AN ABSTRACT OF THE DISSERTATION OF

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This dissertation presents a research series demonstrating the use of pharmacokinetic modeling and simulations as tools to assess drug concentration and disposition in patient populations. For drugs requiring therapeutic drug monitoring, these tools are necessary to ensure patients are receiving a safe and effective dose of medication to address their medical condition.

The second chapter describes a prospective study to validate pharmacokinetic modeling simulation aimed at determining optimal inter and intradialytic dosing of vancomycin for hemodialysis patients. Fifty percent of the patients with evaluable data maintained trough concentrations within the therapeutic range (15-20mg/L). The remaining fifty percent of the patients required individualization of dosing to produce troughs in the therapeutic range. Given this, it is advisable to use a weight-based dosing regimen as a start for patient treatment. Therapeutic drug monitoring and individualization should be implemented as well to ensure therapeutic drug concentrations.

The third chapter involves noncompartmental analysis of aprepitant plasma concentrations in an antiemetic regimen for patients undergoing hematopoietic stem cell transplantation. This study regimen has a first dose of 125mg on day 1, and 80mg daily until 4 days after the hematopoietic stem cell transplant. In spite of drug interactions from concomitant drug therapy, therapeutic concentrations of aprepitant were maintained. The study regimen can be applied in patients undergoing hematopoietic stem cell transplantation.

The fourth chapter examines the unique characteristics of vancomycin pharmacokinetics in patients with Acute Myelogenous Leukemia. (AML) Demographics and vancomycin drug concentration versus time data were gathered from a retrospective cohort. One-compartment pharmacokinetic equations with population pharmacokinetic parameters were used to predict drug concentrations. These were compared with measured concentrations. A shortened half-life and increased clearance for vancomycin was found in AML patients compared to a general population. Because of this, the vancomycin dose in a 24 hour period should be doubled relative to the general population.

The fifth chapter evaluates The University of Southern California Lab of Applied Pharmacokinetics MM-USC*PACK population modeling software using multiple model Bayesian pharmacokinetics for dosing vancomycin in AML patients. Of interest is the ability of the software's included vancomycin population PK database to fit assayed drug concentrations of AML patients given the vancomycin dosing regimen. The root mean squared prediction error was not greater than 5.25 mg/L, given multiple options for estimation of creatinine clearance as a covariate in the modeling. Using the MM-

USC*PACK software with a population model developed from the cohort being evaluated should yield the best predictive performance and be a feasible dosing tool for patient care. Evaluation of pharmacokinetics of clinically available data as applied to improving drug dosing in patients is a consistent and common objective of the research in this thesis.

The Study of Pharmacokinetics in a Clinical Environment

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I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

Sunny Tse, Author

CONTRIBUTION OF AUTHORS

For Chapter 2, Dr. Munar acted as guiding Major Professor for all aspects of the research and thesis. Jean McCormick assisted with logistics of the Institutional Review Board study procedures. Dr. Rueda was the required Physician Principal Investigator for the study and assisted with manuscript revision. Dr. Wahba was originally involved as Physician Principal Investigator but had to withdraw. For Chapter 3, Dr. Munar was guiding Major Professor. Dr. Bubalo reviewed the chapter and provided access to clinical information on the study cohort for analysis. For Chapter 4, Drs. Baker and Jendro collected the data in a mutually developed format. Dr. Baker and I independently generated pharmacokinetic analysis of the data which was compared and combined. Dr. Baker generated an original manuscript draft which I expanded and modified. Chapter 5 was conducted independently with Dr. Ayres acting as an advisor.

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1 GENERAL INTRODUCTION

Sunny Tse

This dissertation is a series of studies demonstrating the use of pharmacokinetic modeling and simulations as tools to assess drug concentration and disposition in patient populations. For drugs requiring therapeutic drug monitoring, these tools are necessary to ensure patients are receiving a safe and effective dose of medication to address their medical condition. These studies demonstrate the implementation of pharmacokinetics to evaluate drug disposition resulting from a given dosing regimen, and how dosage requirements should be adjusted in response to what is observed.

The second chapter describes a prospective study to validate pharmacokinetic modeling simulation aimed at determining optimal dosing of vancomycin for hemodialysis patients. There is currently no nationally recognized standard for dosing vancomycin in hemodialysis patients. The study regimen is a weight-based dosing protocol with a starting dose that can be given off-dialysis or during the last hour of a dialysis session. Subsequent doses are given during the last hour of dialysis, with the end of the infusion coinciding with the end of the dialysis session. Thirty-eight blood samples are reported in 8 patients. Comparisons are made with simulation predictions and dosing recommendations are made.

The third chapter involves noncompartmental analysis of aprepitant plasma concentrations in an antiemetic regimen for patients undergoing hematopoietic stem cell transplantation. Typically, for patients undergoing high emetogenic potential chemotherapy, aprepitant is included in the antiemetic regimen along with a serotonin antagonist and dexamethasone. One hundred twenty five mg of aprepitant is given on the first day of the regimen and 80mg is given daily for two days. This study regimen has a first dose of 125mg on day 1, and 80mg daily until four days after the hematopoietic stem

cell transplant. This regimen provides coverage for the period in which the myeloablative conditioning regimen is given and afterwards for delayed phase chemotherapy induced nausea and vomiting. Drug interactions from concomitant medications and lab values are also discussed.

The fourth chapter examines the unique characteristics of vancomycin pharmacokinetics in patients with Acute Myelogenous Leukemia (AML). Data on demographics and vancomycin drug concentration versus time were gathered from a retrospective cohort. Based upon these data, clinical one-compartment equations and population pharmacokinetic parameters were used to predict serum concentrations. These were compared with actual serum concentrations. Of interest was the shortened half-life and increased clearance in AML patients compared to general population vancomycin.

The fifth chapter evaluates The University of Southern California Lab of Applied Pharmacokinetics MM-USC*PACK population modeling software using multiple model Bayesian pharmacokinetics for dosing vancomycin in AML patients. Of interest is the ability of the software's included vancomycin population pharmacokinetics database to fit assayed serum drug concentrations given the vancomycin dosing regimen of AML patients. Four different estimated creatinine clearance schemes were used as covariates in the modeling. These are discussed in terms of predictive performance. The feasibility of the software for use as a dosing tool is addressed as well.

The research shows the unique pharmacokinetic characteristics of different patient populations and how drug dosing may or may not need to be adjusted accordingly in

clinical practice. Evaluation of pharmacokinetics of clinically available data as applied to improving drug dosing in patients is a consistent and common objective of the research in this thesis.

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2.1 ABSTRACT

Vancomycin is commonly used in renal failure patients who have gram-positive infections of the vascular access. Because vancomycin is cleared renally, this subpopulation of patients require dosing of vancomycin which takes into consideration both drug elimination by high-flux dialysis and residual renal function. The optimal dosing regimen has not been defined. A retrospective study determined that a loading dose of 15mg/kg and maintenance doses of 10mg/kg during the last hour of a hemodialysis session would yield troughs within 15-20mg/L. The purpose of the current study was to test this regimen.

Ten renal failure patients were enrolled to test the regimen. These patients were given the weight-based dosing regimen with dosing individualized if/as needed, and resultant concentrations were assessed.

Evaluable data were collected from eight patients. Four patients adhered to the study regimen with resultant trough concentrations staying within the desired trough concentration range. Four patients required deviation from the study regimen because desired trough concentrations were not consistently achieved. The one-compartment drug concentration versus time simulations for the cohort had a root mean squared prediction error (RMSE) of 4.30mg/L (95% CI: 3.21-5.15). The two-compartment drug concentration versus time simulations for the cohort's first study dosing interval had a RMSE of 14.76mg/L (95% CI: 5.45-20.14). The average trough concentration throughout the study was 18.35mg/L (95% CI: 16.41-20.28mg/L), compared to 17.59mg/L (95% CI: 16.01-19.17) for the weight-based dosing regimen. Safety was acceptable with only one patient removed from the study due to Red Man Syndrome. Patients can have differing pharmacokinetic parameters, so it is not possible to assign a

given dosing regimen and expect desired trough concentrations unilaterally. A patient may or may not have desired drug concentrations resulting from the weight-based dosing regimen. The use of simulations to trial proper dosing is a reasonable start and is less risky and more cost effective than an arbitrary approach. However, patients are unique and will require therapeutic drug monitoring and individualized dosing to ensure desired vancomycin trough concentrations.

2.2 INTRODUCTION

Vancomycin is a tricyclic glycopeptide antibiotic[1] that has excellent efficacy against gram-positive bacteria and is bactericidal for dividing microorganisms.[2] Although vancomycin has been used over 30 years[3], it still remains a first line treatment for methicillin-resistant Staphylococcus aureus (MRSA) infection.[4] It works by interfering with bacterial cell wall construction.[5] Trough concentrations of 15-20 mg/L are recommended.[6] This is based upon evidence that a 24 hour area under the curve divided by the minimum inhibitory concentration (MIC) ratio of ≥ 350 is predictive of cure for S. *aureus* pneumonia.[7] It is important to achieve therapeutic concentrations as vancomycin-intermediate S. *aureus* requires concentrations of 8-16 mg/L for growth inhibition.[8] Vancomycin exhibits time-dependent killing.[9] Therefore, increasing the concentration beyond the MIC has no apparent effect on the rate of killing.[9] Vancomycin is an important agent commonly used in patients who have infections of the vascular access (catheter-related bloodstream infections) and is effective in treating the infecting organisms in these cases.[10] Two of these infecting organisms include *Staphylococcus aureus and S. epidermidis*[1]. Hemodialysis patients, who require catheters for their thrice-

weekly dialysis sessions are a prime example of patients at risk for such catheter-related bloodstream infections.[10]

Since vancomycin is cleared almost exclusively by glomerular filtration,[11] clearance is significantly decreased in renal failure. With normal renal function, vancomycin's elimination half-life is approximately nine hours.[11] In end-stage renal disease, vancomycin's half-life ranges from 54 and 180 hours.[11]

Older low-flux cellulose acetate and cuprophane dialysis membranes had little effect on vancomycin clearance.[1] Newer dialyzer membranes are more permeable to drugs with molecular masses greater than 500 Da.[3] These more efficient, high-flux dialyzers can filter out vancomycin, which has a larger molecular mass of 1448 Da.[12] Vancomycin may be infused during the last hour of a high-flux hemodialysis treatment.[13] Considering the type of high-flux membrane and drug infusion duration, this method of vancomycin administration has resulted in 54% to 87% relative bioavailability with a drug infusion during dialysis compared with 100% bioavailability of infusions administered off dialysis.[13] Therefore, increased drug doses are needed to compensate for supraphysiologic drug clearance during hemodialysis. There are multiple sources of variability when considering vancomycin pharmacokinetics in hemodialysis patients. These include alternating between interdialytic and intradialytic elimination, and the timing of the dose infusion.[1] Also to be considered is the drug elimination via convection during pure ultrafiltration.[14] Given all these factors, dosing vancomycin during dialysis is a complicated matter.

The optimal dosing regimen of vancomycin during dialysis has not been defined.

There are a number of studies that prospectively evaluated vancomycin dosing in hemodialysis.[1, 2, 13, 15, 16] Since these studies tested different types of high-flux dialysis with different clearance characteristics, the results cannot be generalized to other high-flux dialyzer membranes. A retrospective study at Oregon Health and Science University involving chart review of renal failure patients receiving vancomycin tested a previously validated dosing regimen in patients receiving dialysis with commonly used high-flux dialysis membranes. This retrospective study produced a linear correlation between mean simulated concentrations versus mean observed concentrations ($y = 0.9944x - 0.0331$, $R^2 = 0.97$). As a result, a series of simulations were run to determine a regimen that would produce prehemodialysis troughs ranging in between 15-20mg/L.[17] The regimen employed was a 15mg/kg loading dose, followed by maintenance doses of 10mg/kg during the last hour of subsequent hemodialysis sessions. This regimen resulted in predicted trough concentrations of 18-20mg/L, well within the desired trough concentration range. The purpose of the current prospective study was two-fold: Assess the ability of simulations to predict vancomycin serum concentrations and assess the ability of the weight-based regimen to produce prehemodialysis trough concentrations between 18-20mg/L, as originally predicted by the retrospective study simulation. If so, then the simulations are a feasible platform for testing doses and serve as an accurate predictor for drug serum concentrations in humans.

2.3 MATERIALS AND METHODS

2.3.1 PATIENTS

Ten patients, nine males and one female, were enrolled. Ages ranged from 18-68 years, and patients were undergoing hemodialysis three times weekly, and had intravenous vancomycin prescribed by their physician for systemic infection. Since

patients are typically given a one gram dose immediately as prophylaxis prior to culture results, patients with one vancomycin dose given prior to identification could be enrolled for the study. Patients were excluded from the study if they had hypersensitivity to vancomycin, were morbidly obese, were receiving ≥ 2 grams/dose of vancomycin IV, were prescribed the oral dosage form of vancomycin, were special/vulnerable subject populations (for example, the mentally impaired and children), or were pregnant. Patients gave written informed consent. The study was conducted in adherence to the Declaration of Helsinki and approved by the Oregon Health and Science University Institutional Review Board.

2.3.2 STUDY DESIGN

This was an open-label study assessing the pharmacokinetics of vancomycin when given during the last hour of hemodialysis. Ten eligible patients underwent their usual thrice-weekly hemodialysis treatments (egs. 3.5 – 4.5 hour hemodialysis sessions on Monday – Wednesday – Friday, or Tuesday – Thursday – Saturday). Disposable high-flux filters were used in the study. If the patient had received a vancomycin dose prior to enrollment, then a random blood sample was drawn to assess a baseline serum vancomycin concentration. Study patients received an intravenous starting dose of vancomycin 15 mg/kg at a rate ≤ 1 gram per hour outside the hemodialysis session. This was followed in subsequent dialysis sessions by intravenous maintenance doses of vancomycin 10 mg/kg at a rate ≤ 1 gram per hour during hemodialysis, with the end of the drug infusion coinciding with the end of the hemodialysis session. Dosages were rounded to the nearest 50mg. Patients received vancomycin therapy under the study protocol for up to seventeen days. Doses were individualized if the prescribed

maintenance doses of 10mg/kg did not maintain trough concentrations between 15-20mg/L.

Blood samples of 3 ml in volume were drawn from patients. A post-infusion blood sample was taken upon completion of the initial study dose. For the first maintenance dose, a blood sample immediately preceding the start of dialysis and a blood sample immediately preceding the start of the infusion were drawn. For subsequent maintenance doses, a pre-dialysis blood sample was taken directly prior to the start of dialysis.

Data collected included patient demographic data: age, sex, weight, race, cause of end stage renal disease, and reason for treatment. Also collected were information specific to study visits: pre and post hemodialysis weights, dialysis filter type, dialysate flow rates, blood flow rates, vancomycin dosages, study event times, and plasma creatinine values.

2.3.3 PHARMACOKINETIC (PK) METHODS

The one-compartment simulations involved variables which included dose, initial drug concentration, infusion time, volume of distribution, and elimination rate constant (interdialytic or intradialytic). The interdialytic and intradialytic elimination rate constants for the one-compartment simulations were taken from the mean values for the F80 dialyzer subjects in the article by Touchette et al.[18] The elimination rate constant (K_d) was estimated as clearance/volume of distribution. Clearance for pure ultrafiltration was analogous to clearance for continuous venovenous hemofiltration (CVVH) with CVVH clearance = (fraction of drug not bound to protein) * (ultrafiltration rate).[19] No literature sources were available that listed the intradialytic elimination rate constants for

the F160NR, F180NR, or AM-BIO-100 dialyzers which were used in the patient's dialysis. Therefore, the elimination rate constant of the F80 dialyzer was multiplied by a correction factor which involved the in-vitro vitamin B_{12} clearance ratio of the given dialyzer versus the F80 dialyzer. The volume of distribution was assumed to be 0.7L/kg, a middle value between 0.4 and 1.0 L/kg.[9] Excel 2007 was used to perform the simulations for one-compartment drug concentration versus time curves.

