-0.170	-3.44
15	12.0	3.71	4.39	-0.676	-18.2
16	24.0	1.65	1.78	-0.125	-7.61
17	30.0	1.42	1.13	0.290	20.4
			FUNCTION 2		
1	0.167	0.400	0.514	-0.114	-28.5
2	0.250	1.13	0.969	0.161	14.2
3	0.333	1.44	1.36	8.273E-02	5.75
4	0.500	2.11	2.03	7.737E-02	3.67

Text G.1u Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Linda, 20 mg/Kg)

5	0.667	2.67	2.59	8.299E-02	3.11
6	1.00	2.97	3.41	-0.437	-14.7
7	1.50	4.49	4.13	0.357	7.95
8	2.00	4.56	4.48	7.872E-02	1.73
9	3.00	4.97	4.61	0.357	7.18
10	4.00	3.33	4.44	-1.11	-33.2
11	5.00	4.59	4.17	0.421	9.18
12	6.00	4.15	3.88	0.265	6.39
13	8.00	3.48	3.35	0.130	3.75
14	10.0	2.74	2.88	-0.142	-5.18
15	12.0	2.55	2.48	7.114E-02	2.79
16	24.0	1.23	1.00	0.227	18.4
17	30.0	0.840	0.638	0.202	24.0

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 603

MODL ID: THEOPHYLLINE
PLOT ID: F 7 D 2 P 2 X 3176 19-AUG-90 14:48 RS
THEOPHYLLINE 10 MG/KG, TAYLOR LOCK

```
      A         =   7.1067680E-03
    ALPHA       =     1.062159
 T1/2 ALPHA     =   0.6525833
      B         =     569.6794
    BETA        =   7.5361915E-02
 T1/2 BETA      =     9.197579
     AM         =    -21.61092
     AN         =     321.9698
```

DATA SET NUMBER: 12 -FUNFIT- CALL NUMBER: 2
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	1703.28	0.000000E+00	NONE	1.578E-03
2	4.868483E-02	0.000000E+00	NONE	100.
3	45.8087	0.000000E+00	NONE	4.874E-03
4	1.27195	0.000000E+00	NONE	0.779
5	-30.3420	UNCONSTRAINED		5.171E-02
6	819.163	0.000000E+00	NONE	4.309E-03

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	22.3427	80.6973	0.966721
2	17	5.70971	5.42407	0.977787

Text G.1v Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Linda, 20 mg/Kg)

TOTAL 34 28.0524 86.1211 0.985998

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	23.2	22.9	0.321	1.39
2	0.250	33.6	33.5	0.134	0.398
3	0.333	36.5	32.1	4.46	12.2
4	0.500	29.4	29.6	-0.195	-0.663
5	0.667	27.1	27.6	-0.508	-1.87
6	1.00	20.7	24.7	-3.99	-19.3
7	1.50	18.4	21.9	-3.45	-18.7
8	2.00	19.2	20.2	-0.980	-5.10
9	3.00	20.2	18.4	1.85	9.13
10	4.00	18.1	17.3	0.832	4.60
11	5.00	18.1	16.4	1.70	9.43
12	6.00	19.6	15.6	4.06	20.7
13	8.00	16.4	14.1	2.26	13.8
14	10.0	12.0	12.8	-0.858	-7.18
15	12.0	10.6	11.6	-1.07	-10.1
16	24.0	6.84	6.48	0.356	5.21
17	30.0	3.86	4.84	-0.981	-25.4
			FUNCTION 2		
1	0.167	1.00	0.628	0.372	37.2
2	0.250	1.39	1.38	1.211E-02	0.871
3	0.333	2.21	2.22	-1.369E-02	-0.619
4	0.500	3.30	3.66	-0.357	-10.8
5	0.667	4.07	4.79	-0.722	-17.7
6	1.00	5.39	6.39	-0.996	-18.5
7	1.50	7.16	7.69	-0.527	-7.37
8	2.00	8.02	8.25	-0.234	-2.92
9	3.00	8.79	8.44	0.348	3.96
10	4.00	8.53	8.20	0.334	3.92
11	5.00	8.50	7.85	0.652	7.67
12	6.00	7.40	7.49	-8.578E-02	-1.16
13	8.00	7.63	6.79	0.835	10.9
14	10.0	6.46	6.16	0.295	4.57
15	12.0	6.92	5.59	1.33	19.2
16	24.0	3.25	3.12	0.132	4.06
17	30.0	2.04	2.33	-0.298	-14.1

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 455

MODL ID: THEOPHYLLINE

PLOT ID: F 2 D12 P 1 X 3179 19-AUG-90 18:34 RS

THEOPHYLLINE 20 MG/KG, LINDA

A	=	45.80872
ALPHA	=	1.320631
T1/2 ALPHA	=	0.5248608
B	=	1703.278
BETA	=	4.8684884E-02
T1/2 BETA	=	14.23742
AM	=	-30.34198
AN	=	919.1628

Text G.1w Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Average, combo 10 mg/Kg)

[redacted] -FUNFIT- CALL NUMBER: 8

C << 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	597.688	0.000000E+00	NONE	1.630E-03
2	5.519819E-02	0.000000E+00	NONE	100.
3	36.0861	0.000000E+00	NONE	3.154E-03
4	1.23176	0.000000E+00	NONE	1.30
5	-15.7077	UNCONSTRAINED		0.175
6	384.512	0.000000E+00	NONE	1.532E-02

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	1.61576	142.432	0.910355
2	16	0.526578	0.573273	0.987885
TOTAL	33	2.14234	143.005	0.940898

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.170	14.1	12.7	1.42	10.1
2	0.250	29.6	18.1	11.5	38.8
3	0.330	16.3	17.1	-0.842	-5.17
4	0.500	13.4	15.3	-1.85	-13.7
5	0.670	12.3	13.8	-1.54	-12.5
6	1.00	10.9	11.6	-0.710	-6.50
7	1.50	9.75	9.63	0.118	1.21
8	2.00	8.33	8.48	-0.151	-1.81
9	3.00	7.63	7.33	0.304	3.99
10	4.00	7.66	6.74	0.921	12.0
11	5.00	6.88	6.32	0.556	8.08
12	6.00	6.30	5.97	0.330	5.24
13	8.00	5.66	5.34	0.319	5.64
14	10.0	4.91	4.78	0.128	2.60
15	12.0	3.99	4.28	-0.292	-7.32
16	24.0	2.07	2.21	-0.138	-6.67
17	30.0	1.47	1.59	-0.116	-7.86
			FUNCTION 2		
1	0.250	0.890	0.948	-5.823E-02	-6.54
2	0.330	1.61	1.35	0.262	16.3
3	0.500	2.15	2.06	8.511E-02	3.96
4	0.670	2.54	2.63	-9.189E-02	-3.62
5	1.00	3.08	3.41	-0.330	-10.7
6	1.50	3.56	4.05	-0.493	-13.9
7	2.00	4.25	4.33	-7.993E-02	-1.88
8	3.00	4.59	4.40	0.188	4.10
9	4.00	4.22	4.25	-2.969E-02	-0.704
10	5.00	4.07	4.04	2.531E-02	0.622
11	6.00	3.74	3.83	-9.389E-02	-2.51
12	8.00	3.50	3.44	6.466E-02	1.85
13	10.0	3.12	3.08	4.356E-02	1.40
14	12.0	3.01	2.75	0.255	8.48

Text G.1x Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Average, 10 mg/Kg)

15	24.0	1.50	1.42	7.951E-02	5.30
16	30.0	1.08	1.02	5.999E-02	5.55

WGHT. EXP. = -2

FUNCTION EVALUATIONS: 707

MODL ID: THEOPHYLLINE
PLOT ID: F 8 021 P 4 X 3180 19-AUG-90 19:29 RS
THEOPHYLLINE COMBO 10MG/KG (AVERAGE OF 6)

A	=	36.08614
ALPHA	=	1.286957
T1/2 ALPHA	=	0.5385938
B	=	597.6884
BETA	=	5.5198185E-02
T1/2 BETA	=	12.55743
AM	=	-15.70770
AN	=	384.5115

[redacted] -FUNFIT- CALL NUMBER: 6
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	774.194	0.000000E+00	NONE	1.485E-03
2	4.648325E-02	0.000000E+00	NONE	100.
3	35.6713	0.000000E+00	NONE	2.943E-03
4	1.82771	0.000000E+00	NONE	0.613
5	-8.22754	UNCONSTRAINED		0.231
6	360.336	0.000000E+00	NONE	1.339E-02

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	2.31995	270.264	0.921358
2	17	0.682734	0.753265	0.980122
TOTAL	34	3.00268	271.017	0.946419

OBS. NO.	OBSERVED X	Plasma OBSERVED Y	Cai P CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.170	20.4	15.8	4.60	22.5
2	0.250	36.5	22.3	14.2	38.9
3	0.330	24.8	20.4	4.41	17.8
4	0.500	13.3	17.2	-3.92	-29.6
5	0.670	12.0	14.8	-2.84	-23.6
6	1.00	10.8	11.9	-1.14	-10.6
7	1.50	9.74	9.72	1.833E-02	0.188
8	2.00	9.93	8.75	1.18	11.9
9	3.00	8.45	7.95	0.502	5.94
10	4.00	8.30	7.53	0.774	9.33

Text G.1y Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Taylor Lock, 20 mg/Kg)

11	5.00	7.57	7.17	0.396	5.23
12	6.00	7.42	6.85	0.573	7.72
13	8.00	6.62	6.24	0.381	5.76
14	10.0	5.99	5.69	0.305	5.09
15	12.0	4.98	5.18	-0.200	-4.02
16	24.0	2.63	2.97	-0.336	-12.8
17	30.0	1.97	2.24	-0.274	-13.9

---------------------CSF-- FUNCTION 2 csf csf ---------------------------

1	0.167	0.710	0.575	0.135	19.0
2	0.250	0.970	1.09	-0.115	-11.9
3	0.330	1.54	1.50	4.159E-02	2.70
4	0.500	1.92	2.19	-0.269	-14.0
5	0.670	2.42	2.68	-0.262	-10.8
6	1.00	2.86	3.27	-0.406	-14.2
7	1.50	3.61	3.63	-2.249E-02	-0.623
8	2.00	3.67	3.72	-5.208E-02	-1.42
9	3.00	3.85	3.65	0.204	5.30
10	4.00	3.49	3.49	-4.468E-03	-0.128
11	5.00	3.73	3.34	0.392	10.5
12	6.00	3.58	3.19	0.393	11.0
13	8.00	3.09	2.90	0.186	6.03
14	10.0	2.79	2.65	0.144	5.16
15	12.0	2.47	2.41	5.887E-02	2.38
16	24.0	1.40	1.38	1.971E-02	1.41
17	30.0	1.09	1.04	4.565E-02	4.19

WGHT. EXP. = -2

FUNCTION EVALUATIONS: 454

MODL ID: THEOPHYLLINE
PLOT ID: F 6 D20 P 3 X 3180 19-AUG-90 19:26 RS
THEOPHYLLINE AVERAGE 10 MG/KG (AVERAGE OF 6 HORSES)

A	=	35.67131
ALPHA	=	1.874194
T1/2 ALPHA	=	0.3698375
B	=	774.1938
BETA	=	4.6483248E-02
T1/2 BETA	=	14.91176
AM	=	-8.227544
AN	=	360.3359

DATA SET NUMBER: 8 -FUNFIT- CALL NUMBER: 2
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	1003.07	0.000000E+00	NONE	2.757E-03
2	5.800339E-02	0.000000E+00	NONE	100.
3	55.3431	0.000000E+00	NONE	3.335E-03

Text G.1z Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Taylor Lock, 20 mg/Kg)

4	0.947006	0.000000E+00	NONE	1.47 [illegible]
5	-33.7583	UNCONSTRAINED		6.030E-02
6	634.343	0.000000E+00	NONE	7.841E-03

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	14.1252	52.3604	0.973202
2	17	1.97471	1.58997	0.990518
TOTAL	34	16.0999	53.9512	0.985888

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	17.3	18.2	-0.940	-5.44
2	0.250	25.9	26.7	-0.886	-3.43
3	0.333	28.3	25.7	2.65	9.34
4	0.500	22.7	23.8	-1.11	-4.88
5	0.667	25.2	22.2	3.04	12.0
6	1.00	18.3	19.6	-1.30	-7.11
7	1.50	16.0	16.9	-0.911	-5.69
8	2.00	13.3	15.2	-1.87	-14.1
9	3.00	17.9	13.1	4.80	26.8
10	4.00	12.9	11.9	0.959	7.45
11	5.00	12.0	11.1	0.923	7.70
12	6.00	9.24	10.4	-1.14	-12.4
13	8.00	8.56	9.22	-0.657	-7.68
14	10.0	8.14	8.20	-6.367E-02	-0.782
15	12.0	6.76	7.30	-0.545	-8.06
16	24.0	4.03	3.64	0.388	9.64
17	30.0	2.18	2.57	-0.391	-18.0
			FUNCTION 2		
1	0.167	1.05	0.899	0.151	14.4
2	0.250	1.44	1.63	-0.192	-13.3
3	0.333	2.07	2.19	-0.118	-5.72
4	0.500	3.86	3.17	0.693	18.0
5	0.667	3.64	3.98	-0.341	-9.38
6	1.00	5.32	5.21	0.106	2.00
7	1.50	6.60	6.36	0.242	3.67
8	2.00	6.64	6.96	-0.319	-4.80
9	3.00	7.08	7.31	-0.233	-3.29
10	4.00	6.99	7.17	-0.184	-2.63
11	5.00	6.75	6.87	-0.120	-1.77
12	6.00	6.00	6.52	-0.519	-8.65
13	8.00	5.97	5.82	0.147	2.47
14	10.0	5.52	5.19	0.333	6.03
15	12.0	4.78	4.62	0.161	3.36
16	24.0	2.74	2.30	0.437	15.9
17	30.0	1.79	1.63	0.164	9.16

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 407
MODL ID: THEOPHYLLINE
PLOT ID: F 2 D 3 P 1 X 3180 19-AUG-90 19:22 RS
THEOPHYLLINE 20 MG/KG, TAYLOR LOCK
A = 55.34309

Text G.1aa Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Taylor Lock, combo 10 mg/Kg)

```
ALPHA      =    1.005010
T1/2 ALPHA =    0.6896920
B          =    1003.072
BETA       =    5.8003338E-02
T1/2 BETA  =    11.95012
AM         =    -33.75826
AN         =    634.3428
```

[redacted] -FUNFIT- CALL NUMBER: 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	725.084	0.000000E+00	NONE	4.970E-03
2	5.836959E-02	0.000000E+00	NONE	100.
3	16.0845	0.000000E+00	NONE	1.056E-02
4	1.39528	0.000000E+00	NONE	0.711
5	-14.5802	UNCONSTRAINED		0.124
6	344.333	0.000000E+00	NONE	1.203E-02

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	1.95847	5.95044	0.988133
2	16	1.81680	1.37674	0.971161
TOTAL	33	3.77527	7.32715	0.994042

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	11.6	10.5	1.12	9.63
2	0.250	15.6	15.4	0.235	1.50
3	0.333	15.3	14.8	0.543	3.54
4	0.500	12.2	13.8	-1.60	-13.2
5	0.667	12.9	12.9	5.573E-03	4.310E-02
6	1.00	11.0	11.7	-0.671	-6.09
7	1.50	10.2	10.6	-0.351	-3.44
8	2.00	10.2	9.87	0.371	3.62
9	3.00	9.43	9.04	0.394	4.18
10	4.00	8.44	8.46	-1.997E-02	-0.237
11	5.00	7.83	7.97	-0.135	-1.73
12	6.00	7.71	7.51	0.200	2.59
13	8.00	7.24	6.68	0.558	7.71
14	10.0	6.47	5.95	0.524	8.11
15	12.0	5.44	5.29	0.150	2.75
16	24.0	2.20	2.63	-0.426	-19.4
17	30.0	1.58	1.85	-0.270	-17.1
		FUNCTION 2			
1	0.250	0.500	0.546	-4.557E-02	-9.11
2	0.333	1.50	1.03	0.474	31.6
3	0.500	1.74	1.83	-8.696E-02	-5.00
4	0.667	1.91	2.45	-0.535	-28.0
5	1.00	3.19	3.28	-9.117E-02	-2.86
6	1.50	3.93	3.92	1.477E-02	0.376
7	2.00	4.60	4.15	0.445	9.68
8	3.00	4.20	4.17	3.315E-02	0.789
9	4.00	4.23	3.99	0.242	5.71
10	5.00	3.27	3.78	-0.506	-15.5

Text G.1ab Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Moon Mist, 10 mg/Kg)

11	6.00	3.45	3.56	-0.115	-3.33
12	8.00	3.26	3.17	8.699E-02	2.67
13	10.0	2.69	2.82	-0.133	-4.96
14	12.0	2.97	2.51	0.458	15.4
15	24.0	1.36	1.25	0.113	8.30
16	30.0	1.15	0.879	0.271	23.6

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 509
MODL ID: THEOPHYLLINE
PLOT ID: F 3 D14 P 2 X 3180 19-AUG-90 19:24 RS
THEOPHYLLINE COMBO 10 MG/KG, TAYLOR LOCK

A	=	16.08453
ALPHA	=	1.453647
T1/2 ALPHA	=	0.4768331
B	=	725.0836
BETA	=	5.8369592E-02
T1/2 BETA	=	11.87514
AM	=	-14.58018
AN	=	344.3331

DATA SET NUMBER: 1 -FUNFIT- CALL NUMBER: 12
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	1080.06	0.000000E+00	NONE	2.604E-03
2	3.433174E-02	0.000000E+00	NONE	100.
3	99.9183	0.000000E+00	NONE	5.444E-02
4	8.17279	0.000000E+00	NONE	0.287
5	-2.36458	UNCONSTRAINED		1.07
6	333.043	0.000000E+00	NONE	5.363E-03

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	86.3496	2686.25	0.940964
2	17	4.37214	3.94690	0.840550
TOTAL	34	90.7217	2690.19	0.950001

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.167	57.0	80.7	-23.7	-41.6
2	0.250	132.	96.3	35.9	27.2
3	0.333	80.8	53.3	27.5	34.1
4	0.500	12.3	20.3	-8.04	-65.4
5	0.667	10.5	11.9	-1.41	-13.4
6	1.00	11.5	9.19	2.36	20.4

Text G.1ac Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Average, 20 mg/Kg)

7	1.50	10.2	8.85	1.35	13.3
8	2.00	9.56	8.69	0.868	9.08
9	3.00	8.94	8.40	0.541	6.05
10	4.00	8.01	8.12	-0.105	-1.32
11	5.00	8.32	7.84	0.478	5.75
12	6.00	7.95	7.58	0.373	4.69
13	8.00	7.95	7.07	0.876	11.0
14	10.0	6.82	6.60	0.215	3.16
15	12.0	5.69	6.17	-0.476	-8.37
16	24.0	3.38	4.08	-0.704	-20.8
17	30.0	2.90	3.32	-0.424	-14.6
			FUNCTION 2		
1	0.167	0.300	0.140	0.160	53.4
2	0.250	0.650	0.786	-0.136	-20.9
3	0.333	1.35	1.80	-0.445	-33.0
4	0.500	1.69	2.56	-0.867	-51.3
5	0.667	2.09	2.74	-0.649	-31.0
6	1.00	2.34	2.77	-0.430	-18.4
7	1.50	2.84	2.73	0.113	3.99
8	2.00	2.68	2.68	-2.902E-04	-1.083E-02
9	3.00	2.96	2.59	0.370	12.5
10	4.00	2.93	2.50	0.428	14.6
11	5.00	2.99	2.42	0.572	19.1
12	6.00	3.22	2.34	0.884	27.4
13	8.00	2.90	2.18	0.719	24.8
14	10.0	2.52	2.04	0.483	19.2
15	12.0	2.24	1.90	0.339	15.1
16	24.0	1.45	1.26	0.191	13.1
17	30.0	1.10	1.02	7.506E-02	6.82

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 408
MODL ID: THEOPHYLLINE
PLOT ID: F12 D 1 P 2 X 3186 20-AUG-90 06:53 RS
THEOPHYLLINE 10 MG/KG, MOON MIST

A	=	99.91829
ALPHA	=	8.207112
T1/2 ALPHA	=	8.4456891E-02
B	=	1080.062
BETA	=	3.4331739E-02
T1/2 BETA	=	20.18969
AM	=	-2.364578
AN	=	333.0425

DATA SET NUMBER: 19 -FUNFIT- CALL NUMBER: 2
C<< 3

MINI-FUNFIT V.4.3 -NONLINEAR REGRESSION- COPYRIGHT PVP

PAR.NO.	VALUE	LOWER LIM.	UPPER LIM.	REL.SENSITIVITY
1	1987.83	0.000000E+00	NONE	1.285E-03

Text G.1ad Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Average, 20 mg/Kg)

2	4.303d43E-02	0.000000E+00	NONE	100.
3	99.2346	0.000000E+00	NONE	8.329E-03
4	1.49458	0.000000E+00	NONE	0.763
5	-23.5581	UNCONSTRAINED		5.484E-02
6	832.261	UNCONSTRAINED		3.667E-03

FUNCTION	OBSERVATIONS	WEIGHTED SS	SUM OF SQUARES	CORRELATION(R)
1	17	24.9847	171.240	0.974716
2	17	2.20362	2.47644	0.987868
TOTAL	34	27.1883	173.717	0.987444

OBS. NO.	OBSERVED X	OBSERVED Y	CALCULATED Y	DIFFERENCE	DIFFERENCE (PERCENT)
1	0.170	42.0	37.3	4.69	11.2
2	0.250	44.3	53.0	-8.65	-19.5
3	0.330	52.1	49.2	2.90	5.57
4	0.500	48.8	42.6	6.22	12.7
5	0.670	38.4	37.5	0.936	2.44
6	1.00	30.4	30.6	-0.239	-0.786
7	1.50	21.6	24.8	-3.17	-14.6
8	2.00	18.8	21.9	-3.12	-16.6
9	3.00	21.1	19.4	1.73	8.20
10	4.00	18.8	18.2	0.588	3.13
11	5.00	18.5	17.4	1.19	6.41
12	6.00	17.5	16.6	0.916	5.22
13	8.00	15.4	15.2	0.170	1.10
14	10.0	14.3	14.0	0.317	2.22
15	12.0	13.4	12.8	0.610	4.54
16	24.0	7.82	7.65	0.165	2.12
17	30.0	5.20	5.91	-0.713	-13.7
			FUNCTION 2		
1	0.170	0.720	0.648	7.183E-02	9.98
2	0.250	1.48	1.39	9.167E-02	6.19
3	0.330	2.17	2.23	-5.793E-02	-2.67
4	0.500	3.65	3.69	-4.247E-02	-1.16
5	0.670	4.26	4.81	-0.546	-12.8
6	1.00	5.88	6.25	-0.371	-6.31
7	1.50	6.79	7.34	-0.550	-8.10
8	2.00	7.31	7.75	-0.441	-6.03
9	3.00	7.82	7.80	1.700E-02	0.217
10	4.00	8.20	7.56	0.644	7.86
11	5.00	7.99	7.25	0.735	9.20
12	6.00	7.45	6.95	0.497	6.67
13	8.00	6.79	6.38	0.409	6.03
14	10.0	5.97	5.35	0.116	1.94
15	12.0	5.61	5.37	0.238	4.25
16	24.0	3.11	3.20	-9.479E-02	-3.05
17	30.0	2.20	2.48	-0.275	-12.5

WGHT. EXP. = -1

FUNCTION EVALUATIONS: 404

Text G.1ae Computer data output from FUNFIT for individual horses. Function 1 corresponds to plasma theophylline data and Function 2 corresponds to csf theophylline data. (Average, 20 mg/Kg)

```
MODL ID: THEOPHYLLINE
PLOT ID: F 2 019 P 1 X 3186 20-AUG-90 06:42 RS


THEOPHYLLINE AVERAGE 20 MG/KG (AVERAGE OF 6 HORSES)
    A         =    99.28457
  ALPHA       =    1.537622
 T1/2 ALPHA   =    0.4507918
    B         =    1987.830
  BETA        =    4.3038428E-02
 T1/2 BETA    =    16.10531
    AM        =   -23.55806
    AN        =    832.2609
```

Figure G.1 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Moon Mist after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes.

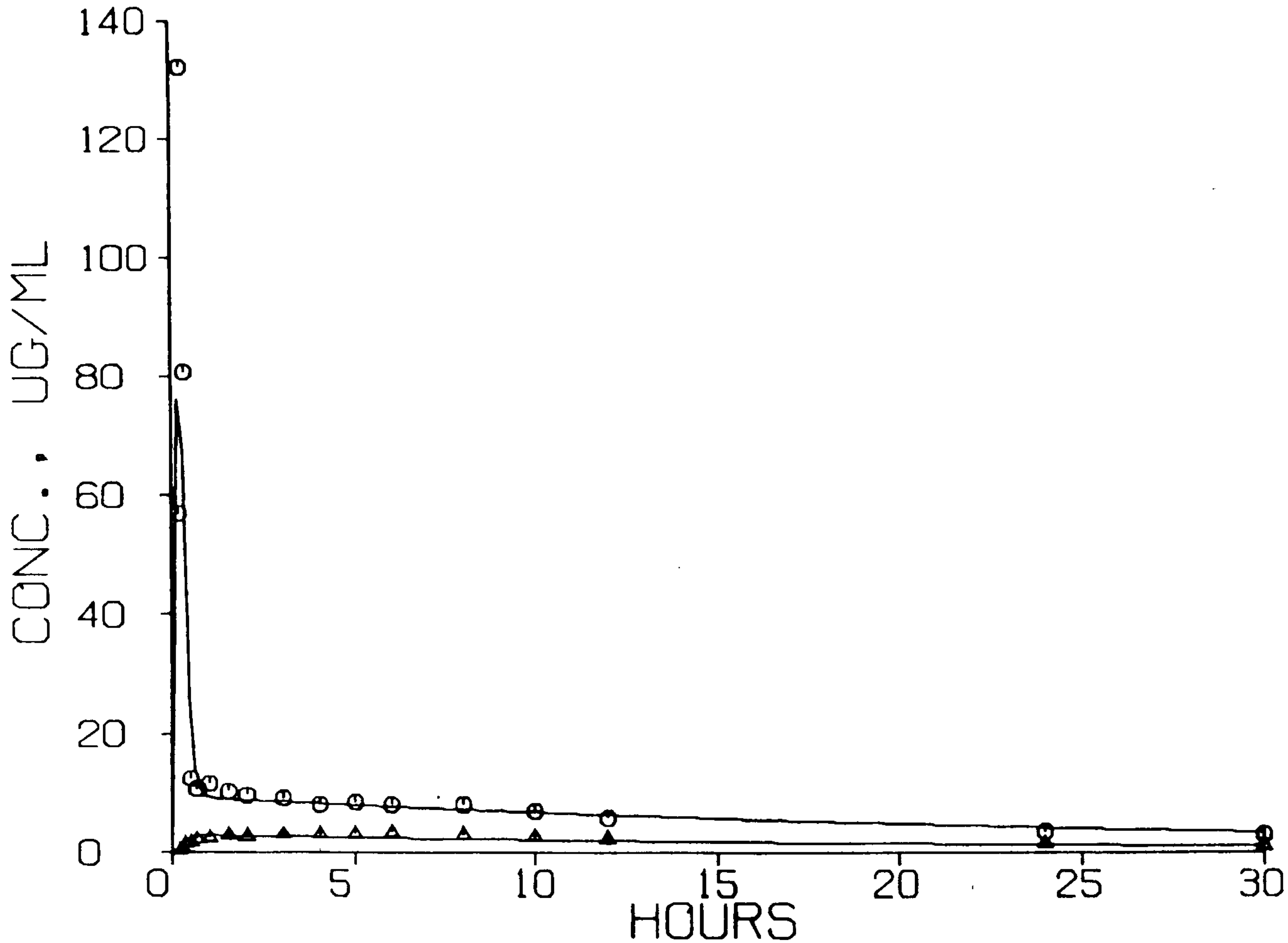


Figure G.2 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Taylor Lock after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes.

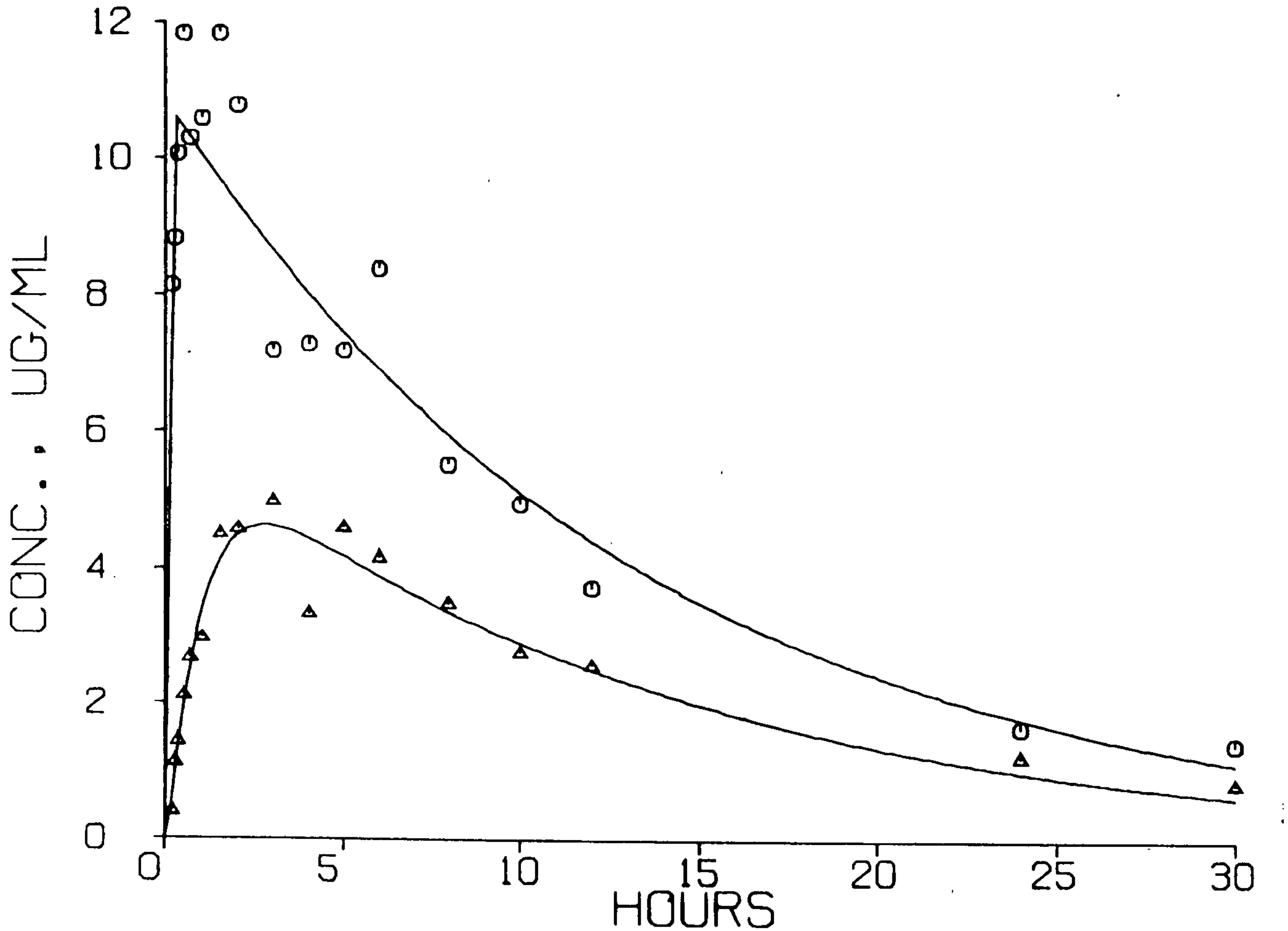


Figure G.3 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Picket Creek after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes.

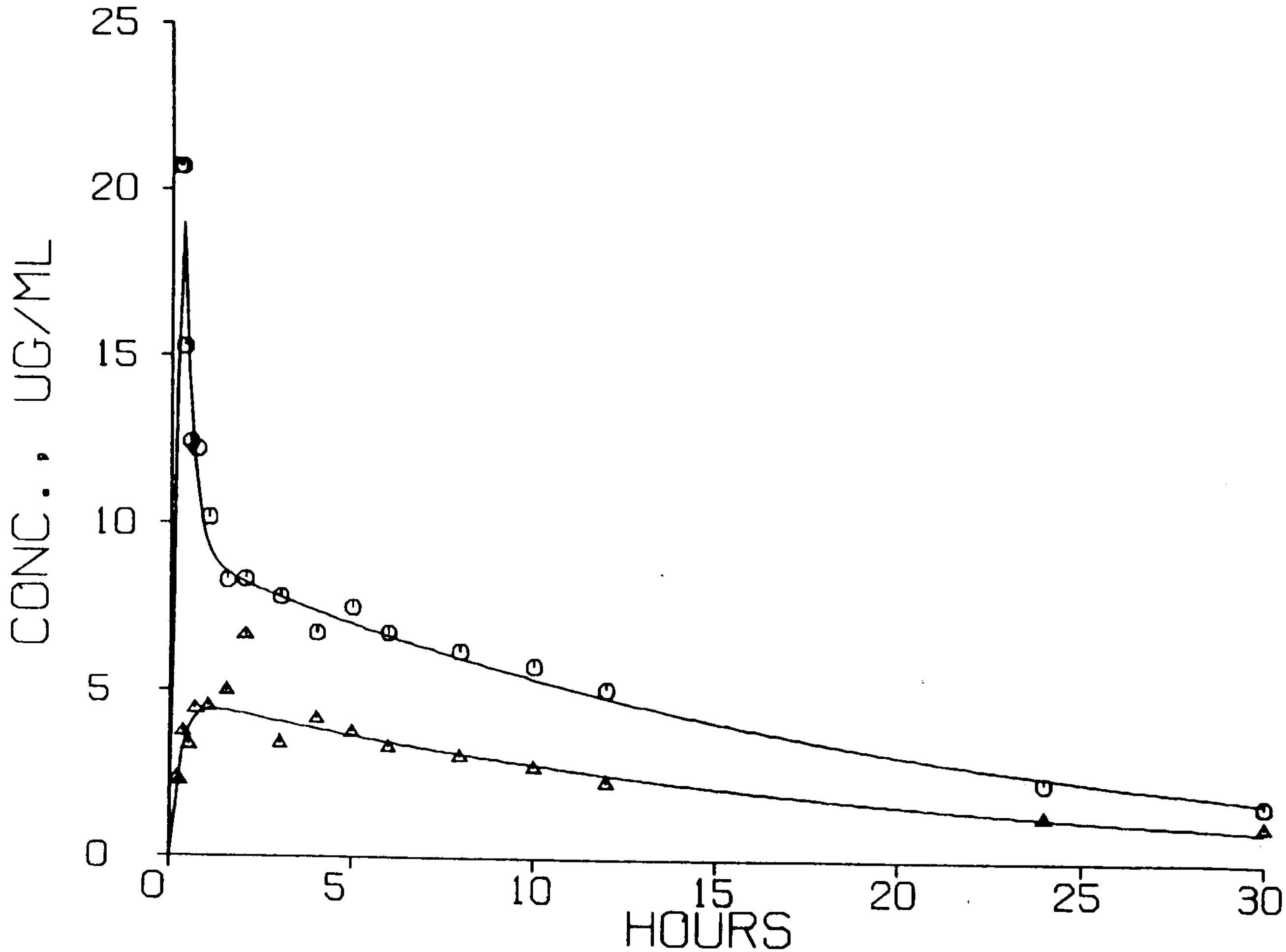


Figure G.4 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Gypsy after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes.

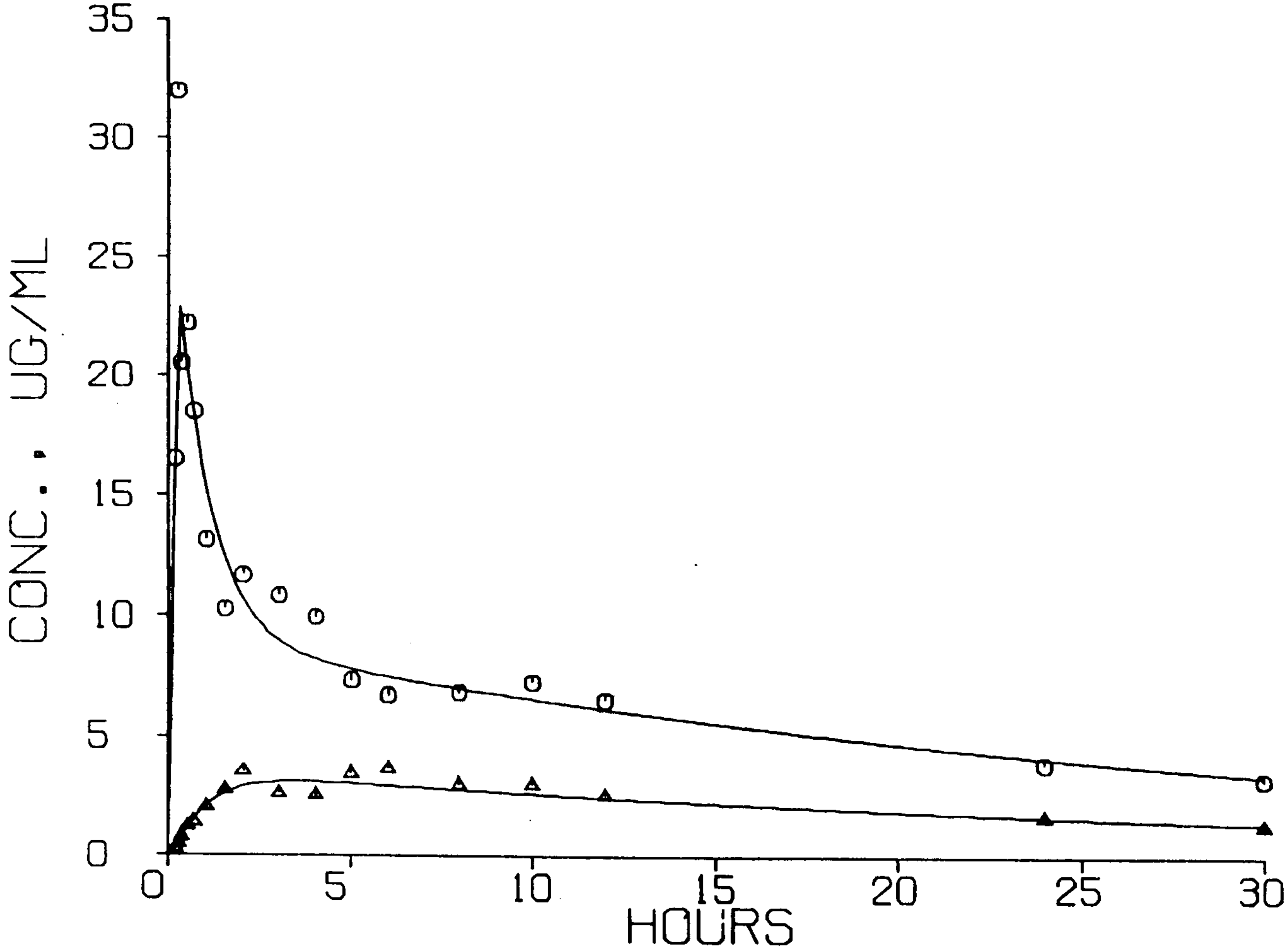


Figure G.5 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Melodee after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes.

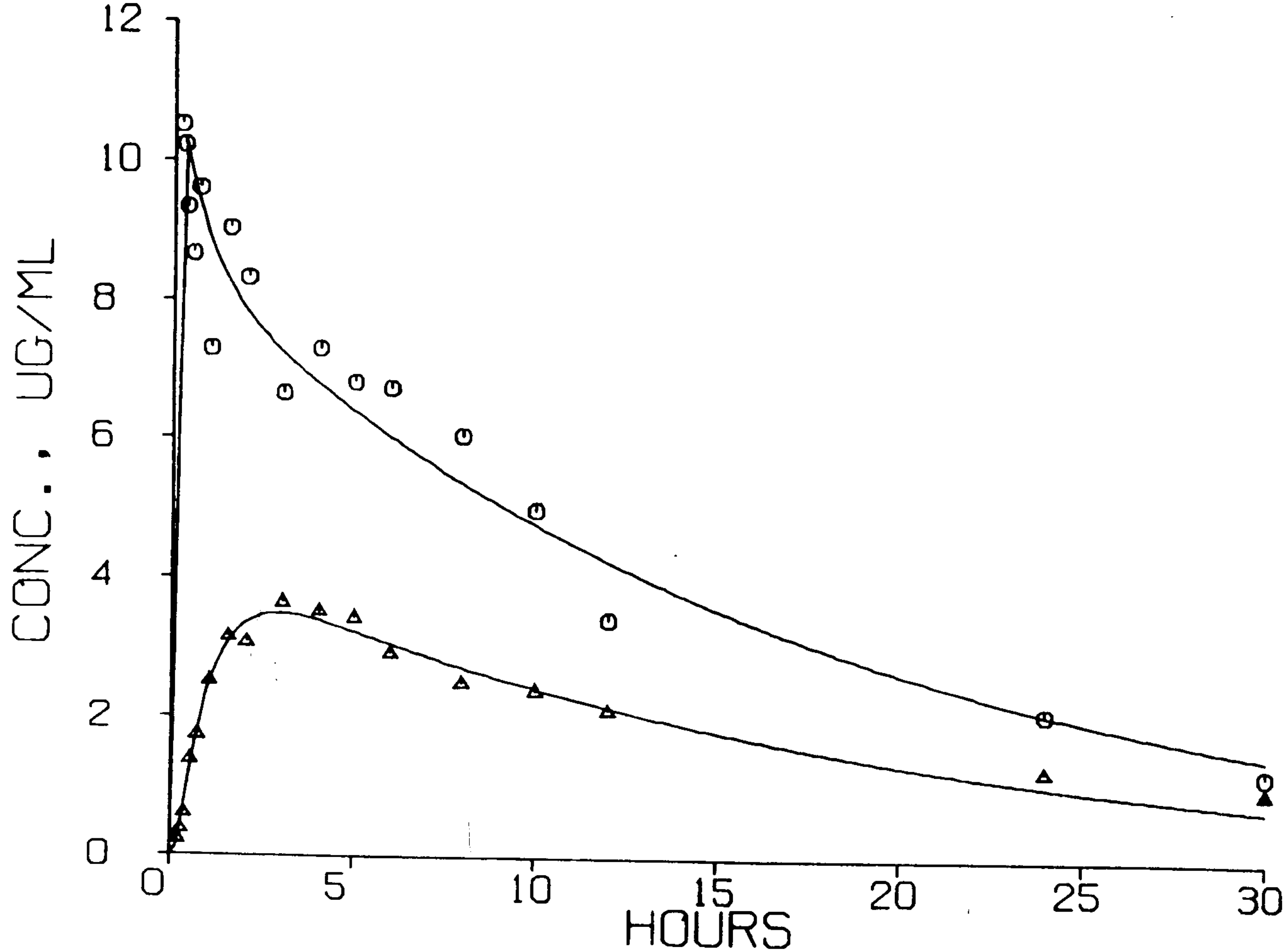


Figure G.6 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Linda after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes.

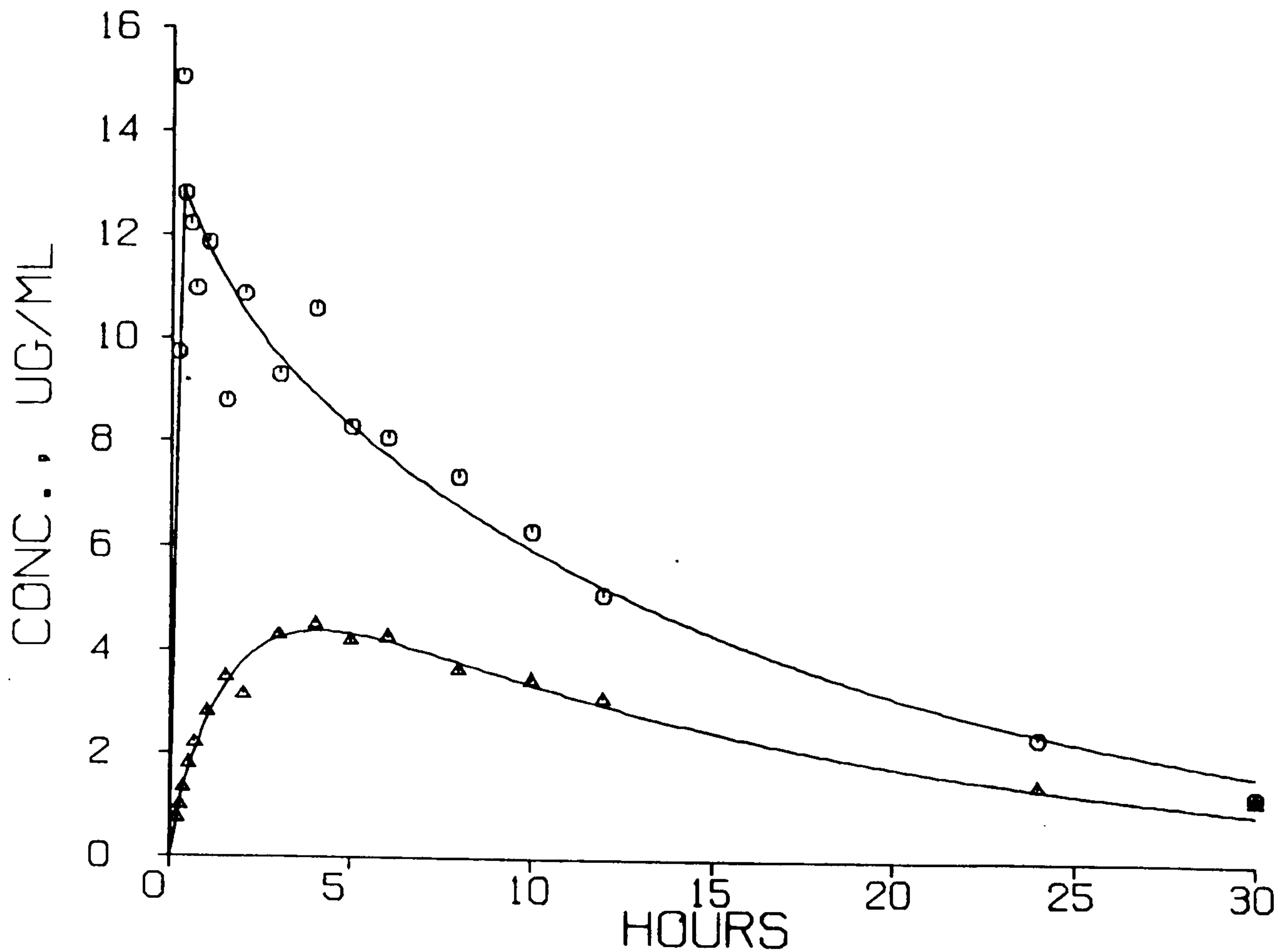


Figure G.7 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for the average of 6 horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes.

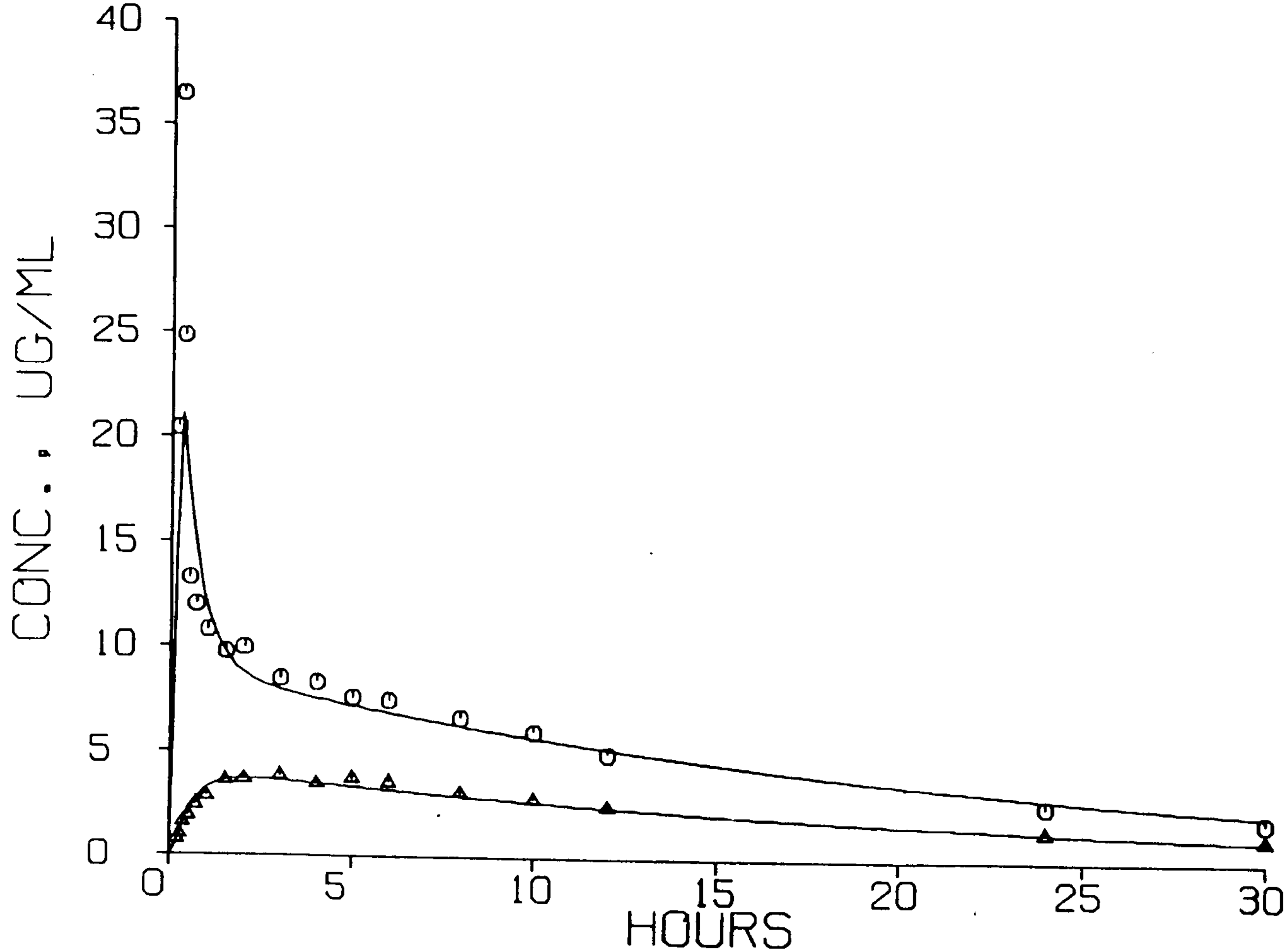


Figure G.8 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Moon Mist after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

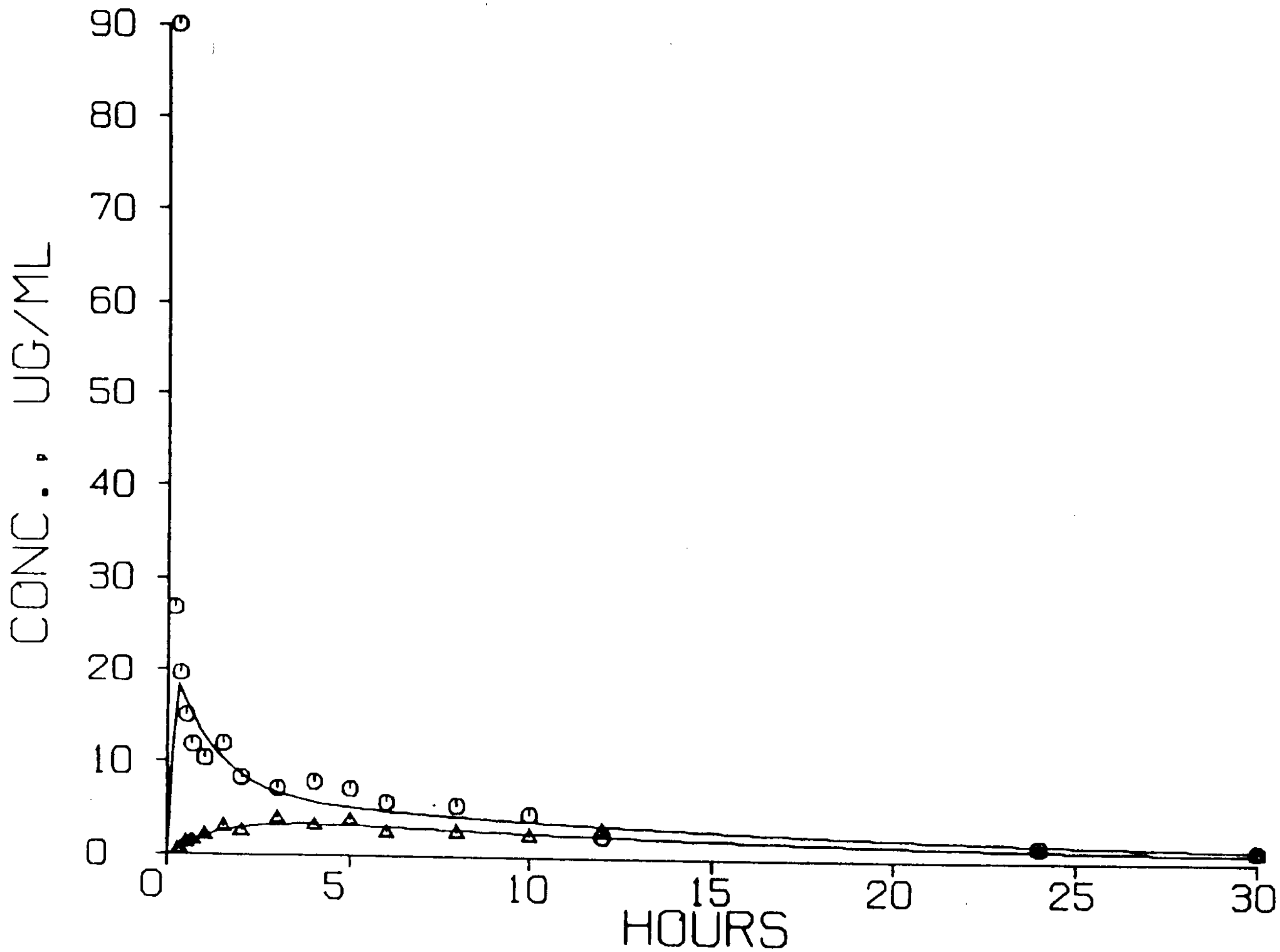


Figure G.9 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Taylor Lock after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

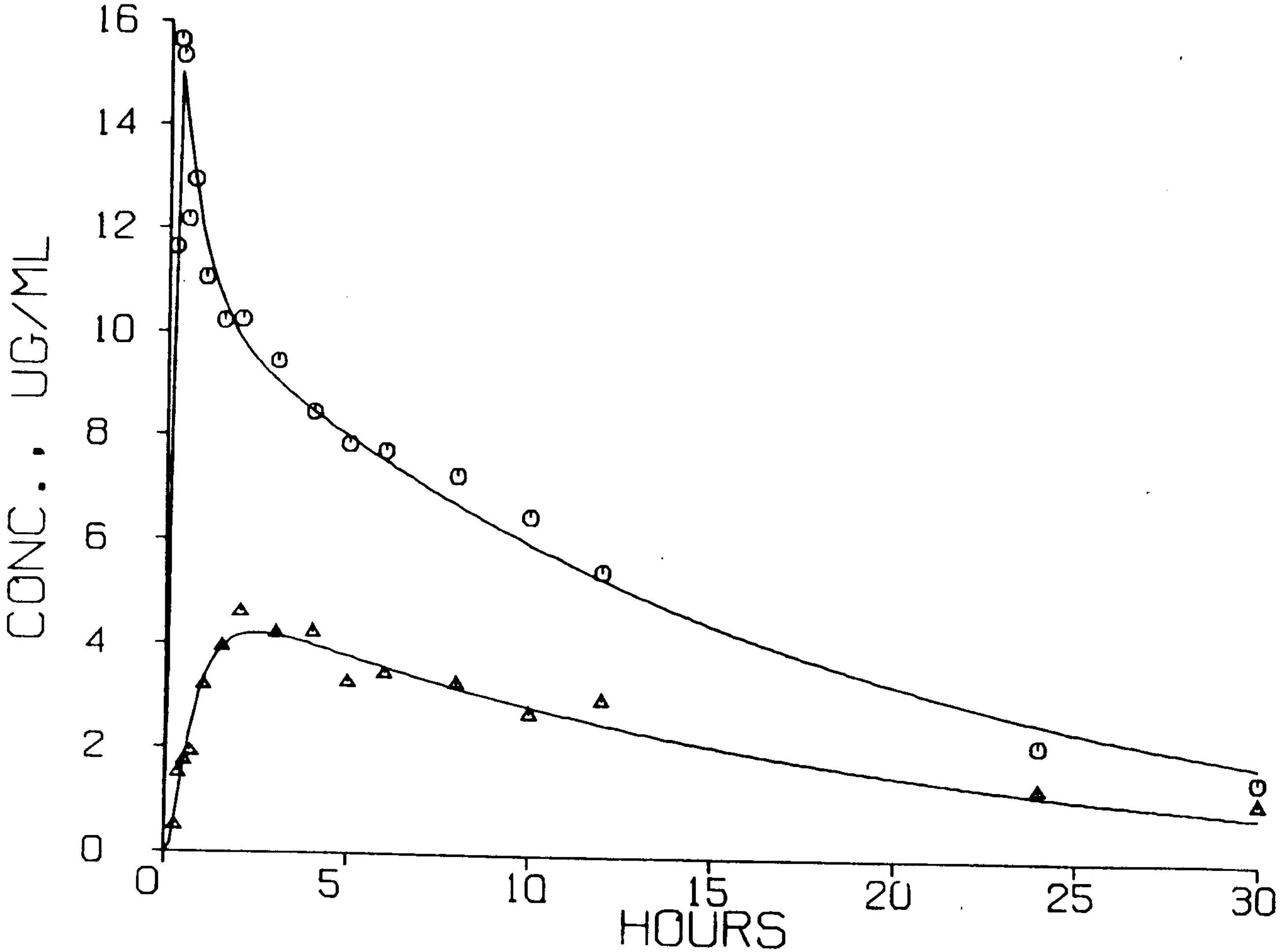


Figure G.10 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Picket Creek after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

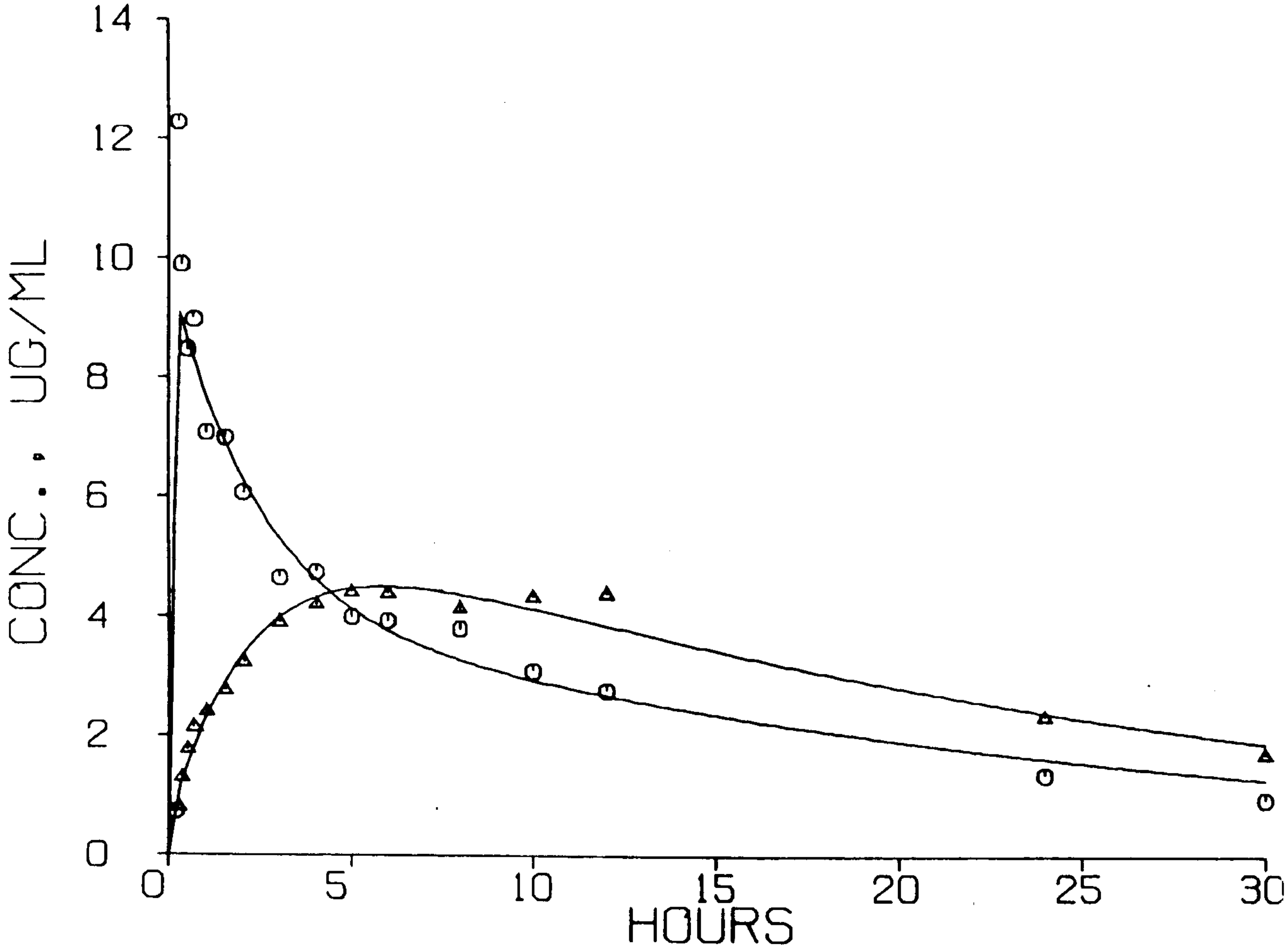


Figure G.11 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Gypsy after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

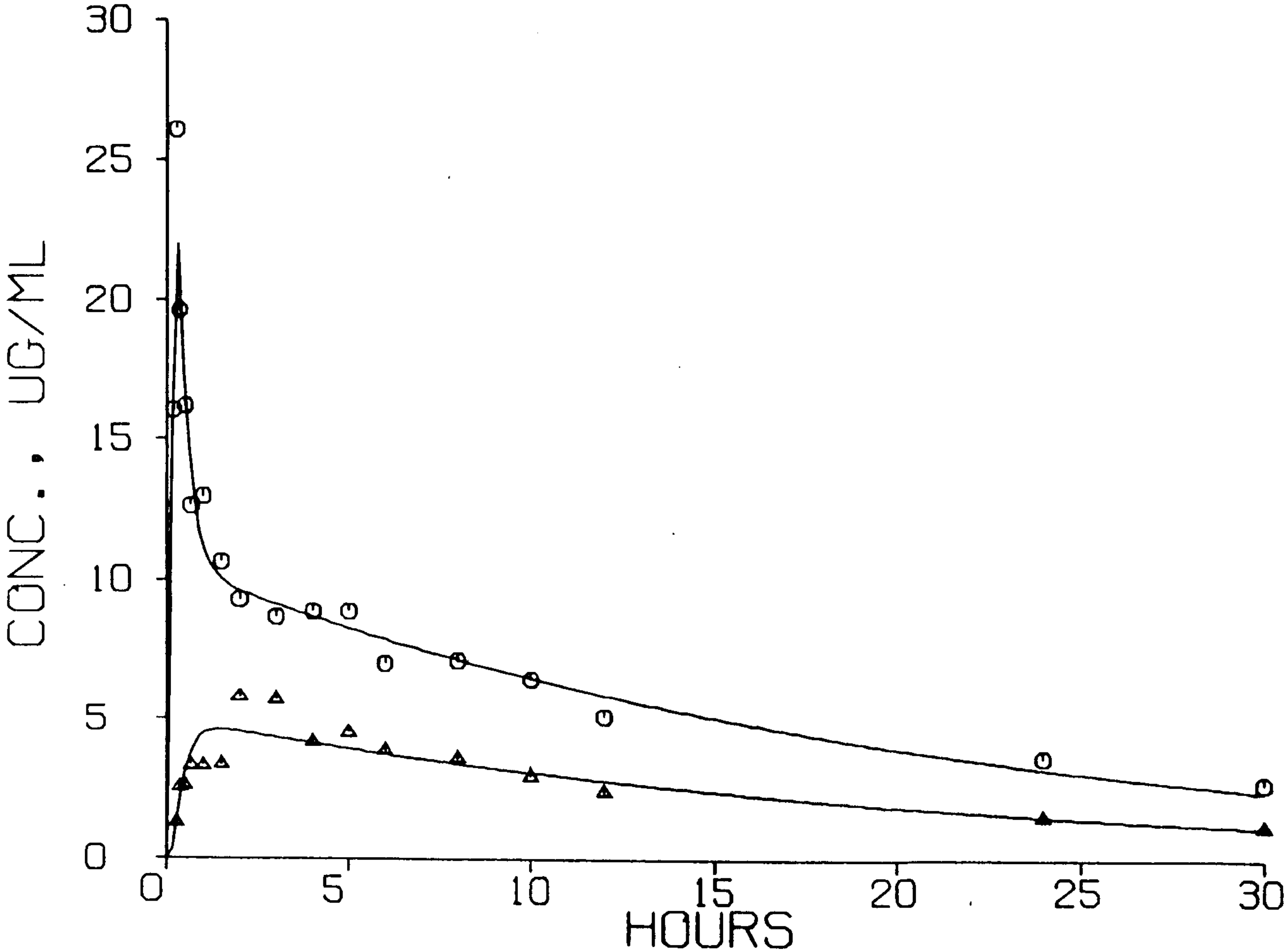


Figure G.12 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Melodee after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

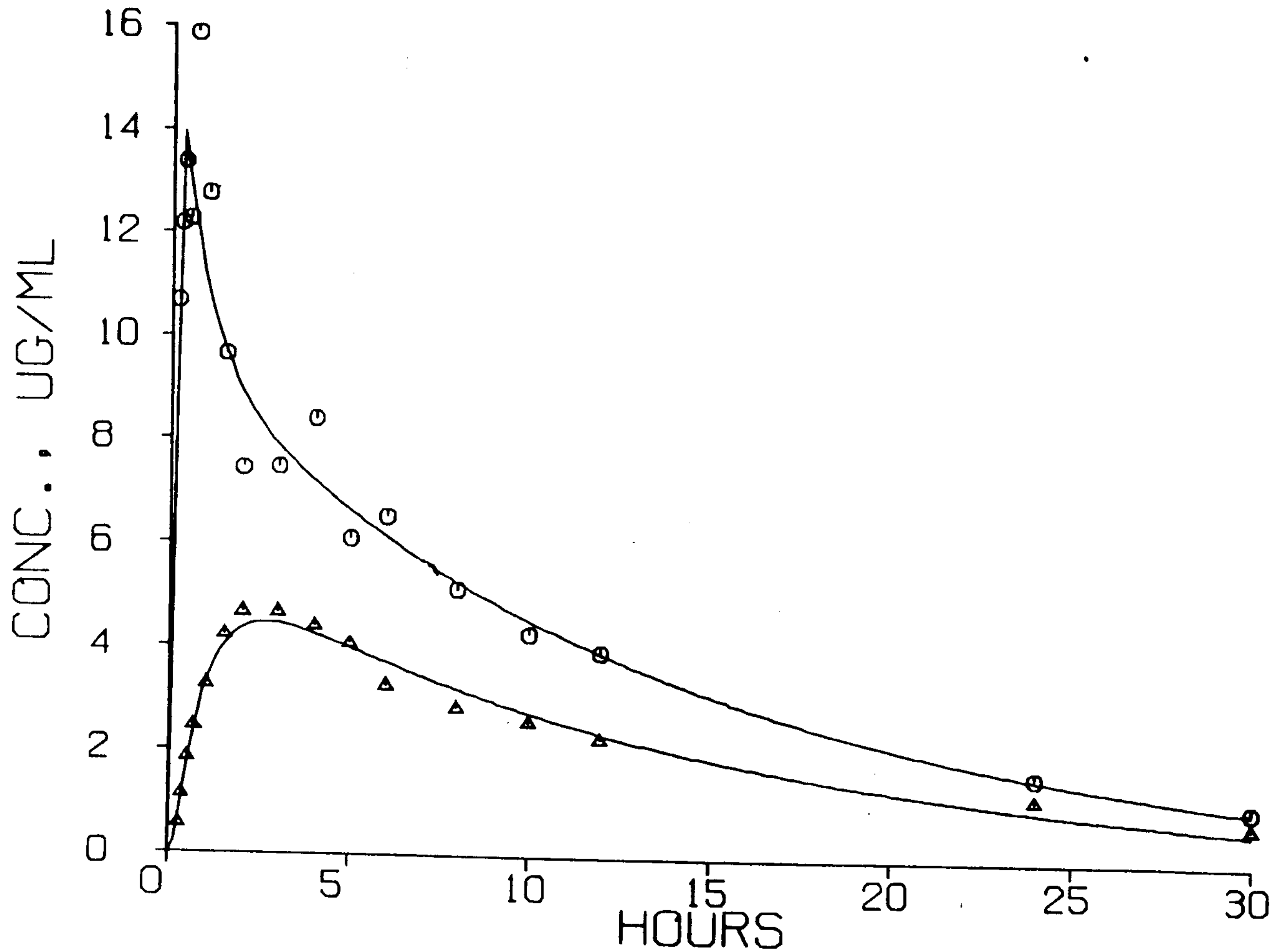


Figure G.13 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Linda after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