Two-compartment pharmacokinetic simulations used parameters taken from mean values listed in the article by Zoer et al.[20] The two-compartment simulations involved variables which included the zero order infusion rate constant, the central compartment volume, the first order rate constant for transfer between the two compartments, and the first order elimination rate constant from the central compartment. WinNonlin Version 5.2 and Excel 2007 were used to generate the two-compartment drug concentration versus time curve simulations.

A major assumption for the simulations was that pharmacokinetic parameters would be constant. In a clinical environment, the patient's renal function is dynamic, as noted by the variability in estimated glomerular filtration rate. Also, because weight can be dynamic due to fluid retention, the volume of distribution can vary throughout treatment. In such circumstances, PK parameters can be variable. These issues would necessitate a change in the dosing for patients to maintain therapeutic concentrations. The original simulation model produced by Osama Mohamed utilized F70NR (inpatient) and CT190G (outpatient) dialyzers. In the current study, most patients were dialyzed mainly with F160NR dialyzers, along with F180NR and AM-BIO-100 dialyzers.

2.3.4 STATISTICAL ANALYSIS

S-Plus, Version 6.2, was used to estimate summary statistics and also used to perform the Kolmogorov-Smirnov Test of Composite Normality to assess the normality of the data distribution(s) when needed. S-Plus was also utilized for power tests. Excel 2007 was used for statistical analyses evaluating the predictive performance of both the one and two-compartment simulation data and produce 95% confidence intervals.

2.3.5 BIOANALYTICAL METHODS

Blood samples were drawn from phlebotomy, catheter, or directly from hemodialysis circuitry. Plasma/serum vancomycin concentrations from blood samples collected in-hospital were analyzed by the in-house laboratory using the Beckman Coulter Synchron Systems. Two different in-house instruments were utilized in the assay of vancomycin concentrations. The lower limit of the analytical range was 3.5mg/L. Linearity was observed between 5-50 mg/L. The intra-day CV for both instruments between 5-50mg/L was less than 1.3%. The inter-day CV for both instruments between 5-50mg/L was less than 1.5%. Vancomycin concentrations from blood samples collected in the outpatient setting were measured by Spectra Laboratories, Milpitas, CA using the Advia Centaur Vancomycin assay. The lower limit of the analytical range was 0.67mg/L. Linearity was observed between 0-87 mg/L. The intra-assay CV between 0-87 mg/L was less than 7%. No inter-assay precision data were available from Spectra Laboratories.

2.4 RESULTS

2.4.1 PRELIMINARY SIMULATIONS

Figures 2.1-2.3 show the simulated drug concentration versus time curves of various considered dosing schemes. Combinations of fixed amounts of drug and weight-based dosing were involved with the simulations. Also factored in was the variability in

the timing of the dose, whether it was on or off-dialysis.[1] The pharmacokinetic parameters from the literature[2] were involved with the simulations. In general, the regimens for Figures 2.2 and 2.3 resulted in higher simulated concentrations. Figure 2.4 simulations involving Table 2.1 PK parameters[2, 9, 18] produced desired drug concentration versus time curves and were used to teach the Institutional Review Board that there was a reason to dose based on weight, and to dose during dialysis. Figure 2.4 shows troughs ranging between 13.10 and 17.76mg/L. See Table 2.2.

2.4.2 DEMOGRAPHIC RESULTS

Between May 2007 and June 2009, ten hemodialysis patients were enrolled. Their reasons for vancomycin administration are listed in Table 2.3. Eight patients had evaluable data. The first patient in the cohort experienced Red Man Syndrome[21] during the first dose and was removed from the study. No data were collected. The fourth patient in the cohort received a 15mg/kg study dose as prophylaxis. A random blood sample was taken immediately prior to the administration the study dose to serve as a baseline concentration. The scheduled peak concentration to be drawn after the completion of the drug infusion was unobtainable. The patient was removed from the study after culture results came back negative. Therefore, no usable pharmacokinetic information were collected from the fourth patient. Patient demographics are listed in Table 2.3. Nine patients were male. One patient was female. Patient ages ranged from 18-68 years. Post hemodialysis weights ranged from 63.27-130.20 kg. (Table 2.4)

2.4.3 SIMULATIONS

Results are shown in Tables 2.5-2.12 for the one-compartment simulations. Tables 2.13-2.20 show results for the two-compartment simulations. The corresponding

Figures 2.5-2.12 and 2.13-2.20 show the graphical representations for the one and two-compartment simulations respectively.

Predictive performance statistics for the one-compartment simulations include prehemodialysis troughs and the random draws during hemodialysis, typically prior to intradialytic drug administration. Peak concentrations following the starting dose were excluded from the estimation of predictive performance statistics as one-compartment pharmacokinetics do not include drug concentrations in the distribution phase.[13] For the one-compartment simulations, 26 drug concentrations were assessed for the predictive performance statistics. The RMSE, equaled 4.30mg/L (95% CI: 3.21, 5.1514).

Predictive performance statistics for the two-compartment simulations involved the drug concentrations taken following the infusion of the regimen starting dose. Fourteen drug concentrations were inspected to assess predictive performance. These included drug concentrations from the first study dosing interval where samples were drawn during the distribution phase and any following trough concentrations for that dosing interval. The RMSE equaled 14.76mg/L (95% CI: 5.45, 20.14)

2.4.4 PROSPECTIVE SIMULATIONS

ONE-COMPARTMENT SIMULATIONS (FIGURES 2.5-2.12)

All patients received starting doses off-dialysis. Patient 2 received a loading dose and a maintenance dose that was given during dialysis. Patient 3 already had a previous dose, so a random draw was done to assess a baseline concentration. Patient 3 was able to maintain acceptable trough concentrations throughout treatment. Patient 5 had a prior dose as well. He was given the regimen starting dose immediately after a dialysis session. The patient was discontinued when the cultures came up negative. Patient 6 required deviation from the study regimen, an increased maintenance dose because

trough concentrations were initially too low. Patient 7 had drug given prior to enrollment. This patient was given one dose off-dialysis and then discharged. Patient 8 was given vancomycin for 3 dosing intervals, with the 3rd dose given off-dialysis. He was discontinued and later reinstated on vancomycin. However, dosing thereafter was individualized. Patient 9 was given a single dose as prophylaxis and was discontinued when the cultures came up negative. Patient 10 had been dosed prior to enrollment. A combined ultrafiltration and dialysis session separated the two study dosing intervals. Resulting drug concentrations were acceptable.

Most of the one-compartment simulations had instances where the simulation under or over-predicted actual drug concentrations. See Figures 2.5-2.12. Patients 3, 6, and 8 were treated with the tested dosing regimen from 229.9 to 427.03 hours (Figures 2.6, 2.8, and 2.10). These figures show, see Figure 2.8– for example, that the simulation calculations and curves account for variable dosing times between the initial dose and the intradialytic doses, and individual patients weight. The most complicated example of this is Patient 8. (See Table 2.10.)

TWO-COMPARTMENT SIMULATIONS (FIGURES 2.13-2.20)

Only the first dosing interval was simulated for the patients since it was the only dosing interval with an actual drug concentration in the distribution phase.

2.4.5 RESULTANT VANCOMYCIN TROUGH CONCENTRATIONS

According to the American Thoracic Society and Infectious Diseases Society of America, troughs should range between 15-20mg/L for methicillin-resistant *Staphylococcus aureus* (MRSA) ventilator-associated pneumonia.[17] Although hemodialysis patients may not have pneumonia, the trough range should be high enough

to cover MRSA, thus the selection of 15-20mg/L for the desired trough range. Eighteen trough concentrations from patients who were dosed during the study both on and off the weight-based regimen had an average of 18.35mg/L (95% CI: 16.41, 20.28). Seven prehemodialysis concentrations were within the desired concentration range of (15-20mg/L)[17]. Five prehemodialysis concentrations were below the desired range. Six prehemodialysis concentrations were above the desired range. The power of the one-tailed test of the hypothesis that the average of all the 18 trough concentrations was greater than 15mg/L equaled 97.8%. The power of the one-tailed test of the hypothesis that the average of all the 18 trough concentrations was less than 20mg/L equaled 56.3%.

The 13 trough concentrations resulting from the weight-based regimen specifically had an average of 17.59 mg/L (95% CI: 16.01, 19.17). Eight prehemodialysis concentrations were within the desired concentration range. Three prehemodialysis concentrations were below the desired concentration range. Two prehemodialysis concentrations were above the desired concentration range. The power of the one-tailed test of the hypothesis that the average of the trough concentrations resulting from the weight-based regimen was greater than 15 equaled 97.3%. The power of the one-tailed test of the hypothesis that the average of the trough concentrations resulting from the weight-based regimen was lower than 20 equaled 95.3%.

2.4.6 INTRADIALYTIC ELIMINATION RATE CONSTANTS

For patients 2, 3, 6, 8, 9, and 10, the intradialytic elimination rate constants were estimated. These are shown in Table 2.21.

2.4.7 SAFETY AND EFFICACY

Two patients (Patients 1 and 6) experienced vancomycin infusion-related histamine release during the study. Patient 1 was discontinued after the first dose. Patient 6 subsequently received parenteral diphenhydramine as prophylaxis prior to vancomycin dosing.

Of the eight evaluable patients (patients 2, 3, 5, 6, 7, 8, 9, 10), there were four patients where adherence to the weight-based regimen resulted in desired concentrations (patients 3, 5, 7, 10). The other four patients (patients 2, 6, 8, 9) in the study required deviation from the weight-based regimen to avoid subtherapeutic concentrations or excessively high concentrations. These patients were not affected clinically by the variability in concentrations. If the trough concentration was above the minimal inhibitory concentration, it was adequate clinically. There was no reported ototoxicity due to the peak vancomycin concentrations after the first study dose, or other concentrations in the distribution phase.

2.5 DISCUSSION

In the literature, there are a number of vancomycin dosing regimens for high-flux hemodialysis patients. Barth and DeVincenzo presented a loading dose of 20mg/kg immediately postdialysis and 500mg after each dialysis session thereafter. This achieved pre-dialysis trough serum concentrations that ranged between 10-15mg/L. Plateau steady-state troughs ranged between 15-25mg/L after 2-3 weeks.[11] Ariano et al. utilized an intradialytic 1 gram loading dose during the last hour of dialysis and 500mg during the last hour of subsequent dialysis sessions. The mean pre-dialysis value was 11 ± 3 mg/L.[13] Zoer et al. recommended a 1000mg loading dose during dialysis and a 500mg maintenance dose during subsequent dialysis sessions. This regimen was determined by

simulations based upon 2 compartment PK parameters of the study cohort.[20] Lucksiri et al. showed a 15mg/kg dose given during the last hour of hemodialysis produced a median pre-dialysis vancomycin concentration of 14.0 mg/L (range 7.7-16.0).[15] With a threshold for re-dosing of 10mg/L, Mason et al. recommend 15mg/kg of vancomycin after dialysis or 30mg/kg given during the last 2 hours of dialysis. These patients will require re-dosing on Day 8. If a patient is dosed at 15mg/kg during the last hour of dialysis, they will require re-dosing on Day 5 of therapy. The author goes on to note that because of variability in residual renal function, dialysis session duration, and dialysis membrane, patients will need vancomycin therapeutic drug monitoring.[2] Touchette et al. have a more complex process for dosing vancomycin in dialysis patients. The loading dose of approximately 1000mg comes first. A trough level 6 hours post dialysis follows. If the post-rebound trough serum vancomycin concentration is $\leq$ 12mg/L, 1000mg vancomycin is given. If the post-rebound trough concentration is between 12-25mg/L, 500mg vancomycin is given. If the post-rebound trough concentration is $\geq$ 25mg/L, the patient should not be given a dose. A trough concentration should be drawn 6 hours following the next dialysis session. When a 6 hour post dialysis trough concentration ranging in between 12-25mg/L is drawn, one may give a 500mg dose of vancomycin after each dialysis session.[18] The most recent definitive study published on vancomycin dosing in hemodialysis patients was published in 2005 by Ariano et al.[13] With such diverse and complex dosing regimens with different dialyzer membranes listed in the literature, there is no standard dosing regimen implemented in the clinical setting. This defined the need for this prospective study with the weight-based dosing regimen that was based upon the retrospective study.

The goals of the present study were to a) evaluate the accuracy of selected pharmacokinetic simulations for prediction of drug concentration versus time data in hemodialysis patients being dosed vancomycin and b) test the ability of the weight-based dosing regimen to produce trough concentrations in the therapeutic range as predicted by the original simulation retrospective study.

One-compartment simulations were used for all patients since these are used clinically. The one-compartment simulation is simpler to use and it includes the clinically relevant prehemodialysis trough concentration.[13] The one-compartment simulation was used in the retrospective study simulations.

The two-compartment simulations were intended to span the dosing interval for the first study dose in order to capture the post starting dose blood sample in the distribution phase as vancomycin can be described a multi-compartmental drug.[20] Although two-compartment simulations were not the basis of the original retrospective simulation study, these were worthy of investigation in the prospective study.

The initial simulations (Figures 2.1-2.4) were important because they served as a platform to compare differing dosing regimens to see which would produce therapeutic trough drug concentrations (15-20 mg/L).[22] This reduces the need to use actual patients to generate candidate regimens and is more cost effective. Because each patient's PK parameters are individualized, and three different dialysis membranes were involved, it is expected that there would be variability between actual and simulated drug concentration versus time data. There was clinically significant prediction error for both the one and two-compartment models, with the RMSE equaling 4.30 and 14.76 mg/L, respectively. The predictive performance of the simulations using the PK parameters from the

literature for the retrospective cohort was stronger.[2] Population based simulations cannot predict every individual's actual serum drug concentration from dosing with acceptable accuracy. However, a desired average trough concentration range was seen, with a 95% confidence interval for the average of the sampled trough concentrations during the study ranging from 16.41 to 20.28mg/L. The 95% confidence interval for average of the sampled trough concentrations utilizing the study regimen was even narrower, ranging from 16.01 to 19.17mg/L. Both ranges were between 15-20 mg/L, and therefore acceptable.[17] These results are impressive given the involvement of different patient characteristics and different dialysis membranes used. Recall that no published clearance data for vancomycin with these membranes was found which made it necessary to estimate the vancomycin clearance based on relative B_{12} clearance.[18, 23] Given the outcome of the prospective study, having a pharmacist proactively involved in dose estimation, utilizing both protocol and individualization of dosing when necessary, produces more desirable serum concentrations than administration of arbitrary doses based upon ease of dose preparation and subjective gauge of a patient's size.

2.6 CONCLUSION

Prospective simulations can serve as a general guide for dosing vancomycin during the last hour of hemodialysis. PK weight-based dosing of vancomycin during the last hour of hemodialysis is a more individualized method of dose estimation that can generate therapeutic drug concentrations in hemodialysis patients.

2.7 REFERENCES

1. Foote EF, Dreitlein WB, Steward CA et al. Pharmacokinetics of vancomycin when administered during high flux hemodialysis. *Clin Nephrol* 1998; **50:** 51-55.

2. Mason NA, Neudeck BL, Welage LS et al. Comparison of 3 vancomycin dosage regimens during hemodialysis with cellulose triacetate dialyzers: post-dialysis versus intradialytic administration. *Clin Nephrol* 2003; **60:** 96-104.

3. Quale JM, O'Halloran JJ, DeVincenzo N et al. Removal of vancomycin by high-flux hemodialysis membranes. *Antimicrob Agents Chemother* 1992; **36:** 1424-1426.

4. Wilcox MH, Tack KJ, Bouza E et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study.[see comment]. *Clin Infect Dis* 2009; **48:** 203-212.

5. Wilhelm MP, Estes L. Symposium on antimicrobial agents--Part XII. Vancomycin. *Mayo Clin Proc* 1999; **74:** 928-935.

6. Rybak MJ, Lomaestro BM, Rotscahfer JC et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis* 2009; **49:** 325-327.