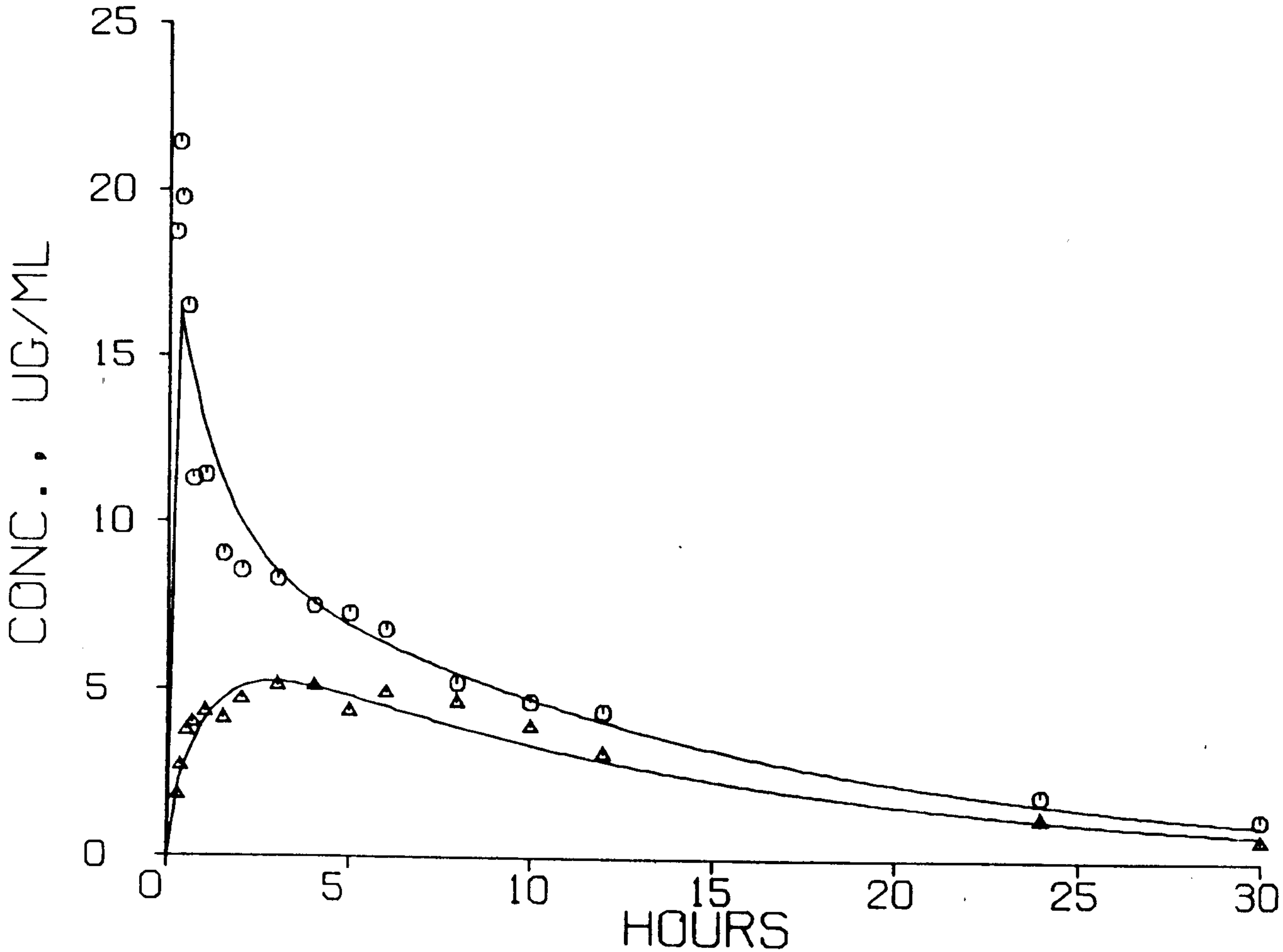


Figure G.14 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for the average of 6 horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

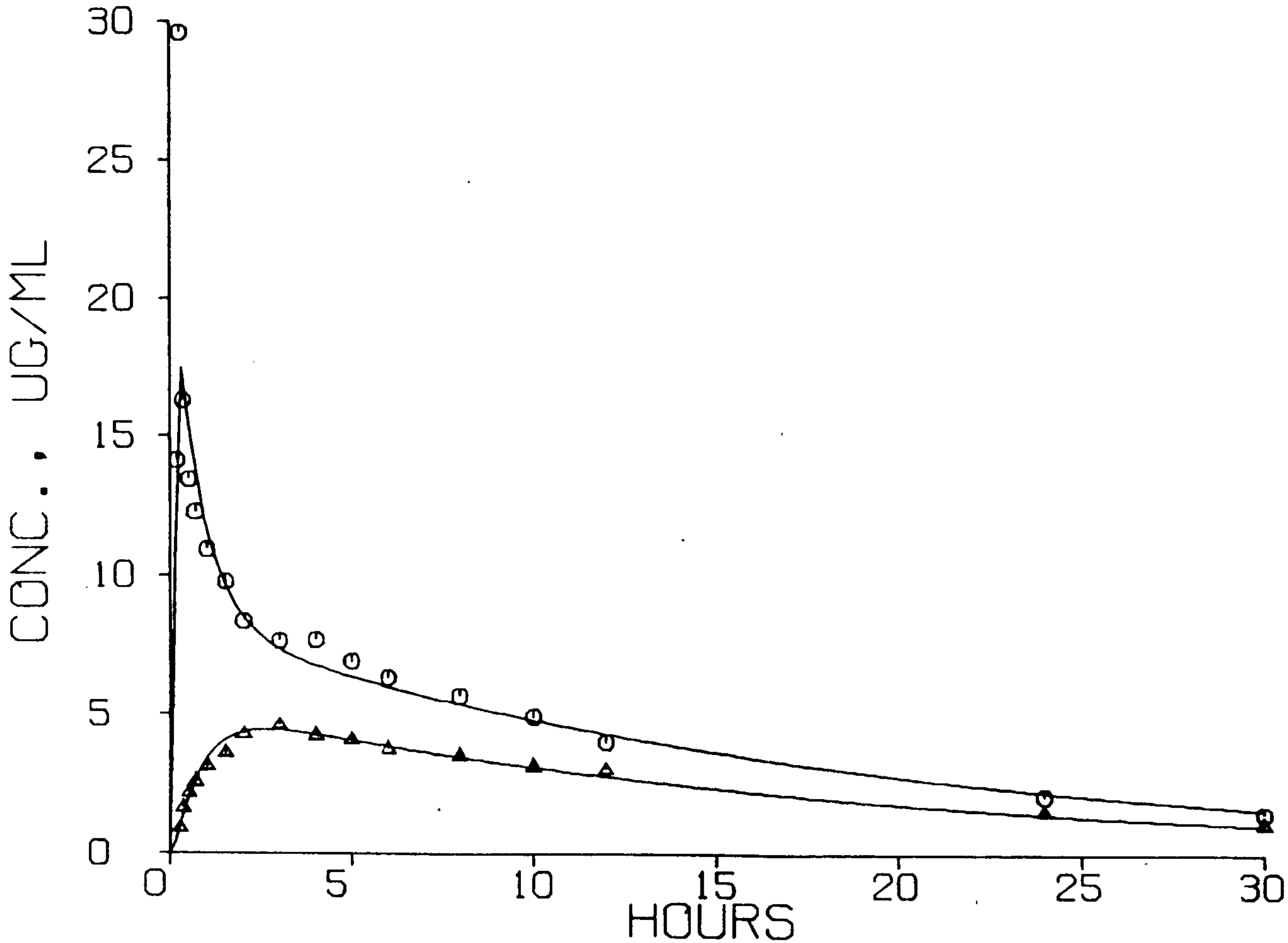


Figure G.15 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Moon Mist after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes.

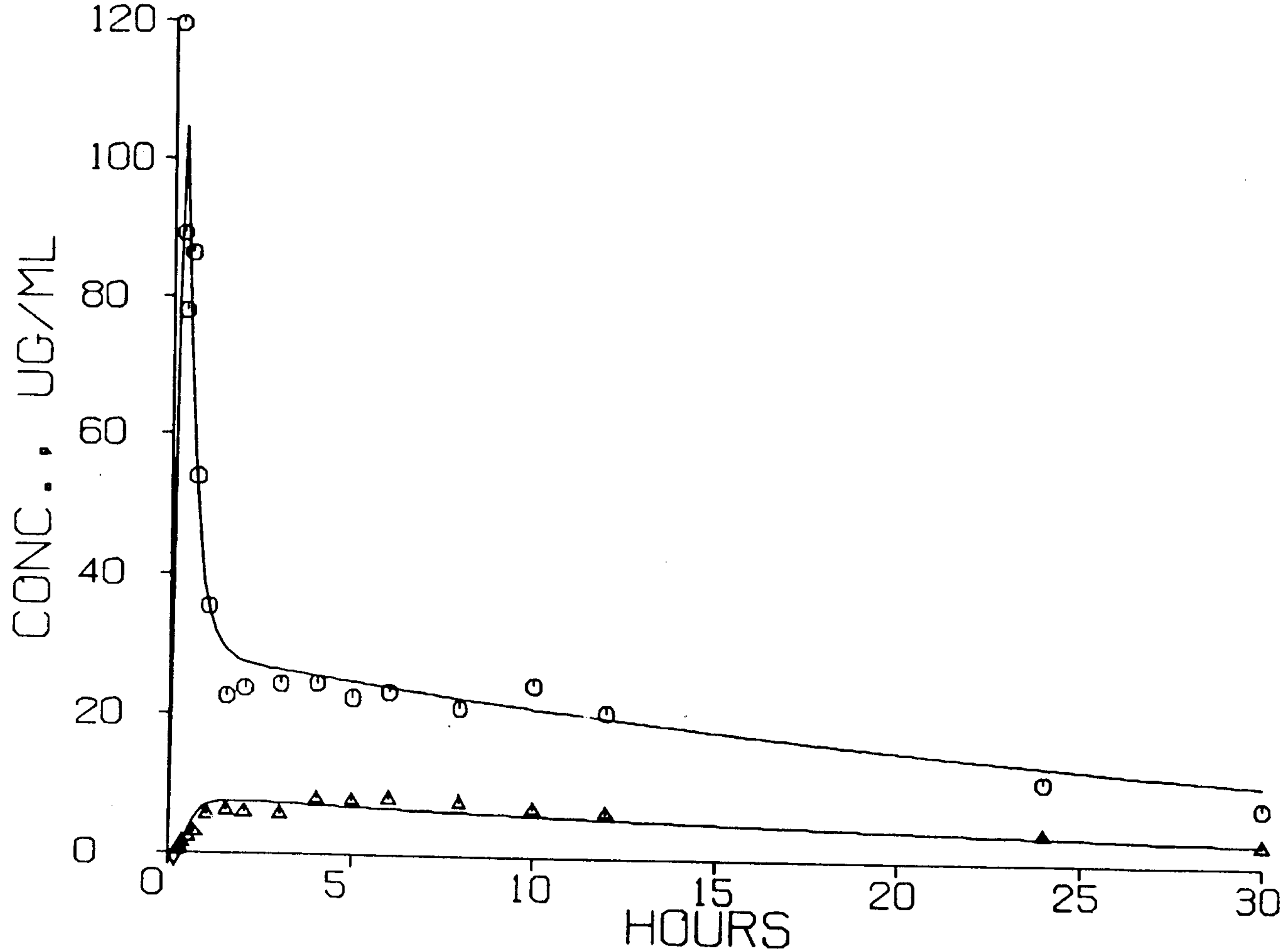


Figure G.16 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Taylor Lock after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes.

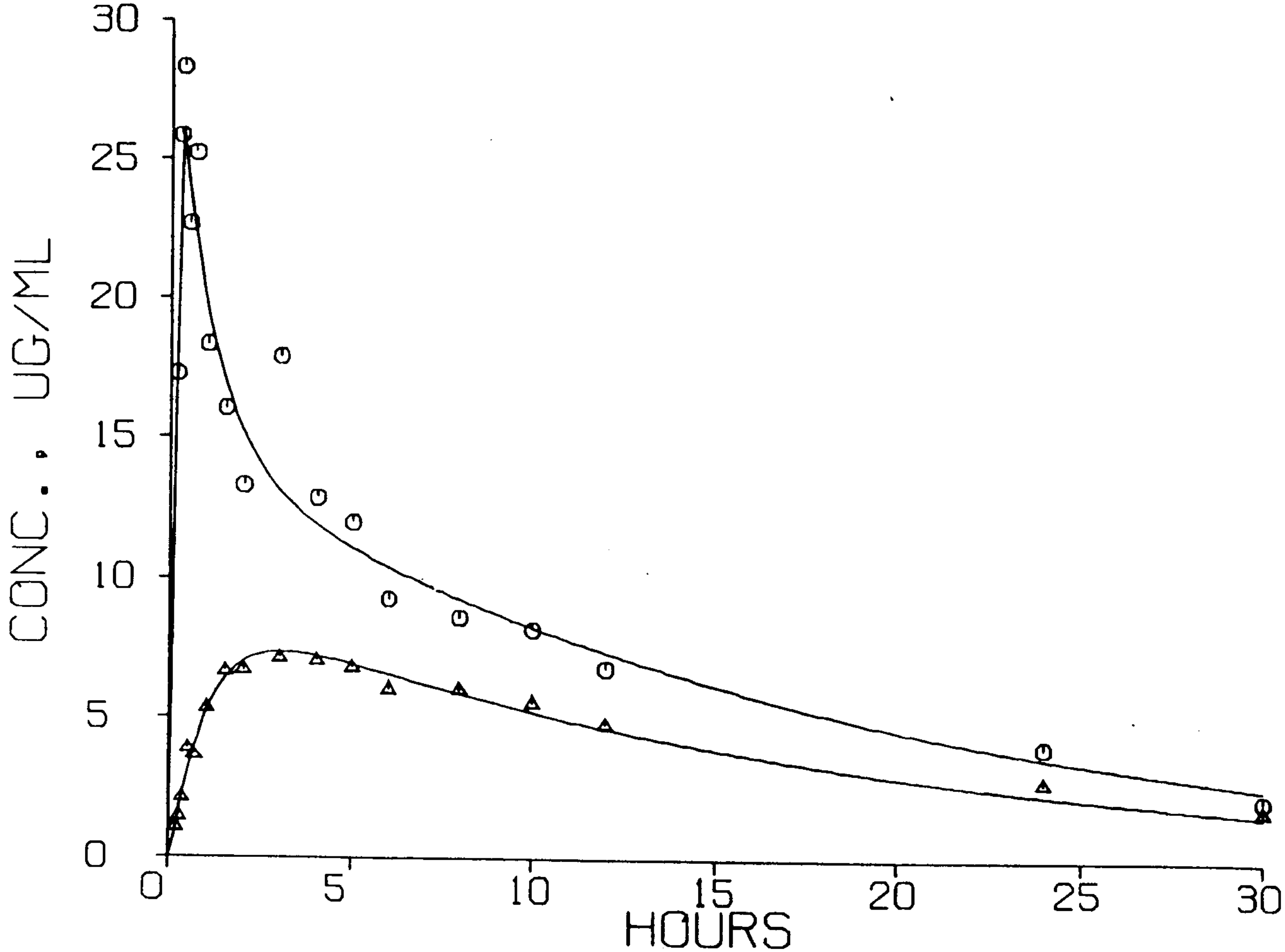


Figure G.17 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Picket Creek after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes.

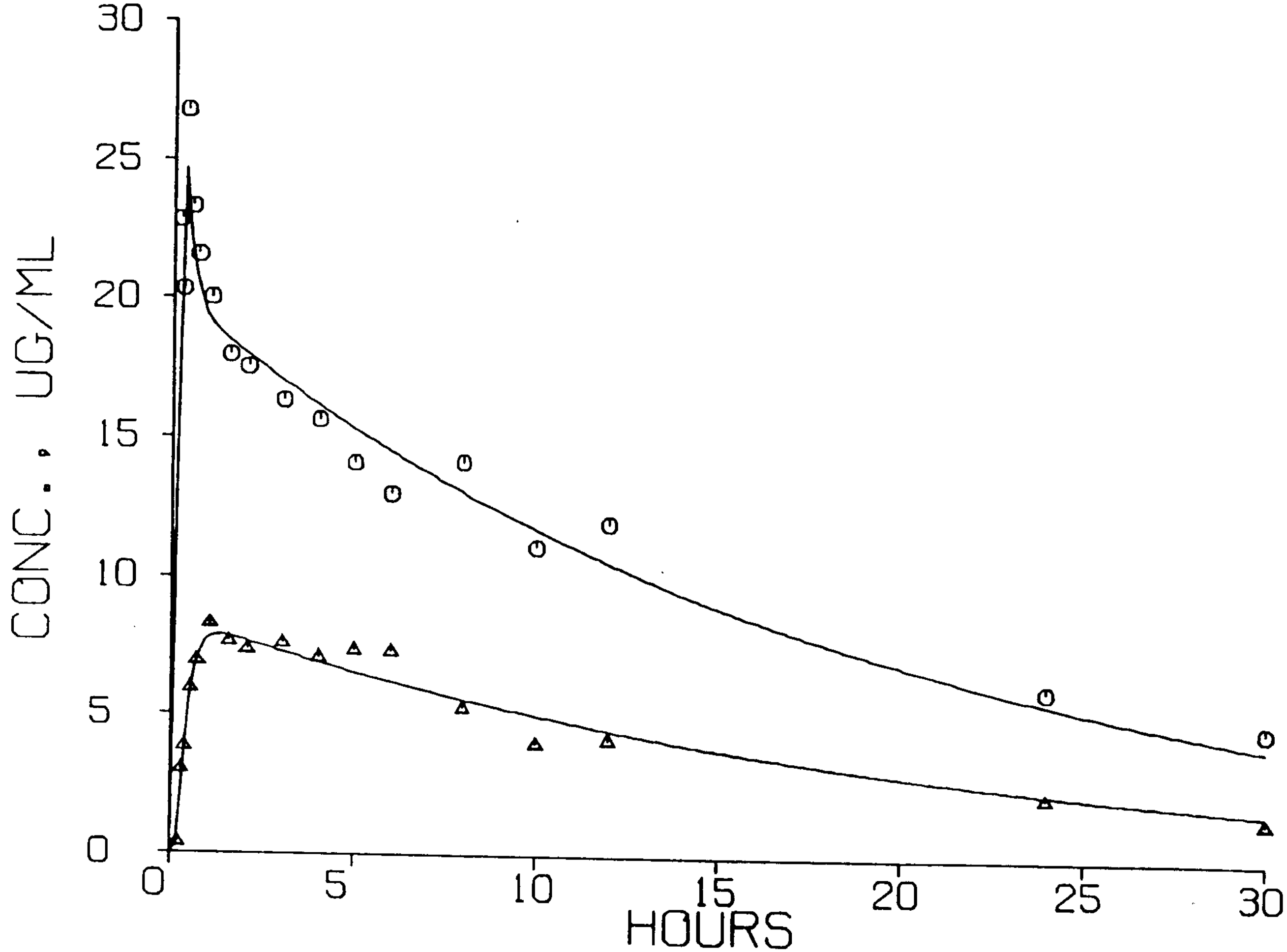


Figure G.18 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Gypsy after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes.

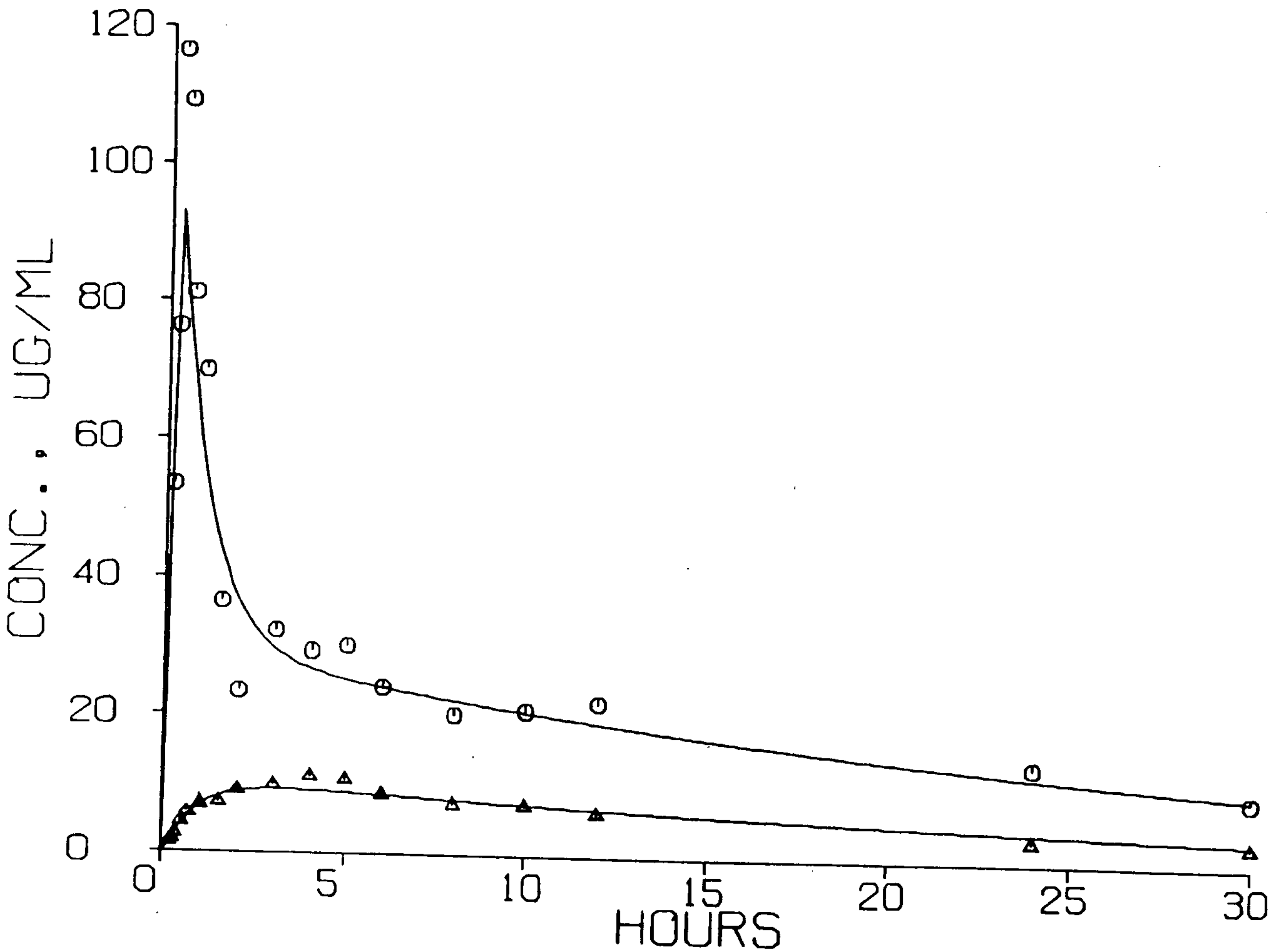


Figure G.19 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Melodee after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes.

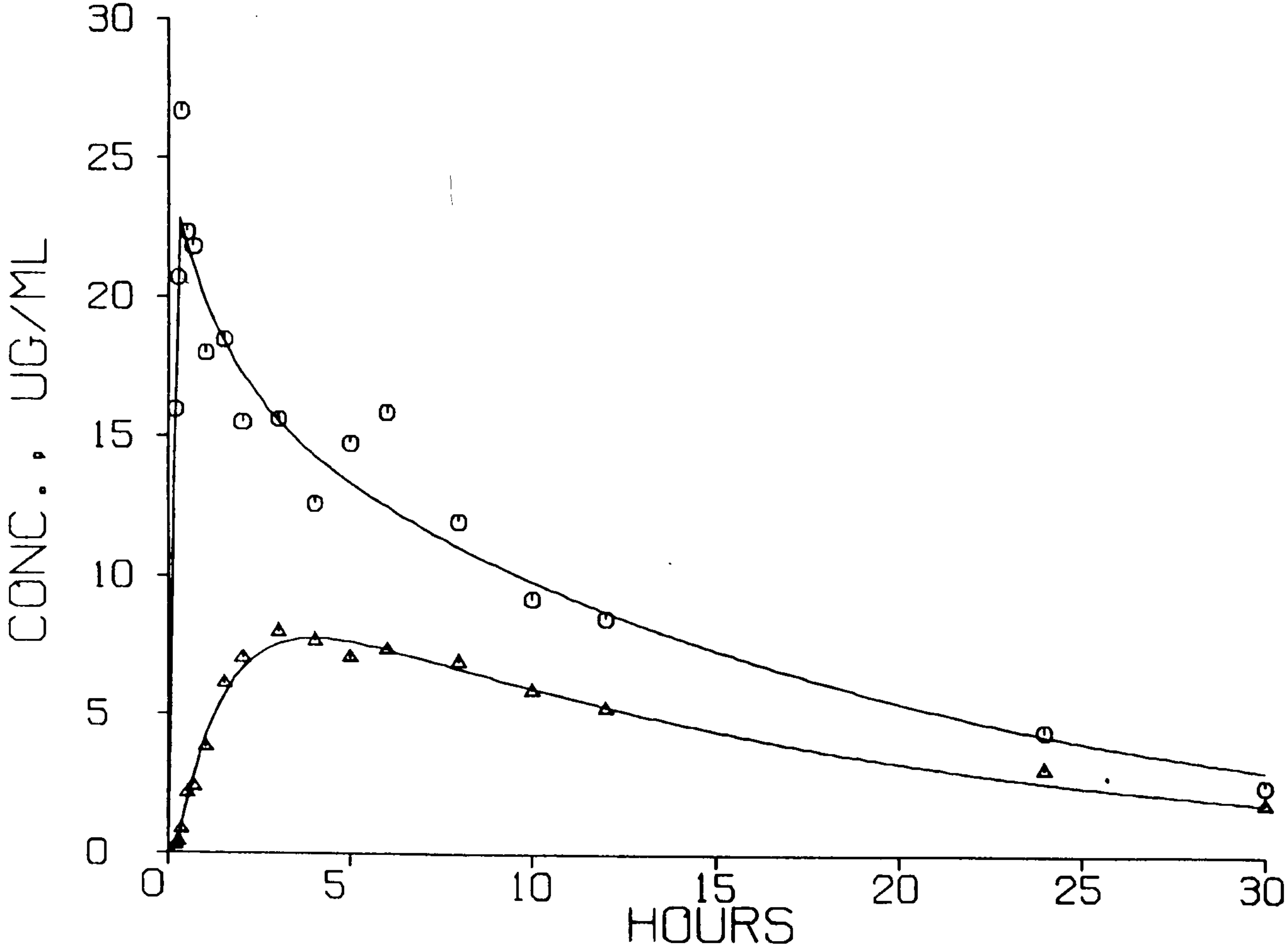


Figure G.20 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for Linda after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes.

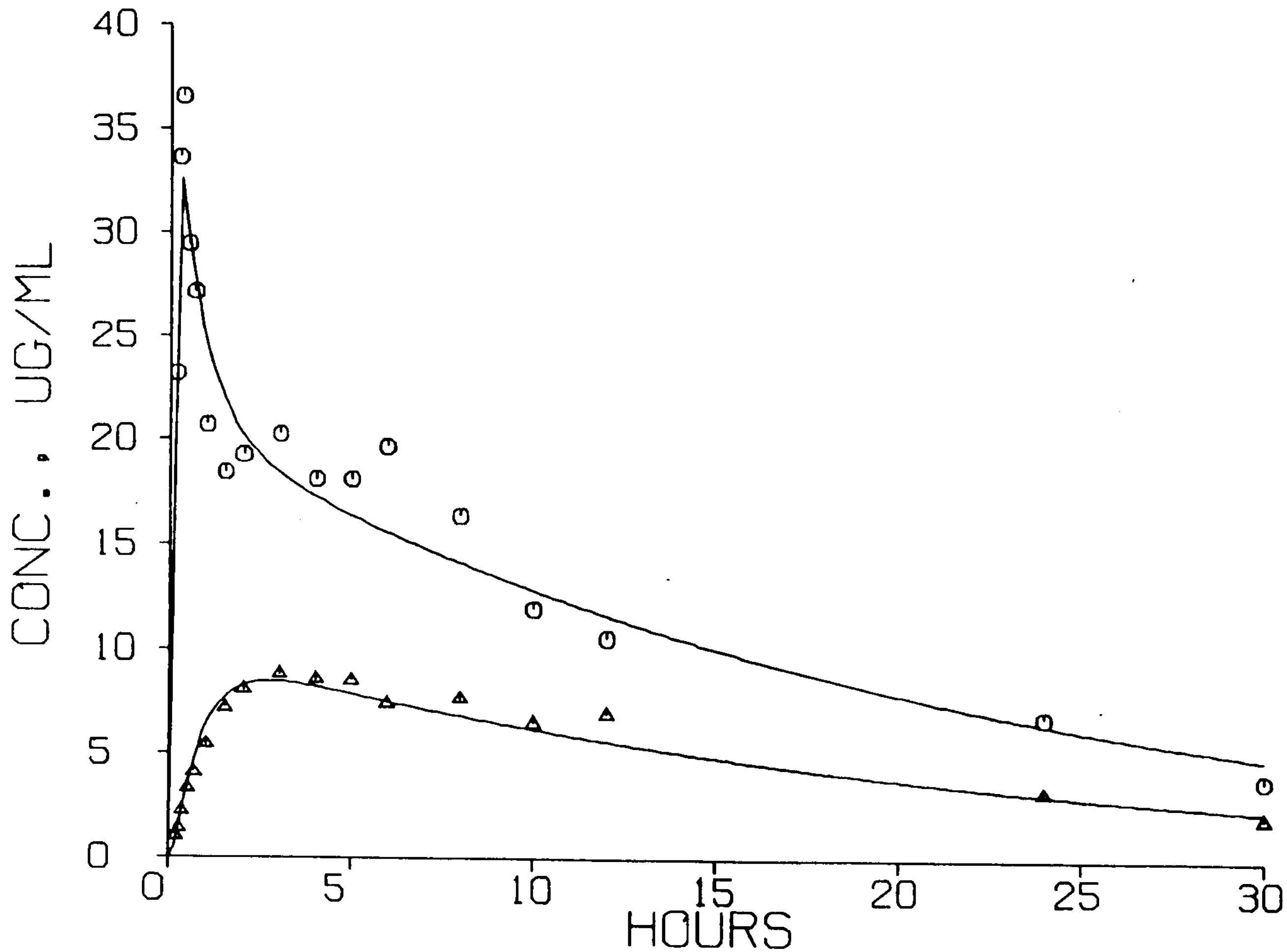


Figure G.21 Plasma and csf theophylline concentration versus time curves fitted simultaneously by FUNFIT for the average of 6 horses after the administration of aminophylline, 20 mg/Kg, infused over 15 minutes

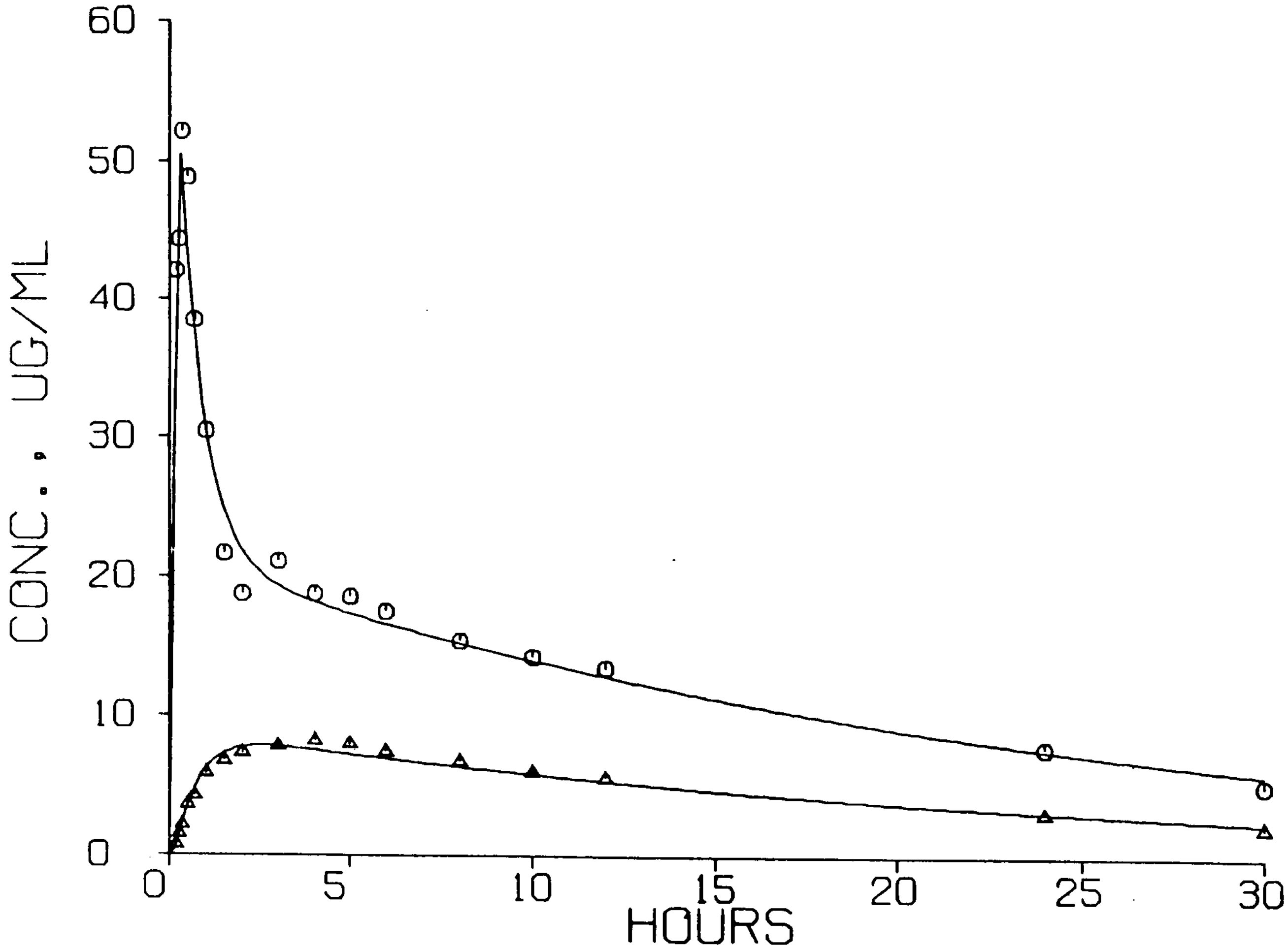


Figure G.22 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Picket Creek after the administration of dyphylline, 20 mg/Kg, iv bolus.

FITTING DYPHYLLINE IV BOLUS AT 20 mg/kg IN 2 COMPARTMENTS
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
 50.0000|
 46.8750|    O
 43.7500|    *
 40.6250|
 37.5000|    +
 34.3750|
 31.2500|     +
 28.1250|      *
 25.0000|      *
 21.8750|      O*
 18.7500|       **
 15.6250|        +*O
 12.5000|          *** O
  9.3750|             ****+*
  6.2500|                  ******+*******+**
  3.1250|                                   ******+******+**************+
   .0000|
        -+-------------+-------------+-------------+-------------+-
       .000          2.000         4.000         6.000         8.00
                                     X
```

***** SUMMARY OF NONLINEAR ESTIMATION *****

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
.1670	43.96	41.50	2.463	.3213E-02	.1762	11.91
.2500	37.42	34.95	2.466	.4435E-02	.1394	10.58
.3330	28.59	29.72	-1.131	.7597E-02	.1314	-4.755
.5000	21.43	22.12	-.6869	.1352E-01	.1259	-2.854
.6670	14.61	17.18	-2.572	.2909E-01	.1633	-11.85
1.000	14.62	11.73	2.893	.2905E-01	.1200	11.87
1.500	9.630	8.233	1.397	.6696E-01	.1171	5.700
2.000	6.850	6.564	.2862	.1323	.1291	1.198
3.000	4.180	4.607	-.4271	.3554	.1349	-1.812
4.000	3.520	3.305	.2152	.5012	.1023	.8553
5.000	2.190	2.375	-.1849	1.295	.1192	-.7573
6.000	1.750	1.707	.4312E-01	2.028	.1236	.1783
8.000	.8530	.8817	-.2874E-01	8.535	.1948	-.1518

CORRECTED SUM OF SQUARED OBSERVATIONS = 2449.35
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 49.5602
SUM OF SQUARED RESIDUALS = 31.1792
SUM OF WEIGHTED SQUARED RESIDUALS = .782749
S = .334397 **WITH** 7 **DEGREES OF FREEDOM**
CORRELATION (Y,YHAT) = .994

Figure G.23 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Picket Creek after the administration of dyphylline, 20 mg/Kg, iv bolus.

FUNCTION 2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
5.0000|          O
4.6875|
4.3750|
4.0625|       O
3.7500|        ******
3.4375|      *       ***
3.1250|     +          ***
2.8125|             O  O ***
2.5000|    O*                *****O
2.1875|    *                      ****
1.8750|                              *****
1.5625|   *                              O*****
1.2500|   O                                   ***+***   O
 .9375|                                              **********   O
 .6250|   +                                                   **********
 .3125|
 .0000|
       -+-------------+--------------+--------------+--------------+-
       .000         2.000          4.000          6.000          8.00
                                     X
```

*** SUMMARY OF NONLINEAR ESTIMATION ***

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
.1670	.5000	.4754	.2457E-01	5.302	.2611	.3286
.2500	1.150	1.366	-.2159	1.002	.1370	-.9206
.3330	2.230	2.043	.1865	.2665	.1040	.7433
.5000	2.820	2.935	-.1150	.1667	.1115	-.4644
.6670	4.000	3.402	.5979	.8284E-01	.8426E-01	2.315
1.000	4.980	3.658	1.322	.5345E-01	.6573E-01	5.014
1.500	2.630	3.386	-.7564	.1916	.1127	-3.060
2.000	2.600	2.940	-.3402	.1961	.1007	-1.349
3.000	2.270	2.132	.1383	.2572	.8700E-01	.5375
4.000	1.360	1.533	-.1732	.7166	.1112	-.6988
5.000	1.070	1.102	-.3203E-01	1.158	.1111	-.1292
6.000	1.060	.7921	.2679	1.180	.8951E-01	1.045
8.000	.7390	.4092	.3298	2.427	.8254E-01	1.274

CORRECTED SUM OF SQUARED OBSERVATIONS = 21.0035
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 5.55432
SUM OF SQUARED RESIDUALS = 3.11787
SUM OF WEIGHTED SQUARED RESIDUALS = .693043
S = .314652 WITH 7 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .927

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 34.2970
SUM OF WEIGHTED SQUARED RESIDUALS = 1.47579
S = .271642 WITH 20 DEGREES OF FREEDOM

Figure G.24 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Gypsy after the administration of dyphylline, 20 mg/Kg, iv bolus.

FUNCTION 1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
 70.0000|    O
 65.6250|    +
 61.2500|
 56.8750|    *
 52.5000|     *
 48.1250|     O*
 43.7500|      O*
 39.3750|        *+
 35.0000|         **
 30.6250|           +*
 26.2500|            ***O
 21.8750|              *****O
 17.5000|                 *****
 13.1250|                      ****+**
  8.7500|                             ****+********+
  4.3750|                                          *******+**************+
   .0000|
         -+-------------+-------------+-------------+-------------+-
        .000          2.000         4.000         6.000         8.00
                                     X
```

***** SUMMARY OF NONLINEAR ESTIMATION *****

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
.1670	68.21	62.18	6.031	.2245E-02	.4810	9.378
.2500	63.75	56.42	7.330	.2570E-02	.3818	10.37
.3330	44.15	51.43	-7.283	.5359E-02	.4293	-10.73
.5000	41.68	43.28	-1.603	.6013E-02	.3458	-2.211
.6670	35.45	37.05	-1.604	.8312E-02	.3757	-2.260
1.000	29.73	28.41	1.321	.1182E-01	.3916	1.884
1.500	23.26	20.68	2.583	.1931E-01	.3760	3.640
2.000	17.72	15.94	1.782	.3327E-01	.3883	2.534
3.000	12.95	10.15	2.799	.6228E-01	.3330	3.830
4.000	7.430	6.643	.7871	.1892	.3338	1.078
5.000	4.700	4.370	.3296	.4728	.3127	.4455
6.000	2.560	2.878	-.3183	1.594	.3964	-.4557
8.000	.9930	1.249	-.2559	10.59	.6613	-.5616

CORRECTED SUM OF SQUARED OBSERVATIONS = 6088.58
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 100.156
SUM OF SQUARED RESIDUALS = 168.616
SUM OF WEIGHTED SQUARED RESIDUALS = 2.30780
S = .574183 **WITH** 7 **DEGREES OF FREEDOM**
CORRELATION (Y,YHAT) = .987

Figure G.25 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Gypsy after the administration of dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

 4.0000|
 3.7500|                O
 3.5000|           O
 3.2500|        O
 3.0000|
 2.7500|         ******    O         O
 2.5000|     O*         ***
 2.2500|     *            ***                O         O        O
 2.0000|    *                ****
 1.7500|   *O                    ****                                    O
 1.5000|   +                         ****
 1.2500|   *                              ****
 1.0000|                                       *****
  .7500|                                             ********
  .5000|                                                     *************
  .2500|                                                                 ******
  .0000|
      -+-------------+-------------+-------------+-------------+-
      .000         2.000         4.000         6.000         8.0(
                                   X
```

*** SUMMARY OF NONLINEAR ESTIMATION ***

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZ RESIDUA
.1670	1.300	1.128	.1720	2.258	.6465	.3609
.2500	1.260	1.529	-.2686	2.403	.4768	-.4156
.3330	1.620	1.846	-.2261	1.454	.4061	-.3263
.5000	2.430	2.287	.1432	.6462	.3745	.2016
.6670	3.190	2.532	.6577	.3749	.3250	.8955
1.000	3.320	2.666	.6539	.3462	.3248	.8903
1.500	3.600	2.451	1.149	.2944	.2981	1.541
2.000	2.540	2.091	.4491	.5914	.4111	.6509
3.000	2.520	1.419	1.101	.6008	.3373	1.510
4.000	2.210	.9403	1.270	.7812	.2829	1.689
5.000	2.200	.6200	1.580	.7883	.2038	2.034
6.000	2.170	.4085	1.761	.8103	.1475	2.231
8.000	1.520	.1773	1.343	1.651	.1069	1.687

CORRECTED SUM OF SQUARED OBSERVATIONS = 6.83277
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 5.14860
SUM OF SQUARED RESIDUALS = 12.7814
SUM OF WEIGHTED SQUARED RESIDUALS = 10.5927
S = 1.23014 WITH 7 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .652

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 181.398
SUM OF WEIGHTED SQUARED RESIDUALS = 12.9005
S = .803134 WITH 20 DEGREES OF FREEDOM

Figure G.26 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Melodee after the administration of dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

   25.0000|    O
   23.4375|    *
   21.8750|    +O
   20.3125|     **
   18.7500|      *
   17.1875|      O*
   15.6250|        *
   14.0625|        O**
   12.5000|          O** O
   10.9375|              **
    9.3750|                **+*
    7.8125|                   *****
    6.2500|                        **+***
    4.6875|                              ***+******
    3.1250|                                        *+*******+**********
    1.5625|                                                            ****+
     .0000|
          -+--------------+--------------+--------------+--------------+-
          .000          2.000          4.000          6.000          8.0C
                                         X
```

*** SUMMARY OF NONLINEAR ESTIMATION ***

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
.1670	23.54	22.08	1.465	.2390E-01	.1717	5.864
.2500	21.36	20.84	.5235	.2903E-01	.1546	2.008
.3330	21.52	19.69	1.829	.2860E-01	.1274	6.652
.5000	17.04	17.64	-.5978	.4561E-01	.1226	-2.157
.6670	13.22	15.88	-2.655	.7578E-01	.1422	-9.922
1.000	12.40	13.05	-.6513	.8613E-01	.1501	-2.474
1.500	12.35	10.05	2.302	.8683E-01	.1358	8.496
2.000	8.690	8.001	.6891	.1754	.1536	2.638
3.000	5.850	5.461	.3888	.3870	.1454	1.462
4.000	3.730	3.957	-.2268	.9519	.1648	-.8916
5.000	2.660	2.951	-.2914	1.872	.1665	-1.151
6.000	2.190	2.231	-.4103E-01	2.761	.1602	-.1595
8.000	1.430	1.293	.1367	6.477	.2510	.8051

CORRECTED SUM OF SQUARED OBSERVATIONS = 743.229
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 86.6461
SUM OF SQUARED RESIDUALS = 19.6790
SUM OF WEIGHTED SQUARED RESIDUALS = 1.67761
S = .489550 WITH 7 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .987

Figure G.27 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Melodee after the administration of dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

 1.6000|
 1.5125|
 1.4250|       O
 1.3375|         O
 1.2500|             O  O        O
 1.1625|         ***********
 1.0750|       **          *****
  .9875|  OOO*                 ****
  .9000|    **                    **** O
  .8125|    *                         ****
  .7250|   *                             *****
  .6375|  *                                  *****
  .5500|  *                                    O  *****
  .4625|  O                                           +******
  .3750|                                                    ********
  .2875|                                                            *+
  .2000|
       -+---------------+---------------+---------------+---------------+-
       .000           2.000           4.000           6.000           8.00
                                    X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
.1670	.4000	.5280	-.1280	1.659	.2627	-.8475
.2500	.9120	.6266	.2854	.3192	.1018	.9998
.3330	.9210	.7132	.2078	.3130	.9642E-01	.7231
.5000	.9580	.8561	.1019	.2893	.1004	.3563
.6670	1.422	.9633	.4587	.1313	.7705E-01	1.565
1.000	1.330	1.095	.2348	.1501	.9714E-01	.8177
1.500	1.210	1.157	.5332E-01	.1813	.1120	.1893
2.000	1.230	1.126	.1044	.1755	.1034	.3666
3.000	1.170	.9552	.2148	.1939	.8698E-01	.7397
4.000	.8400	.7612	.7880E-01	.3762	.9561E-01	.2740
5.000	.5260	.5919	-.6587E-01	.9595	.1222	-.2375
6.000	.3830	.4555	-.7255E-01	1.810	.1359	-.2678
8.000	.2030	.2670	-.6405E-01	6.442	.1718	-.2565

CORRECTED SUM OF SQUARED OBSERVATIONS = 1.88288
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 1.21625
SUM OF SQUARED RESIDUALS = .496721
SUM OF WEIGHTED SQUARED RESIDUALS = .159430
S = .150916 WITH 7 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .933

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 20.1757
SUM OF WEIGHTED SQUARED RESIDUALS = 1.83704
S = .303071 WITH 20 DEGREES OF FREEDOM

Figure G.28 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Linda after the administration of dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

   25.0000|
   23.4375|     O
   21.8750|     *
   20.3125|     *
   18.7500|     O+
   17.1875|       *
   15.6250|      +*O
   14.0625|       **
   12.5000|        ***
   10.9375|          +*
    9.3750|            ***
    7.8125|              +***+
    6.2500|                  ****
    4.6875|                     ****+**
    3.1250|                           *****+*****
    1.5625|                                     ***+******+**************+
     .0000|
         -+--------------+--------------+--------------+--------------+-
         .000          2.000          4.000          6.000          8.000
                                        X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1670	23.29	21.70	1.592	.1656E-02	.2520	5.591
.2500	17.83	19.52	-1.691	.2825E-02	.2260	-5.530
.3330	18.40	17.77	.6253	.2653E-02	.1613	1.816
.5000	15.23	15.15	.8050E-01	.3872E-02	.1450	.2290
.6670	14.53	13.27	1.257	.4255E-02	.1429	3.568
1.000	9.470	10.67	-1.201	.1002E-01	.1964	-3.688
1.500	7.690	8.044	-.3544	.1519E-01	.1801	-1.058
2.000	7.320	6.150	1.170	.1676E-01	.1337	3.286
3.000	4.110	3.617	.4928	.5317E-01	.1208	1.367
4.000	2.270	2.129	.1410	.1743	.1263	.3930
5.000	1.500	1.253	.2468	.3992	.1280	.6894
6.000	.5500	.7376	-.1876	2.969	.2505	-.6558
8.000	.3100	.2555	.5445E-01	9.347	.2270	.1785

CORRECTED SUM OF SQUARED OBSERVATIONS = 714.733
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 8.58824
SUM OF SQUARED RESIDUALS = 10.6720
SUM OF WEIGHTED SQUARED RESIDUALS = .232281
S = .182162 WITH 7 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .993

Figure G.29 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Linda after the administration of dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

2.0000|
1.8750|
1.7500|       ***
1.6250|       *   +*
1.5000|       * O  ***
1.3750|              *+
1.2500|      *O       ***O
1.1250|      O          **       O      O       O
1.0000|     *             **
 .8750|     O               **                         O
 .7500|                       ***                                     O
 .6250|                         ****
 .5000|     +                      *****
 .3750|                                *******
 .2500|                                      ***********
 .1250|                                                ****************
 .0000|
        -+--------------+---------------+--------------+--------------+-
         .000          2.000           4.000          6.000          8.000
                                    X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1670	.5000	.4305	.6953E-01	3.326	.3676	.7157
.2500	.8410	.9098	-.6877E-01	1.176	.2103	-.2171
.3330	1.050	1.234	-.1838	.7542	.2201	-.5927
.5000	1.130	1.578	-.4479	.6512	.2157	-1.430
.6670	1.470	1.682	-.2120	.3848	.1568	-.6120
1.000	1.510	1.592	-.8190E-01	.3647	.1712	-.2412
1.500	1.290	1.278	.1164E-01	.4997	.2038	.3627E-01
2.000	1.173	.9893	.1837	.6043	.1884	.5562
3.000	1.090	.5835	.5065	.6999	.1291	1.416
4.000	1.080	.3435	.7365	.7129	.8401E-01	1.986
5.000	1.050	.2022	.8478	.7542	.5675E-01	2.255
6.000	.7790	.1190	.6600	1.370	.5056E-01	1.751
8.000	.6990	.4123E-01	.6578	1.702	.2444E-01	1.733

CORRECTED SUM OF SQUARED OBSERVATIONS = 1.01244
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 1.10673
SUM OF SQUARED RESIDUALS = 2.71564
SUM OF WEIGHTED SQUARED RESIDUALS = 2.65968
S = .616405 WITH 7 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .745

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 13.3876
SUM OF WEIGHTED SQUARED RESIDUALS = 2.89196
S = .380261 WITH 20 DEGREES OF FREEDOM

Figure G.30 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Taylor Lock after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

   70.0000|    O
   65.6250|    *
   61.2500|
   56.8750|
   52.5000|
   48.1250|
   43.7500|
   39.3750|    *
   35.0000|
   30.6250|
   26.2500|    O*
   21.8750|     *
   17.5000|      *O
   13.1250|        ***+****
    8.7500|               O ****+*****+**** O
    4.3750|                                 *******+*****+***********+
     .0000|
          -+-----------+-----------+-----------+-----------+-----------+-
          .000       2.000       4.000       6.000       8.000      10.0(
                                   X
```

FUNCTION 1

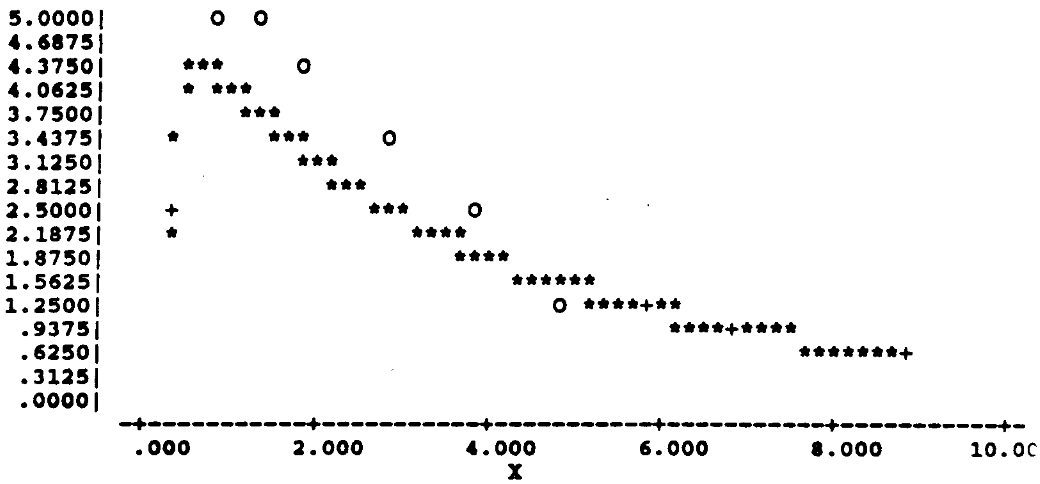
X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZ: RESIDUA:
.1700	68.12	65.40	2.718	.2367E-02	.3624	55.57
.3330	23.24	25.13	-1.894	.2033E-01	.3543	-20.85
.6670	15.97	13.07	2.897	.4306E-01	.1533	8.724
1.170	10.67	10.93	-.2562	.9646E-01	.1856	-.8131
1.670	8.530	9.513	-.9832	.1509	.1856	-3.120
2.670	7.470	7.218	.2516	.1968	.1361	.7411
3.670	5.680	5.477	.2028	.3404	.1218	.5880
4.670	4.770	4.156	.6140	.4827	.1104	1.761
5.670	2.950	3.154	-.2035	1.262	.1518	-.6116
6.670	2.400	2.393	.7175E-02	1.907	.1675	.2207E-(
8.670	1.300	1.378	-.7767E-01	6.498	.2514	-.2924

CORRECTED SUM OF SQUARED OBSERVATIONS = 3673.49
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 58.9199
SUM OF SQUARED RESIDUALS = 20.9277
SUM OF WEIGHTED SQUARED RESIDUALS = .903979
S = .425201 WITH 5 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .998

Figure G.31 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Taylor Lock after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

FUNCTION 2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed



FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAI
.1670	2.240	2.027	.2130	.3193	.3610	3.639
.3330	2.460	3.982	-1.522	.2647	.2120	-5.106
.6670	4.720	4.151	.5686	.7190E-01	.1154	1.638
1.170	4.940	3.637	1.303	.6564E-01	.9539E-01	3.690
1.670	4.270	3.168	1.102	.8786E-01	.9465E-01	3.118
2.670	3.390	2.404	.9858	.1394	.8876E-01	2.779
3.670	2.500	1.824	.6758	.2563	.9126E-01	1.908
4.670	1.180	1.384	-.2042	1.150	.1493	-.6116
5.670	1.150	1.050	.9969E-01	1.211	.1203	.2886
6.670	.8300	.7970	.3304E-01	2.325	.1325	.9694E-(
8.670	.5600	.4588	.1012	5.108	.1275	.2951

CORRECTED SUM OF SQUARED OBSERVATIONS = 24.9438
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 6.50175
SUM OF SQUARED RESIDUALS = 7.08689
SUM OF WEIGHTED SQUARED RESIDUALS = 1.23611
S = .497215 WITH 5 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .871

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 28.0146
SUM OF WEIGHTED SQUARED RESIDUALS = 2.14009
S = .365726 WITH 16 DEGREES OF FREEDOM

Figure G.32 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Picket Creek after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

  40.0000|
  37.5000|    O
  35.0000|    *
  32.5000|
  30.0000|
  27.5000|     *
  25.0000|
  22.5000|     *
  20.0000|
  17.5000|     O* O
  15.0000|       ****
  12.5000|          ***+***+
  10.0000|                  ********+**
   7.5000|                             ******+********
   5.0000|                                            *+*******+********+
   2.5000|
    .0000|
          ---+--------+--------+--------+--------+--------+--------+--------+---
           .000    1.000    2.000    3.000    4.000    5.000    6.000    7.000
                                         X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARDIZE RESIDUAL
.1700	35.51	34.41	1.099	.2764E-01	.7400	16.50
.3300	17.40	18.83	-1.431	.1151	.7261	-9.088
.6700	16.31	13.20	3.111	.1310	.3436	4.722
1.170	12.42	11.49	.9263	.2259	.3930	1.469
1.670	10.47	10.18	.2893	.3179	.3656	.4474
2.670	7.670	7.991	-.3210	.5925	.3094	-.4752
3.670	5.590	6.272	-.6823	1.115	.3020	-1.005
4.670	4.970	4.923	.4674E-01	1.411	.3039	.6894E-0
5.670	3.620	3.864	-.2444	2.660	.4177	-.3977
6.670	3.200	3.033	.1668	3.404	.4734	.2912

CORRECTED SUM OF SQUARED OBSERVATIONS = 859.089
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 102.831
SUM OF SQUARED RESIDUALS = 14.5326
SUM OF WEIGHTED SQUARED RESIDUALS = 2.59433
S = .805346 WITH 4 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .992

Figure G.33 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN^R and corresponding computer data output for Picket Creek after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

 2.5000|       .
 2.3438|      **                                                        O
 2.1875|      * **
 2.0313|     *   **  O     O
 1.8750|         O**            O
 1.7188|       O    ***
 1.5625|              ***            O     O
 1.4063|     +           ***
 1.2500|                    ***                  O
 1.0938|                       ****
  .9375|                           *****
  .7813|                               ******
  .6250|                                     *******
  .4688|                                            ***********
  .3125|
  .1563|
  .0000|
        -+-----------+-----------+-----------+-----------+-----------+-
        .000        2.000       4.000       6.000       8.000       10.0
                                  X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
8.670	2.240	.3151	1.925	.5035	.5567E-01	2.598
.1670	1.320	1.342	-.2203E-01	1.450	.7312	-.1675
.3330	1.390	2.116	-.7259	1.308	.4139	-1.177
.6670	1.670	2.175	-.5053	.9058	.3712	-.7851
1.170	1.800	1.937	-.1372	.7797	.3094	-.2031
1.670	1.890	1.716	.1736	.7072	.2615	.2496
2.670	1.970	1.347	.6227	.6509	.1998	.8702
3.670	1.800	1.057	.7425	.7797	.1767	1.029
4.670	1.540	.8300	.7100	1.065	.1690	.9813
5.670	1.480	.6515	.8285	1.153	.1452	1.137
6.670	1.220	.5114	.7086	1.697	.1464	.9728

CORRECTED SUM OF SQUARED OBSERVATIONS = .953273
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = .845056
SUM OF SQUARED RESIDUALS = 7.16874
SUM OF WEIGHTED SQUARED RESIDUALS = 5.68558
S = 1.06636 WITH 5 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = ********

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 21.7013
SUM OF WEIGHTED SQUARED RESIDUALS = 8.27991
S = .742963 WITH 15 DEGREES OF FREEDOM

Figure G.34 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Gypsy after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

 140.0000|
 131.2500|    O
 122.5000|    *
 113.7500|
 105.0000|
  96.2500|
  87.5000|
  78.7500|
  70.0000|     *
  61.2500|
  52.5000|
  43.7500|     *
  35.0000|     O*
  26.2500|      **O    O
  17.5000|       **********+********
   8.7500|                         +********+********+*******+*********+
    .0000|
          ---+-------+-------+-------+-------+-------+-------+-------+---
            .000   1.000   2.000   3.000   4.000   5.000   6.000   7.000
                                     X
```

FUNCTION 1

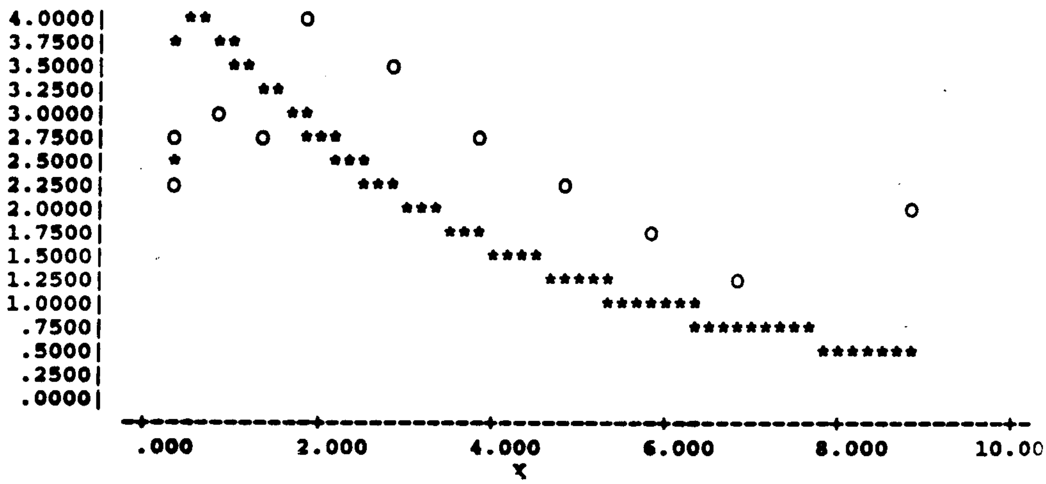
X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZ RESIDUA
.1700	123.4	122.0	1.463	.2096E-02	1.002	31.14
.3330	30.27	31.72	-1.452	.3484E-01	.9990	-15.11
.6670	22.89	15.69	7.198	.6093E-01	.4237	7.912
1.170	17.96	13.34	4.620	.9897E-01	.4339	5.105
1.670	10.80	11.55	-.7460	.2737	.5511	-.8894
2.670	8.180	8.650	-.4702	.4771	.4293	-.5184
3.670	5.540	6.481	-.9408	1.040	.4239	-1.034
4.670	4.680	4.855	-.1754	1.458	.4217	-.1926
5.670	3.470	3.638	-.1677	2.651	.5411	-.1984
6.670	2.860	2.725	.1347	3.903	.6284	.1721

CORRECTED SUM OF SQUARED OBSERVATIONS = 11958.4
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 123.075
SUM OF SQUARED RESIDUALS = 79.1407
SUM OF WEIGHTED SQUARED RESIDUALS = 6.71580
S = 1.29574 WITH 4 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .997

Figure G.35 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Gypsy after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

FUNCTION 2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed



FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
8.670	1.920	.3728	1.547	1.128	.1154	1.552
.1670	2.190	2.321	-.1307	.8669	.9991	-1.376
.3330	2.690	3.864	-1.174	.5746	.5180	-1.365
.6670	2.820	3.754	-.9339	.5228	.5009	-1.074
1.170	2.550	3.251	-.7007	.6394	.4749	-.7926
1.670	3.940	2.814	1.126	.2678	.2650	1.164
2.670	3.450	2.108	1.342	.3493	.2304	1.374
3.670	2.690	1.579	1.111	.5746	.2315	1.137
4.670	2.220	1.183	1.037	.8436	.2245	1.060
5.670	1.730	.8865	.8435	1.389	.2338	.8643
6.670	1.040	.6642	.3758	3.844	.3178	.3948

CORRECTED SUM OF SQUARED OBSERVATIONS = 6.38245
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 6.42554
SUM OF SQUARED RESIDUALS = 11.3817
SUM OF WEIGHTED SQUARED RESIDUALS = 8.39157
S = 1.29550 WITH 5 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .613

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 90.5224
SUM OF WEIGHTED SQUARED RESIDUALS = 15.1074
S = 1.00357 WITH 15 DEGREES OF FREEDOM

Figure G.36 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Melodee after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

FUNCTION 1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
50.0000|
46.8750|    O
43.7500|
40.6250|
37.5000|    *
34.3750|
31.2500|     *
28.1250|
25.0000|     *
21.8750|     O*
18.7500|      **O
15.6250|       **
12.5000|         *****
 9.3750|              +****+*********+
 6.2500|                               ********+*********+***
 3.1250|                                                        *****+*********+
  .0000|
        ---+---------+---------+---------+---------+---------+---------+---------+---
         .000      1.000     2.000     3.000     4.000     5.000     6.000     7.000
                                         X
```

FUNCTION 1

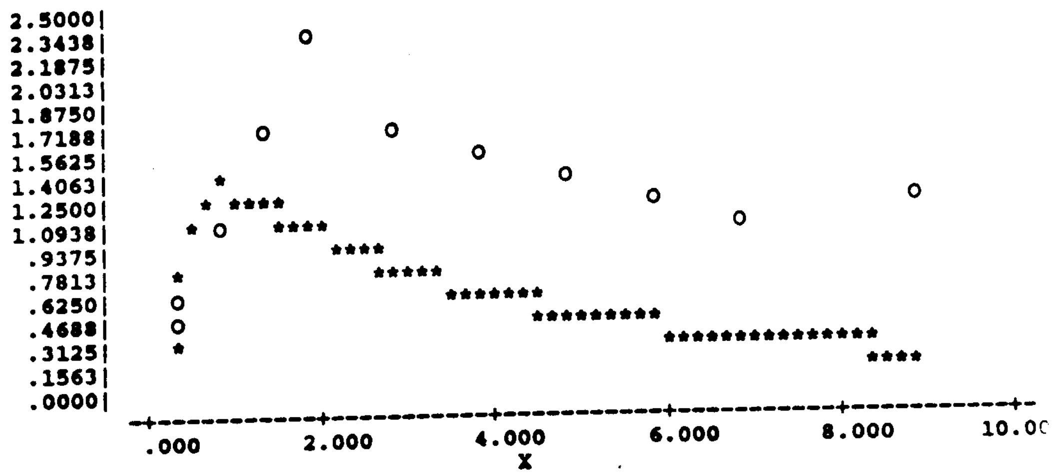
X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZI RESIDUAI
.1700	45.00	36.88	8.117	.8123E-02	.6160	31.14
.3300	18.81	23.00	-4.188	.4649E-01	.5840	-12.84
.6670	18.33	13.01	5.324	.[illegible]895E-01	.3801	9.674
1.170	8.900	9.672	-.7716	.2077	.4129	-1.466
1.670	7.940	8.258	-.3183	.2609	.3879	-.5842
2.670	7.960	6.203	1.757	.2596	.2325	2.802
3.670	4.300	4.666	-.3663	.8896	.2788	-.6025
4.670	3.560	3.511	.4948E-01	1.298	.2741	.8110E-(
5.670	2.750	2.641	.1090	2.175	.3365	.1885
6.670	1.850	1.987	-.1369	4.806	.4834	-.2961

CORRECTED SUM OF SQUARED OBSERVATIONS = 1536.93
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 65.6293
SUM OF SQUARED RESIDUALS = 115.721
SUM OF WEIGHTED SQUARED RESIDUALS = 3.92817
S = .990980 WITH 4 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .973

Figure G.37 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Melodee after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

FUNCTION 2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed



FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZI RESIDUAL
8.670	1.150	.1389	1.011	.5101	.4824E-01	1.516
.1670	.3700	.2818	.8817E-01	4.928	.6554	.6611
.3330	.5200	.9303	-.4103	2.495	.4860	-.8928
.6670	1.000	1.249	-.2491	.6746	.3655	-.4446
1.170	1.620	1.166	.4543	.2571	.2271	.7221
1.670	2.200	1.018	1.182	.1394	.1491	1.813
2.670	1.680	.7663	.9137	.2390	.1499	1.402
3.670	1.500	.5765	.9235	.2998	.1292	1.407
4.670	1.300	.4337	.8663	.3992	.1153	1.315
5.670	1.200	.3263	.8737	.4685	.9705E-01	1.320
6.670	1.070	.2455	.8245	.5893	.8482E-01	1.243

CORRECTED SUM OF SQUARED OBSERVATIONS = 2.70222
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 2.07559
SUM OF SQUARED RESIDUALS = 6.74552
SUM OF WEIGHTED SQUARED RESIDUALS = 2.78255
S = .745996 WITH 5 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .326

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 122.467
SUM OF WEIGHTED SQUARED RESIDUALS = 6.71072
S = .668866 WITH 15 DEGREES OF FREEDOM

Figure G.38 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Linda after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

  50.0000|     O
  46.8750|
  43.7500|
  40.6250|
  37.5000|
  34.3750|     *
  31.2500|      *
  28.1250|      **
  25.0000|      O*
  21.8750|       *
  18.7500|        *
  15.6250|        O***
  12.5000|          **+
   9.3750|             ***+***
   6.2500|                   *****+********+******* O
   3.1250|                                          ********+********+
    .0000|
          --+-------+-------+-------+-------+-------+-------+-------+---
          .000   1.000   2.000   3.000   4.000   5.000   6.000   7.000
                                   X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARDIZE[D] RESIDUAL
.1700	48.38	33.22	15.16	.5926E-02	.2850	39.31
.3330	23.67	26.28	-2.613	.2476E-01	.3424	-7.778
.6670	14.63	17.10	-2.472	.6480E-01	.2979	-6.577
1.170	11.15	10.33	.8236	.1116	.2856	2.137
1.670	7.570	7.334	.2358	.2420	.2819	.6076
2.670	5.340	4.939	.4009	.4864	.2500	.9794
3.670	3.930	3.831	.9876E-01	.8980	.2435	.2390
4.670	3.370	3.063	.3067	1.221	.2028	.7055
5.670	2.450	2.464	-.1370E-01	2.311	.2414	-.3306E-0
6.670	1.730	1.984	-.2536	4.634	.3502	-.7740

CORRECTED SUM OF SQUARED OBSERVATIONS = 1867.10
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 55.6528
SUM OF SQUARED RESIDUALS = 243.951
SUM OF WEIGHTED SQUARED RESIDUALS = 2.51727
S = .793296 WITH 4 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .956

Figure G.39 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Linda after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

FUNCTION 2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
2.5000|        *****O
2.3750|       **  ***
2.2500|      **      **  O
2.1250|      *         **
2.0000|     *   O        **
1.8750|     *              **  O
1.7500|                      **
1.6250|    *                   **    O
1.5000|      O                   ***
1.3750|    *                        ***    O
1.2500|   O                           ****
1.1250|   *                              ****                O
1.0000|   O                                 ******O
 .8750|                                         *****
 .7500|   *                                         ******
 .6250|                                                  *****
 .5000|
      -+-----------+-----------+-----------+-----------+-----------+-
      .000       2.000       4.000       6.000       8.000       10.0
                                    X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
8.670	1.030	.5542	.4758	1.594	.1668	1.058
.1670	.8900	.7163	.1737	2.135	.4307	.8229
.3330	1.140	1.340	-.1998	1.301	.2598	-.4955
.6670	1.500	2.054	-.5537	.7517	.2612	-1.377
1.170	1.970	2.393	-.4226	.4358	.2220	-.9940
1.670	2.420	2.360	.6043E-01	.2888	.1713	.1349
2.670	2.250	2.007	.2434	.3341	.1549	.5361
3.670	1.820	1.632	.1879	.5106	.1625	.4163
4.670	1.530	1.317	.2131	.7225	.1690	.4748
5.670	1.320	1.061	.2591	.9706	.1754	.5803
6.670	.9300	.8545	.7552E-01	1.955	.2254	.1784

CORRECTED SUM OF SQUARED OBSERVATIONS = 2.80482
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 1.79727
SUM OF SQUARED RESIDUALS = .998082
SUM OF WEIGHTED SQUARED RESIDUALS = .933503
S = .432089 **WITH** 5 **DEGREES OF FREEDOM**
CORRELATION (Y,YHAT) = .882

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 244.949
SUM OF WEIGHTED SQUARED RESIDUALS = 3.45078
S = .479637 **WITH** 15 **DEGREES OF FREEDOM**

Figure G.40 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Moon Mist after the administration of dyphylline, 40 mg/Kg, iv bolus.