7. Harigaya Y, Bulitta JB, Forrest A et al. Pharmacodynamics of vancomycin at simulated epithelial lining fluid concentrations against methicillin-resistant Staphylococcus aureus (MRSA): implications for dosing in MRSA pneumonia. *Antimicrob Agents Chemother* 2009; **53:** 3894-3901.

8. Fridkin SK, Hageman J, McDougal LK et al. Epidemiological and microbiological characterization of infections caused by Staphylococcus aureus with reduced susceptibility to vancomycin, United States, 1997-2001. *Clin Infect Dis* 2003; **36:** 429-439.

9. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis* 2006; **42 Suppl 1:** S35-39.

10. Allon M. Dialysis catheter-related bacteremia: treatment and prophylaxis. *Am J Kidney Dis* 2004; **44:** 779-791.

11. Barth RH, DeVincenzo N. Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy. *Kidney Int* 1996; **50:** 929-936.

12. Welage LS, Mason NA, Hoffman EJ et al. Influence of cellulose triacetate hemodialyzers on vancomycin pharmacokinetics. *J Am Soc Nephrol* 1995; **6:** 1284-1290.

13. Ariano RE, Fine A, Sitar DS et al. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. *Am J Kidney Dis* 2005; **46:** 681-687.

14. Susla GM. The impact of continuous renal replacement therapy on drug therapy. *Clin Pharmacol Ther* 2009; **86:** 562-565.

15. Lucksiri A, Scott MK, Mueller BA et al. CAHP-210 dialyzer influence on intra-dialytic vancomycin removal. *Nephrol Dial Transplant* 2002; **17:** 1649-1654.

16. Scott MK, Macias WL, Kraus MA et al. Effects of dialysis membrane on intradialytic vancomycin administration. *Pharmacotherapy* 1997; **17:** 256-262.

17. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia.[see comment]. *Am J Respir Crit Care Med* 2005; **171:** 388-416.

18. Touchette MA, Patel RV, Anandan JV et al. Vancomycin removal by high-flux polysulfone hemodialysis membranes in critically ill patients with end-stage renal disease. *Am J Kidney Dis* 1995; **26:** 469-474.

19. Bouman CS, van Kan HJ, Koopmans RP et al. Discrepancies between observed and predicted continuous venovenous hemofiltration removal of antimicrobial agents in critically ill patients and the effects on dosing. *Intensive Care Med* 2006; **32:** 2013-2019.

20. Zoer J, Schrander-van der Meer AM, van Dorp WT. Dosage recommendation of vancomycin during haemodialysis with highly permeable membranes. *Pharm World Sci* 1997; **19:** 191-196.

21. Wazny LD, Daghigh B. Desensitization protocols for vancomycin hypersensitivity. *Ann Pharmacother* 2001; **35:** 1458-1464.

22. Pea F, Viale P. Should the currently recommended twice-daily dosing still be considered the most appropriate regimen for treating MRSA ventilator-associated pneumonia with vancomycin? *Clin Pharmacokinet* 2008; **47:** 147-152.

23. Ronco C, Orlandini G, Brendolan A et al. Enhancement of convective transport by internal filtration in a modified experimental hemodialyzer: technical note. *Kidney Int* 1998; **54:** 979-985.

2.8 TABLES

2.1 PHARMACOKINETIC PARAMETERS FOR THE SIMULATIONS

Weight of patient	**70 Kg (assumed)**
Drug Clearance of patient or Interdialytic clearance (CLID)	**0.392 L/hr (6.53 ml/min)**
Clearance during hemodialysis or Intradialytic clearance (CLHD) F70 dialyzer clearance (estimated approximately equal to F80 dialyzer clearance) CT190G dialyzer clearance	**5.93 L/hr (98.8 ml/min)** **7.007 L/hr (116.8 ml/min)**
Volume of distribution (Vd)	**49 L**
Elimination rate constant during the hemodialysis session F70 dialyzer elimination rate constant (estimated approximately equal to F80 dialyzer elimination rate constant) CT190G dialyzer elimination rate constant	 **0.134 1/hr** **0.143 1/hr**
Elimination rate constant interdialytic	**0.008 1/hr**
Time of dialysis session	**4 hr (assumed)**

Ref: Clin Nephrol 2003; 60: 96-104[2]
Am J Kidney Dis 1995;26(3):469-74[18]
Clin Infect Dis 2006; 42 Suppl 1: S35-39[9]

2.2 SIMULATED PHARMACOKINETIC PARAMETERS

-PROPOSED DOSING METHOD

	Peak (mg/L)	Trough (mg/L)
After loading dose	21.34	17.76
After maintenance dose 1	25.19	17.72
After maintenance dose 2	23.31	16.39
After last maintenance dose listed	22.56	13.10

By giving the 10mg/kg dose at the end of hemodialysis, the drug plasma concentration will decrease more slowly as the drug is cleared only by the patient's renal function during the interdialytic period. Thus the plasma concentration will stay in the desired Cmax range longer for greater pharmacodynamic effect. The patient is redosed before the drug plasma concentration drops below the MIC.

2.3 PATIENT DEMOGRAPHICS

Patient	Age (yrs)	Sex	Weight (kg)	Race	Cause of ESRD	Reason for treatment
1	18	M	64.5	Hispanic	Unknown etiology	Line infection
2	59	M	66	Caucasian	Hepatorenal syndrome	MRSA septicemia
3	50	M	78.2	Caucasian	Membranous glomerulonephritis	L forearm abscess
4	63	M	72.6	Caucasian	Diabetes	Prophylaxis
5	62	M	95.4	Caucasian	Amyloidosis	Prophylaxis
6	34	M	65.5	Black	Sickle cell nephropathy	Coagulase-negative Staphylococcus species, catheter tip
7	67	F	83.5	Caucasian	Diabetes	Right fistula post-operative wound infection
8	44	M	128.7	Caucasian	Acute tubular necrosis	Coagulase-negative Staphylococcus species bacteremia
9	30	M	80.5	Hispanic	Hypertension	Coagulase-negative Staphylococcus species bacteremia
10	68	M	72	Asian	Diabetes	Coagulase-negative Staphylococcus species, central line
Min	**18**		**64.5**			
Max	**68**		**128.7**			

Notes regarding Patient 1:
Original physician orders form that would have listed weight lost
Patient 1 was given a rounded loading dose of 950mg vancomycin IV
Patient 1 prehemodialysis weight listed from hemodialysis flowsheet 2 days after start of antibiotic treatment

2.4 POST HEMODIALYSIS PATIENT WEIGHTS (KG)

patient	1	2	3	4	5	6	7	8	9	10
			78.8	72.6	95.4	77.1	83.5	128.3	78	65.5
			78.2			63.6		133.2		69.7
			77.1			67.4		129.1		
			76.7			66.9				
			77.2			64.1				
			78			60.3				
			77.9			57.2				
						56.1				
						56.7				
average			**77.70**	**72.60**	**95.40**	**63.27**	**83.50**	**130.20**	**78.00**	**67.60**

Cohort min **63.27**

Cohort max **130.20**

2.5 ONE-COMPARTMENT SIMULATION EVENT LOG, PATIENT 2

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	Vanco Cp (mg/L)
dose start	0	1000		inter	0.00	0
dose stop	1			inter	21.56	
postdose blood sample	1.07			inter	21.55	59.7
preHD trough	16.72			inter	19.01	13.6
start HD	16.95		F160NR	inter	18.98	
predose blood sample	19.08			intra	14.10	7.9
dose start	19.22	700		intra	13.83	
dose stop and stop HD	20.22			intra	26.18	

2.6 ONE-COMPARTMENT SIMULATION EVENT LOG, PATIENT 3

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	Vanco Cp (mg/L)
start HD	-53.95			intra		
stop HD	-49.95			intra		
dose start	-42.85	1000		inter		
dose stop	-41.85			inter		
start HD	-7.53			inter		
stop HD	-3.33			intra		
predose blood sample	0			inter	12.10	12.1
dose start	0.07	586.2656		inter	12.09	
dose stop	1.67			inter	30.69	
dose start	1.83	38.168		inter	30.65	
dose stop	1.87			inter	31.34	
dose start	1.87	632.07		inter	31.34	
dose stop	2.63			inter	42.66	
postdose blood sample	3.53			inter	42.35	38
preHD trough	61.38			inter	26.66	20.31

start HD	61.43		F160NR	inter	26.65	
predose blood sample	64.45			intra	17.50	12.5
dose start	64.46	750		intra	17.47	
dose stop	65.36			intra	28.29	
stop HD	65.45			intra	27.94	
preHD trough	109.4			inter	19.66	17.47
start HD	109.45		F180NR	inter	19.65	
dose start	112.2	750		intra	12.86	
dose stop	113.2			intra	23.73	
stop HD	113.47			intra	22.76	
preHD trough	157.3			inter	16.03	18.12
start HD	157.35		F180NR	inter	16.02	
dose start	160.52	750		intra	9.83	
dose stop	161.4			intra	21.40	
stop HD	161.62			intra	20.69	
preHD trough	229.38			inter	12.03	19.84
start HD	229.48		F180NR	inter	12.02	
dose start	232.66	750		intra	7.37	
dose stop	233.56			intra	19.21	
stop HD	233.63			intra	19.00	
preHD trough	277.75			inter	13.35	19.32
start HD	277.67		F180NR	inter	13.36	
dose start	280.45	750		intra	8.71	
dose stop	281.45			intra	20.16	
stop HD	281.75			intra	19.25	
start HD	325.5		F180NR	inter	13.57	
dose start	328.55	750		intra	8.48	
dose stop	329.47			intra	20.14	
stop HD	329.67			intra	19.53	

2.7 ONE-COMPARTMENT SIMULATION EVENT LOG, PATIENT 5

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
dose start	-26.48	1000		inter		
dose stop	-25.48			inter		
start HD	-3.98			inter		
stop HD	-0.48			intra		
predose blood sample	0			inter	6.20	6.2
dose start	0.28	1400		inter	6.19	
dose stop	1.78			inter	26.95	
postdose blood sample	1.82			inter	26.94	37.8
preHD trough	43.51			inter	19.30	18.7

2.8 ONE-COMPARTMENT SIMULATION EVENT LOG, PATIENT 6

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	Vanco Cp (mg/L)
dose start	0	1000		inter	0.00	
dose stop	2.03			inter	21.63	
postdose blood sample	2.6			inter	21.54	22.8
preHD trough	36.67			inter	16.40	14.1
start HD	36.74		F160NR	inter	16.39	
predose blood sample	39.64			intra	10.94	8.6
dose start	39.67	700		intra	10.90	
dose stop	40.64			intra	23.80	
stop HD	40.8			intra	23.27	
preHD trough	84			inter	16.47	13.8
start HD	84.08		F160NR	inter	16.46	
dose start	87.08	1000		intra	10.84	
dose stop	88.08			intra	29.79	
stop HD	88.1			intra	29.70	
start UF	113.35		F160NR	inter	24.27	

stop UF	115.38			intra	22.42	
preHD trough	155.88			inter	16.21	11.8
start HD	155.93		F160NR	inter	16.21	
dose start	158.68	1250		intra	11.05	
dose stop	159.93			intra	34.30	
stop HD	159.98			intra	34.07	
preHD trough	206.6			inter	23.46	20.55
start HD	206.7		F180NR	inter	23.44	
dose start	209.63	1000		intra	14.93	
dose stop	210.62			intra	33.05	
stop HD	210.73			intra	32.49	
preHD trough	254.77			inter	22.84	23.79
start HD	254.84		F180NR	inter	22.83	
dose start	257.85	1000		intra	14.36	
dose stop	258.79			intra	32.73	
stop HD	258.87			intra	32.33	
start HD	273.68		F160NR	inter	28.72	
dose start	276.55	500		intra	19.25	
dose stop	277.01			intra	28.62	
stop HD	277.06			intra	28.42	
preHD trough	327.02			inter	19.06	24.26
start HD	327.1		F180NR	inter	19.05	
stop HD	331.1			intra	10.29	
preHD trough	374.65			inter	7.26	14.47
start HD	374.68		F180NR	inter	7.26	
dose start	377.65	750		intra	4.59	
dose stop	378.63			intra	19.13	
stop HD	378.75			intra	18.78	
start HD	422.95		F180NR	inter	13.19	
dose start	425.98	750		intra	8.27	
dose stop	427.03			intra	22.14	

stop HD	427.03			intra	22.14	

2.9 ONE-COMPARTMENT SIMULATION EVENT LOG, PATIENT 7

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
dose start	-22.07	1000		inter		
dose stop	-21.07			inter		
start HD	-11.42			inter		
stop HD	-8.47			intra		
predose blood sample	0			inter	12.00	12
dose start	0.17	1250		inter	11.98	
dose stop	1.42			inter	33.14	
postdose blood sample	1.62			inter	33.09	41.2

2.10 ONE-COMPARTMENT SIMULATION EVENT LOG, PATIENT 8

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	Vanco Cp (mg/L)
dose start	0	1900		inter	0.00	
dose stop	2.08			inter	20.92	
postdose blood sample	2.15			inter	20.90	39.3
preHD trough	9.78			inter	19.67	17.1
start HD	9.78		F160NR	inter	19.67	
predose blood sample	12.46			intra	13.54	12.7
dose start	12.46	1300		intra	13.54	
dose stop	13.76			intra	24.49	
stop HD	13.86			intra	24.15	
predose blood sample	59			inter	16.83	16.2
dose start	59.02	1300		inter	16.83	
dose stop	60.32			inter	31.01	
start HD	65.35		F160NR	inter	29.79	
stop HD	67.45			intra	22.23	

start HD	82.02		F160NR	inter	19.79	
stop HD	86.19			intra	11.07	
dose start	95.03	1110		inter	10.31	
dose stop	96.15			inter	22.49	
start UF	163.85		F160NR	inter	13.08	
stop UF	165.85			intra	12.47	
start HD	180.77		F160NR	inter	11.07	
stop HD	184.77			intra	6.34	
random blood sample	205.98			inter	5.35	13.3
start UF	207.65		F160NR	inter	5.28	
change Quf	207.93			intra UF	5.25	
dose start	208.15	1500		intra UF	5.22	
dose stop	209.65			intra UF	21.36	
stop UF	209.71			intra UF	21.32	
preHD trough	225.85			inter	18.74	24.7
start HD	225.88		F160NR	inter	18.74	
stop HD	229.9			intra	10.70	

2.11 ONE-COMPARTMENT SIMULATION EVENT LOG, PATIENT 9

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	Vanco Cp (mg/L)
dose start	0	1200		inter	0.00	
dose stop	1.2			inter	21.19	
postdose blood sample	1.2			inter	21.19	45.7
preHD trough	10.58			inter	19.66	22.1
start HD	10.65		F160NR	inter	19.65	
random blood sample	13.35			intra	13.49	13
stop HD	14.2			intra	11.98	

2.12 ONE-COMPARTMENT SIMULATION EVENT LOG, PATIENT 10

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
dose start	-67.9	1000		inter		
dose stop	-66.9			inter		
start HD	-9.57			inter		
stop HD	-9.15			intra		
start HD	-8.9			inter		
stop HD	-7.95			intra		
start HD	-7.6			inter		
stop HD	-6.48			intra		
predose blood sample	0			inter	10.60	10.6
dose start	0.05	1000		inter	10.60	
dose stop	1.15			inter	30.26	
postdose blood sample	1.17			inter	30.25	42.3
start UF	18.83		AM-BIO-100	inter	26.27	
stop UF	19.85			intra	25.63	
start HD	19.85		AM-BIO-100	intra	25.63	
stop HD	21.9			intra	21.16	
preHD trough	36.82			inter	18.78	18
start HD	36.87		AM-BIO-100	inter	18.77	
predose blood sample	39.1			intra	15.24	16.5
dose start	39.14	700		intra	15.19	
dose stop	40.15			intra	27.07	
stop HD	40.15			intra	27.07	

2.13 TWO-COMPARTMENT SIMULATION EVENT LOG, PATIENT 2

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
dose start	0	1000		inter		
dose stop	1			inter		
postdose blood sample	1.07			inter	68.57	59.7
preHD trough	16.72			inter	16.85	13.6