FUNCTION 1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
 250.0000|
 234.3750|    O
 218.7500|
 203.1250|
 187.5000|
 171.8750|    *
 156.2500|
 140.6250|
 125.0000|
 109.3750|    O
  93.7500|    *
  78.1250|
  62.5000|    O*
  46.8750|     +*O
  31.2500|      **+**+**+******
  15.6250|                   O*****+*****+*****+**********+**********+
    .0000|
        -+---------+----------+----------+----------+----------+-
       .000      2.000      4.000      6.000      8.000      10.00
                              X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
.1700	230.0	170.1	59.95	.1249E-02	.6349	131.0
.2500	94.84	100.3	-5.501	.7344E-02	.5085	-9.247
.3330	57.47	64.13	-6.660	.2000E-01	.5624	-12.24
.5000	37.04	36.90	.1353	.4815E-01	.4824	.2195
.6670	34.42	29.56	4.863	.5576E-01	.3060	6.752
1.000	27.07	25.54	1.531	.9015E-01	.3585	2.201
1.500	21.50	22.44	-.9436	.1429	.3758	-1.375
2.000	22.93	19.81	3.124	.1256	.2846	4.286
3.000	15.00	15.43	-.4251	.2936	.2883	-.5843
4.000	10.29	12.01	-1.724	.6239	.2986	-2.383
5.000	9.050	9.357	-.3065	.8066	.2716	-.4176
6.000	7.600	7.287	.3129	1.144	.2867	.4296
8.000	4.030	4.420	-.3902	4.067	.4659	-.6206
10.00	3.170	2.681	.4888	6.574	.4920	.8032

CORRECTED SUM OF SQUARED OBSERVATIONS = 46404.1
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 487.183
SUM OF SQUARED RESIDUALS = 3708.54
SUM OF WEIGHTED SQUARED RESIDUALS = 12.7653
S = 1.26320 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .983

Figure G.41 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Moon Mist after the administration of dyphylline, 40 mg/Kg, iv bolus.

```
FUNCTION   2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

 2.5000|
 2.3438|
 2.1875|     * O O
 2.0313|    **+*    O    O
 1.8750|   *O   **
 1.7188|   O     **
 1.5625|           ***        O
 1.4063|   O        ****
 1.2500|   *           ****
 1.0938|                  ****     O
  .9375|   O                 *****
  .7813|                        ******
  .6250|                             ***+***     O
  .4688|                                   **********      O
  .3125|                                          ************
  .1563|
  .0000|
         -+---------+---------+---------+---------+---------+-
         .000      2.000     4.000     6.000     8.000     10.00
                               X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
.1670	.8330	1.100	-.2672	.9354	.7495	-1.187
.2500	1.320	1.659	-.3392	.3725	.3039	-.4703
.3330	1.620	1.910	-.2896	.2473	.2779	-.3959
.5000	1.860	2.037	-.1765	.1876	.2842	-.2421
.6670	1.900	2.002	-.1019	.1798	.2812	-.1395
1.000	2.160	1.856	.3042	.1391	.2312	.4068
1.500	2.160	1.639	.5214	.1391	.2042	.6902
2.000	1.910	1.446	.4639	.1779	.2037	.6140
3.000	1.930	1.126	.8037	.1742	.1571	1.048
4.000	1.430	.8772	.5528	.3174	.1653	.7227
5.000	.9440	.6832	.2608	.7283	.1956	.3442
6.000	.5870	.5321	.5493E-01	1.884	.2459	.7394E-0
8.000	.5730	.3227	.2503	1.977	.1544	.3262
10.00	.3150	.1958	.1192	6.541	.1729	.1562

CORRECTED SUM OF SQUARED OBSERVATIONS = 5.26481
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 3.19839
SUM OF SQUARED RESIDUALS = 1.99100
SUM OF WEIGHTED SQUARED RESIDUALS = .708663
S = .297629 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .843

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 3710.53
SUM OF WEIGHTED SQUARED RESIDUALS = 13.4740
S = .782595 WITH 22 DEGREES OF FREEDOM

Figure G.42 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN^{R} and corresponding computer data output for Taylor Lock after the administration of dyphylline, 40 mg/Kg, iv bolus.

FUNCTION 1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
50.0000|     O
46.8750|     *
43.7500|
40.6250|     +
37.5000|     O*
34.3750|      *
31.2500|      O*
28.1250|       *+
25.0000|        +
21.8750|          ***
18.7500|            +**+
15.6250|                *****O
12.5000|                    *******
 9.3750|                           +*****+**
 6.2500|                                   ***+************
 3.1250|                                                   +***********+
  .0000|
        -+-----------+-----------+-----------+-----------+-----------+-
        .000       2.000       4.000       6.000       8.000       10.00
                                 X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
.1700	46.98	43.84	3.136	.1410E-01	.3152	9.098
.2500	39.02	39.75	-.7277	.2044E-01	.2610	-1.879
.3330	35.71	36.23	-.5222	.2440E-01	.2179	-1.264
.5000	29.61	30.86	-1.254	.3549E-01	.2261	-3.069
.6670	25.84	27.09	-1.251	.4660E-01	.2477	-3.159
1.000	24.13	22.30	1.834	.5344E-01	.2116	4.404
1.500	17.63	18.24	-.6077	.1001	.2133	-1.463
2.000	17.11	15.59	1.520	.1063	.1872	3.551
3.000	13.68	11.77	1.915	.1663	.1666	4.388
4.000	7.890	8.943	-1.053	.4998	.2001	-2.495
5.000	7.210	6.802	.4078	.5986	.1614	.9304
6.000	4.790	5.174	-.3841	1.356	.1954	-.9055
8.000	2.650	2.994	-.3438	4.431	.2678	-.8983
10.00	2.180	1.732	.4478	6.547	.2533	1.141

CORRECTED SUM OF SQUARED OBSERVATIONS = 2691.85
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 238.715
SUM OF SQUARED RESIDUALS = 25.2214
SUM OF WEIGHTED SQUARED RESIDUALS = 4.04689
S = .711239 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .995

Figure G.43 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Taylor Lock after the administration of dyphylline, 40 mg/Kg, iv bolus.

```
FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

  12.0000|        O
  11.2500|       *** O
  10.5000|      *O ***
   9.7500|     *     ***
   9.0000|     +       +*
   8.2500|    +          *** O
   7.5000|    O            ***
   6.7500|    *               **
   6.0000|                      ***
   5.2500|                         +***
   4.5000|                            *****
   3.7500|                               O ****+
   3.0000|                                    *******
   2.2500|                                           *****+***
   1.5000|                                                    ********+
    .7500|
    .0000|
          -+-----------+-----------+-----------+-----------+-----------+-
          .000       2.000       4.000       6.000       8.000       10.00
                                   X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1670	6.820	6.373	.4472	.1645	.3753	1.608
.2500	7.830	7.654	.1759	.1248	.2350	.4357
.3330	7.850	8.622	-.7723	.1242	.2168	-1.867
.5000	8.900	9.867	-.9668	.9662E-01	.2144	-2.330
.6670	10.20	10.47	-.2672	.7356E-01	.1955	-.6299
1.000	11.73	10.61	1.116	.5562E-01	.1571	2.537
1.500	11.15	9.782	1.368	.6156E-01	.1415	3.073
2.000	8.840	8.669	.1710	.9794E-01	.1565	.3886
3.000	7.830	6.635	1.195	.1248	.1337	2.671
4.000	4.590	5.050	-.4596	.3633	.1727	-1.059
5.000	3.580	3.841	-.2612	.5972	.1714	-.6013
6.000	3.180	2.922	.2581	.7568	.1530	.5849
8.000	1.662	1.691	-.2862E-01	2.771	.1936	-.6733E-01
10.00	.9440	.9782	-.3420E-01	8.588	.2320	-.8436E-01

```
CORRECTED SUM OF SQUARED OBSERVATIONS =  155.632
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS =  55.8782
SUM OF SQUARED RESIDUALS =            6.75490
SUM OF WEIGHTED SQUARED RESIDUALS =  .752222
S =  .306640      WITH      8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .979

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS =            31.9762
SUM OF WEIGHTED SQUARED RESIDUALS =  4.79911
S =  .467056      WITH     22 DEGREES OF FREEDOM
```

Figure G.44 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Picket Creek after the administration of dyphylline, 40 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

   25.0000|
   23.4375|
   21.8750|        O
   20.3125|   O+*+
   18.7500|   +    ****  O
   17.1875|   O       +***
   15.6250|              ***
   14.0625|                 ***
   12.5000|                    +***
   10.9375|                        **+*
    9.3750|                           *****
    7.8125|                                ******
    6.2500|                                O    *+*******
    4.6875|                                            ******+****
    3.1250|                                                      ********+
    1.5625|
     .0000|
          -+-----------+-----------+-----------+-----------+-----------+-
          .000       2.000       4.000       6.000       8.000       10.00
                                   X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZE RESIDUAL
.1670	20.16	18.38	1.783	.1057	.4145	3.057
.2500	18.52	18.65	-.1344	.1253	.3757	-.2206
.3330	16.44	18.84	-2.404	.1590	.3617	-3.892
.5000	19.66	19.01	.6544	.1112	.2465	.9740
.6670	18.89	18.94	-.5091E-01	.1204	.2413	-.7556E-0
1.000	21.34	18.37	2.972	.9436E-01	.2232	4.371
1.500	16.22	16.94	-.7172	.1633	.3065	-1.109
2.000	18.15	15.29	2.858	.1304	.2601	4.286
3.000	11.60	12.16	-.5618	.3193	.3118	-.8721
4.000	9.600	9.569	.3054E-01	.4663	.2671	.4600E-C
5.000	6.200	7.510	-1.310	1.118	.3069	-2.027
6.000	5.940	5.891	.4938E-01	1.218	.2672	.7438E-0
8.000	3.940	3.623	.3174	2.768	.3479	.5076
10.00	2.460	2.228	.2324	7.101	.4848	.4414

CORRECTED SUM OF SQUARED OBSERVATIONS = 578.222
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 258.794
SUM OF SQUARED RESIDUALS = 29.1132
SUM OF WEIGHTED SQUARED RESIDUALS = 5.97389
S = .864139 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .976

Figure G.45 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN^{R} and corresponding computer data output for Picket Creek after the administration of dyphylline, 40 mg/Kg, iv bolus.

```
FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

    12.0000|         O  O
    11.2500|        O   *  O
    10.5000|         *** ****
     9.7500|        **      ***
     9.0000|       *          ***
     8.2500|      O*             O**   O
     7.5000|      *                 ***
     6.7500|                           ***
     6.0000|      *                       ***+
     5.2500|                                 ****
     4.5000|    +                                *****
     3.7500|    +                                 O   *****
     3.0000|    *                                          ****+**
     2.2500|                                                      **********
     1.5000|                                                               O
      .7500|
      .0000|
           -+-----------+-----------+-----------+-----------+-----------+-
          .000        2.000       4.000       6.000       8.000       10.0
                                    X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1670	3.530	2.698	.8317	1.030	.6018	2.147
.2500	3.700	4.155	-.4552	.9375	.4029	-.7696
.3330	4.110	5.389	-1.279	.7598	.4279	-2.230
.5000	8.140	7.311	.8290	.1937	.3277	1.303
.6670	10.68	8.641	2.039	.1125	.2930	3.124
1.000	12.00	10.08	1.923	.8913E-01	.2618	2.887
1.500	11.88	10.50	1.382	.9094E-01	.2268	2.036
2.000	10.97	9.985	.9849	.1067	.2313	1.454
3.000	7.940	8.228	-.2882	.2036	.2936	-.4415
4.000	7.840	6.528	1.312	.2088	.2407	1.946
5.000	5.450	5.134	.3160	.4321	.2653	.4755
6.000	3.190	4.029	-.8387	1.261	.3480	-1.341
8.000	3.000	2.478	.5221	1.426	.2371	.7732
10.00	1.340	1.524	-.1838	7.148	.3774	-.3022

CORRECTED SUM OF SQUARED OBSERVATIONS = 175.966
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 66.4590
SUM OF SQUARED RESIDUALS = 16.8728
SUM OF WEIGHTED SQUARED RESIDUALS = 5.29426
S = .813500 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .974

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 45.9860
SUM OF WEIGHTED SQUARED RESIDUALS = 11.2681
S = .715674 WITH 22 DEGREES OF FREEDOM

Figure G.46 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Gypsy after the administration of dyphylline, 40 mg/Kg, iv bolus.

FUNCTION 1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
100.0000|
 93.7500|    O
 87.5000|    *
 81.2500|
 75.0000|    +
 68.7500|     *
 62.5000|     +*
 56.2500|      *O
 50.0000|       **
 43.7500|        +*
 37.5000|         **
 31.2500|           +*
 25.0000|             *+*
 18.7500|                ****+*
 12.5000|                      ****+*****+*****
  6.2500|                                     *+***********+***********+
   .0000|
        -+-----------+-----------+-----------+-----------+-----------+-
       .000        2.000       4.000       6.000       8.000      10.000
                                 X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1700	92.39	81.83	10.56	.5308E-02	.2457	25.81
.2500	73.04	75.85	-2.813	.8493E-02	.2563	-6.982
.3330	73.35	70.21	3.139	.8421E-02	.2110	7.330
.5000	56.32	60.36	-4.039	.1428E-01	.2010	-9.325
.6670	50.88	52.21	-1.326	.1750E-01	.1866	-3.017
1.000	38.41	39.85	-1.442	.3071E-01	.2242	-3.420
1.500	27.51	27.95	-.4397	.5987E-01	.2678	-1.112
2.000	21.73	20.81	.9193	.9595E-01	.2544	2.275
3.000	14.31	13.37	.9395	.2213	.2143	2.202
4.000	10.03	9.728	.3018	.4504	.2278	.7193
5.000	7.230	7.498	-.2684	.8667	.2470	-.6569
6.000	5.750	5.917	-.1668	1.370	.2340	-.4009
8.000	3.670	3.764	-.9378E-01	3.364	.2512	-.2310
10.00	2.460	2.409	.5052E-01	7.487	.3498	.1555

CORRECTED SUM OF SQUARED OBSERVATIONS = 11868.7
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 369.151
SUM OF SQUARED RESIDUALS = 151.656
SUM OF WEIGHTED SQUARED RESIDUALS = 1.54850
S = .439957 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .994

Figure G.47 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Gypsy after the administration of dyphylline, 40 mg/Kg, iv bolus.

FUNCTION 2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
20.0000|
18.7500|
17.5000|     O
16.2500|
15.0000|
13.7500|
12.5000|     O
11.2500|      O O
10.0000|     ***
 8.7500|       **+**
 7.5000|     O      +****
 6.2500|               O*******
 5.0000|                     O*****+**
 3.7500|                               ***+*****+*
 2.5000|                                         **********+********
 1.2500|                                                             ****+
  .0000|
         -+-----------+-----------+-----------+-----------+-----------+-
          .000       2.000       4.000       6.000       8.000       10.000
                                  X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1670	7.410	9.864	-2.454	.1570	.3457	-7.452
.2500	11.37	9.648	1.722	.6668E-01	.2002	3.973
.3330	17.20	9.440	7.760	.2914E-01	.1181	16.77
.5000	10.02	9.041	.9794	.8586E-01	.1646	2.185
.6670	10.35	8.666	1.684	.8047E-01	.1348	3.676
1.000	7.790	7.983	-.1926	.1420	.1488	-.4246
1.500	6.450	7.084	-.6344	.2072	.1694	-1.421
2.000	6.180	6.307	-.1270	.2257	.1712	-.2851
3.000	4.520	5.024	-.5042	.4219	.1984	-1.161
4.000	3.920	4.015	-.9467E-01	.5610	.1811	-.2143
5.000	3.210	3.212	-.1639E-02	.8366	.1753	-.3691E-02
6.000	2.700	2.570	.1297	1.182	.1711	.2909
8.000	1.730	1.647	.8307E-01	2.880	.2012	.1919
10.00	1.100	1.055	.4462E-01	7.124	.2542	.1104

CORRECTED SUM OF SQUARED OBSERVATIONS = 255.149
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 53.1111
SUM OF SQUARED RESIDUALS = 73.7496
SUM OF WEIGHTED SQUARED RESIDUALS = 3.46677
S = .658291 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .869

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 225.405
SUM OF WEIGHTED SQUARED RESIDUALS = 5.01527
S = .477459 WITH 22 DEGREES OF FREEDOM

Figure G.48 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Melodee after the administration of dyphylline, 40 mg/Kg, iv bolus.

FUNCTION 1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
 80.0000|   O
 75.0000|
 70.0000|
 65.0000|
 60.0000|   *
 55.0000|   O
 50.0000|   *
 45.0000|   O*
 40.0000|     *
 35.0000|    O**
 30.0000|      O*
 25.0000|       O**
 20.0000|          +**O
 15.0000|             ******O
 10.0000|                  *******+*****+****
  5.0000|                                   *+***********+***********+
   .0000|
       -+-----------+-----------+-----------+-----------+-----------+-
       .000        2.000       4.000       6.000       8.000      10.000
                                 X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1670	75.47	55.19	20.28	.4399E-02	.2388	40.49
.2500	54.74	50.53	4.210	.8362E-02	.2674	8.660
.3330	43.93	46.36	-2.431	.1298E-01	.2735	-5.036
.5000	34.81	39.25	-4.441	.2068E-01	.2476	-8.946
.6670	28.65	33.55	-4.900	.3053E-01	.2453	-9.848
1.000	23.88	25.28	-1.399	.4394E-01	.2527	-2.833
1.500	17.18	17.81	-.6316	.8490E-01	.2926	-1.340
2.000	15.26	13.60	1.659	.1076	.2566	3.373
3.000	10.37	9.350	1.020	.2330	.2471	2.054
4.000	7.800	7.166	.6344	.4119	.2439	1.273
5.000	6.530	5.701	.8288	.5876	.2188	1.626
6.000	4.850	4.590	.2605	1.065	.2265	.5143
8.000	2.650	2.999	-.3486	3.568	.3031	-.7502
10.00	1.790	1.963	-.1726	7.821	.3944	-.4425

CORRECTED SUM OF SQUARED OBSERVATIONS = 6317.28
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 204.930
SUM OF SQUARED RESIDUALS = 485.980
SUM OF WEIGHTED SQUARED RESIDUALS = 5.14168
S = .801692 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .967

Figure G.49 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Melodee after the administration of dyphylline, 40 mg/Kg, iv bolus.

```
FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

     7.0000|
     6.5625|                *******
     6.1250|             O*     O ****O
     5.6875|             *   O        ****
     5.2500|            *                 *** O
     4.8125|           *                     ***
     4.3750|           *O                       ****
     3.9375|          *                            *+**   O
     3.5000|                                           *****
     3.0625|          +                                    *****
     2.6250|         O                                         ******  O
     2.1875|         +                                               *******
     1.7500|                                                                ********O
     1.3125|         +                                                              *
      .8750|
      .4375|
      .0000|
           -+-----------+-----------+-----------+-----------+-----------+-
           .000       2.000       4.000       6.000       8.000      10.000
                                        X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1670	1.000	.9226	.7736E-01	5.712	.5006	.3236
.2500	1.870	1.788	.8235E-01	1.633	.2330	.1636
.3330	2.440	2.540	-.9955E-01	.9594	.2123	-.1942
.5000	2.890	3.760	-.8704	.6839	.2629	-1.782
.6670	4.080	4.662	-.5822	.3431	.2296	-1.153
1.000	5.890	5.770	.1202	.1646	.1869	.2300
1.500	5.590	6.363	-.7730	.1828	.2030	-1.497
2.000	5.990	6.300	-.3099	.1592	.1850	-.5925
3.000	5.820	5.491	.3289	.1686	.1756	.6249
4.000	5.140	4.538	.6021	.2162	.1770	1.145
5.000	3.870	3.695	.1754	.3814	.2063	.3406
6.000	3.630	2.995	.6352	.4335	.1932	1.221
8.000	2.380	1.962	.4181	1.008	.2298	.8279
10.00	1.710	1.284	.4256	1.953	.2497	.8590

CORRECTED SUM OF SQUARED OBSERVATIONS = 38.9257
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 22.7141
SUM OF SQUARED RESIDUALS = 3.08792
SUM OF WEIGHTED SQUARED RESIDUALS = 1.62930
S = .451290 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .966

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 489.068
SUM OF WEIGHTED SQUARED RESIDUALS = 6.77098
S = .554772 WITH 22 DEGREES OF FREEDOM

Figure G.50 Plasma dyphylline concentration versus time curve fitted simultaneously with csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Linda after the administration of dyphylline, 40 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

  80.0000|    O
  75.0000|
  70.0000|
  65.0000|
  60.0000|
  55.0000|
  50.0000|    *
  45.0000|    +*
  40.0000|     *
  35.0000|     O**
  30.0000|       O*
  25.0000|         **
  20.0000|        O  ***
  15.0000|           O  +***
  10.0000|                **+******
   5.0000|                        O*****+*****+**********+***********+
    .0000|
          -+-----------+-----------+-----------+-----------+-----------+-
          .000       2.000       4.000       6.000       8.000      10.000
                                   X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1670	75.25	47.90	27.35	.9056E-03	.2052	43.13
.2500	41.44	44.75	-3.315	.2986E-02	.3264	-5.703
.3330	41.84	41.85	-.6068E-02	.2929E-02	.2838	-.1006E-01
.5000	34.18	36.63	-2.448	.4389E-02	.2711	-4.020
.6670	28.17	32.15	-3.982	.6462E-02	.2645	-6.509
1.000	19.17	25.02	-5.854	.1395E-01	.2867	-9.728
1.500	15.00	17.62	-2.619	.2279E-01	.2956	-4.383
2.000	12.41	12.82	-.4145	.3330E-01	.3028	-.6980
3.000	9.450	7.528	1.922	.5742E-01	.2549	3.120
4.000	4.690	4.983	-.2934	.2331	.3088	-.4966
5.000	3.660	3.589	.7097E-01	.3828	.2585	.1155
6.000	2.640	2.717	-.7742E-01	.7357	.2686	-.1269
8.000	1.610	1.665	-.5543E-01	1.978	.3016	-.9325E-01
10.00	.6980	1.051	-.3535	10.52	.5038	-.8097

CORRECTED SUM OF SQUARED OBSERVATIONS = 5957.72
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 50.7074
SUM OF SQUARED RESIDUALS = 826.293
SUM OF WEIGHTED SQUARED RESIDUALS = 3.03880
S = .616320 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .936

Figure G.51 Csf dyphylline concentration versus time curve fitted simultaneously with plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for Linda after the administration of dyphylline, 40 mg/Kg, iv bolus.

```
FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

  12.0000|
  11.2500|
  10.5000|    O    ******      O
   9.7500|      ***     +****
   9.0000|     +*OO  O       ****
   8.2500|    **                ***
   7.5000|    +                    *+*
   6.7500|    O                       ****
   6.0000|                               ****   O
   5.2500|                                O  *****
   4.5000|                                       ******
   3.7500|                                            ******+
   3.0000|                                                  ********
   2.2500|                                                          ****+
   1.5000|
    .7500|
    .0000|
         -+-----------+-----------+-----------+-----------+-----------+-
         .000       2.000       4.000       6.000       8.000      10.000
                                  X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1670	6.680	7.023	-.3429	.6031	.4645	-.7172
.2500	7.490	7.492	-.2075E-02	.4797	.3521	-.3666E-02
.3330	10.33	7.906	2.424	.2522	.2258	3.865
.5000	8.920	8.591	.3294	.3382	.2384	.5291
.6670	8.680	9.104	-.4236	.3572	.2573	-.6889
1.000	8.760	9.723	-.9625	.3507	.2944	-1.610
1.500	8.600	9.946	-1.346	.3639	.3217	-2.306
2.000	9.130	9.661	-.5311	.3228	.2910	-.8857
3.000	9.980	8.431	1.549	.2702	.2215	2.464
4.000	6.860	7.001	-.1415	.5718	.2628	-.2310
5.000	4.720	5.691	-.9713	1.208	.3187	-1.659
6.000	5.880	4.581	1.299	.7783	.2238	2.068
8.000	3.320	2.936	.3843	2.441	.3422	.6717
10.00	2.180	1.873	.3075	5.663	.4609	.6385

CORRECTED SUM OF SQUARED OBSERVATIONS = 79.3722
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 94.6906
SUM OF SQUARED RESIDUALS = 14.5929
SUM OF WEIGHTED SQUARED RESIDUALS = 6.73631
S = .917626 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .912

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 840.886
SUM OF WEIGHTED SQUARED RESIDUALS = 9.77511
S = .666576 WITH 22 DEGREES OF FREEDOM

Figure G.52 Mean plasma dyphylline concentration versus time curve fitted simultaneously with mean csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for the average of 4 horses after the administration of dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

  40.0000|    O
  37.5000|
  35.0000|    *
  32.5000|    +
  30.0000|     *
  27.5000|     O*
  25.0000|       *
  22.5000|      O**
  20.0000|        +*
  17.5000|          *
  15.0000|          O**
  12.5000|             *+
  10.0000|               **+*
   7.5000|                  ****** O
   5.0000|                        ********+****
   2.5000|                                     ***+******+**************+
    .0000|
        -+--------------+--------------+--------------+--------------+-
        .000          2.000          4.000          6.000          8.000
                                       X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1700	39.13	33.79	5.336	.2907E-02	.1303	20.58
.2500	30.86	31.27	-.4079	.4674E-02	.1386	-1.600
.3300	25.92	28.96	-3.044	.6626E-02	.1396	-11.97
.5000	21.90	24.71	-2.811	.9282E-02	.1217	-10.67
.6700	17.63	21.20	-3.570	.1432E-01	.1235	-13.60
1.000	14.54	16.01	-1.468	.2106E-01	.1280	-5.638
1.500	11.62	10.92	.6968	.3297E-01	.1384	2.732
2.000	9.040	7.847	1.193	.5447E-01	.1414	4.710
3.000	5.630	4.609	1.021	.1404	.1307	3.943
4.000	3.520	3.036	.4838	.3593	.1280	1.858
5.000	2.320	2.119	.2008	.8271	.1292	.7731
6.000	1.430	1.517	-.8729E-01	2.177	.1533	-.3543
8.000	.6900	.7979	-.1079	9.350	.2296	-.6082

CORRECTED SUM OF SQUARED OBSERVATIONS = 1815.10
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 39.1362
SUM OF SQUARED RESIDUALS = 63.9555
SUM OF WEIGHTED SQUARED RESIDUALS = .929254
S = .364350 WITH 7 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .982

Figure G.53 Mean csf dyphylline concentration versus time curve fitted simultaneously with mean plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for the average of 4 horses after the administration of dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

     3.0000|
     2.8125|         O
     2.6250|       O  ********
     2.4375|        **       ****
     2.2500|        *    O      ****
     2.0625|       *        O      ****
     1.8750|      O*                O ****
     1.6875|      *                      ****
     1.5000|     O*                        O****
     1.3125|     *                             ***+
     1.1250|    +                                 ***** O
      .9375|                                          ******               O
      .7500|    +                                          *******
      .5625|                                                      ******
      .3750|
      .1875|
      .0000|
           -+--------------+--------------+--------------+--------------+-
           .000          2.000          4.000          6.000          8.000
                                          X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1700	.6800	.7375	-.5750E-01	3.275	.2464	-.3753
.2500	1.040	1.029	.1100E-01	1.400	.1374	.4305E-01
.3300	1.480	1.284	.1960	.6913	.1021	.7216
.5000	1.810	1.721	.8881E-01	.4622	.1135	.3326
.6700	2.520	2.040	.4801	.2385	.9999E-01	1.763
1.000	2.790	2.407	.3826	.1945	.1049	1.414
1.500	2.180	2.561	-.3809	.3186	.1300	-1.468
2.000	1.890	2.459	-.5689	.4239	.1328	-2.205
3.000	1.760	1.997	-.2369	.4889	.1155	-.8899
4.000	1.380	1.515	-.1349	.7951	.1291	-.5191
5.000	1.210	1.121	.8858E-01	1.034	.1305	.3418
6.000	1.100	.8224	.2776	1.251	.1256	1.061
8.000	.7900	.4383	.3517	2.426	.1273	1.349

```
CORRECTED SUM OF SQUARED OBSERVATIONS =  5.03148
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS =  3.09778
SUM OF SQUARED RESIDUALS =          1.17830
SUM OF WEIGHTED SQUARED RESIDUALS =  .754611
S =  .328331      WITH      7 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .898


TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS =           65.1338
SUM OF WEIGHTED SQUARED RESIDUALS =  1.68387
S =  .290161      WITH     20 DEGREES OF FREEDOM
```

Figure G.54 Mean plasma dyphylline concentration versus time curve fitted simultaneously with mean csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for the average of 6 horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

   70.0000|     *
   65.6250|     O
   61.2500|
   56.8750|
   52.5000|
   48.1250|
   43.7500|
   39.3750|     *
   35.0000|
   30.6250|
   26.2500|     O*
   21.8750|         O
   17.5000|      **
   13.1250|       ********+*
    8.7500|                 *****+*****+*****
    4.3750|                                  +*****+*****+***********+
     .0000|
          -+-----------+------------+------------+------------+------------+-
          .000        2.000        4.000        6.000        8.000        10.000
                                         X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1700	64.09	67.33	-3.244	.3171E-02	.6019	-86.41
.3300	22.68	23.66	-.9844	.2532E-01	.5969	-11.49
.6700	17.63	12.25	5.378	.4191E-01	.2323	9.663
1.170	12.22	10.48	1.737	.8723E-01	.2823	3.259
1.670	9.060	9.224	-.1643	.1587	.3044	-.3155
2.670	7.320	7.145	.1751	.2431	.2403	.3165
3.670	5.010	5.534	-.5243	.5189	.2344	-.9437
4.670	4.270	4.287	-.1680E-01	.7144	.2074	-.2966E-01
5.670	3.050	3.320	-.2705	1.400	.2518	-.4936
6.670	2.410	2.572	-.1620	2.243	.2972	-.3087
8.670	1.530	1.543	-.1313E-01	5.564	.4098	-.2967E-01

CORRECTED SUM OF SQUARED OBSERVATIONS = 3252.91
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 63.4215
SUM OF SQUARED RESIDUALS = 43.8670
SUM OF WEIGHTED SQUARED RESIDUALS = 1.84999
S = .608275 WITH 5 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .995

Figure G.55 Mean csf dyphylline concentration versus time curve fitted simultaneously with mean plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for the average of 6 horses after the administration of aminophylline, 10 mg/Kg, infused over 15 minutes followed by dyphylline, 20 mg/Kg, iv bolus.