2.14 TWO-COMPARTMENT SIMULATION EVENT LOG, PATIENT 3

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
blood sample	0			inter	12.1	12.1
starting dose	0.07	586.2656		inter		
stopping dose	1.67			inter		
starting dose	1.83	38.168		inter		
stopping dose	1.87			inter		
starting dose	1.87	632.07		inter		
stopping dose	2.63			inter		
blood sample	3.53			inter	42.33	38
preHD trough	61.38			inter	16.58	20.31

2.15 TWO-COMPARTMENT SIMULATION EVENT LOG, PATIENT 5

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
blood sample	0			inter	6.2	6.2
vanco start	0.28	1400		inter		
vanco stop	1.78			inter		
blood sample	1.82			inter	63.07	37.8
preHD trough	43.51			inter	15.70	18.7

2.16 TWO-COMPARTMENT SIMULATION EVENT LOG, PATIENT 6

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
dose start	0	1000		inter		
dose stop	2.03			inter		
postdose blood sample	2.6			inter	33.61	22.8
preHD trough	36.67			inter	13.51	14.1

2.17 TWO-COMPARTMENT SIMULATION EVENT LOG, PATIENT 7

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
blood sample	0			inter	12	12
start vanco	0.17	1250		inter		
stop vanco	1.42			inter		
blood sample	1.62			inter	65.66	41.2

2.18 TWO-COMPARTMENT SIMULATION EVENT LOG, PATIENT 8

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
dose start	0	1900		inter		
dose stop	2.08			inter		
postdose blood sample	2.15			inter	47.21	39.3
preHD trough	9.78			inter	17.93	17.1

2.19 TWO-COMPARTMENT SIMULATION EVENT LOG, PATIENT 9

event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
dose start	0	1200		inter		
dose stop	1.2			inter		
postdose blood sample	1.2			inter	67.24	45.7

preHD trough	10.58			inter	17.84	22.1

2.20 TWO-COMPARTMENT SIMULATION EVENT LOG, PATIENT 10

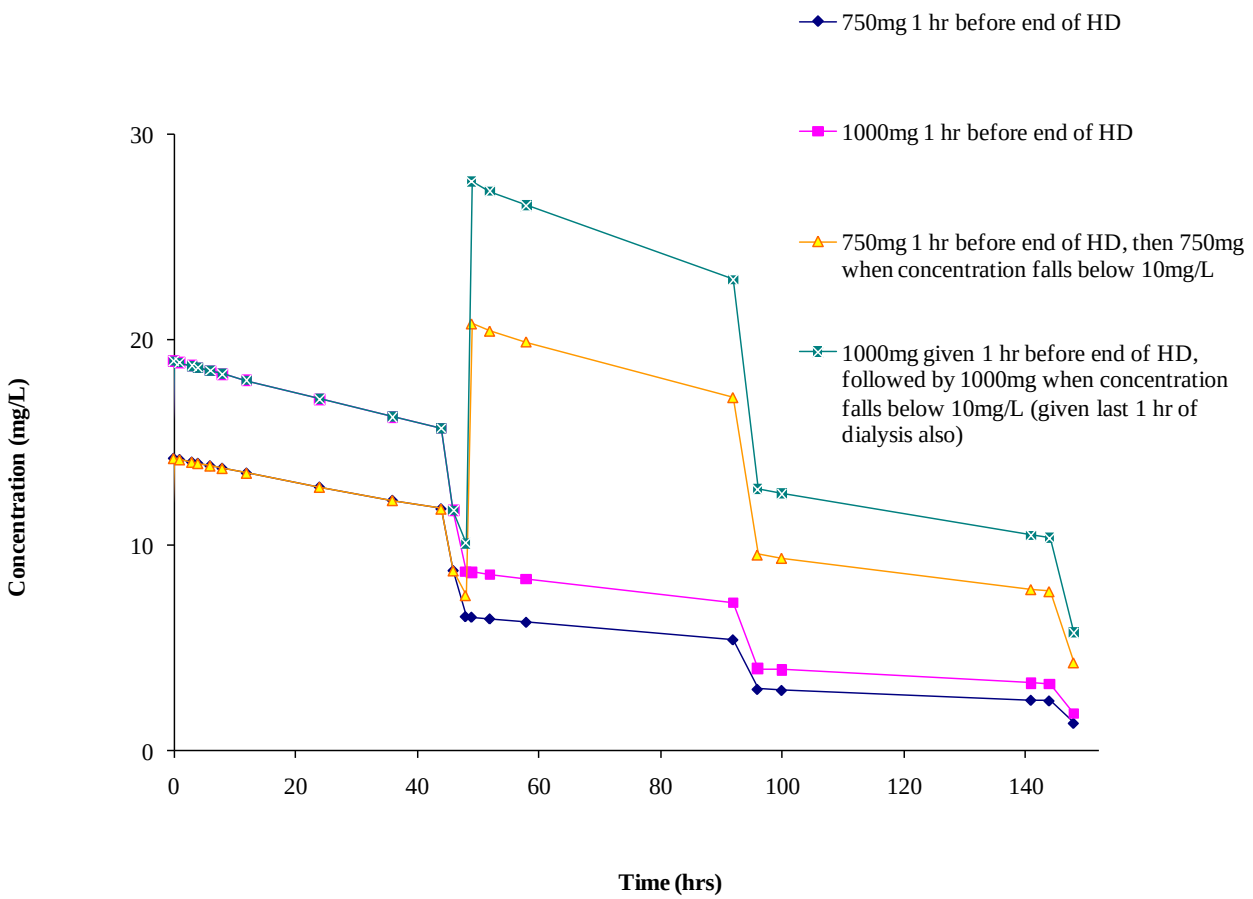
event	elapsed time (hrs)	dose (mg)	HD filter	inter/intra HD	simulated vanco Cp (mg/L)	vanco Cp (mg/L)
blood sample	0			inter	10.6	10.6
start vanco	0.05	1000		inter		
stop vanco	1.15			inter		
blood sample	1.17			inter	74.21	42.3
start UF	18.83		AM-BIO-100	inter		

2.21 INTRADIALYTIC ELIMINATION RATE CONSTANTS

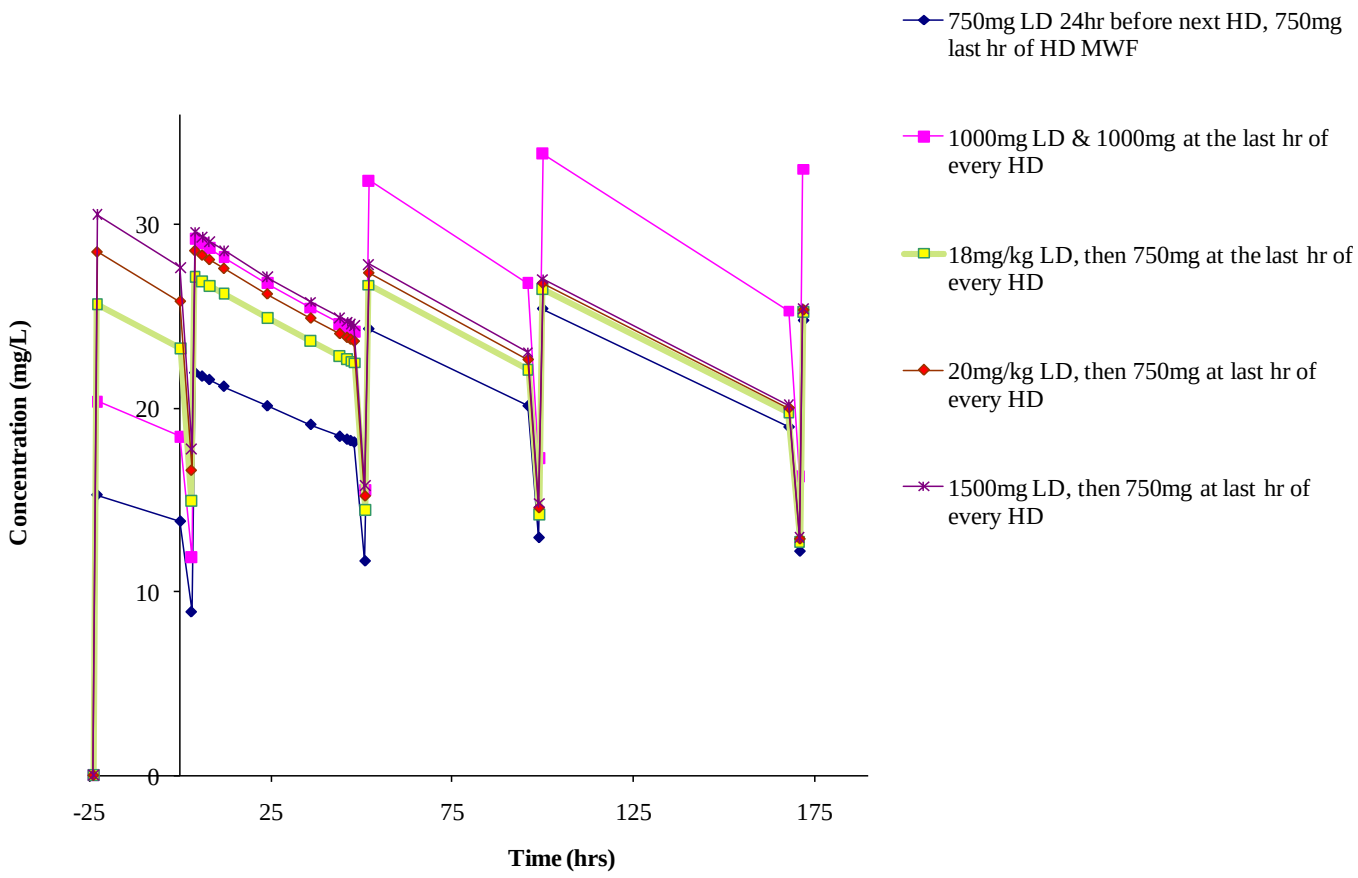
Patient	Dialysis Filter	Intradialytic k (1/hr)
2	F160NR	0.230
3	F160NR	0.158
6	F160NR	0.166
8	F160NR	0.111
9	F160NR	0.192
10	AM-BIO-100	0.038

2.9 FIGURES

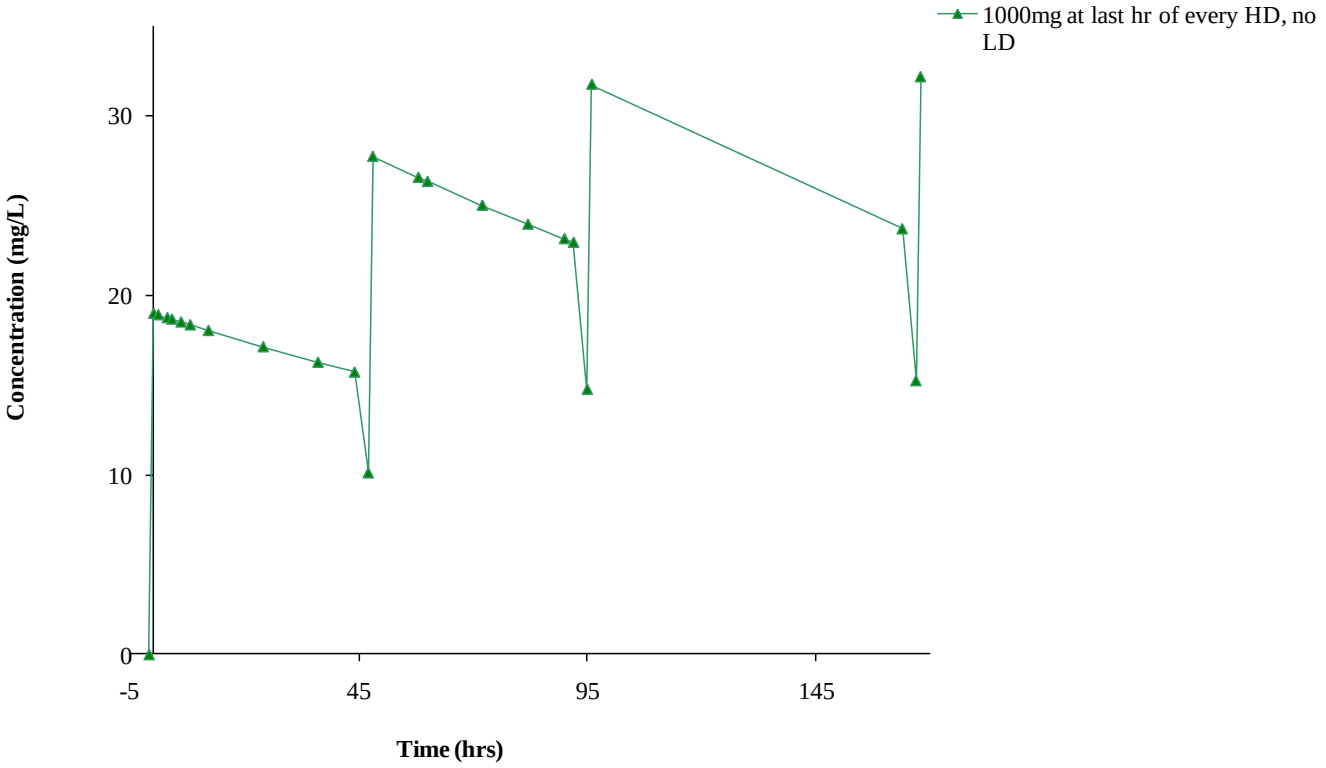
2.1 GRAPH PRELIMINARY SIMULATIONS 1



2.2 GRAPH PRELIMINARY SIMULATIONS 2

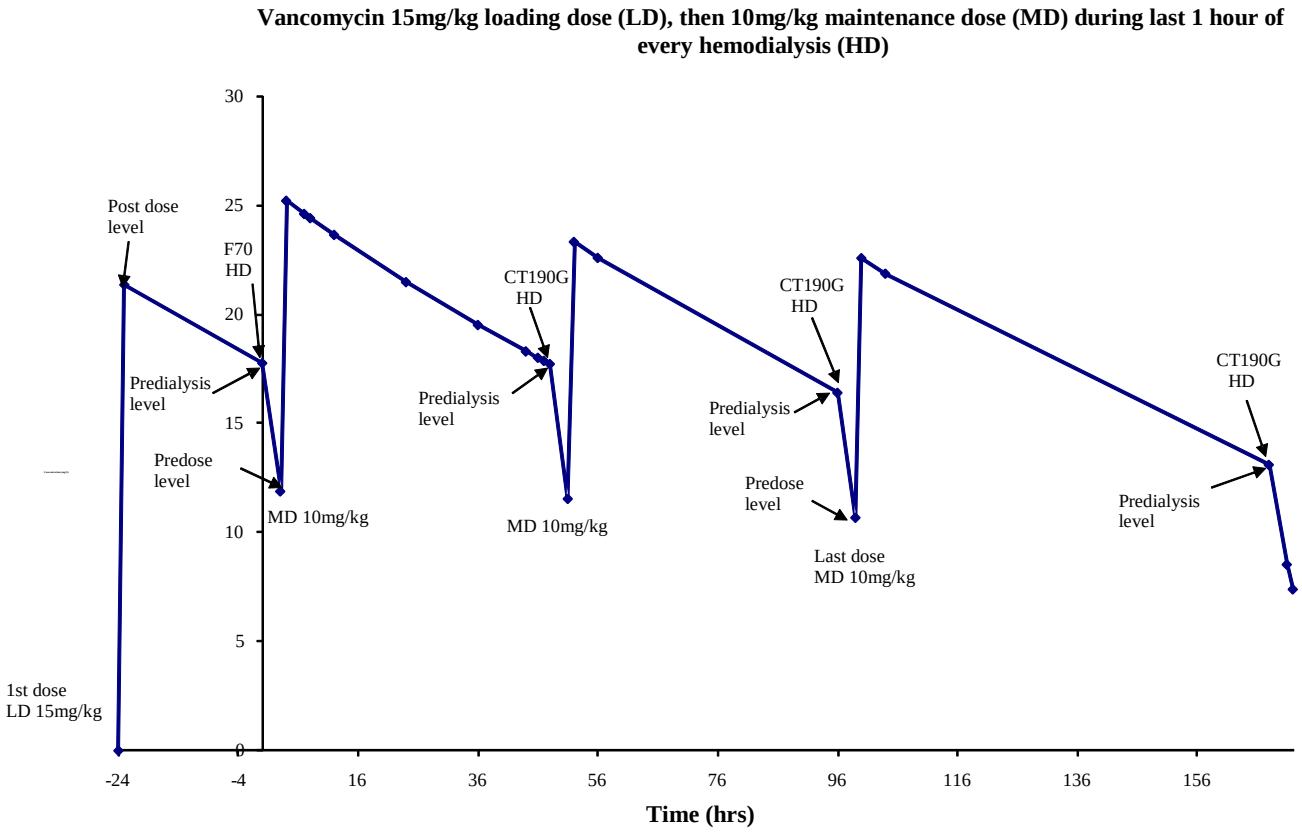


2.3 GRAPH PRELIMINARY SIMULATIONS 3



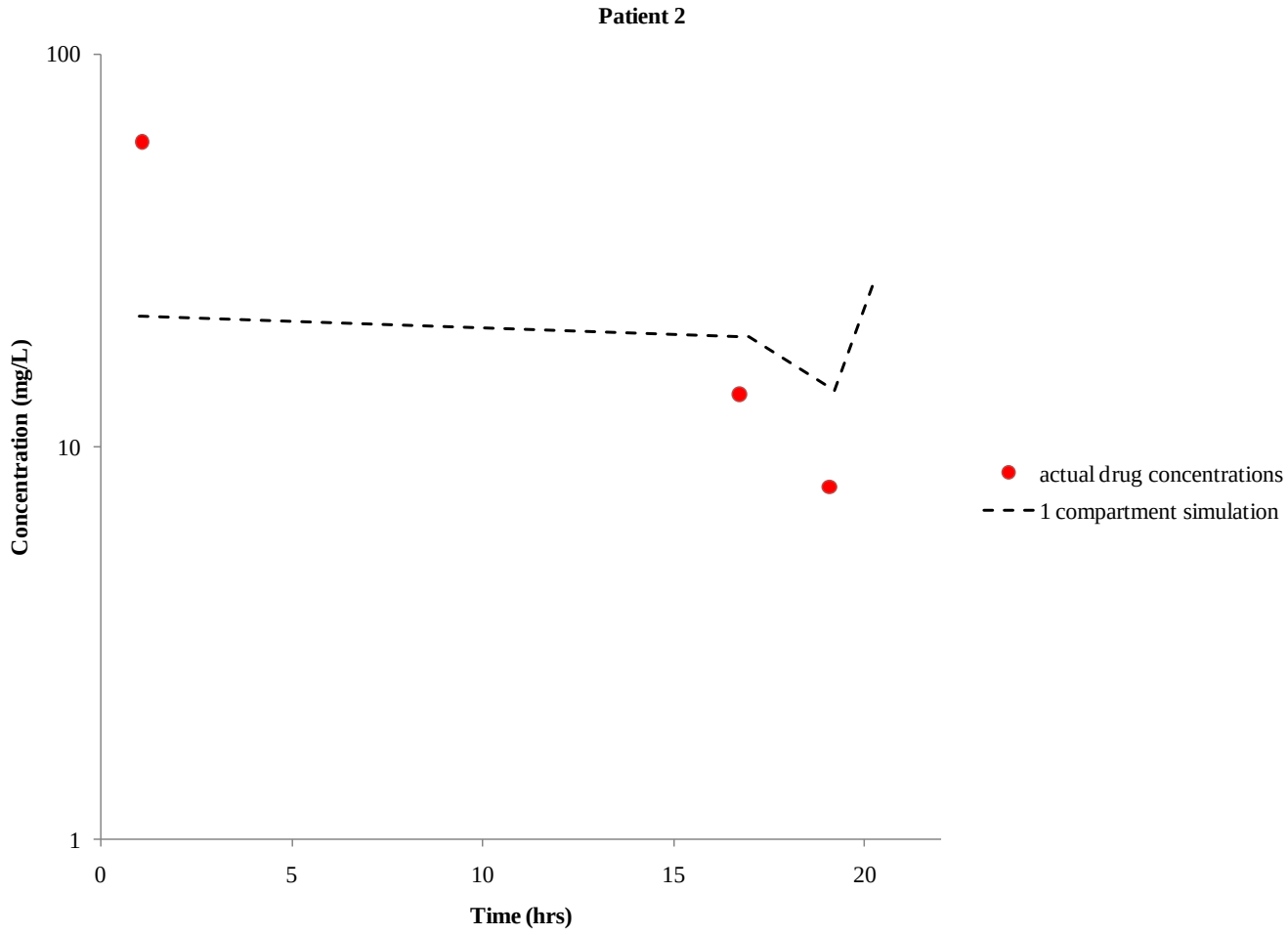
Pharmacokinetic simulations were performed to determine a good regimen for dosing vancomycin during dialysis. One-compartment, linear intravenous infusion model equations were used to determine the predicted plasma concentrations. Out of a series of simulations, a 15mg/kg loading dose, then a maintenance dose of 10mg/kg during the last hour of every hemodialysis was selected. This simulation resulted in desired plasma concentrations greater than the MIC of 10mg/L and Cmax within 20–30mg/L. The assumptions used in performing the simulations are listed in Table 2.1.

2.4 GRAPH VANCOMYCIN PK SIMULATIONS

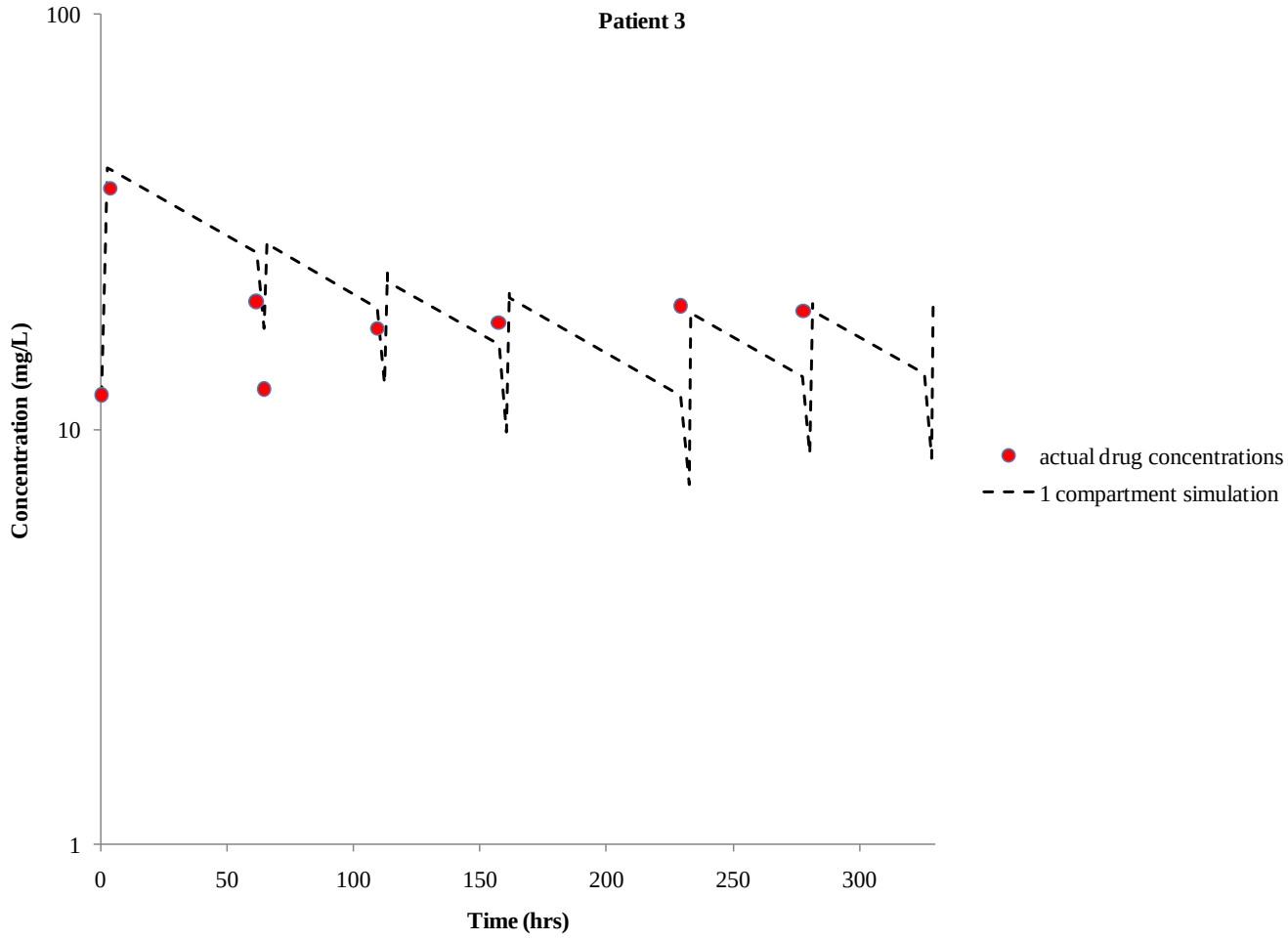


Using the pharmacokinetic parameters from Table 2.1, the figure shows the predicted plasma concentration versus time curve for the proposed dosing modality. The loading dose is given 24 to 72 hours before the next dialysis session. Maintenance doses are given during the last hour of dialysis 3 times/week. If a patient is hemodialyzed for 4 hours, there are 44 or 68 hours between dialysis sessions.)

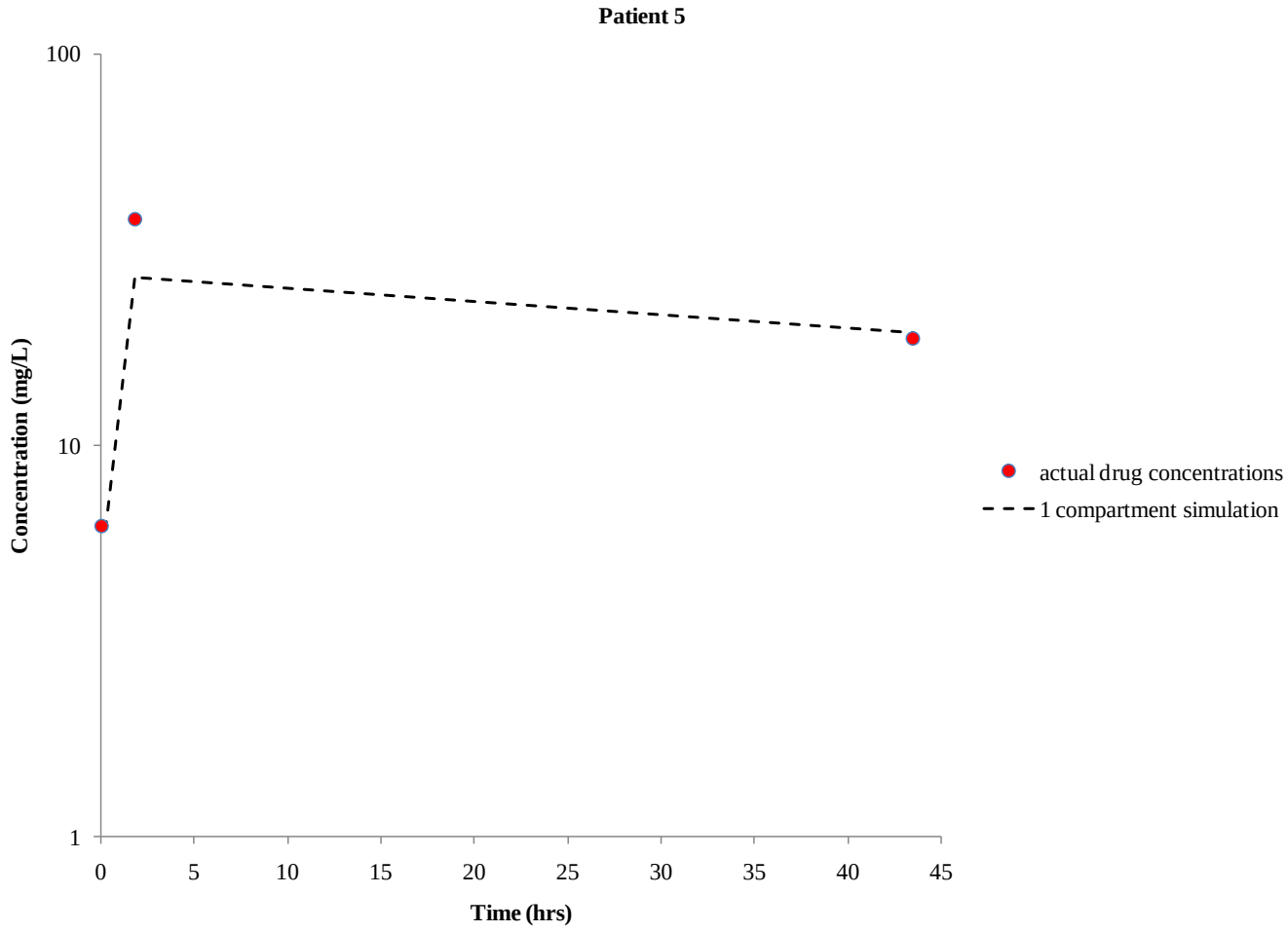
2.5 GRAPH ONE-COMPARTMENT SIMULATION, PATIENT 2



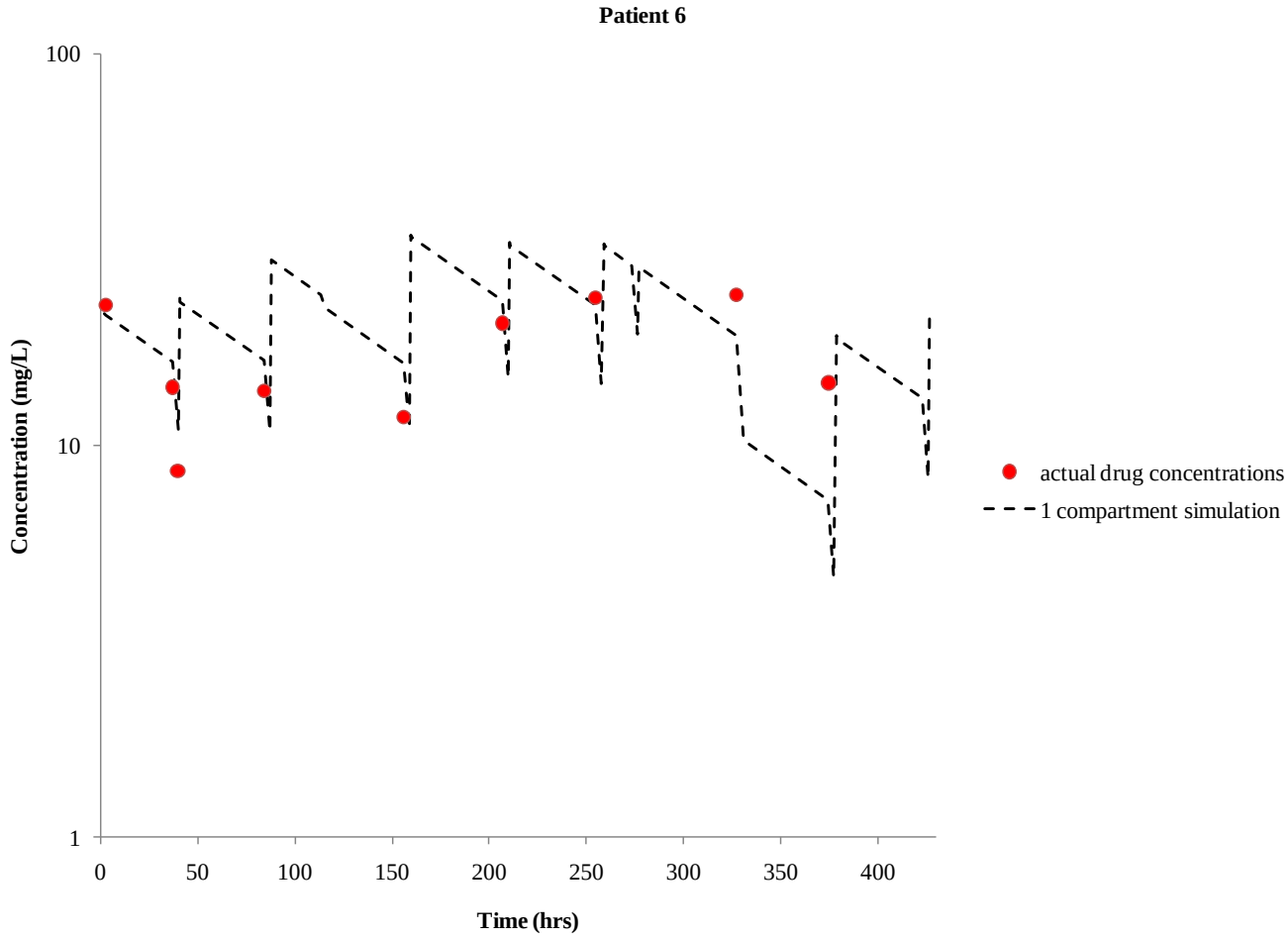
2.6 GRAPH ONE-COMPARTMENT SIMULATION, PATIENT 3