```
FUNCTION  2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

  3.0000|              O
  2.8125|
  2.6250|     ***  O         O
  2.4375|    *  O**
  2.2500|         ***
  2.0625|    *      ***            O
  1.8750|              ***
  1.6875|    O           ***             O
  1.5000|    O              ***                O
  1.3125|                      ****
  1.1250|                         ******             O
   .9375|                              ******                    O
   .7500|                                   *******
   .5625|                                          ***********
   .3750|                                                   *****
   .1875|
   .0000|
         --+------------+------------+------------+------------+------------+-
          .000        2.000        4.000        6.000        8.000       10.000
                                     X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1700	1.400	1.957	-.5569	1.048	.5974	-6.758
.3300	1.640	2.561	-.9214	.7639	.3508	-1.878
.6700	2.340	2.506	-.1657	.3752	.2716	-.3077
1.170	2.580	2.210	.3697	.3087	.2169	.6571
1.670	2.940	1.945	.9947	.2377	.1668	1.716
2.670	2.550	1.507	1.043	.3160	.1496	1.786
3.670	2.060	1.167	.8929	.4842	.1464	1.526
4.670	1.550	.9040	.6460	.8552	.1559	1.109
5.670	1.380	.7003	.6797	1.079	.1419	1.160
6.670	1.020	.5424	.4776	1.975	.1569	.8202
8.670	.7600	.3254	.4346	3.557	.1427	.7417

CORRECTED SUM OF SQUARED OBSERVATIONS = 4.92816
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 3.67399
SUM OF SQUARED RESIDUALS = 5.49447
SUM OF WEIGHTED SQUARED RESIDUALS = 3.96878
S = .890930 WITH 5 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .644

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 49.3614
SUM OF WEIGHTED SQUARED RESIDUALS = 5.81877
S = .603053 WITH 16 DEGREES OF FREEDOM

Figure G.56 Mean plasma dyphylline concentration versus time curve fitted simultaneously with mean csf dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for the average of 6 horses after the administration of dyphylline, 40 mg/Kg, iv bolus.

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

  100.0000|
   93.7500|     O
   87.5000|
   81.2500|
   75.0000|     *
   68.7500|
   62.5000|     *
   56.2500|     O
   50.0000|     O*
   43.7500|      *
   37.5000|      O*
   31.2500|       *+O
   25.0000|         ***O
   18.7500|            ***+****
   12.5000|                    *+******+*****+***
    6.2500|                                      **+***********+***********+
     .0000|
          -+-----------+-----------+-----------+-----------+-----------+-
          .000       2.000       4.000       6.000       8.000      10.000
                                   X
```

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1700	90.04	73.07	16.97	.4163E-02	.3713	35.77
.2500	53.60	60.51	-6.907	.1175E-01	.3760	-14.68
.3300	44.79	50.90	-6.110	.1682E-01	.3160	-11.91
.5000	35.27	37.25	-1.976	.2713E-01	.3361	-3.953
.6700	31.14	29.32	1.815	.3481E-01	.3369	3.635
1.000	25.67	21.77	3.902	.5122E-01	.2674	7.228
1.500	19.17	17.30	1.872	.9184E-01	.2512	3.420
2.000	17.93	14.96	2.973	.1050	.2331	5.353
3.000	12.40	11.64	.7636	.2195	.2369	1.379
4.000	8.380	9.101	-.7207	.4806	.2450	-1.309
5.000	6.650	7.119	-.4690	.7632	.2293	-.8418
6.000	5.260	5.569	-.3088	1.220	.2344	-.5565
8.000	3.090	3.408	-.3177	3.53[illegible]	.3117	-.6162
10.00	2.130	2.085	.4477E-01	7.439	.3707	.9428E-01

CORRECTED SUM OF SQUARED OBSERVATIONS = 7829.68
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 266.029
SUM OF SQUARED RESIDUALS = 409.292
SUM OF WEIGHTED SQUARED RESIDUALS = 5.67133
S = .841972 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .975

Figure G.57 Mean csf dyphylline concentration versus time curve fitted simultaneously with mean plasma dyphylline concentrations by PCNONLIN[R] and corresponding computer data output for the average of 6 horses after the administration of dyphylline, 40 mg/Kg, iv bolus.

FUNCTION 2
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
 10.0000|
  9.3750|      ****
  8.7500|      *    ***
  8.1250|    * OO  O***
  7.5000|   O*         +**
  6.8750|    O            *** O
  6.2500|   *                ***
  5.6250|   O                   ****
  5.0000|   O                       **+*
  4.3750|   *                           ****
  3.7500|                                   *+***  O
  3.1250|                                        ******
  2.5000|                                             ******** O
  1.8750|                                                     ***********   O
  1.2500|                                                                *****
   .6250|
   .0000|
       -+-----------+-----------+-----------+-----------+-----------+-
       .000       2.000       4.000       6.000       8.000       10.000
                                X
```

FUNCTION 2

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.1700	4.380	4.127	.2531	.5666	.5160	.8143
.2500	5.600	5.707	-.1072	.3466	.2974	-.2046
.3300	7.260	6.853	.4074	.2062	.2222	.7276
.5000	6.790	8.297	-1.507	.2358	.2646	-2.785
.6700	7.650	8.911	-1.261	.1857	.2410	-2.285
1.000	8.060	9.004	-.9438	.1673	.2200	-1.683
1.500	7.640	8.255	-.6148	.1862	.2119	-1.090
2.000	7.170	7.352	-.1820	.2114	.2006	-.3204
3.000	6.340	5.761	.5794	.2704	.1767	1.006
4.000	4.960	4.507	.4535	.4419	.1804	.7890
5.000	3.630	3.525	.1047	.8249	.2029	.1847
6.000	3.190	2.758	.4324	1.068	.1943	.7582
8.000	2.110	1.687	.4225	2.442	.2148	.7508
10.00	1.260	1.033	.2274	6.847	.2647	.4202

CORRECTED SUM OF SQUARED OBSERVATIONS = 63.8048
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 52.7159
SUM OF SQUARED RESIDUALS = 6.37561
SUM OF WEIGHTED SQUARED RESIDUALS = 2.31249
S = .537644 WITH 8 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .978

TOTALS FOR ALL CURVES COMBINED
SUM OF SQUARED RESIDUALS = 415.667
SUM OF WEIGHTED SQUARED RESIDUALS = 7.98382
S = .602412 WITH 22 DEGREES OF FREEDOM

APPENDIX H

SAS[R] STATISTICAL COMPUTER PROGRAMS

Text H.1 SAS[R] computer program to statistically compare temperature decrement readings over time for each ibuprofen input regimen versus each other ibuprofen input regimen. (Mean control temperature decrement readings from each appropriate input regimen were subtracted from each experimental rat's temperature decrement reading)

```
TITLE 'TWO WAY ANOVA WITH A REPEATED MEASURE';
TITLE 'CONTROLS WERE SUBTRACTED OUT FROM EXPERIMENTAL RATS'
TITLE 'TEMPERATURE DECREMENT'
DATA IV;
INPUT SUBJECT GROUP $ TEMPA TEMPB TEMPC TEMPD TEMPE TEMPF;
CARDS;

;
PROC GLM;
CLASSES GROUP;
MODEL TEMPA TEMPB TEMPC TEMPD TEMPE TEMPF=GROUP /NOUNI;
REPEATED TIME 6 (0 0.5 1 2 3 4) POLYNOMIAL/SUMMARY;
MEANS GROUP/TUKEY;
RUN;
QUIT;
```

Text H.2 SAS[R] computer program to statistically compare temperature (°C) readings over time for an ibuprofen input regimen versus control rats.

```
TITLE 'TWO WAY ANOVA WITH A REPEATED MEASURE';
TITLE 'OBJ1, SUSPENSION, CONTROL VS EXPERIMENTAL'
DATA IV;
INPUT SUBJECT GROUP $ TEMPA TEMPB TEMPC TEMPD TEMPE TEMPF;
CARDS;
1 C 39 39 39.1 38.9 39.1 38.3
2 C 38.8 39 39 38.9 38.2 38.1
3 C 38.8 [illegible].9 38.6 38.8 39 38.5
4 C 38.1 39 38.9 38.8 38.9 38.5
5 C 39.1 39.5 39.1 39 38.7 38.8
6 C 39.1 39.2 39.3 39.1 38.8 38.8
7 C 38.8 38.5 39.2 39.1 39.3 38.9
8 C 38.9 38.9 38.9 39 39 38.6
9 C 38.9 39.2 39 39 38.9 38.2
10 C 38.9 38.8 39 38.5 38.4 38.1
11 C 38.2 38.5 39 39.1 39 39
1 E 39.1 38.5 37.9 37.9 37.9 38
2 E 39 38.3 38.3 37.2 37.2 37.3
3 E 38.8 38.2 37.8 37.8 37.6 37.3
4 E 39.2 38.8 38.2 38 37.9 37.6
5 E 39 38.2 38.1 37.9 38 38.1
6 E 38.8 37.9 37.9 37.8 37.8 37.7
7 E 38.8 38 37.8 37.7 37.7 37.5
8 E 38.8 37.4 37.5 37.4 37.8 37.9
9 E 39.1 38.2 38.3 37.[illegible] 37.8 38.2
10 E 39 38.5 38.4 37.8 38.1 37.5
11 E 39.2 38.5 38.7 38.2 38.4 38.7
12 E 38.8 38.2 38 37.8 37.6 37.9
13 E 38.8 38.8 38.2 37.8 38 37.8
14 E 39.1 38.5 38.1 38.2 38.5 38.2
;
PROC GLM;
CLASSES GROUP;
MODEL TEMPA TEMPB TEMPC TEMPD TEMPE TEMPF=GROUP / NOUNI;
REPEATED TIME 6 (0 0.5 1 2 3 4) POLYNOMIAL/SUMMARY;
MEANS GROUP/TUKEY;
RUN;
QUIT;
```

Text H.3 SAS[R] computer program to statistically compare temperature decrement slopes from 0 to 30 minutes for each ibuprofen input regimen versus each other ibuprofen input regimen. (Mean control temperature decrement readings from each appropriate input regimen were subtracted from each experimental rat's temperature decrement reading)

```
TITLE 'REGRESSION ANALYSIS, CONTROLS ARE SUBTRACTED OUT'
TITLE 'SLOPE COMPARISON FROM 0 - 30 MINUTES'
DATA IV;
INPUT REGIMEN ANIMAL TIME TD;
CARDS;
```

```
PROC GLM;
CLASSES REGIMEN ANIMAL;
MODEL TD=REGIMEN ANIMAL(REGIMEN) TIME TIME*REGIMEN / SOLUTION;
RUN;
QUIT;
```

APPENDIX I

TEMPERATURE READINGS (°C) AND TEMPERATURE DECREMENT READINGS FOR INDIVIDUAL RATS ADMINISTERED IBUPROFEN

Table I.1 Temperature (°C) after administering ibuprofen oral suspension (7.5 mg/Kg) to rats with yeast induced fever.

TIME VERSUS TEMPERATURE (°C)

TIME	53R	6A	14B	25C	43E	44E	55R
0	39.1	39.0	38.8	39.2	39.0	38.8	38.8
30 MIN	38.5	38.3	38.2	38.8	38.2	37.9	38.0
1 HR	37.9	38.3	37.8	38.2	38.1	37.9	37.8
2 HR	37.9	37.2	37.8	38.0	37.9	37.8	37.7
3 HR	37.9	37.2	37.6	37.9	38.0	37.8	37.7
4 HR	38.0	37.3	37.3	37.6	38.1	37.7	37.5
5 HR	37.9	37.2	38.0	37.5	38.0	38.0	37.7
6 HR	37.8	37.8	38.0	38.2	38.0	38.0	37.3
(BODY°C)	(37.4)	(37.4)	(37.3)	(37.8)	(37.7)	(37.5)	(37.7)

TIME	45E	50F	55F	56F	73H	75H	76H
0	38.8	39.1	39.0	39.2	38.8	38.8	39.1
30 MIN	37.4	38.2	38.5	38.5	38.2	38.8	38.5
1 HR	37.5	38.3	38.4	38.7	38.0	38.2	38.1
2 HR	37.4	37.8	37.8	38.2	37.8	37.8	38.2
3 HR	37.8	37.8	38.1	38.4	37.6	38.0	38.5
4 HR	37.9	38.2	37.5	38.7	37.9	37.8	38.2
5 HR	38.0	37.7	37.2	38.1	37.7	37.7	38.2
6 HR	38.0	37.7	37.2	38.2	37.8	37.5	38.1
(BODY°C)	(37.7)	(37.4)	(37.7)	(37.8)	(37.5)	(37.5)	(37.7)

TIME	MEAN	SD
0	39.0	0.2
30 MIN	38.3	0.4
1 HR	38.1	0.3
2 HR	37.8	0.3
3 HR	37.9	0.3
4 HR	37.8	0.4
5 HR	37.8	0.3
6 HR	37.8	0.3

Table I.2 Temperature (°C) after administering ibuprofen iv bolus (0.83 mg/Kg) followed by ibuprofen iv infusion to rats with yeast induced fever.

TEMPERATURE (°C)

TIME	3P TEMP	4P TEMP	12P TEMP	14P TEMP	21P TEMP	22P TEMP	30P TEMP
0 MIN	39.2	39.1	38.8	39.0	38.9	39.7	39.1
10	39.2	38.3	38.2	38.2	39.2	38.8	38.6
20	38.1	37.9	37.7	38.1	38.8	38.4	38.1
30	38.0	37.4	37.5	37.9	38.2	38.0	37.8
40	37.9	37.2	37.8	37.9	38.0	37.8	37.8
50	37.9	37.3	37.7	37.2	37.6	37.6	37.8
60	37.9	37.3	37.6	37.3	37.5	37.2	37.8
120	37.8	36.8	36.8	37.2	37.1	36.9	37.4
180	37.5	36.8	37.5	37.8	37.7	36.0	37.2
240	37.0	36.8	37.2	36.9	37.0	36.3	36.8

TIME	33P TEMP	45P TEMP	MEAN	SD
0 MIN	39.2	39.8	39.2	0.3
10	38.8	39.0	38.7	0.4
20	38.2	39.1	38.3	0.4
30	38.1	38.9	38.0	0.4
40	37.9	38.8	37.9	0.4
50	37.9	38.1	37.7	0.3
60	37.8	38.0	37.6	0.3
120	38.0	38.0	37.3	0.5
180	37.5	38.2	37.4	0.6
240	37.8	38.2	37.1	0.6

Table I.3 Temperature (°C) after administering ibuprofen iv infusion to rats with yeast induced fever.

TEMPERATURE (°C)

TIME	62Q	64Q	67Q	72Q	74Q	90V	91V
0 MIN.	39.8	39.0	39.0	39.0	39.0	39.0	39.8
10	39.7	38.7	38.5	38.5	39.0	39.0	39.5
20	39.1	38.4	38.0	38.2	39.0	38.9	39.3
30	38.5	38.0	37.9	38.1	39.0	38.9	38.7
40	38.1	38.1	37.5	38.0	38.9	38.6	39.0
50	38.2	38.2	37.2	37.9	38.9	38.2	38.9
60	38.0	38.0	37.0	37.9	38.6	38.1	38.8
120	38.2	37.5	36.6	37.3	38.3	38.2	39.0
180	37.8	37.3	36.2	37.2	37.9	38.0	39.0
240	37.8	37.0	36.5	37.6	37.0	37.7	38.2

TIME	95V	97V	MEAN	SD
0 MIN.	39.0	38.8	39.2	0.4
10	39.0	38.9	39.0	0.4
20	38.8	38.3	38.7	0.5
30	38.8	37.9	38.4	0.4
40	38.2	38.2	38.3	0.5
50	38.3	38.0	38.2	0.5
60	38.2	37.9	38.1	0.5
120	38.2	37.9	37.9	0.7
180	38.2	37.2	37.6	0.8
240	38.1	37.0	37.4	0.6

Table I.4 Temperature (°C) after administering ibuprofen iv bolus (0.83 mg/Kg) to rats with yeast induced fever.

TEMPERATURE (°C)

TIME	96V	100V	2Z	3Z	4Z	5Z	8Z
0 MIN.	38.8	38.8	39.0	38.8	39.0	39.0	39.1
10	38.2	38.9	38.6	38.5	39.2	38.9	39.1
20	38.1	38.8	38.5	38.3	39.0	38.5	38.8
30	38.0	38.2	38.0	38.1	39.0	38.5	38.9
40	38.2	38.2	38.5	38.5	39.0	38.4	38.6
50	37.5	38.2	38.5	38.4	39.0	38.3	38.4
60	37.8	38.2	38.0	38.3	39.0	38.2	37.8
120	38.8	38.2	38.2	38.2	38.9	37.9	37.8
180	38.6	38.0	38.2	38.8	38.8	38.0	37.4
240	38.5	38.1	38.2	38.8	38.1	38.7	38.1

TIME	MEAN	SD
0 MIN.	38.9	0.1
10	38.8	0.4
20	38.6	0.3
30	38.4	0.4
40	38.5	0.3
50	38.3	0.4
60	38.2	0.4
120	38.3	0.4
180	38.3	0.5
240	38.4	0.3

Table I.5 Temperature decrement (°C) readings after the administration of an ibuprofen oral suspension (7.5 mg/Kg) to rats with yeast induced fever. (No controls were subtracted out of the temperature decrement readings for individual rats)

TEMPERATURE DECREMENT (°C)

TIME	53R	6A	14B	25C	43E	44E	55R
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30 MIN	0.6	0.7	0.6	0.4	0.8	0.9	0.8
1 HR	1.2	0.7	1.0	1.0	0.9	0.9	1.0
2 HR	1.2	1.8	1.0	1.2	1.1	1.0	1.1
3 HR	1.2	1.8	1.2	1.3	1.0	1.0	1.1
4 HR	1.1	1.7	1.5	1.6	0.9	1.1	1.3
5 HR	1.2	1.8	0.8	1.7	1.0	0.8	1.1
6 HR	1.3	1.2	0.8	1.0	1.0	0.8	1.5

TIME	45E	50F	55F	56F	73H	75H	76H
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30 MIN	1.4	0.9	0.5	0.7	0.6	0.0	0.6
1 HR	1.3	0.8	0.6	0.5	0.8	0.6	1.0
2 HR	1.4	1.3	1.2	1.0	1.0	1.0	0.9
3 HR	1.0	1.3	0.9	0.8	1.2	0.8	0.6
4 HR	0.9	0.9	1.5	0.5	0.9	1.0	0.9
5 HR	0.8	1.4	1.8	1.1	1.1	1.1	0.9
6 HR	0.8	1.4	1.8	1.0	1.0	1.3	1.0

TIME	MEAN	SD
0	0.0	0.0
30 MIN	0.7	0.3
1 HR	0.9	0.2
2 HR	1.2	0.2
3 HR	1.1	0.3
4 HR	1.1	0.3
5 HR	1.2	0.4
6 HR	1.1	0.3

Table I.6 Temperature decrement (°C) readings after the administration of an ibuprofen iv bolus (0.83 mg/Kg) followed by ibuprofen infusion to rats with yeast induced fever. (No controls were subtracted out of the temperature decrement readings for individual rats)

TEMPERATURE DECREMENT (°C)

TIME	3P	4P	12P	14P	21P	22P
0	0.0	0.0	0.0	0.0	0.0	0.0
10 MIN	0.0	0.8	0.6	0.8	-0.3	0.9
20 MIN	1.1	1.2	1.1	0.9	0.1	1.3
30 MIN	1.2	1.7	1.3	1.1	0.7	1.7
40 MIN	1.3	1.9	1.0	1.1	0.9	1.9
50 MIN	1.3	1.8	1.1	1.8	1.3	2.1
60 MIN	1.3	1.8	1.2	1.7	1.4	2.5
120 MIN	1.4	2.3	2.0	1.8	1.8	2.8
180 MIN	1.7	2.3	1.3	1.2	1.2	3.7
240 MIN	2.2	2.3	1.6	2.1	1.9	3.4

TIME	30P	33P	45P	MEAN	SD
0	0.0	0.0	0.0	0.0	0.0
10 MIN	0.5	0.4	0.8	0.5	0.4
20 MIN	1.0	1.0	0.7	0.9	0.4
30 MIN	1.3	1.1	0.9	1.2	0.3
40 MIN	1.3	1.3	1.0	1.3	0.4
50 MIN	1.3	1.3	1.7	1.5	0.3
60 MIN	1.3	1.4	1.8	1.6	0.4
120 MIN	1.7	1.2	1.8	1.9	0.5
180 MIN	1.9	1.7	1.6	1.8	0.8
240 MIN	2.3	1.4	1.6	2.1	0.6

Table I.7 Temperature decrement (°C) readings after the administration of an ibuprofen infusion to rats with yeast induced fever. (No controls were subtracted out of the temperature decrement readings for individual rats)

TEMPERATURE DECREMENT (°C)

TIME	90V	91V	95V	97V	62Q	64Q
0	0.0	0.0	0.0	0.0	0.0	0.0
10 MIN	0.1	0.3	0.5	0.5	0.0	0.0
20 MIN	0.7	0.6	1.0	0.8	0.0	0.1
30 MIN	1.3	1.0	1.1	0.9	0.0	0.1
40 MIN	1.7	0.9	1.5	1.0	0.1	0.4
50 MIN	1.6	0.8	1.8	1.1	0.1	0.8
60 MIN	1.8	1.0	2.0	1.1	0.4	0.9
120 MIN	1.6	1.5	2.4	1.7	0.7	0.8
180 MIN	2.0	1.7	2.8	1.8	1.1	1.0
240 MIN	2.0	2.0	2.5	1.4	2.0	1.3

TIME	67Q	72S	74S	MEAN	SD
0	0.0	0.0	0.0	0.0	0.0
10 MIN	0.3	0.0	-0.1	0.2	0.2
20 MIN	0.5	0.2	0.5	0.5	0.3
30 MIN	1.1	0.2	0.9	0.7	0.5
40 MIN	0.8	0.8	0.6	0.9	0.5
50 MIN	0.9	0.7	0.8	1.0	0.5
60 MIN	1.0	0.8	0.9	1.1	0.5
120 MIN	0.8	0.8	0.9	1.2	0.6
180 MIN	0.8	0.8	1.6	1.5	0.7
240 MIN	1.6	0.9	1.8	1.7	0.5

Table I.8 Temperature decrement (°C) readings after the administration of an ibuprofen iv bolus (0.83 mg/Kg) to rats with yeast induced fever. (No controls were subtracted out of the temperature decrement readings for individual rats)

TEMPERATURE DECREMENT (°C)

TIME	96V	100V	2Z	3Z	4Z	5Z
0	0.0	0.0	0.0	0.0	0.0	0.0
10 MIN	0.6	-0.1	0.4	0.3	-0.2	0.1
20 MIN	0.7	0.0	0.5	0.5	0.0	0.5
30 MIN	0.8	0.6	1.0	0.7	0.0	0.5
40 MIN	0.6	0.6	0.5	0.3	0.0	0.6
50 MIN	1.3	0.6	0.5	0.4	0.0	0.7
60 MIN	1.0	0.6	1.0	0.5	0.0	0.8
120 MIN	0.0	0.6	0.8	0.6	0.1	1.1
180 MIN	0.2	0.8	0.8	0.0	0.2	1.0
240 MIN	0.3	0.7	0.8	0.0	0.9	0.3

TIME	8Z	MEAN	SD
0	0.0	0.0	0.0
10 MIN	0.0	0.2	0.3
20 MIN	0.3	0.4	0.3
30 MIN	0.2	0.5	0.3
40 MIN	0.5	0.4	0.2
50 MIN	0.7	0.6	0.4
60 MIN	1.3	0.7	0.4
120 MIN	1.3	0.6	0.5
180 MIN	1.7	0.7	0.6
240 MIN	1.0	0.6	0.4

Table I.9 Temperature decrement (°C) readings after the administration of an ibuprofen oral suspension (7.5 mg/Kg) to rats with yeast induced fever. (Controls were subtracted out of the temperature decrement readings for individual rats)

TIME	53R	6A	14B	25C	43E	44E	55R
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30 MIN	0.8	0.9	0.8	0.6	1.0	1.1	1.0
1 HR	1.4	0.9	1.2	1.2	1.1	1.1	1.2
2 HR	1.3	1.9	1.1	1.3	1.2	1.1	1.2
3 HR	1.3	1.9	1.3	1.4	1.1	1.1	1.2
4 HR	0.8	1.4	1.2	1.3	0.6	0.8	1.0
5 HR	0.8	1.4	0.4	1.3	0.6	0.4	0.7
6 HR	0.9	0.8	0.4	0.6	0.6	0.4	1.1

TIME	45E	50F	55F	56F	73H	75H	76H
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30 MIN	1.6	1.1	0.7	0.9	0.8	0.2	0.8
1 HR	1.5	1.0	0.8	0.7	1.0	0.8	1.2
2 HR	1.5	1.4	1.3	1.1	1.1	1.1	1.0
3 HR	1.1	1.4	1.0	0.9	1.3	0.9	0.7
4 HR	0.6	0.6	1.2	0.2	0.6	0.7	0.6
5 HR	0.4	1.0	1.4	0.7	0.7	0.7	0.5
6 HR	0.4	1.0	1.4	0.6	0.6	0.9	0.6

EXP. RAT TEMPERATURE- CONTROL MEAN DEC TIME	MEAN	SD	CONTROL TEMPERATURE MEAN VALUE DECREMENT
0	0.0	0.0	0.0
30 MIN	0.9	0.3	-0.2
1 HR	1.1	0.2	-0.2
2 HR	1.3	0.2	-0.1
3 HR	1.1	0.3	-0.1
4 HR	0.9	0.3	0.3
5 HR	0.8	0.4	0.4
6 HR	0.7	0.3	0.4

Table I.10 Temperature decrement (°C) readings after the administration of an ibuprofen iv bolus (0.83 mg/Kg) followed by ibuprofen infusion to rats with yeast induced fever. (Controls were subtracted out of the temperature decrement readings for individual rats)

TIME	3P	4P	12P	14P	21P	22P
0	0.0	0.0	0.0	0.0	0.0	0.0
10 MIN	-0.3	0.5	0.3	0.5	-0.6	0.6
20 MIN	0.7	0.8	0.7	0.5	-0.3	0.9
30 MIN	0.7	1.2	0.8	0.6	0.2	1.2
40 MIN	0.9	1.5	0.6	0.7	0.5	1.5
50 MIN	0.8	1.3	0.6	1.3	0.8	1.6
60 MIN	0.8	1.3	0.7	1.2	0.9	2.0
120 MIN	0.8	1.7	1.4	1.2	1.2	2.2
180 MIN	0.8	1.4	0.4	0.3	0.3	2.8
240 MIN	0.8	0.9	0.2	0.7	0.5	2.0

TIME	30P	33P	45P	MEAN	SD
0	0.0	0.0	0.0	0.0	0.0
10 MIN	0.2	0.1	0.5	0.2	0.4
20 MIN	0.6	0.6	0.3	0.5	0.4
30 MIN	0.8	0.6	0.4	0.8	0.3
40 MIN	0.9	0.9	0.6	0.9	0.4
50 MIN	0.8	0.8	1.2	1.0	0.3
60 MIN	0.8	0.9	1.3	1.1	0.4
120 MIN	1.1	0.6	1.2	1.2	0.5
180 MIN	1.0	0.8	0.7	0.9	0.8
240 MIN	0.9	0.0	0.2	0.7	0.6

CONTROL TEMPERATURE MEAN VALUE DECREMENT SUBTRACTED FROM EACH RAT
0.0
0.3
0.4
0.5
0.4
0.5
0.5
0.6
0.9
1.4

Table I.11 Temperature decrement (°C) readings after the administration of an ibuprofen infusion to rats with yeast induced fever. (Controls were subtracted out of the temperature decrement readings for individual rats)

TIME	90V	91V	95V	97V	62Q	64Q
0	0.0	0.0	0.0	0.0	0.0	0.0
10 MIN	-0.1	0.1	0.3	0.3	-0.2	-0.2
20 MIN	0.6	0.5	0.9	0.7	-0.1	0.0
30 MIN	1.2	0.9	1.0	0.8	-0.1	-0.0
40 MIN	1.6	0.8	1.4	0.9	0.0	0.3
50 MIN	1.4	0.6	1.6	0.9	-0.1	0.6
60 MIN	1.5	0.7	1.7	0.8	0.1	0.6
120 MIN	1.1	1.0	1.9	1.2	0.2	0.3
180 MIN	1.5	1.2	2.3	1.3	0.6	0.5
240 MIN	1.3	1.3	1.8	0.7	1.3	0.6

TIME	67Q	72S	74S	MEAN	SD
0	0.0	0.0	0.0	0.0	0.0
10 MIN	0.1	-0.2	-0.3	0.0	0.2
20 MIN	0.4	0.1	0.4	0.4	0.3
30 MIN	1.0	0.1	0.8	0.6	0.5
40 MIN	0.7	0.7	0.5	0.8	0.5
50 MIN	0.7	0.5	0.6	0.8	0.5
60 MIN	0.7	0.5	0.6	0.8	0.5
120 MIN	0.3	0.3	0.4	0.8	0.6
180 MIN	0.3	0.3	1.1	1.0	0.7
240 MIN	0.9	0.2	1.1	1.1	0.5

CONTROL TEMPERATURE MEAN VALUE DECREMENT SUBTRACTED FROM EACH RAT
0.0
0.2
0.1
0.1
0.1
0.2
0.3
0.5
0.5
0.7

Table I.12 Temperature decrement (°C) readings after the administration of an ibuprofen iv bolus (0.83 mg/Kg) to rats with yeast induced fever. (Controls were subtracted out of the temperature decrement readings for individual rats)

TIME	96V	100V	2Z	3Z	4Z	5Z
0	0.0	0.0	0.0	0.0	0.0	0.0
10 MIN						
20 MIN						
30 MIN	1.0	0.8	1.2	0.9	0.2	0.7
40 MIN						
50 MIN						
60 MIN	1.2	0.8	1.2	0.7	0.2	1.0
120 MIN	0.1	0.7	0.9	0.7	0.2	1.2
180 MIN	0.3	0.9	0.9	0.1	0.3	1.1
240 MIN	0.0	0.4	0.5	-0.3	0.6	0.0

TIME	8Z	MEAN	SD	CONTROL TEMPERATURE MEAN VALUE DECREMENT
0	0.0	0.0	0.0	0.0
10 MIN				
20 MIN				
30 MIN	0.4	0.7	0.3	-0.2
40 MIN				
50 MIN				
60 MIN	1.5	1.0	0.4	-0.2
120 MIN	1.4	0.8	0.5	-0.1
180 MIN	1.8	0.7	0.6	-0.1
240 MIN	0.7	0.3	0.4	0.3

APPENDIX J

TEMPERATURE READINGS (°C) AND TEMPERATURE DECREMENT READINGS FOR INDIVIDUAL RATS ADMINISTERED SALINE (CONTROLS)

Table J.1 Temperature readings (°C) after the administration of saline by gavage to rats with yeast induced fever. (Controls for regimen 1)

TIME	2A	4A	8A	73R	10B	11B	26C
0	39.0	38.8	38.8	38.1	39.1	39.1	38.8
30 MIN	39.0	39.0	38.9	39.0	39.5	39.2	38.5
1 HR	39.1	39.0	38.6	38.9	39.1	39.3	39.2
2 HR	38.9	38.9	38.8	38.8	39.0	39.1	39.1
3 HR	39.1	38.2	39.0	38.9	38.7	38.8	39.3
4 HR	38.3	38.1	38.5	38.5	38.8	38.8	38.9
5 HR	37.8	38.0	38.1	38.6	38.6	38.8	39.3
6 HR	38.2	38.0	37.9	38.1	38.8	38.8	38.8
(BODY C)	(37.6)	(38.0)	(38.2)	(37.1)	(37.8)	(37.7)	(37.5)

TIME	28C	47E	51F	54F	MEAN	SD
0	38.9	38.9	38.9	38.2	38.8	0.3
30 MIN	38.9	39.2	38.8	38.5	39.0	0.3
1 HR	38.9	39.0	39.0	39.0	39.0	0.2
2 HR	39.0	39.0	38.5	39.1	38.9	0.2
3 HR	39.0	38.9	38.4	39.0	38.8	0.3
4 HR	38.6	38.2	38.1	39.0	38.5	0.3
5 HR	38.3	38.2	37.8	38.7	38.4	0.5
6 HR	38.5	38.2	37.9	38.6	38.3	0.4
(BODY C)	(37.5)	(37.9)	(37.6)	(37.9)		

Table J.2 Temperature readings (°C) after the administration of saline iv bolus followed by saline infusion to rats with yeast induced fever. (Controls for regimen 2)

TIME	1P	8P	13P	17P	31P	32P
0 MIN	39.2	39.6	39.0	38.8	39.3	39.9
10	38.9	39.2	38.9	38.0	39.1	40.0
20	39.0	39.0	38.9	38.1	39.4	39.1
30	39.0	38.7	38.8	38.1	39.0	39.1
40	39.1	38.8	38.6	38.2	39.1	39.0
50	38.9	38.2	38.8	38.2	39.0	39.3
60	38.8	38.5	38.5	38.6	39.0	39.2
120	38.4	38.2	38.8	38.8	38.8	38.9
180	38.8	37.9	39.0	38.5	38.2	38.3
240	38.3	37.8	38.8	37.3	37.5	38.0

TIME	43P	44P	25P	MEAN	SD
0 MIN	39.8	39.7	38.8	39.3	0.4
10	39.2	39.3	38.8	39.0	0.5
20	39.2	39.0	38.8	38.9	0.4
30	39.5	39.0	38.8	38.9	0.4
40	39.7	38.8	38.8	38.9	0.4
50	39.6	38.9	38.7	38.8	0.5
60	39.4	38.8	39.0	38.9	0.3
120	39.0	38.9	38.7	38.7	0.3
180	38.2	38.5	38.3	38.4	0.3
240	37.8	38.5	37.9	38.0	0.5

Table J.3 Temperature readings (°C) after the administration of saline infusion to rats with yeast induced fever. (Controls for regimen 3)

TIME	60Q	63Q	68Q	75S	76S	92V	93V
0 MIN	38.8	38.8	38.8	38.8	38.8	38.7	38.9
10	38.5	38.9	38.8	38.8	38.4	38.8	39.0
20	39.0	39.0	38.8	38.8	38.3	38.2	39.2
30	38.7	38.8	38.5	38.9	38.3	38.7	39.0
40	38.3	38.8	38.8	38.8	38.5	38.6	39.0
50	38.2	38.8	38.3	38.5	38.4	38.8	39.0
60	38.4	38.5	38.1	38.5	38.1	38.6	39.0
120	38.2	38.4	38.0	38.2	38.2	38.6	39.0
180	38.2	38.2	38.0	38.8	38.0	38.4	39.0
240	38.0	38.0	38.0	38.1	37.8	38.5	38.9

TIME	98V	99V	MEAN	SD
0 MIN	38.7	39.5	38.9	0.2
10	38.2	38.9	38.7	0.3
20	38.2	39.8	38.8	0.5
30	38.4	39.3	38.7	0.3
40	38.9	39.2	38.8	0.3
50	39.0	39.1	38.7	0.3
60	39.2	39.1	38.6	0.4
120	38.2	38.8	38.4	0.3
180	38.0	38.8	38.4	0.4
240	37.8	38.8	38.2	0.4

Table J.4 Temperature decrement readings (°C) after the administration of saline by gavage to rats with yeast induced fever. (Controls for regimen 1)

TEMPERATURE DECREMENT (°C)

TIME	2A	4A	8A	73R	10B	11B	26C
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30 MIN	0.0	-0.2	-0.1	-0.9	-0.4	-0.1	0.3
1 HR	-0.1	-0.2	0.2	-0.8	0.0	-0.2	-0.4
2 HR	0.1	-0.1	0.0	-0.7	0.1	0.0	-0.3
3 HR	-0.1	0.6	-0.2	-0.8	0.4	0.3	-0.5
4 HR	0.7	0.7	0.3	-0.4	0.3	0.3	-0.1
5 HR	1.2	0.8	0.7	-0.5	0.5	0.3	-0.5
6 HR	0.8	0.8	0.9	0.0	0.3	0.3	0.0

TIME	28C	47E	51F	54F	MEAN	SD
0	0.0	0.0	0.0	0.0	0.0	0.0
30 MIN	0.0	-0.3	0.1	-0.3	-0.2	0.3
1 HR	0.0	-0.1	-0.1	-0.8	-0.2	0.3
2 HR	-0.1	-0.1	0.4	-0.9	-0.1	0.4
3 HR	-0.1	0.0	0.5	-0.8	-0.1	0.5
4 HR	0.3	0.7	0.8	-0.8	0.3	0.5
5 HR	0.6	0.7	1.1	-0.5	0.4	0.6
6 HR	0.4	0.7	1.0	-0.4	0.4	0.4

Table J.5 Temperature decrement readings (°C) after the administration of saline iv bolus followed by saline infusion to rats with yeast induced fever. (Controls for regimen 2)

TEMPERATURE DECREMENT (°C)

TIME	1P	8P	13P	17P	31P	32P
0 MIN	0.0	0.0	0.0	0.0	0.0	0.0
10	0.3	0.4	0.1	0.8	0.2	-0.1
20	0.2	0.6	0.1	0.7	-0.1	0.8
30	0.2	0.9	0.2	0.7	0.3	0.8
40	0.1	0.8	0.4	0.6	0.2	0.9
50	0.3	1.4	0.2	0.6	0.3	0.6
60	0.4	1.1	0.5	0.2	0.3	0.7
120	0.8	1.4	0.2	0.0	0.5	1.0
180	0.4	1.7	0.0	0.3	1.1	1.6
240	0.9	1.8	0.2	1.5	1.8	1.9

TIME	43P	44P	25P	MEAN	SD
0 MIN	0.0	0.0	0.0	0.0	0.0
10	0.6	0.4	0.0	0.3	0.3
20	0.6	0.7	0.0	0.4	0.3
30	0.3	0.7	0.0	0.5	0.3
40	0.1	0.9	0.0	0.4	0.4
50	0.2	0.8	0.1	0.5	0.4
60	0.4	0.9	-0.2	0.5	0.4
120	0.8	0.8	0.1	0.6	0.5
180	1.6	1.2	0.5	0.9	0.6
240	2.0	1.2	0.9	1.4	0.6

Table J.6 Temperature decrement readings (°C) after the administration of saline infusion to rats with yeast induced fever. (Controls for regimen 3)

TEMPERATURE DECREMENT (°C)

TIME	60Q	63Q	68Q	75S	76S	92V	93V
0 MIN	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10	0.3	-0.1	0.0	0.0	0.4	-0.1	-0.1
20	-0.2	-0.2	0.0	0.0	0.5	0.5	-0.3
30	0.1	0.0	0.3	-0.1	0.5	0.0	-0.1
40	0.5	0.0	0.0	0.0	0.3	0.1	-0.1
50	0.6	0.0	0.5	0.3	0.4	-0.1	-0.1
60	0.4	0.3	0.7	0.3	0.7	0.1	-0.1
120	0.6	0.4	0.8	0.6	0.6	0.1	-0.1
180	0.6	0.6	0.8	0.0	0.8	0.3	-0.1
240	0.8	0.8	0.8	0.7	1.0	0.2	0.0

TIME	98V	99V	MEAN	SD
0 MIN	0.0	0.0	0.0	0.0
10	0.5	0.6	0.2	0.3
20	0.5	-0.3	0.1	0.4
30	0.3	0.2	0.1	0.2
40	-0.2	0.3	0.1	0.2
50	-0.3	0.4	0.2	0.3
60	-0.5	0.4	0.3	0.4
120	0.5	0.7	0.5	0.3
180	0.7	0.7	0.5	0.3
240	0.9	0.7	0.7	0.3

APPENDIX K

PLASMA IBUPROFEN CONCENTRATIONS AND TEMPERATURE READINGS (°C) FOR INDIVIDUAL RATS

Table K.1 Plasma ibuprofen concentrations ($\mu g/ml$) after administering ibuprofen oral suspension (7.5 mg/Kg) to rats with yeast induced fever.