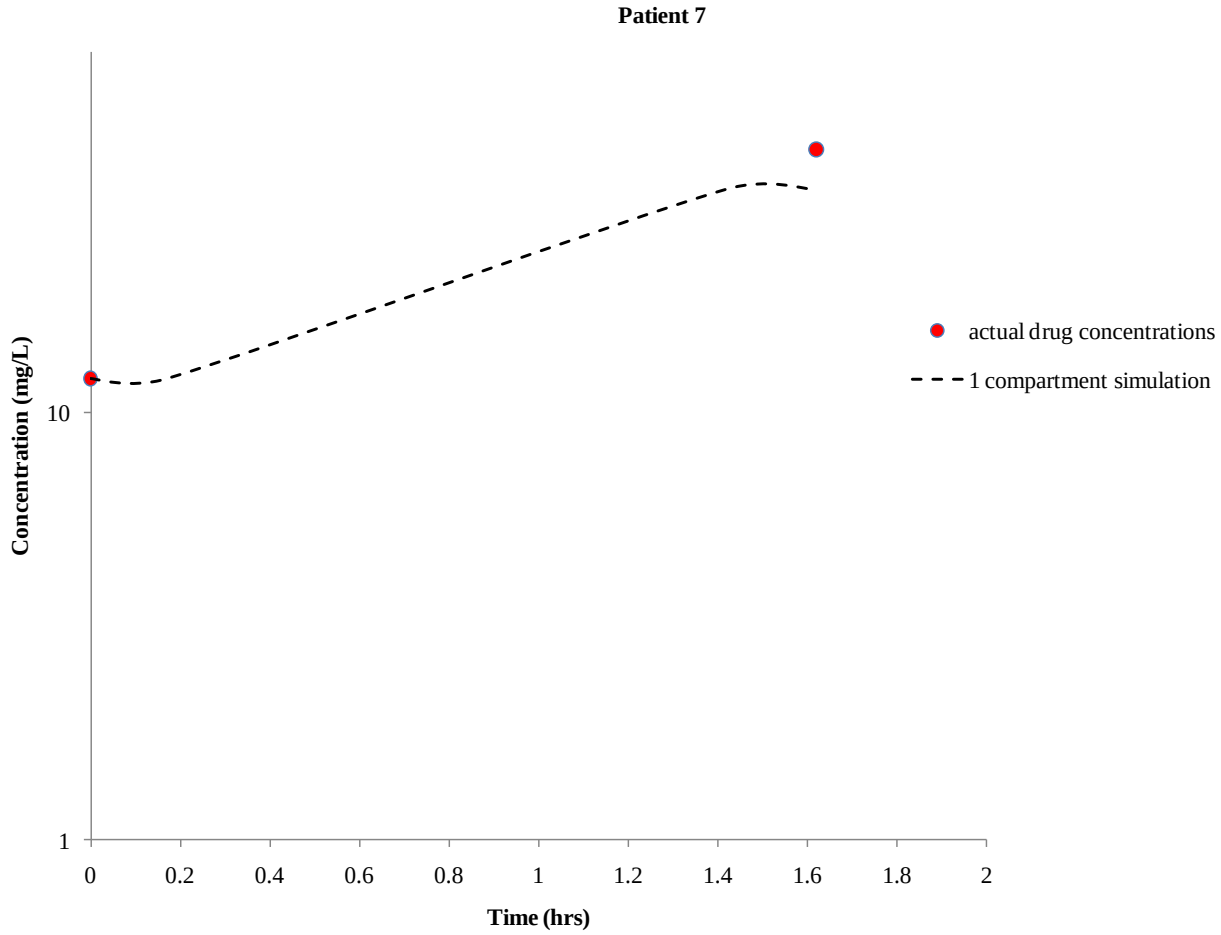
2.7 GRAPH ONE-COMPARTMENT SIMULATION, PATIENT 5



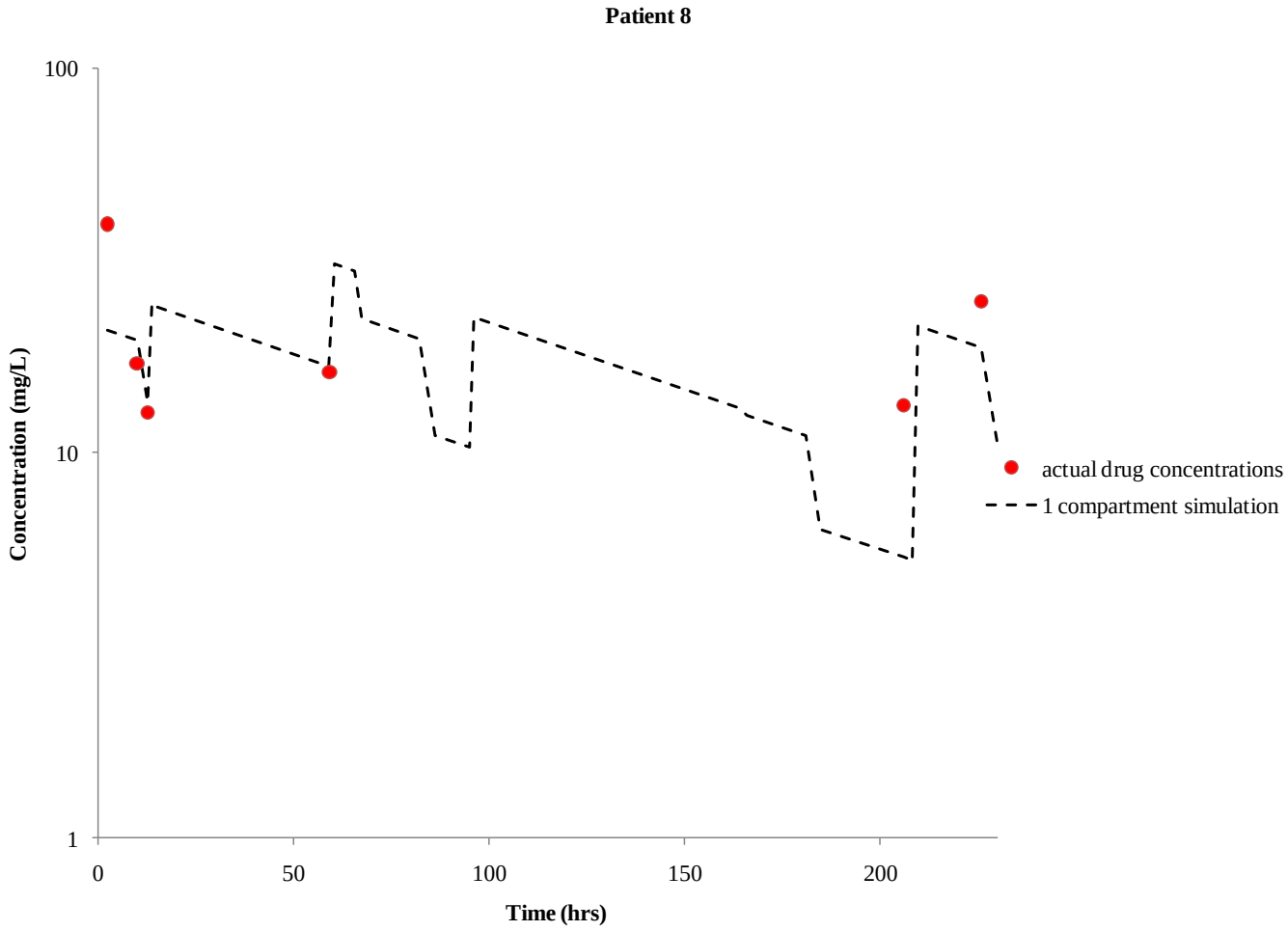
2.8 GRAPH ONE-COMPARTMENT SIMULATION, PATIENT 6



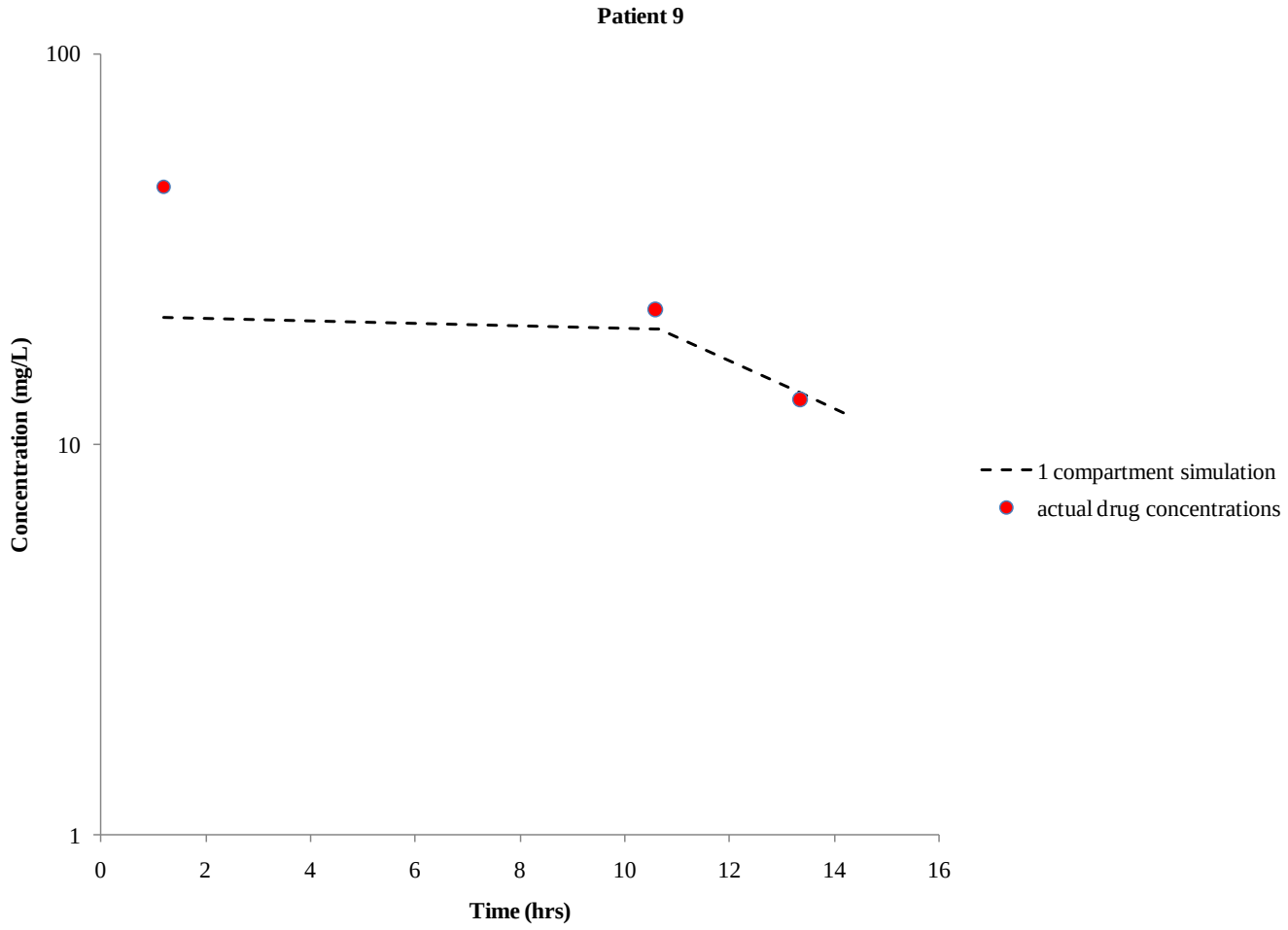
2.9 GRAPH ONE-COMPARTMENT SIMULATION, PATIENT 7



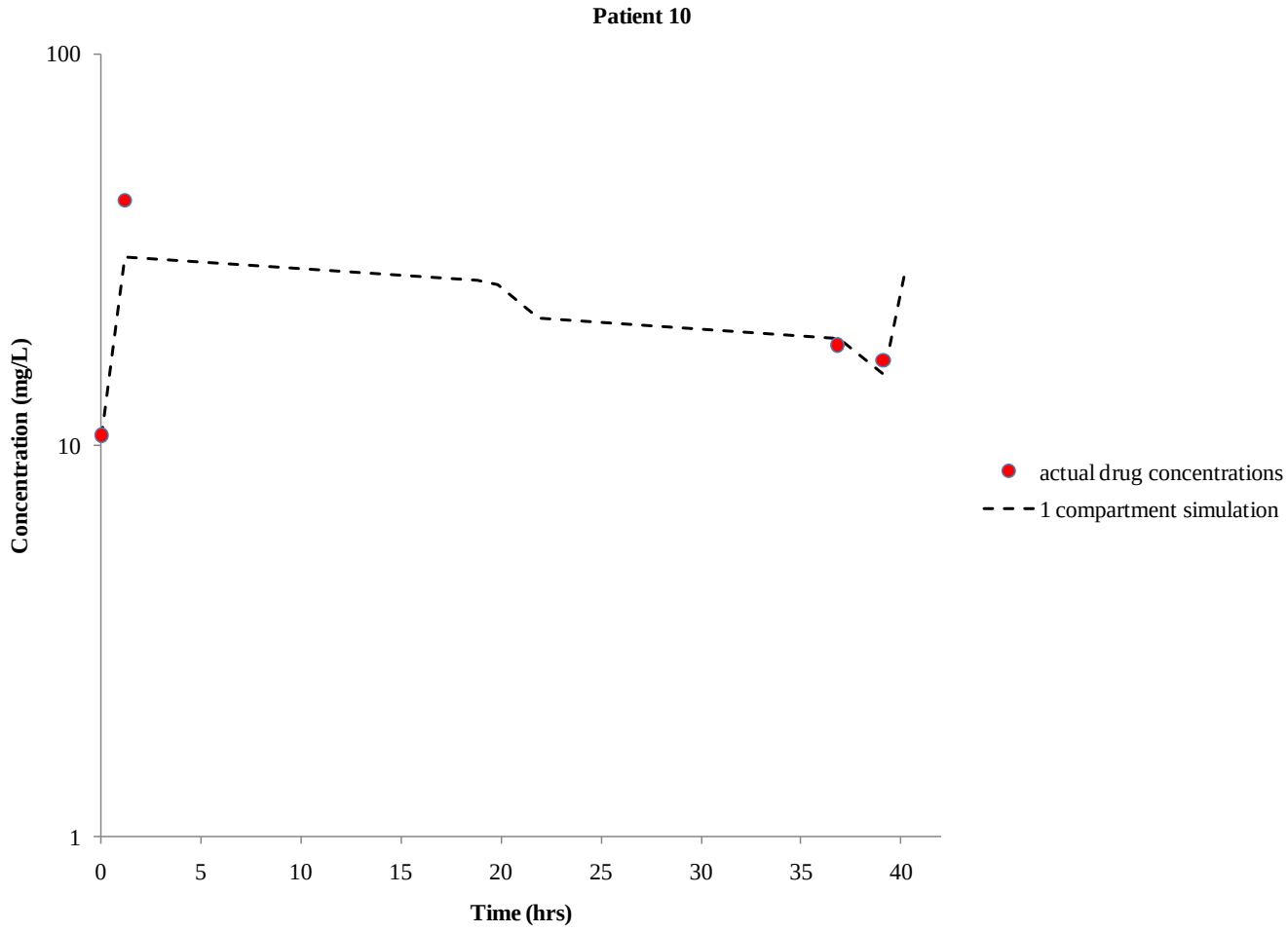
2.10 GRAPH ONE-COMPARTMENT SIMULATION, PATIENT 8



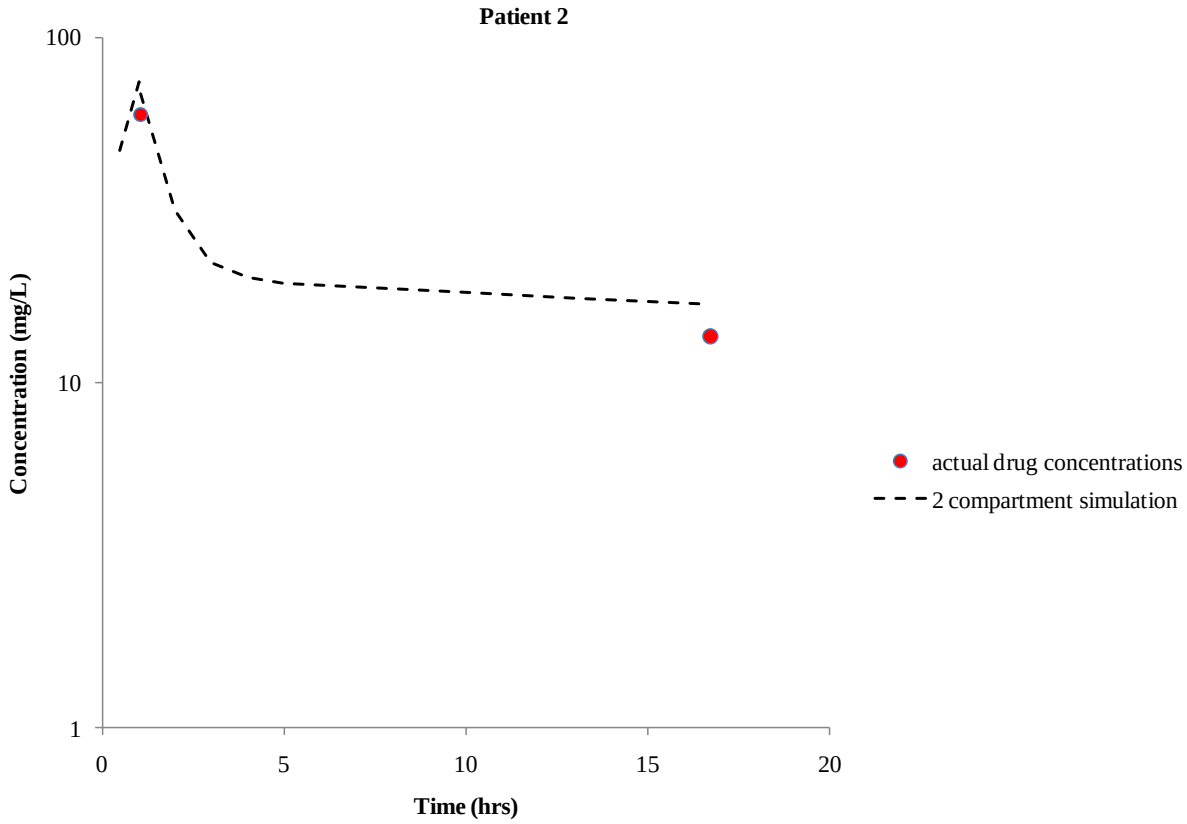
2.11 GRAPH ONE-COMPARTMENT SIMULATION, PATIENT 9



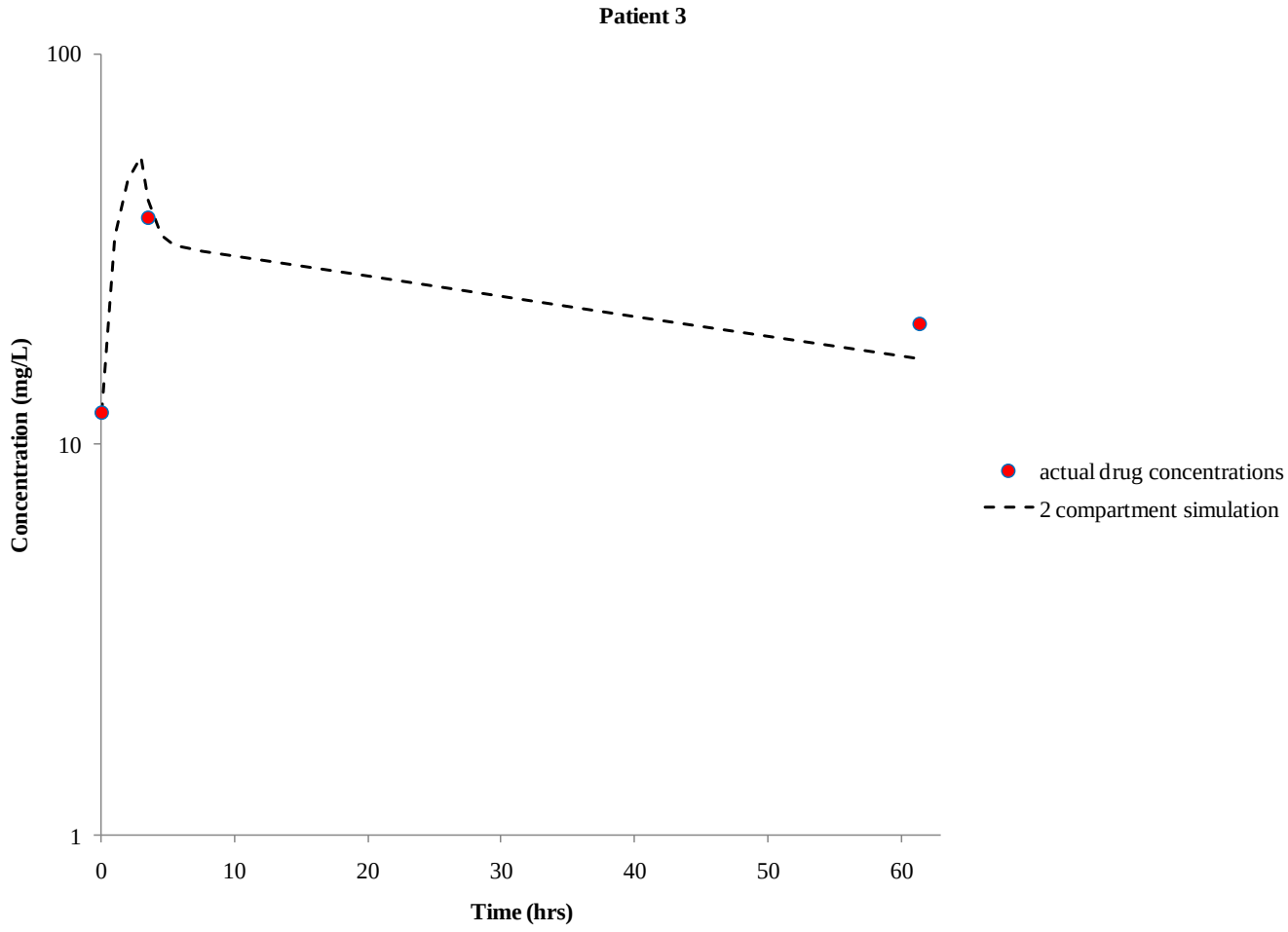
2.12 GRAPH ONE-COMPARTMENT SIMULATION, PATIENT 10



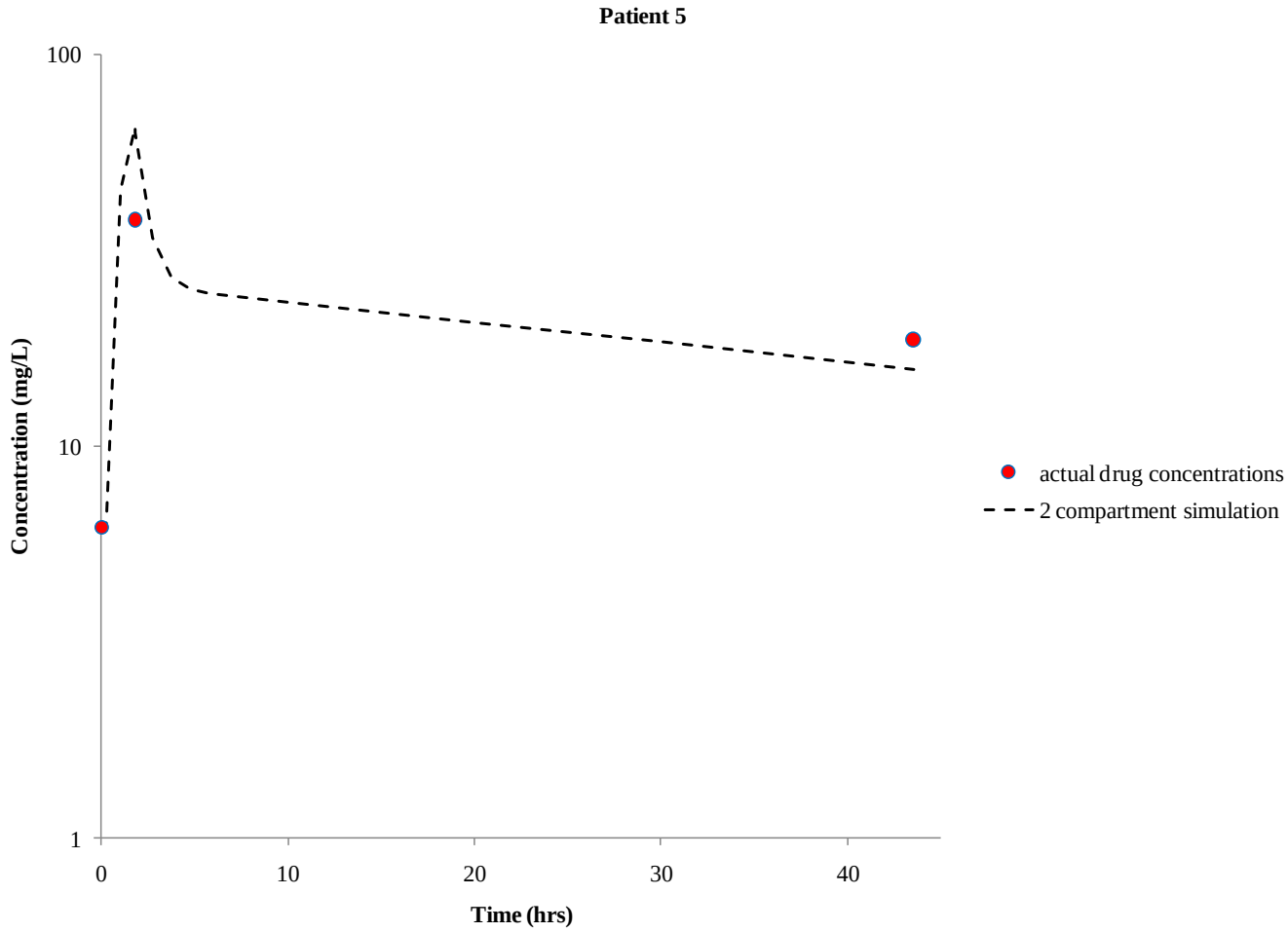
2.13 GRAPH TWO-COMPARTMENT SIMULATION, PATIENT 2



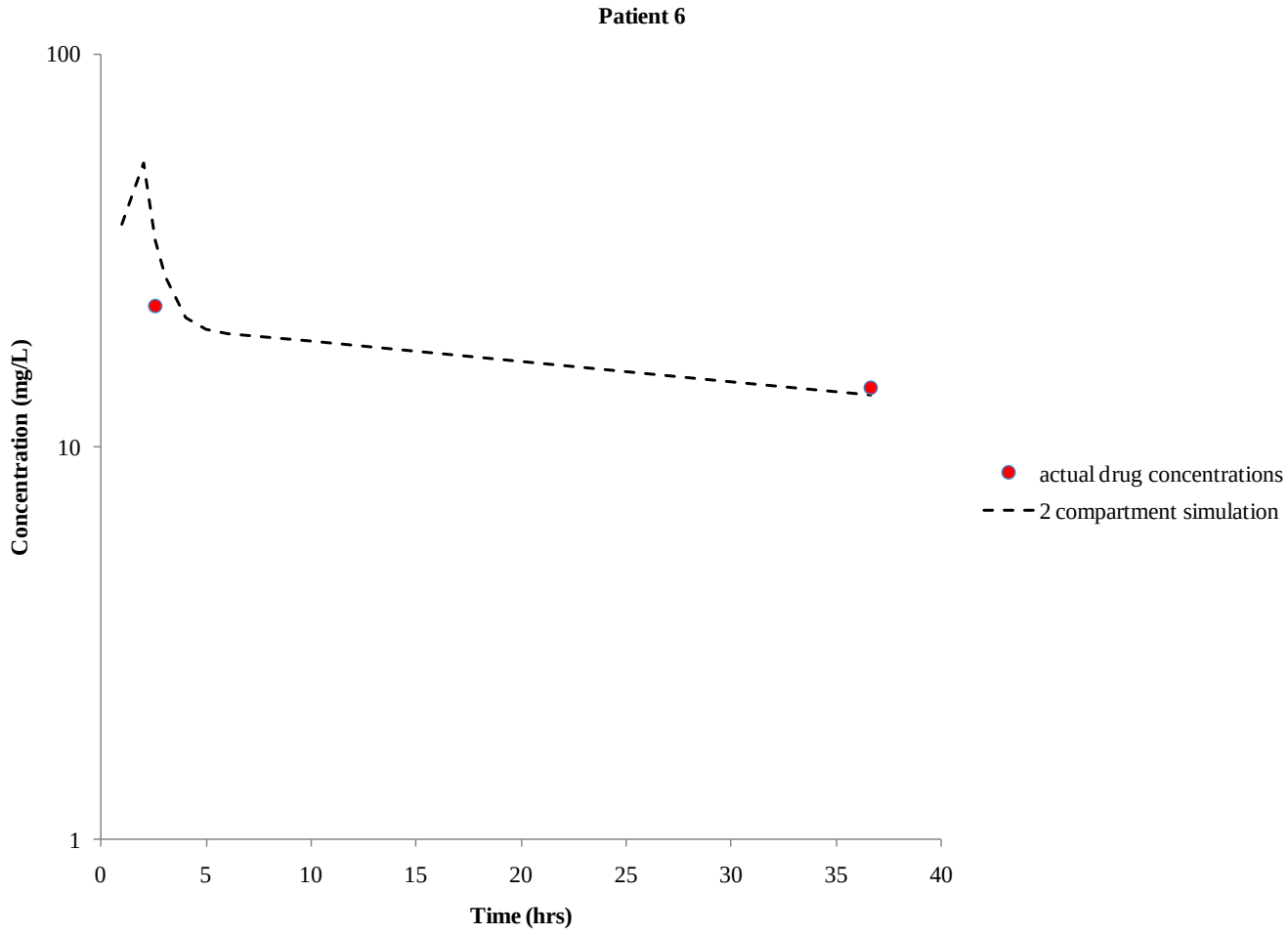
2.14 GRAPH TWO-COMPARTMENT SIMULATION, PATIENT 3