TIME	43E	44E	45E	50F	55F	56F	73H
30 MIN	8.59	4.82	4.81	3.03	2.69	6.93	2.12
1 HR	9.19	3.15	6.23	4.76	4.16	8.03	1.87
2 HR	10.35	5.59	5.98	6.18	4.50	13.40	2.31
3 HR	7.74	6.74	3.07	5.93	4.32	4.20	2.24
4 HR	5.33	4.60	3.95	3.25	1.38	2.80	2.15
5 HR	3.40	3.72	3.30	2.62	0.96	1.34	1.21

TIME	75H	76H	25C	53R	55R	6A	14B
30 MIN	2.31	2.41	5.15	3.12	16.30	3.46	1.78
1 HR	1.77	2.90	5.00	4.00	13.10	5.48	2.68
2 HR	1.71	2.90	3.95	4.53	11.74	5.01	2.38
3 HR	1.45	2.66	3.41	4.89	9.75	5.07	1.58
4 HR	1.25	2.41	2.03	3.42	5.37	2.40	0.78
5 HR	1.18	1.75	1.57	3.27	3.17	2.12	0.70

TIME	MEAN	SD
30 MIN	4.82	3.84
1 HR	5.17	3.15
2 HR	5.75	3.62
3 HR	4.50	2.41
4 HR	2.94	1.46
5 HR	2.17	1.05

Table K.2 Plasma ibuprofen concentrations ($\mu g/ml$) after administering ibuprofen iv bolus (0.83 mg/Kg) followed by ibuprofen iv infusion to rats with yeast induced fever.

TIME	3P CONC.	4P CONC.	12P CONC.	14P CONC.	21P CONC.	22P CONC.	30P CONC.
0 MIN							
10	4.98	2.59	4.41	4.95	6.39	4.88	2.28
30	3.92	2.64	5.39	5.75	6.70	4.47	1.73
60	3.65	2.81	5.63	5.56	5.92	3.88	1.62
120	3.19	2.85	6.43	3.82	6.85	4.03	1.55
180	3.25	2.76	6.44	4.27	7.04	3.83	1.72
240	3.91	2.86	6.58	5.46	6.59	3.00	1.61

TIME	33P CONC.	45P CONC.	MEAN	SD
0 MIN				
10	2.11	4.39	4.11	1.46
30	2.10	4.29	4.11	1.70
60	2.37	4.02	3.94	1.53
120	2.05	4.14	3.88	1.79
180	2.38	4.06	3.97	1.78
240	2.18	4.00	4.02	1.83

Table K.3 Plasma ibuprofen concentrations ($\mu g/ml$) after administering ibuprofen iv infusion to rats with yeast induced fever.

TIME	90V	91V	95V	97V	62Q	64Q	67Q
10 MIN	0.64	0.91	3.49	3.97	2.06	3.88	3.30
20 MIN	1.76	0.95	4.75	7.42	2.75	3.94	4.62
30 MIN	4.05	0.98	6.70	9.67	3.54	5.00	6.20
1 HR	6.83	1.06	7.30	9.34	4.27	4.57	5.65
2 HR	8.42	1.35	6.23	12.12	4.20	3.93	6.73
3 HR	10.47	2.31	7.36	13.16	4.44	3.92	5.72
4 HR	9.60	7.20	5.90	9.31	6.75	2.33	4.64

TIME	72S	74S	MEAN	SD
10 MIN	1.77	1.51	2.39	1.29
20 MIN	4.89	3.02	3.79	1.93
30 MIN	5.01	5.05	5.13	2.38
1 HR	5.32	6.04	5.60	2.29
2 HR	6.30	7.28	6.28	3.04
3 HR	7.19	8.34	6.99	3.38
4 HR	5.90	8.50	6.68	2.33

Table K.4 Plasma ibuprofen concentrations ($\mu g/ml$) after administering ibuprofen iv bolus (0.83 mg/Kg) to rats with yeast induced fever.

TIME	96V	100V	2Z	3Z	4Z	5Z	8Z
10 MIN	3.95	5.47	5.00	2.88	4.10	3.74	3.30
20 MIN	3.27	4.00	2.26	2.72	3.60	3.88	3.04
30 MIN	1.87	3.15	3.35	2.29	2.91	3.12	2.84
1 HR	1.03	2.42	2.48	2.15	2.72	2.68	2.03
2 HR	1.03	1.56	1.57	1.32	2.15	1.79	1.29
3 HR	0.80	1.22	0.88	1.07	1.22	1.21	0.89
4 HR	0.62	0.93	0.70	0.68	0.99	1.04	0.82

TIME	MEAN	SD
10 MIN	4.06	0.91
20 MIN	3.25	0.63
30 MIN	2.79	0.53
1 HR	2.22	0.58
2 HR	1.53	0.37
3 HR	1.04	0.18
4 HR	0.73	0.36

Table K.5a Plasma ibuprofen concentrations ($\mu g/ml$) and temperature decrement (°C) readings after the administration of an ibuprofen oral suspension (7.5 mg/Kg) to rats with yeast induced fever.

TIME	RAT 43E CONC.	TEMP.	DIFF. FROM 0 MIN. TIME
0 MIN.	--	39.00	0.00
30 MIN.	8.59	38.20	0.80
1 HR.	9.19	38.10	0.90
2 HR.	10.35	37.90	1.10
3 HR.	7.74	38.00	1.00
4 HR.	5.33	38.10	0.90
5 HR.	3.40	38.00	1.00
6 HR.		38.00	1.00

NORMAL BODY TEMP. (37.7 C)

TIME	RAT 44E CONC.	TEMP.	DIFF. FROM 0 MIN. TIME
0 MIN.	--	38.80	0.00
30 MIN.	4.82	37.90	0.90
1 HR.	3.15	37.90	0.90
2 HR.	5.59	37.80	1.00
3 HR.	6.74	37.80	1.00
4 HR.	4.60	37.70	1.10
5 HR.	3.72	38.00	0.80
6 HR.		38.00	0.80

NORMAL BODY TEMP. (37.5 C)

TIME	RAT 45E CONC.	TEMP.	DIFF. FROM 0 MIN. TIME
0 MIN.	--	38.80	0.00
30 MIN.	4.81	37.40	1.40
1 HR.	6.23	37.50	1.30
2 HR.	5.98	37.40	1.40
3 HR.	3.07	37.80	1.00
4 HR.	3.95	37.90	0.90
5 HR.	3.30	38.00	0.80
6 HR.		38.00	0.80

NORMAL BODY TEMP. (37.7 C)

TIME	RAT 50F CONC.	TEMP.	DIFF. FROM 0 MIN. TIME
0 MIN.	--	39.10	0.00
30 MIN.	3.03	38.20	0.90
1 HR.	4.76	38.30	0.80
2 HR.	6.18	37.80	1.30
3 HR.	5.93	37.80	1.30
4 HR.	3.25	38.20	0.90
5 HR.	2.62	37.70	1.40
6 HR.		37.70	1.40

NORMAL BODY TEMP. (37.4 C)

TIME	RAT 55F CONC.	TEMP.	DIFF. FROM 0 MIN. TIME
0 MIN.	--	39.00	0.00
30 MIN.	2.69	38.50	0.50
1 HR.	4.16	38.40	0.60
2 HR.	4.50	37.80	1.20
3 HR.	4.32	38.10	0.90
4 HR.	1.38	37.50	1.50
5 HR.	0.96	37.20	1.80
6 HR.		37.20	1.80

NORMAL BODY TEMP. (37.7 C)

TIME	RAT 56F CONC.	TEMP.	DIFF. FROM 0 MIN. TIME
0 MIN.	--	39.20	0.00
30 MIN.	6.93	38.50	0.70
1 HR.	8.03	38.70	0.50
2 HR.	13.40	38.20	1.00
3 HR.	4.20	38.40	0.80
4 HR.	2.80	38.70	0.50
5 HR.	1.34	38.10	1.10
6 HR.		38.20	1.00

NORMAL BODY TEMP. (37.8 C)

Table K.5b Plasma ibuprofen concentrations ($\mu g/ml$) and temperature decrement (°C) readings after the administration of an ibuprofen oral suspension (7.5 mg/Kg) to rats with yeast induced fever.

TIME	RAT 73H CONC.	TEMP.	DIFF. FROM 0 MIN. TIME	RAT 75H CONC.	TEMP.	DIFF. FROM 0 MIN. TIME
0 MIN.	--	38.80	0.00	--	38.80	0.00
30 MIN.	2.12	38.20	0.60	2.31	38.80	0.00
1 HR.	1.87	38.00	0.80	1.77	38.20	0.60
2 HR.	2.31	37.80	1.00	1.71	37.80	1.00
3 HR.	2.24	37.60	1.20	1.45	38.00	0.80
4 HR.	2.15	37.90	0.90	1.25	37.80	1.00
5 HR.	1.21	37.70	1.10	1.18	37.70	1.10
6 HR.	0.84	37.80	1.00	1.05	37.50	1.30
	NORMAL BODY TEMP.	(37.5 C)		NORMAL BODY TEMP.	(37.5 C)	

TIME	RAT 76H CONC.	TEMP.	DIFF. FROM 0 MIN. TIME	RAT 25C CONC.	TEMP.	DIFF. FROM 0 MIN. TIME
0 MIN.	--	39.10	0.00	--	39.20	0.00
30 MIN.	2.41	38.50	0.60	5.15	38.80	0.40
1 HR.	2.90	38.10	1.00	2.98	38.20	1.00
2 HR.	2.90	38.20	0.90	3.41	38.00	1.20
3 HR.	2.66	38.50	0.60	2.03	37.90	1.30
4 HR.	2.41	38.20	0.90		37.60	1.60
5 HR.	1.75	38.20	0.90		37.50	1.70
6 HR.	1.70	38.10	1.00		38.20	1.00
	NORMAL BODY TEMP.	(37.7 C)		NORMAL BODY TEMP.	(37.8 C)	

Table K.5c Plasma ibuprofen concentrations ($\mu g/ml$) and temperature decrement (°C) readings after the administration of an ibuprofen oral suspension (7.5 mg/Kg) to rats with yeast induced fever.

TIME	RAT 53R CONC.	TEMP.	DIFF. FROM 0 MIN. TIME	RAT 55R CONC.	TEMP.	DIFF. FROM 0 MIN. TIME
0 MIN.	--	39.10	0.00	--	38.80	0.00
10 MIN.		39.00	0.10		38.20	0.60
20 MIN.		39.00	0.10		37.90	0.90
30 MIN.	3.12	38.50	0.60	16.30	38.00	0.80
1 HR.	4.00	37.90	1.20	13.10	37.80	1.00
2 HR.	4.53	37.90	1.20	11.74	37.70	1.10
3 HR.	4.89	37.90	1.20	9.75	37.70	1.10
4 HR.	3.42	38.00	1.10	5.37	37.50	1.30
5 HR.	3.27	37.90	1.20	3.17	37.70	1.10
6 HR.		37.80	1.30		37.30	1.50
	NORMAL BODY TEMP.		(37.4 C)	NORMAL BODY TEMP.		(37.7 C)

TIME	RAT 6A CONC.	TEMP.	DIFF. FROM 0 MIN. TIME	RAT 14B CONC.	TEMP.	DIFF. FROM 0 MIN. TIME
0 MIN.	--	39.00	0.00	--	38.80	0.00
30 MIN.	3.46	38.30	0.70	1.78	38.20	0.60
1 HR.	4.99	38.30	0.70	2.68	37.80	1.00
2 HR.	4.63	37.20	1.80	2.38	37.80	1.00
3 HR.	5.07	37.20	1.80	1.58	37.60	1.20
4 HR.	1.06	37.30	1.70	0.78	37.30	1.50
5 HR.		37.20	1.80		38.00	0.80
6 HR.		37.80	1.20		38.00	0.80
	NORMAL BODY TEMP.		(37.4 C)	NORMAL BODY TEMP.		(37.3 C)

Table K.6 Plasma ibuprofen concentrations ($\mu g/ml$) and temperature decrement (°C) readings after the administration of an ibuprofen iv bolus (0.83 mg/Kg) followed by ibuprofen infusion to rats with yeast induced fever.

PLASMA (ug/ml) TEMPERATURE (ºC)

TIME	RAT 3P CONC.	TEMP	RAT 4P CONC.	TEMP	RAT 12P CONC.	TEMP
0 MIN		39.20		39.10		38.80
10 MIN	4.98	39.20	2.59	38.30	4.41	38.20
20 MIN		38.10		37.90		37.70
30 MIN	3.92	38.00	2.64	37.40	5.39	37.50
40 MIN		37.90		37.20		37.80
50 MIN		37.90		37.30		37.70
60 MIN	3.65	37.90	2.81	37.30	5.63	37.60
120 MIN	3.19	37.80	2.85	36.80	6.43	36.80
180 MIN	3.25	37.50	2.76	36.80	6.44	37.50
240 MIN	3.91	37.00	2.86	36.80	6.58	37.20

TIME	RAT 14P CONC.	TEMP	RAT 21P CONC.	TEMP	RAT 22P CONC.	TEMP
0 MIN		39.00		38.90		39.70
10 MIN	4.95	38.20	6.39	39.20	4.88	38.80
20 MIN		38.10		38.80		38.40
30 MIN	5.75	37.90	6.70	38.20	4.47	38.00
40 MIN		37.90		38.00		37.80
50 MIN		37.20		37.60		37.60
60 MIN	5.56	37.30	5.92	37.50	3.88	37.20
120 MIN	3.82	37.20	6.85	37.10	4.03	36.90
180 MIN	4.27	37.80	7.04	37.70	3.83	36.00
240 MIN	5.46	36.90	6.59	37.00	3.00	36.30

TIME	RAT 30P CONC.	TEMP	RAT 33P CONC.	TEMP	RAT 45P CONC.	TEMP
0 MIN		39.10		39.20		39.80
10 MIN	2.28	38.60	2.11	38.80	4.39	39.00
20 MIN		38.10		38.20		39.10
30 MIN	1.73	37.80	2.10	38.10	4.29	38.90
40 MIN		37.80		37.90		38.80
50 MIN		37.80		37.90		38.10
60 MIN	1.62	37.80	2.37	37.80	4.02	38.00
120 MIN	1.55	37.40	2.05	38.00	4.14	38.00
180 MIN	1.72	37.20	2.38	37.50	4.06	38.20
240 MIN	1.61	36.80	2.18	37.80	4.00	38.20

Table K.7 Plasma ibuprofen concentrations ($\mu g/ml$) and temperature decrement (°C) readings after the administration of an ibuprofen infusion to rats with yeast induced fever.

PLASMA (ug/ml) -- TEMPERATURE (°C)

	RAT 90V		RAT 91V		RAT 95V	
TIME	CONC.	TEMP	CONC.	TEMP	CONC.	TEMP
0 MIN		39.80		39.00		39.00
10 MIN	0.64	39.70	0.91	38.70	3.49	38.50
20 MIN	1.76	39.10	0.95	38.40	4.75	38.00
30 MIN	4.05	38.50	0.98	38.00	6.70	37.90
40 MIN		38.10		38.10		37.50
50 MIN		38.20		38.20		37.20
60 MIN	6.83	38.00	1.06	38.00	7.30	37.00
120 MIN	8.42	38.20	1.35	37.50	6.23	36.60
180 MIN	10.47	37.80	2.31	37.30	7.36	36.20
240 MIN	9.60	37.80	7.20	37.00	5.90	36.50

	RAT 97V		RAT 62Q		RAT 64Q	
TIME	CONC.	TEMP	CONC.	TEMP	CONC.	TEMP
0 MIN		39.00		39.00		39.00
10 MIN	3.97	38.50	2.06	39.00	3.88	39.00
20 MIN	7.42	38.20	2.75	39.00	3.94	38.90
30 MIN	9.67	38.10	3.54	39.00	5.00	38.90
40 MIN		38.00		38.90		38.60
50 MIN		37.90		38.90		38.20
60 MIN	9.34	37.90	4.27	38.60	4.57	38.10
120 MIN	12.12	37.30	4.20	38.30	3.93	38.20
180 MIN	13.16	37.20	4.44	37.90	3.92	38.00
240 MIN	9.31	37.60	6.75	37.00	2.33	37.70

	RAT 67Q		RAT 72S		RAT 74S	
TIME	CONC.	TEMP	CONC.	TEMP	CONC.	TEMP
0 MIN		39.80		39.00		38.80
10 MIN	3.30	39.50	1.77	39.00	1.51	38.90
20 MIN	4.62	39.30	4.89	38.80	3.02	38.30
30 MIN	6.20	38.70	5.01	38.80	5.05	37.90
40 MIN		39.00		38.20		38.20
50 MIN		38.90		38.30		38.00
60 MIN	5.65	38.80	5.32	38.20	6.04	37.90
120 MIN	6.73	39.00	6.30	38.20	7.28	37.90
180 MIN	5.72	39.00	7.19	38.20	8.34	37.20
240 MIN	4.64	38.20	5.90	38.10	8.50	37.00

Table K.8 Plasma ibuprofen concentrations ($\mu g/ml$) and temperature decrement (°C) readings after the administration of an ibuprofen iv bolus (0.83 mg/Kg) to rats with yeast induced fever.

PLASMA (ug/ml) TEMPERATURE (°C)

	RAT 96V		RAT 100V		RAT 2Z	
TIME	CONC.	TEMP	CONC.	TEMP	CONC.	TEMP
0 MIN		38.80		38.80		39.00
10 MIN	3.95	38.20	5.47	38.90	5.00	38.60
20 MIN	3.27	38.10	4.00	38.80	2.26	38.50
30 MIN	1.87	38.00	3.15	38.20	3.35	38.00
40 MIN		38.20		38.20		38.50
50 MIN		37.50		38.20		38.50
60 MIN	1.03	37.80	2.42	38.20	2.48	38.00
120 MIN	1.03	38.80	1.56	38.20	1.57	38.20
180 MIN	0.80	38.60	1.22	38.00	0.88	38.20
240 MIN	0.62	38.50	0.93	38.10	0.70	38.20

	RAT 3Z		RAT 4Z		RAT 5Z	
TIME	CONC.	TEMP	CONC.	TEMP	CONC.	TEMP
0 MIN		38.80		39.00		39.00
10 MIN	2.88	38.50	4.10	39.20	3.74	38.90
20 MIN	2.72	38.30	3.60	39.00	3.88	38.50
30 MIN	2.29	38.10	2.91	39.00	3.12	38.50
40 MIN		38.50		39.00		38.40
50 MIN		38.40		39.00		38.30
60 MIN	2.15	38.30	2.72	39.00	2.68	38.20
120 MIN	1.32	38.20	2.15	38.90	1.79	37.90
180 MIN	1.07	38.80	1.22	38.80	1.21	38.00
240 MIN	--	38.80	0.99	38.10	1.04	38.70

	RAT 8Z	
TIME	CONC.	TEMP
0 MIN		39.10
10 MIN	3.30	39.10
20 MIN	3.04	38.80
30 MIN	2.84	38.90
40 MIN		38.60
50 MIN		38.40
60 MIN	2.03	37.80
120 MIN	1.29	37.80
180 MIN	0.89	37.40
240 MIN	0.82	38.10

APPENDIX L

PLASMA IBUPROFEN CONCENTRATIONS AND TEMPERATURE DECREMENT DATA FROM PUBLISHED LITERATURE AND INDIVIDUAL WEIGHTS FOR RATS FOR ALL IBUPROFEN INPUT RATE REGIMENS

Table L.1 Data from Walson, et al., (Ibuprofen, acetaminophen, and placebo treatment of febrile children. Clin. Pharmacol. Ther., July 1989, 9-17).

TEMPERATURE DECREMENT (°C)

TIME	IBUPROFEN 5 MG/KG	IBUPROFEN 10 MG/KG
0 HR	0.00	0.00
0.50	0.34	0.28
1.00	0.78	0.84
2.00	1.40	1.57
3.00	1.57	1.68
4.00	1.57	1.74
5.00	1.40	1.68
6.00	1.18	1.46
8.00	0.62	0.95

PLASMA CONCENTRATION (ug/ml)

TIME	IBUPROFEN 5 MG/KG	IBUPROFEN 10 MG/KG
0 HR	0.30	0.20
0.50	15.50	24.70
1.00	21.70	28.40
1.50	23.50	39.70
2.00	20.20	31.50
3.00	12.50	25.30
4.00	8.40	14.70
5.00	5.10	9.00
6.00	3.50	6.00
8.00	1.40	4.50

Table L.2a Weights of individual rats for all ibuprofen input regimens.

REGIMEN 1: IBUPROFEN ORAL SUSPENSION (7.5 MG/KG)

EXPERIMENTAL RATS RAT ID	(KG)	CONTROL RATS RAT ID	(KG)
43E	0.428	2A	0.314
44E	0.379	4A	0.271
45E	0.374	8A	0.315
50F	0.408	73R	0.384
55F	0.351	10B	0.317
56F	0.350	11B	0.303
53F	0.401	26C	0.342
55F	0.375	28C	0.390
6A	0.377	47E	0.390
73H	0.368	51F	0.404
75H	0.356	54F	0.381
76H	0.379		
14B	0.355	MEAN	0.346
19B	0.380		
MEAN	0.377		

REGIMEN 2: IBUPROFEN IV BOLUS FOLLOWED BY IBUPROFEN INFUSION.

EXPERIMENTAL RATS RAT ID	(KG)	CONTROL RATS RAT ID	(KG)
3P	0.405	1P	0.316
4P	0.433	8P	0.336
12P	0.379	17P	0.374
14P	0.364	13P	0.354
22P	0.414	31P	0.412
21P	0.309	32P	0.361
30P	0.428	25P	0.442
33P	0.352	43P	0.360
45P	0.400	44P	0.395
MEAN	0.387	MEAN	0.372

Table L.2b Weights of individual rats for all ibuprofen input regimens.

REGIMEN 3: IBUPROFEN INFUSION

EXPERIMENTAL RATS RAT ID	(KG)	CONTROL RATS RAT ID	(KG)
62Q	0.391	60Q	0.350
64Q	0.361	63Q	0.375
67Q	0.388	68Q	0.393
72S	0.423	75S	0.380
74S	0.394	76S	0.353
90V	0.421	92V	0.363
91V	0.361	93V	0.310
95V	0.392	98V	0.361
97V	0.385	99V	0.485
MEAN	0.391	MEAN	0.374

REGIMEN 4: IBUPROFEN IV BOLUS

EXPERIMENTAL RATS RAT ID	(KG)
96V	0.485
100V	0.436
2Z	0.423
3Z	0.346
4Z	0.350
5Z	0.475
8Z	0.391
MEAN	0.415

APPENDIX M

NONPARAMETRIC ANALYSIS FOR RATS AND CHILDREN

Table M.1 Pharmacokinetic/Pharmacodynamic modelling by Verotta and Sheiner computer program. Mean data from the administration of ibuprofen oral suspension (7.5 mg/Kg) to rats with yeast induced fever.

INITIAL ESTIMATES

NAME	LOWER BOUND	PARAMETER	UPPER BOUND
KVO	0.1000E+07	0.1000E+07	0.1000E+07
KEO	0.0000E+00	0.3000E+01	0.8000E+01

GRID SEARCH, KVO GRID 1 KEO GRID 10
GRID SEARCH ENDS
SUCCESSFULLY TERMINATED

OBJECTIVE FUNCTION VALUE=0.7446E-01

NAME	LOWER BOUND	PARAMETER	UPPER BOUND
KVO	0.1000E+07	0.1000E+07	0.1000E+07
KEO	0.0000E+00	0.3636E+01	0.8000E+01

SIMPLEX SEARCH
TERMINATED DUED TO MAXIMAL NUMBER OF FUNCT. EVAL

NUMBER OF FUNCTION EVALUATIONS 11
NUMBER OF SIGNIFICANT DIGITS 0.1000E+01

FINAL RESULTS:

OBJECTIVE FUNCTION VALUE=0.7424E-01

DATA SET 1 OBJ.FUNCTION=0.7424E-01

NAME	LOWER BOUND	PARAMETER	UPPER BOUND
KVO	0.1000E+07	0.1000E+07	0.1000E+07
KEO	0.0000E+00	0.3680E+01	0.8000E+01

PRED.CE	PRED.CP	EFF	PRED.EFF	TIME	SET
0.0000E+00	0.0000E+00	0.0000E+00	0.0000E+00	0.0000E+00	1
0.1609E+01	0.1400E+01	0.7000E+00	0.6268E+00	0.6000E+01	1
0.2385E+01	0.2170E+01	0.8000E+00	0.8101E+00	0.5000E+01	1
0.2616E+01	0.4820E+01	0.9000E+00	0.8619E+00	0.5000E+00	1
0.3362E+01	0.2940E+01	0.9000E+00	0.9365E+00	0.4000E+01	1
0.4660E+01	0.5170E+01	0.1100E+01	0.1088E+01	0.1000E+01	1
0.4834E+01	0.4500E+01	0.1100E+01	0.1114E+01	0.3000E+01	1
0.5876E+01	0.5750E+01	0.1300E+01	0.1300E+01	0.2000E+01	1

PRED.CE	PRED.CP	EFF	PRED.EFF	TIME	SET
0.0000E+00	0.0000E+00	0.0000E+00	0.0000E+00	0.0000E+00	1
0.2616E+01	0.4820E+01	0.9000E+00	0.8619E+00	0.5000E+00	1
0.4660E+01	0.5170E+01	0.1100E+01	0.1088E+01	0.1000E+01	1
0.5876E+01	0.5750E+01	0.1300E+01	0.1300E+01	0.2000E+01	1
0.4834E+01	0.4500E+01	0.1100E+01	0.1114E+01	0.3000E+01	1
0.3362E+01	0.2940E+01	0.9000E+00	0.9365E+00	0.4000E+01	1
0.2385E+01	0.2170E+01	0.8000E+00	0.8101E+00	0.5000E+01	1
0.1609E+01	0.1400E+01	0.7000E+00	0.6268E+00	0.6000E+01	1

Table M.2 Pharmacokinetic/Pharmacodynamic modelling by Verotta and Sheiner computer program. Mean data from the administration of ibuprofen oral suspension (5 mg/Kg) to children with fever.

INITIAL ESTIMATES

NAME	LOWER BOUND	PARAMETER	UPPER BOUND
KVO	0.1000E+07	0.1000E+07	0.1000E+07
KEO	0.0000E+00	0.5000E+00	0.6000E+01

GRID SEARCH, KVO GRID 1 KEO GRID 10
GRID SEARCH ENDS
SUCCESSFULLY TERMINATED

OBJECTIVE FUNCTION VALUE=0.7662E+00

NAME	LOWER BOUND	PARAMETER	UPPER BOUND
KVO	0.1000E+07	0.1000E+07	0.1000E+07
KEO	0.0000E+00	0.5455E+00	0.6000E+01

SIMPLEX SEARCH
TERMINATED DUED TO MAXIMAL NUMBER OF FUNCT. EVAL

NUMBER OF FUNCTION EVALUATIONS 10
NUMBER OF SIGNIFICANT DIGITS 0.3010E+00

FINAL RESULTS:

OBJECTIVE FUNCTION VALUE=0.1246E+00

DATA SET 1 OBJ.FUNCTION=0.1246E+00

NAME	LOWER BOUND	PARAMETER	UPPER BOUND
KVO	0.1000E+07	0.1000E+07	0.1000E+07
KEO	0.0000E+00	0.4053E+00	0.6000E+01

PRED.CE	PRED.CP	EFF	PRED.EFF	TIME	SET
0.0000E+00	0.3000E+00	0.0000E+00	0.0000E+00	0.0000E+00	1
0.1496E+01	0.1550E+02	0.3400E+00	0.3400E+00	0.5000E+00	1
0.4653E+01	0.2170E+02	0.7800E+00	0.7800E+00	0.1000E+01	1
0.4875E+01	0.1400E+01	0.6200E+00	0.7118E+00	0.8000E+01	1
0.8081E+01	0.3500E+01	0.1180E+01	0.1162E+01	0.6000E+01	1
0.9997E+01	0.5100E+01	0.1400E+01	0.1374E+01	0.5000E+01	1
0.1049E+02	0.2020E+02	0.1400E+01	0.1425E+01	0.2000E+01	1
0.1168E+02	0.8400E+01	0.1570E+01	0.1539E+01	0.4000E+01	1
0.1236E+02	0.1250E+02	0.1570E+01	0.1570E+01	0.3000E+01	1

PRED.CE	PRED.CP	EFF	PRED.EFF	TIME	SET
0.0000E+00	0.3000E+00	0.0000E+00	0.0000E+00	0.0000E+00	1
0.1496E+01	0.1550E+02	0.3400E+00	0.3400E+00	0.5000E+00	1
0.4653E+01	0.2170E+02	0.7800E+00	0.7800E+00	0.1000E+01	1
0.1049E+02	0.2020E+02	0.1400E+01	0.1425E+01	0.2000E+01	1
0.1236E+02	0.1250E+02	0.1570E+01	0.1570E+01	0.3000E+01	1
0.1168E+02	0.8400E+01	0.1570E+01	0.1539E+01	0.4000E+01	1
0.9997E+01	0.5100E+01	0.1400E+01	0.1374E+01	0.5000E+01	1
0.8081E+01	0.3500E+01	0.1180E+01	0.1162E+01	0.6000E+01	1
0.4875E+01	0.1400E+01	0.6200E+00	0.7118E+00	0.8000E+01	1

TABLE M.3 Pharmacokinetic/Pharmacodynamic modelling by Verotta and Sheiner computer program. Mean data from the administration of ibuprofen oral suspension (10 mg/Kg) to children with fever.

INITIAL ESTIMATES

NAME	LOWER BOUND	PARAMETER	UPPER BOUND
KVO	0.1000E+07	0.1000E+07	0.1000E+07
KEO	0.0000E+00	0.2000E+01	0.6000E+01

GRID SEARCH, KVO GRID 1 KEO GRID 10
GRID SEARCH ENDS .
SUCCESSFULLY TERMINATED

OBJECTIVE FUNCTION VALUE=0.1088E+01

NAME	LOWER BOUND	PARAMETER	UPPER BOUND
KVO	0.1000E+07	0.1000E+07	0.1000E+07
KEO	0.0000E+00	0.5455E+00	0.6000E+01

SIMPLEX SEARCH
TERMINATED DUED TO MAXIMAL NUMBER OF FUNCT. EVAL

NUMBER OF FUNCTION EVALUATIONS 10
NUMBER OF SIGNIFICANT DIGITS 0.3010E+00

FINAL RESULTS:

OBJECTIVE FUNCTION VALUE=0.5726E-01

DATA SET 1 OBJ.FUNCTION=0.5726E-01

NAME	LOWER BOUND	PARAMETER	UPPER BOUND
KVO	0.1000E+07	0.1000E+07	0.1000E+07
KEO	0.0000E+00	0.4053E+00	0.6000E+01

PRED.CE	PRED.CP	EFF	PRED.EFF	TIME	SET
0.0000E+00	0.2000E+00	0.0000E+00	0.0000E+00	0.0000E+00	1
0.2360E+01	0.2470E+02	0.2800E+00	0.2800E+00	0.5000E+00	1
0.6780E+01	0.2810E+02	0.8400E+00	0.8400E+00	0.1000E+01	1
0.9058E+01	0.4500E+01	0.9500E+00	0.9839E+00	0.8000E+01	1
0.1394E+02	0.6000E+01	0.1460E+01	0.1429E+01	0.6000E+01	1
0.1613E+02	0.3150E+02	0.1570E+01	0.1589E+01	0.2000E+01	1
0.1721E+02	0.9000E+01	0.1680E+01	0.1640E+01	0.5000E+01	1
0.1998E+02	0.1470E+02	0.1740E+01	0.1708E+01	0.4000E+01	1
0.2015E+02	0.2530E+02	0.1680E+01	0.1680E+01	0.3000E+01	1

PRED.CE	PRED.CP	EFF	PRED.EFF	TIME	SET
0.0000E+00	0.2000E+00	0.0000E+00	0.0000E+00	0.0000E+00	1
0.2360E+01	0.2470E+02	0.2800E+00	0.2800E+00	0.5000E+00	1
0.6780E+01	0.2810E+02	0.8400E+00	0.8400E+00	0.1000E+01	1
0.1613E+02	0.3150E+02	0.1570E+01	0.1589E+01	0.2000E+01	1
0.2015E+02	0.2530E+02	0.1680E+01	0.1680E+01	0.3000E+01	1
0.1998E+02	0.1470E+02	0.1740E+01	0.1708E+01	0.4000E+01	1
0.1721E+02	0.9000E+01	0.1680E+01	0.1640E+01	0.5000E+01	1
0.1394E+02	0.6000E+01	0.1460E+01	0.1429E+01	0.6000E+01	1
0.9058E+01	0.4500E+01	0.9500E+00	0.9839E+00	0.8000E+01	1

APPENDIX N

PCNONLIN[R] COMPUTER PROGRAMS AND OUTPUTS FOR FITTING SIGMOID Emax MODEL CURVE TO PREDICTED UNBOUND IBUPROFEN EFFECT COMPARTMENT CONCENTRATION VERSUS PREDICTED TEMPERATURE DECREMENT EFFECT FOR CHILDREN AND RATS ADMINISTERED IBUPROFEN ORAL SUSPENSION

Text N.1 PCNONLIN[R] nonlinear estimation program for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (10 mg/Kg).

PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

```
LISTING OF INPUT COMMANDS

REMARK   SMAX FITTED BY PCNONLIN
REMARK   HUMAN 10 MG/KG IBUPROFEN ORAL SUSPENSION (UNBOUND)
MODEL
TEMP
A=P(1)
B=P(2)
C=P(3)
D=P(4)
REMARK A = EC0
REMARK B = N (FUNCTION OF SLOPE)
REMARK C = EC50:DOSE TO GET REPONSE AT (A+D)/2
REMARK D = EMAX
END
FUNC1
F = ((A-D)/(1+(X/C)**B)) + D
END
EOM
NOBS 9
DATA
NPAR 4
INITIAL VALUES 0 1.24 2 1.6
LOWER VALUES 0 0 0 0
UPPER VALUES .5 3 5 2.5
BEGIN
```

Text N.2a Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (10 mg/Kg).

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION WEIGHTED SS          1            2            3            4

    0      1.62440           .0000        1.240        2.000        1.600

                  RANK =  4 COND = .1883E+05
    1     .524252E-01       .5000E-06    1.525        1.499        1.997

                  RANK =  4 COND = .9479E+06
    2     .323025E-01       .5000E-06    1.441        1.783        2.156

                  RANK =  4 COND = .8695E+06
    3     .240941E-01       .5000E-06    1.407        1.969        2.268

                  RANK =  4 COND = .8167E+06
    4     .192918E-01       .5000E-06    1.392        2.101        2.352

                  RANK =  4 COND = .7820E+06
    5     .164620E-01       .5001E-06    1.384        2.190        2.411

                  RANK =  4 COND = .7611E+06
    6     .148323E-01       .5001E-06    1.378        2.246        2.451

                  RANK =  4 COND = .7496E+06
    7     .129870E-01       .5002E-06    1.382        2.281        2.482

                  RANK =  4 COND = .7476E+06
    8     .118545E-01       .5003E-06    1.392        2.262        2.490

                  RANK =  4 COND = .7586E+06
    9     .118358E-01       .5005E-06    1.390        2.269        2.494

                  RANK =  4 COND = .7564E+06
   10     .118168E-01       .5010E-06    1.388        2.275        2.498

                  RANK =  4 COND = .7544E+06
   11     .118043E-01       .5019E-06    1.388        2.274        2.499

                  RANK =  4 COND = .7538E+06
   12     .118016E-01       .5041E-06    1.387        2.277        2.500

                  RANK =  4 COND = .7499E+06
   13     .117987E-01       .5109E-06    1.387        2.276        2.500

                  RANK =  4 COND = .7407E+06

CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN    .000100
   13     .117982E-01       .5517E-06    1.387        2.276        2.500
```

Text N.2b Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (10 mg/Kg).

PCNONLIN NONLINEAR ESTIMATION PROGRAM

PARAMETER	ESTIMATE	STANDARD ERROR	95% CONFIDENCE LIMITS		
1	.000001	.047830	-.122948	.122949	UNIVARIATE
			-.221742	.221743	PLANAR
2	1.387250	.241952	.765302	2.009198	UNIVARIATE
			.265545	2.508955	PLANAR
3	2.276497	.568702	.814623	3.738372	UNIVARIATE
			-.360046	4.913040	PLANAR
4	2.499989	.401648	1.467535	3.532444	UNIVARIATE
			.637920	4.362058	PLANAR

*** CORRELATION MATRIX OF THE ESTIMATES ***

	1	2	3	4
1	1.00000			
2	.49176	1.00000		
3	-.22012	-.89693	1.00000	
4	-.34266	-.93991	.98741	1.00000

*** EIGENVALUES OF (Var - Cov) MATRIX ***

NUMBER	EIGENVALUE
1	5.310
2	1.492
3	.2046
4	.4435E-02

Condition number = 34.60

Text N.2c Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (10 mg/Kg).

```
FUNCTION  1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

2.0000|
1.8750|
1.7500|                                           O *****++
1.6250|                                      **+*****
1.5000|                                 **+***
1.3750|                             *****
1.2500|                         *****
1.1250|                      ****
1.0000|                   ****O
 .8750|                **+*
 .7500|              ***
 .6250|            ***
 .5000|          **
 .3750|       +**
 .2500|     ***
 .1250| ****
 .0000| O
       -+-----------+-----------+-----------+-----------+-----------+-
       .000       1.000       2.000       3.000       4.000       5.000
                                  X
```

*** SUMMARY OF NONLINEAR ESTIMATION ***

FUNCTION 1

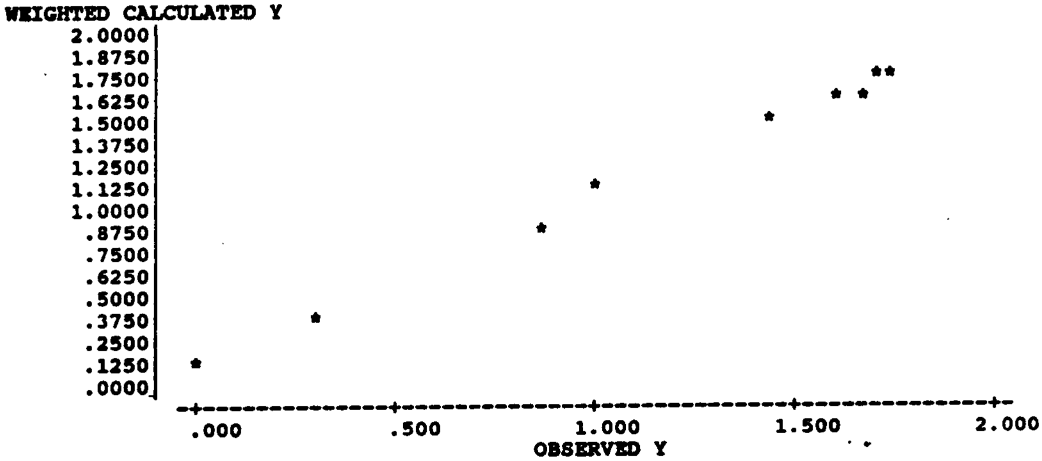
X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.0000	.0000	.5517E-06	-.5517E-06	1.000	.4783E-01	-.6504E-04
.4720	.2800	.2533	.2672E-01	1.000	.4351E-01	1.237
1.356	.8400	.8192	.2082E-01	1.000	.3167E-01	.5653
3.226	1.589	1.546	.4251E-01	1.000	.2144E-01	.9753
4.030	1.680	1.721	-.4080E-01	1.000	.2990E-01	-1.066
3.996	1.710	1.714	-.4486E-02	1.000	.2911E-01	-.1154
3.442	1.640	1.599	.4108E-01	1.000	.2129E-01	.9407
2.788	1.430	1.425	.5419E-02	1.000	.2536E-01	.1308
1.812	.9800	1.054	-.7377E-01	1.000	.3095E-01	-1.970

CORRECTED SUM OF SQUARED OBSERVATIONS = 3.30563
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 3.30563
SUM OF SQUARED RESIDUALS = .117982E-01
SUM OF WEIGHTED SQUARED RESIDUALS = .117982E-01
S = .485761E-01 WITH 5 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .998

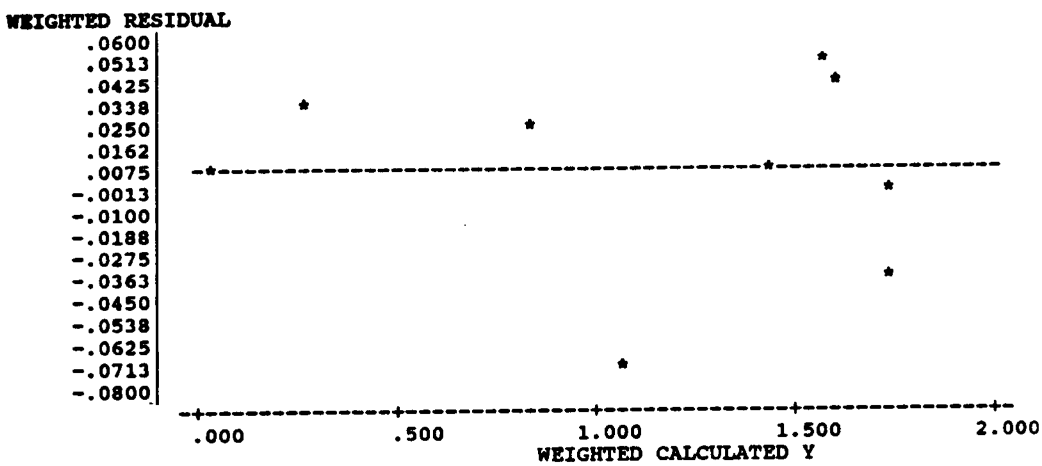
AIC criteria = -31.95827
SC criteria = -35.56382

Text N.2d Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (10 mg/Kg).

FUNCTION 1
PLOT OF OBSERVED Y VS. WEIGHTED CALCULATED Y



FUNCTION 1
PLOT OF WEIGHTED CALCULATED Y VS. WEIGHTED RESIDUAL



Text N.2e Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (10 mg/Kg).

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  1
PLOT OF X VS WEIGHTED RESIDUAL Y

WEIGHTED RESIDUAL
  .1000|
  .0875|
  .0750|
  .0625|
  .0500|                                         *  *
  .0375|      *
  .0250|                 *
  .0125|                                    *
  .0000|*-------------------------------------------------*------------
 -.0125|
 -.0250|
 -.0375|                                                  *
 -.0500|
 -.0625|                       *
 -.0750|
 -.0875|
 -.1000|
       -+-----------+-----------+-----------+-----------+-----------+-
       .000       1.000       2.000       3.000       4.000       5.000
                                    X
```

Text N.3 PCNONLIN[R] nonlinear estimation program for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (5 mg/Kg).

PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

LISTING OF INPUT COMMANDS

```
REMARK   SMAX FITTED BY PCNONLIN
REMARK   HUMAN 5 MG/KG IBUPROFEN ORAL SOLUTION (UNBOUND)
NEWP 0,1
NPAR 4
INITIAL VALUES 0 1.24 1 1.6
LOWER VALUES 0 0 0 0
UPPER VALUES .5 3 3 3
NOBS 9
DATA
BEGIN
```

Text N.4a Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (5 mg/Kg).

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION WEIGHTED SS         1           2            3            4

     0     .410735         .0000       1.240        1.000        1.600

                 RANK =  4 COND = .2434E+05
     1     .480024E-01     .5000E-06   1.468        1.311        2.059

                 RANK =  4 COND = .9507E+06
     2     .328027E-01     .5000E-06   1.251        1.679        2.423

                 RANK =  4 COND = .7070E+06
     3     .241159E-01     .5000E-06   1.253        1.913        2.640

                 RANK =  4 COND = .5874E+06
     4     .220261E-01     .5001E-06   1.205        2.096        2.788

                 RANK =  4 COND = .5100E+06
     5     .209674E-01     .5001E-06   1.201        2.071        2.793

                 RANK =  4 COND = .5151E+06
     6     .200893E-01     .5001E-06   1.185        2.181        2.871

                 RANK =  4 COND = .4923E+06
     7     .196655E-01     .5001E-06   1.177        2.238        2.914

                 RANK =  4 COND = .4872E+06
     8     .190302E-01     .5002E-06   1.177        2.285        2.958

                 RANK =  4 COND = .4867E+06
     9     .187741E-01     .5003E-06   1.172        2.315        2.981

                 RANK =  4 COND = .4876E+06
    10     .186487E-01     .5006E-06   1.169        2.329        2.992

                 RANK =  4 COND = .4882E+06
    11     .185404E-01     .5017E-06   1.169        2.334        2.998

                 RANK =  4 COND = .4879E+06
    12     .184714E-01     .5074E-06   1.170        2.328        3.000

                 RANK =  4 COND = .4833E+06
    13     .184684E-01     .5575E-06   1.170        2.327        3.000

                 RANK =  4 COND = .5730E+06

CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN    .000100
    13     .184680E-01     .2802E-05   1.170        2.327        3.000
```

Text N.4b Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (5 mg/Kg).

PCNONLIN NONLINEAR ESTIMATION PROGRAM

PARAMETER	ESTIMATE	STANDARD ERROR	95% CONFIDENCE LIMITS		
1	.000003	.060179	-.154689	.154695	UNIVARIATE
			-.278990	.278996	PLANAR
2	1.169838	.334478	.310047	2.029629	UNIVARIATE
			-.380825	2.720501	PLANAR
3	2.326784	1.828318	-2.372989	7.026556	UNIVARIATE
			-6.149424	10.802991	PLANAR
4	3.000000	1.421738	-.654640	6.654639	UNIVARIATE
			-3.591274	9.591273	PLANAR

PCNONLIN NONLINEAR ESTIMATION PROGRAM

***** CORRELATION MATRIX OF THE ESTIMATES *****

	1	2	3	4
1	1.00000			
2	.47554	1.00000		
3	-.29387	-.95298	1.00000	
4	-.32860	-.95450	.99839	1.00000

***** EIGENVALUES OF (Var - Cov) MATRIX *****

NUMBER	EIGENVALUE
1	6.239
2	.7706
3	.3121
4	.6762E-03

Condition number = 96.05

Text N.4c Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (5 mg/Kg).

PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
2.0000|
1.8750|
1.7500|
1.6250|                                                            +***+
1.5000|                                                    **+******
1.3750|                                              ******+*
1.2500|                                        **+***
1.1250|                                   *****
1.0000|                              *****
 .8750|                         *+*****
 .7500|                      **** O
 .6250|                  ****
 .5000|              ****
 .3750|           +***
 .2500|        ****
 .1250|  *****
 .0000|  O
       -+-----------+-----------+-----------+-----------+-----------+-
       .000        .500       1.000       1.500       2.000       2.500
                                 X
```

***** SUMMARY OF NONLINEAR ESTIMATION *****

FUNCTION 1

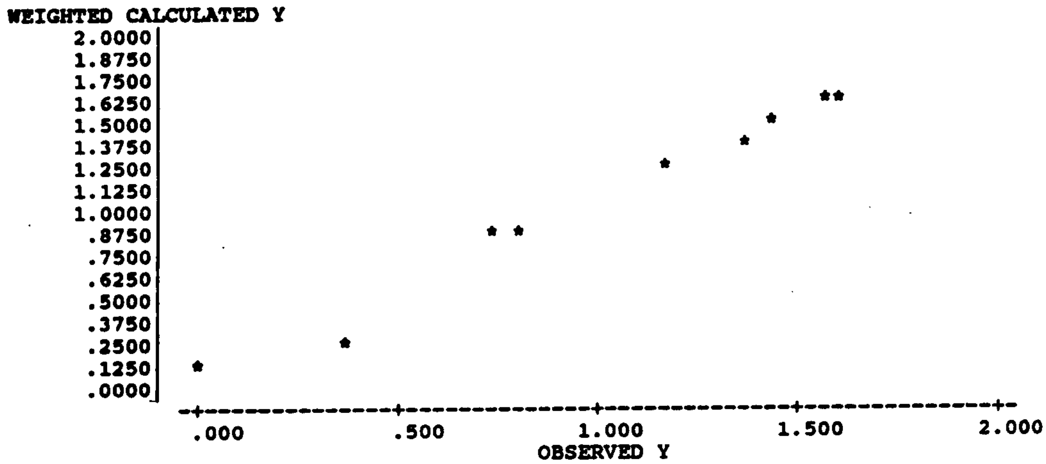
X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.0000	.0000	.2802E-05	-.2802E-05	1.000	.6018E-01	-.3300E-03
.2980	.3400	.2486	.9144E-01	1.000	.5527E-01	3.619
.9300	.7800	.7646	.1539E-01	1.000	.3622E-01	.3153
2.098	1.425	1.409	.1570E-01	1.000	.2705E-01	.2884
2.472	1.570	1.553	.1690E-01	1.000	.4117E-01	.3781
2.336	1.539	1.503	.3553E-01	1.000	.3343E-01	.7000
1.999	1.347	1.367	-.2013E-01	1.000	.2727E-01	-.3706
1.616	1.162	1.185	-.2293E-01	1.000	.3447E-01	-.4581
.9750	.7120	.7965	-.8453E-01	1.000	.3619E-01	-1.731

CORRECTED SUM OF SQUARED OBSERVATIONS = 2.50791
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 2.50791
SUM OF SQUARED RESIDUALS = .184680E-01
SUM OF WEIGHTED SQUARED RESIDUALS = .184680E-01
S = .607750E-01 WITH 5 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .996

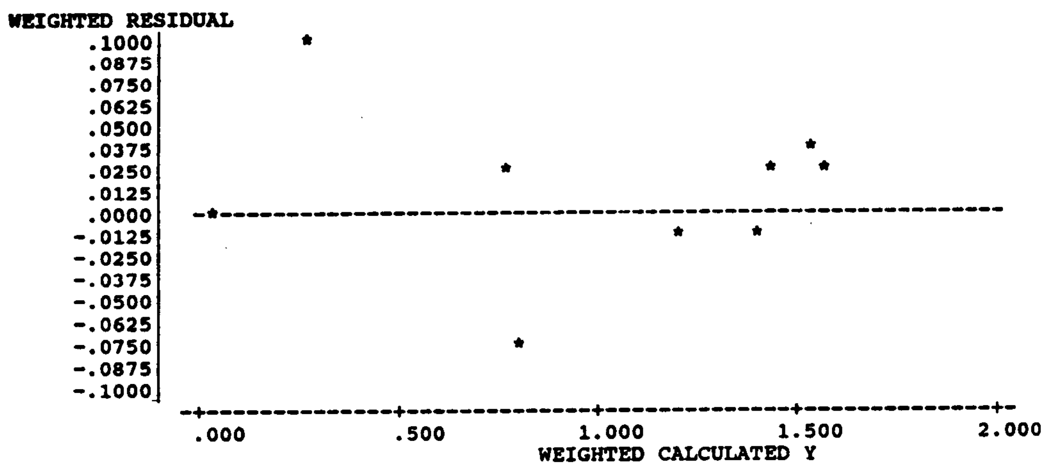
AIC criteria = -27.92545
SC criteria = -31.53100

Text N.4d Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children adminis.ered ibuprofen oral solution (5 mg/Kg).

FUNCTION 1
PLOT OF OBSERVED Y VS. WEIGHTED CALCULATED Y



FUNCTION 1
PLOT OF WEIGHTED CALCULATED Y VS. WEIGHTED RESIDUAL



Text N.4e Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for children administered ibuprofen oral solution (5 mg/Kg).

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  1
PLOT OF X VS WEIGHTED RESIDUAL Y

WEIGHTED RESIDUAL
  .1000|          *
  .0875|
  .0750|
  .0625|
  .0500|
  .0375|                                                          *
  .0250|                        *                           *        *
  .0125|
  .0000|  *----------------------------------------------------------
 -.0125|                                        *        *
 -.0250|
 -.0375|
 -.0500|
 -.0625|
 -.0750|                         *
 -.0875|
 -.1000|
        -+-----------+-----------+-----------+-----------+-----------+-
        .000        .500       1.000       1.500       2.000       2.500
                                     X
```

Text N.5 PCNONLIN^R nonlinear estimation program for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for rats administered ibuprofen oral solution (7.5 mg/Kg).

PCNONLIN NONLINEAR ESTIMATION PROGRAM (V03.0)

LISTING OF INPUT COMMANDS

```
REMARK   SMAX FITTED BY PCNONLIN
REMARK   RAT 7.5 MG/KG IBUPROFEN ORAL SOLUTION (UNBOUND)
NEWP 0,1
NPAR 4
INITIAL VALUES 0 1.24 1 1.6
LOWER VALUES 0 0 0 0
UPPER VALUES .5 5 5 3
NOBS 8
DATA
BEGIN
```

Text N.6a Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for rats administered ibuprofen oral solution (7.5 mg/Kg).

PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION	WEIGHTED SS	1	2	3	4
0	.172524E-01	.0000	1.240	1.000	1.600
	RANK =	4 COND = .2484E+05			
1	.105886E-01	.5001E-06	.9996	1.249	1.843
	RANK =	4 COND = .8887E+06			
2	.817605E-02	.5001E-06	.8642	1.743	2.165
	RANK =	4 COND = .7273E+06			
3	.728459E-02	.5001E-06	.8094	2.306	2.435
	RANK =	4 COND = .6801E+06			
4	.682332E-02	.5001E-06	.7942	2.637	2.582
	RANK =	4 COND = .6996E+06			
5	.644419E-02	.5001E-06	.7890	2.892	2.698
	RANK =	4 COND = .7292E+06			
6	.620732E-02	.5001E-06	.7819	3.088	2.785
	RANK =	4 COND = .7562E+06			
7	.617682E-02	.5001E-06	.7755	3.205	2.827
	RANK =	4 COND = .7719E+06			
8	.609500E-02	.5001E-06	.7693	3.340	2.880
	RANK =	4 COND = .7922E+06			
9	.607764E-02	.5001E-06	.7663	3.405	2.902
	RANK =	4 COND = .8019E+06			
10	.606401E-02	.5002E-06	.7638	3.461	2.921
	RANK =	4 COND = .8104E+06			
11	.605344E-02	.5002E-06	.7617	3.510	2.938
	RANK =	4 COND = .8181E+06			
12	.604569E-02	.5002E-06	.7598	3.554	2.953
	RANK =	4 COND = .8250E+06			
13	.602176E-02	.5002E-06	.7581	3.549	2.953
	RANK =	4 COND = .8240E+06			
14	.601213E-02	.5002E-06	.7579	3.581	2.965
	RANK =	4 COND = .8297E+06			
15	.600619E-02	.5002E-06	.7571	3.614	2.976
	RANK =	4 COND = .8352E+06			
16	.600129E-02	.5003E-06	.7565	3.632	2.982
	RANK =	4 COND = .8383E+06			
17	.599777E-02	.5003E-06	.7561	3.647	2.987

Text N.6b Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for rats administered ibuprofen oral solution (7.5 mg/Kg).

```
18      .599525E-02     .5004E-06   .7556       3.659       2.991

                RANK =  4 COND = .8426E+06
19      .599084E-02     .5004E-06   .7545       3.658       2.991

                RANK =  4 COND = .8422E+06
20      .598764E-02     .5004E-06   .7566       3.653       2.993

                RANK =  4 COND = .8429E+06
21      .598583E-02     .5006E-06   .7556       3.667       2.996

                RANK =  4 COND = .8444E+06
22      .598448E-02     .5010E-06   .7553       3.673       2.998

                RANK =  4 COND = .8448E+06
23      .598382E-02     .5017E-06   .7552       3.676       2.999

                RANK =  4 COND = .8440E+06

CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN    .000100
  23    .598330E-02     .5017E-06   .7548       3.676       2.999
```

PCNONLIN NONLINEAR ESTIMATION PROGRAM

PARAMETER	ESTIMATE	STANDARD ERROR	95% CONFIDENCE LIMITS		
1	.000001	.038674	-.107374	.107375	UNIVARIATE
			-.198378	.198379	PLANAR
2	.754820	.431136	-.442190	1.951829	UNIVARIATE
			-1.456707	2.966346	PLANAR
3	3.675754	10.776104	-26.243102	33.594610	UNIVARIATE
			-51.600602	58.952110	PLANAR
4	2.999297	3.589393	-6.966320	12.964915	UNIVARIATE
			-15.412604	21.411198	PLANAR

Text N.6c Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for rats administered ibuprofen oral solution (7.5 mg/Kg).

PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

Legend : * = predicted, O = observed, + = predicted & observed

```
 1.4000|
 1.3125|                                                                 **+
 1.2250|                                                          ********
 1.1375|                                                    ******+*O
 1.0500|                                               *******
  .9625|                                       *****+
  .8750|                                  +**+**
  .7875|                              ****
  .7000|                         *+***
  .6125|                     ****
  .5250|                  ***
  .4375|               ***
  .3500|           **
  .2625|        **
  .1750|      *
  .0875|    **
  .0000|   O
        -+----------+----------+----------+----------+----------+-
        .000       .500      1.000      1.500      2.000      2.500
                                  X
```

***** SUMMARY OF NONLINEAR ESTIMATION *****

FUNCTION 1

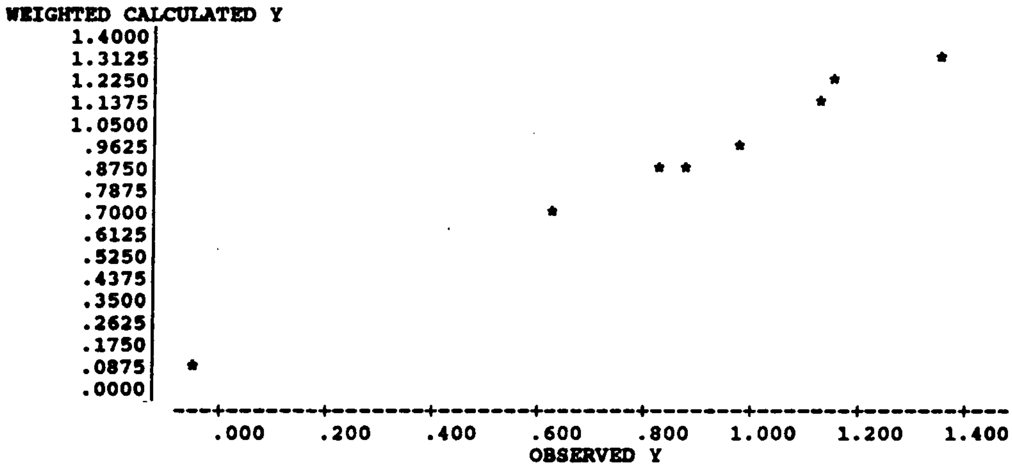
X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.0000	.0000	.5017E-06	-.5017E-06	1.000	.3867E-01	-.1241E-02
1.044	.8620	.8364	.2560E-01	1.000	.2051E-01	.7806
1.864	1.088	1.124	-.3553E-01	1.000	.1975E-01	-1.068
2.350	1.300	1.249	.5116E-01	1.000	.3324E-01	2.588
1.934	1.114	1.143	-.2915E-01	1.000	.1987E-01	-.8784
1.345	.9370	.9565	-.1945E-01	1.000	.2310E-01	-.6270
.9540	.8100	.7960	.1402E-01	1.000	.2009E-01	.4241
.6440	.6300	.6349	-.4928E-02	1.000	.3521E-01	-.3082

CORRECTED SUM OF SQUARED OBSERVATIONS = 1.10862
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 1.10862
SUM OF SQUARED RESIDUALS = .598330E-02
SUM OF WEIGHTED SQUARED RESIDUALS = .598330E-02
S = .386759E-01 WITH 4 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .997

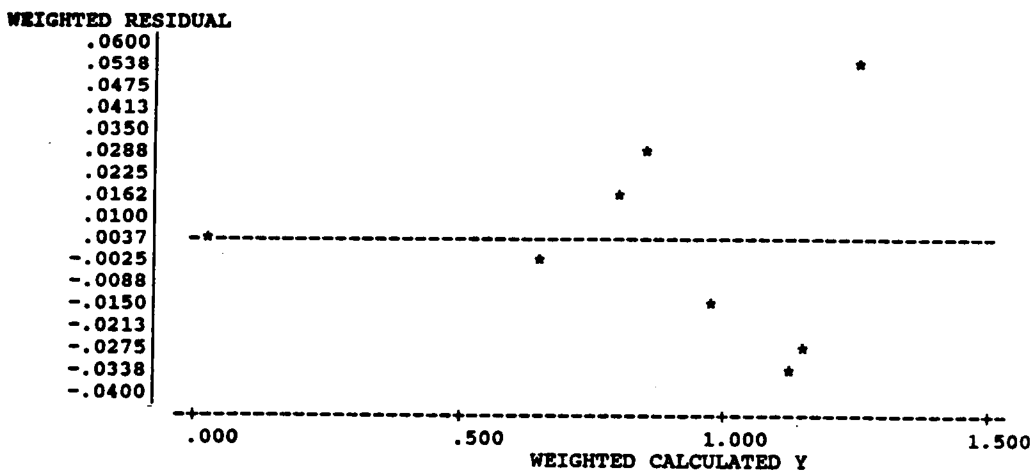
AIC criteria = -32.95027
SC criteria = -36.79139

Text N.6d Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for rats administered ibuprofen oral solution (7.5 mg/Kg).

FUNCTION 1
PLOT OF OBSERVED Y VS. WEIGHTED CALCULATED Y



FUNCTION 1
PLOT OF WEIGHTED CALCULATED Y VS. WEIGHTED RESIDUAL



Text N.6e Computer program output from PCNONLIN[R] for fitting a sigmoid Emax model curve to predicted unbound ibuprofen effect compartment concentration versus predicted temperature decrement effect for rats administered ibuprofen oral solution (7.5 mg/Kg).

PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF X VS WEIGHTED RESIDUAL Y

```
WEIGHTED RESIDUAL
   .0600|
   .0538|                                                           *
   .0475|
   .0413|
   .0350|
   .0288|                            *
   .0225|
   .0162|                         *
   .0100|
   .0037|  *-------------------------------------------------------------
  -.0025|                  *
  -.0088|
  -.0150|                                   *
  -.0213|
  -.0275|                                                 *
  -.0338|                                               *
  -.0400|
          -+-----------+-----------+-----------+-----------+-----------+-
          .000         .500      1.000       1.500       2.000       2.500
                                          X
```

PCNONLIN NONLINEAR ESTIMATION PROGRAM

***** CORRELATION MATRIX OF THE ESTIMATES *****

	1	2	3	4
1	1.00000			
2	.10515	1.00000		
3	-.04607	-.99226	1.00000	
4	-.05503	-.98996	.99963	1.00000

***** EIGENVALUES OF (Var - Cov) MATRIX *****

NUMBER	EIGENVALUE
1	7.400
2	.5121
3	.1503
4	.1158E-04

Condition number = 799.4

Text N.7 Raw data for predicted total or unbound ibuprofen effect compartment concentration and predicted temperature decrement effect for children and rats.

Predicted total ibuprofen effect compartment concentration.

TIME	CE human UG/ML(5)	TEMP DEC	CE human UG/ML(10)	TEMP DEC	CE rat UG/ML(7.5	TEMP DEC
0	0.000	0.000	0.000	0.000	0.000	0.000
0.5	1.490	0.340	2.360	0.280	2.610	0.862
1	4.650	0.780	6.780	0.840	4.660	1.088
2	10.490	1.425	16.130	1.589	5.876	1.300
3	12.360	1.570	20.150	1.680	4.834	1.114
4	11.680	1.539	19.980	1.710	3.362	0.937
5	9.997	1.374	17.210	1.640	2.385	0.810
6	8.081	1.162	13.940	1.430	1.609	0.630
8	4.875	0.712	9.058	0.980		

Predicted unbound ibuprofen effect compartment concentration.

TIME	(.2) human UG/ML(5)	TEMP DEC	(.2) human UG/ML(10)	TEMP DEC	(.4) rat UG/ML(7.5	TEMP DEC
0	0.000	0.000	0.000	0.000	0.000	0.000
0.5	0.298	0.340	0.472	0.280	1.044	0.862
1	0.930	0.780	1.356	0.840	1.864	1.088
2	2.098	1.425	3.226	1.589	2.350	1.300
3	2.472	1.570	4.030	1.680	1.934	1.114
4	2.336	1.539	3.996	1.710	1.345	0.937
5	1.999	1.374	3.442	1.640	0.954	0.810
6	1.616	1.162	2.788	1.430	0.644	0.630
8	0.975	0.712	1.812	0.980		