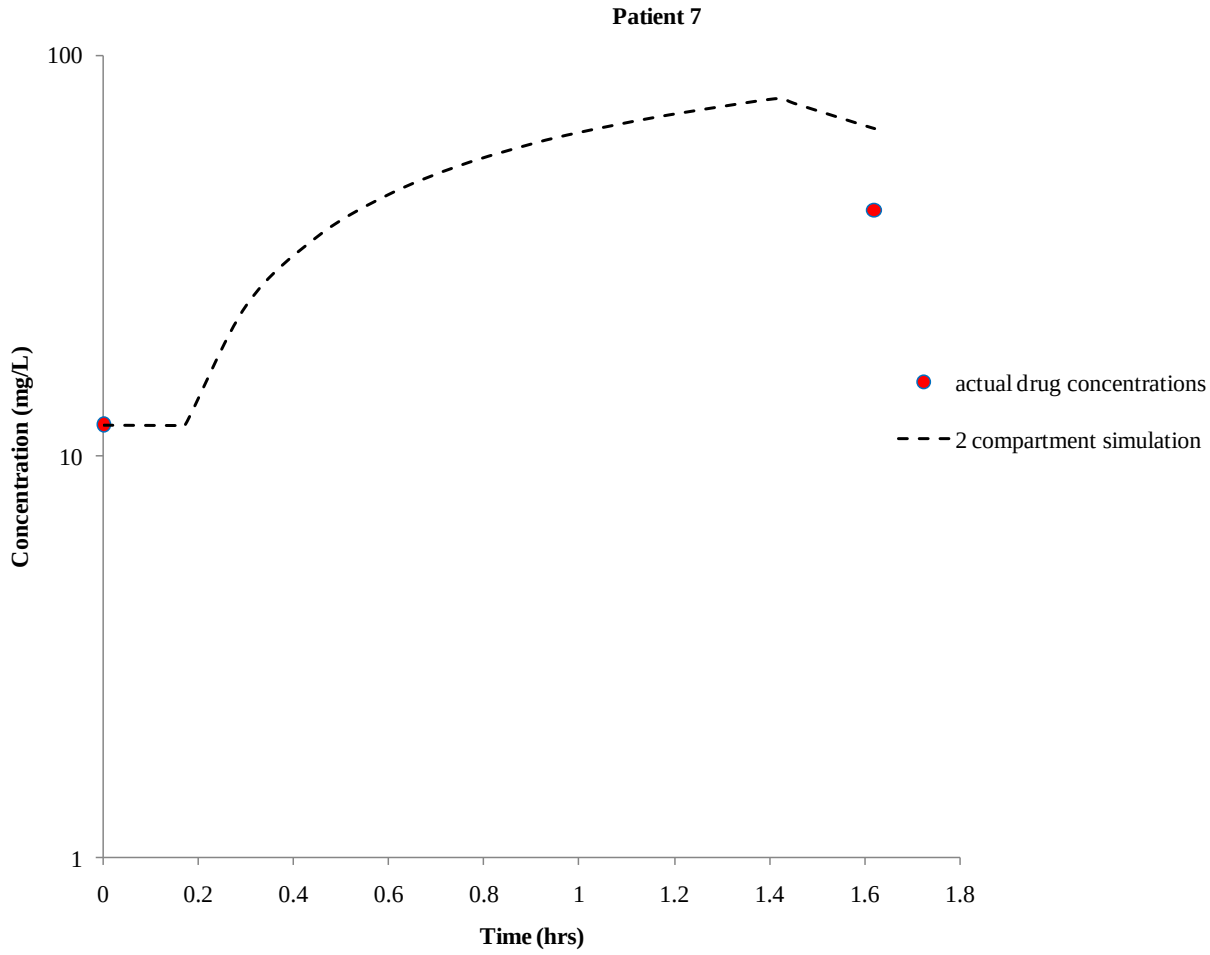
2.15 GRAPH TWO-COMPARTMENT SIMULATION, PATIENT 5



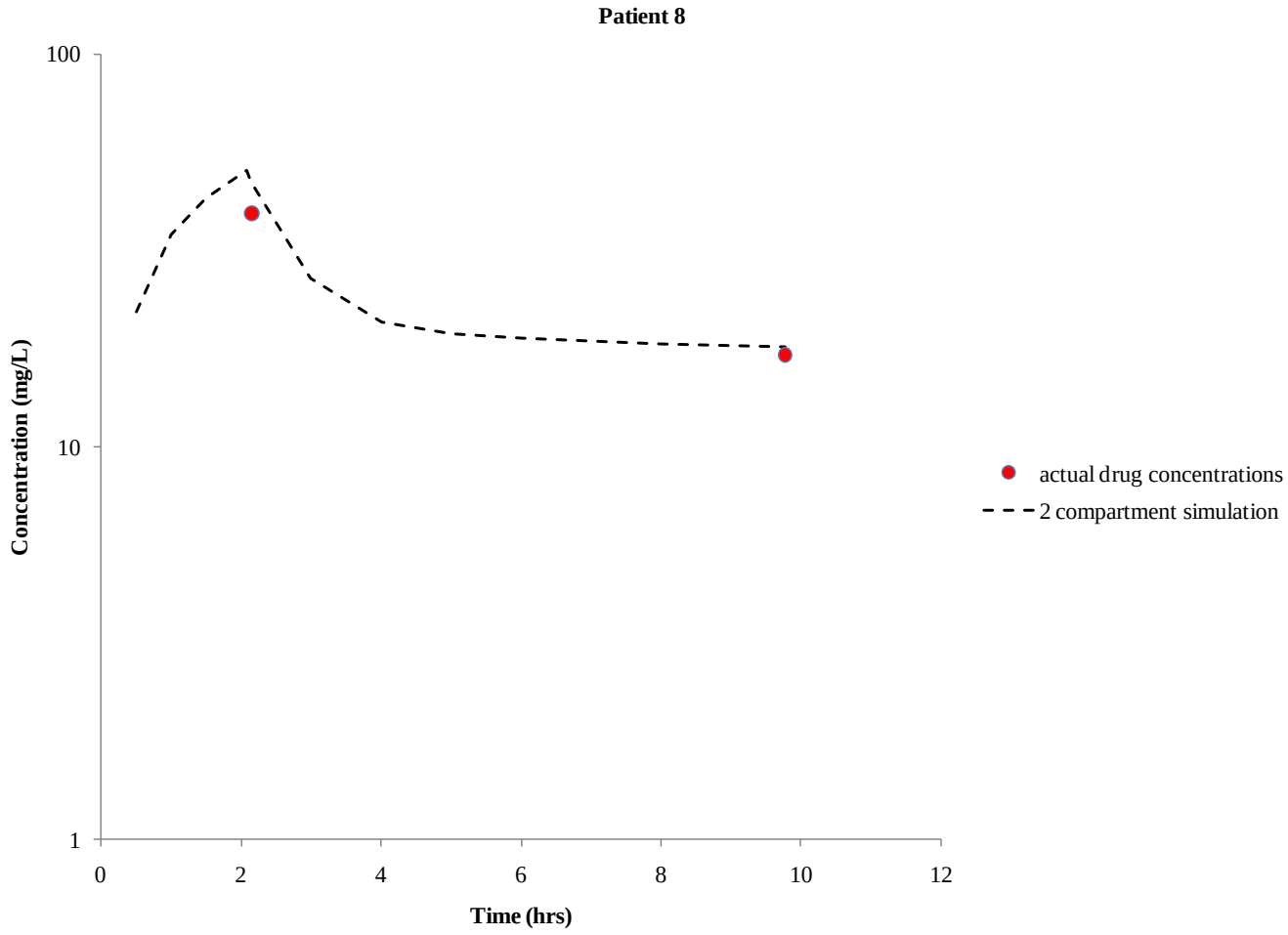
2.16 GRAPH TWO-COMPARTMENT SIMULATION, PATIENT 6



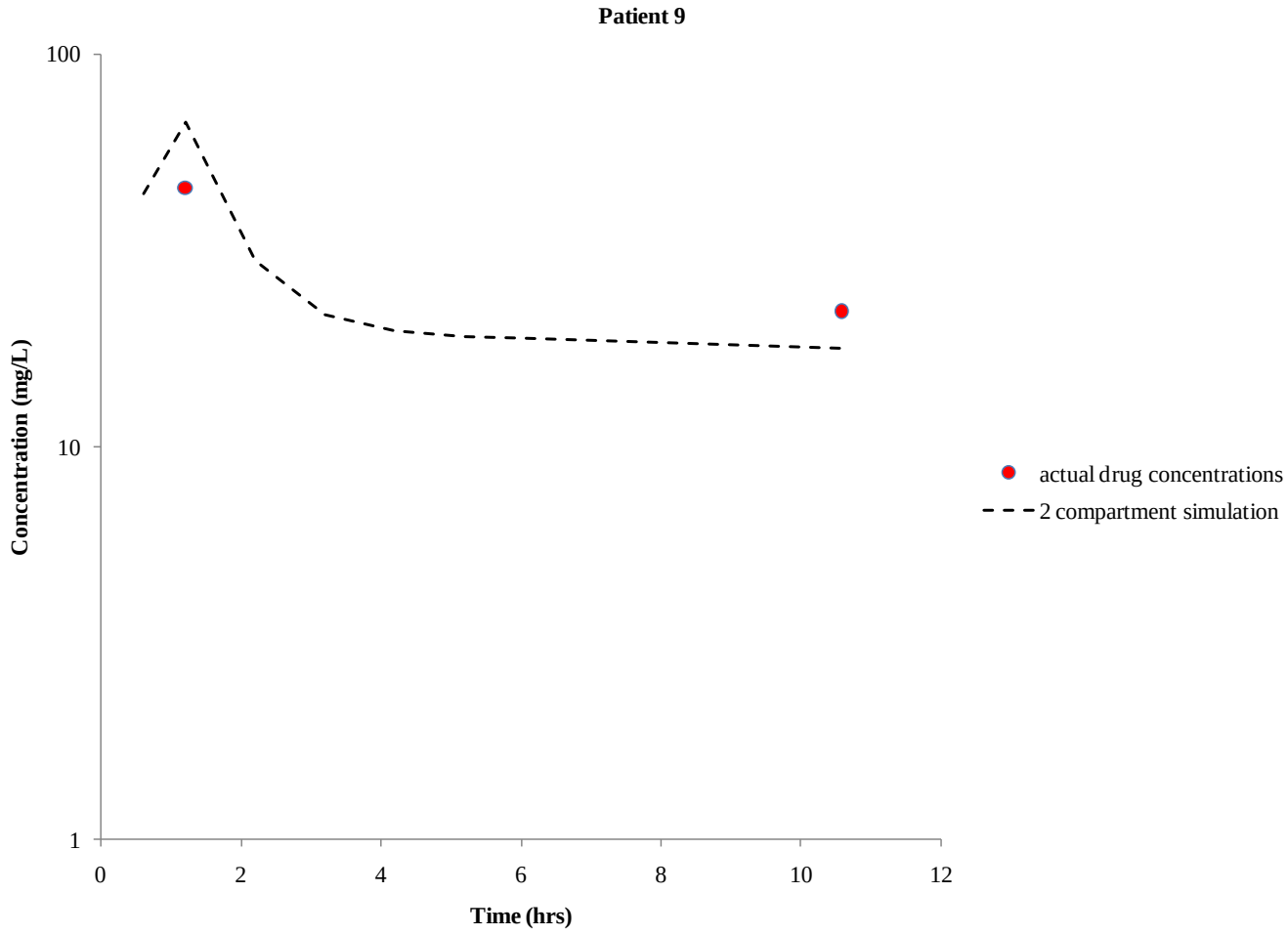
2.17 GRAPH TWO-COMPARTMENT SIMULATION, PATIENT 7



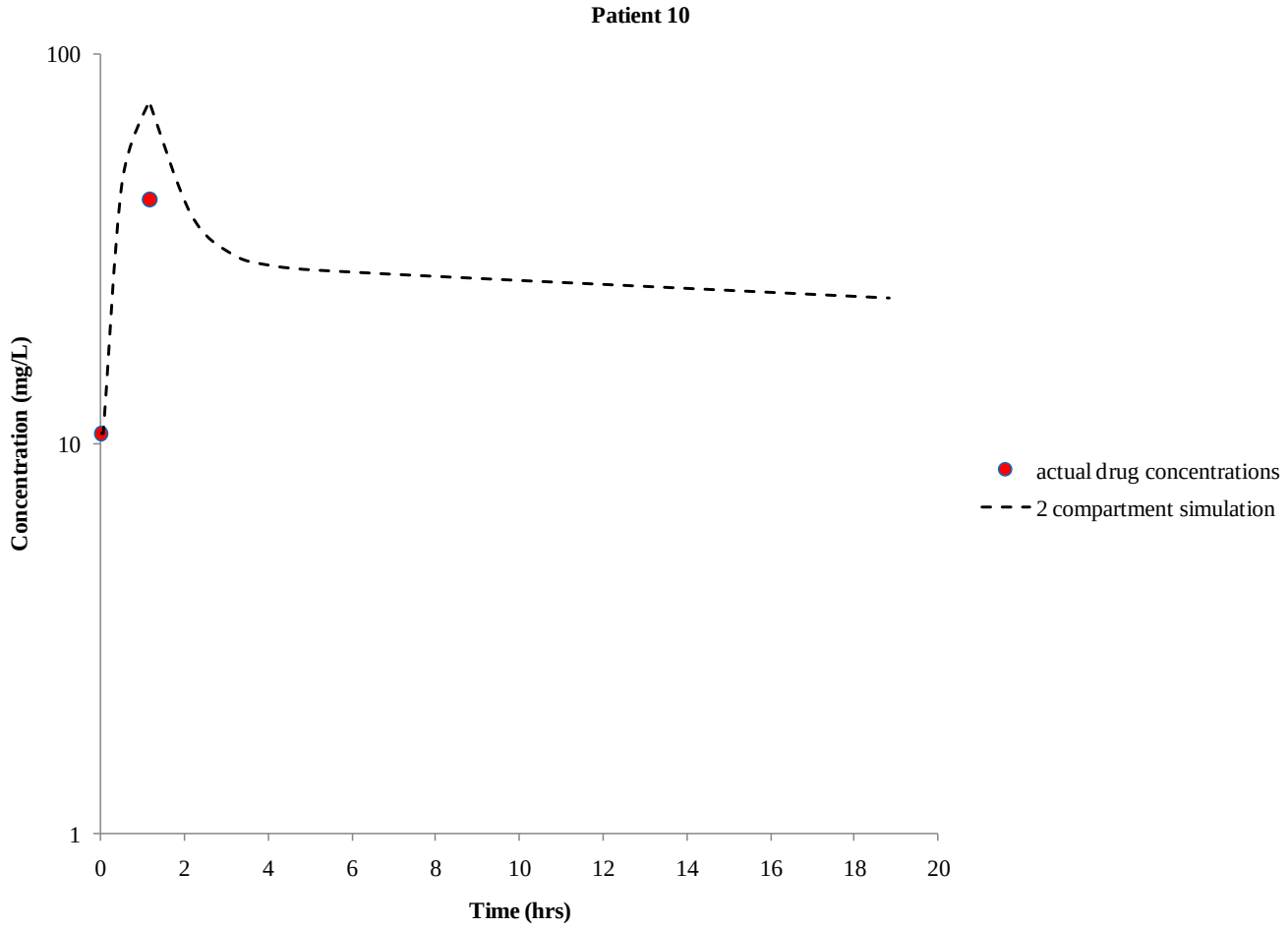
2.18 GRAPH TWO-COMPARTMENT SIMULATION, PATIENT 8



2.19 GRAPH TWO-COMPARTMENT SIMULATION, PATIENT 9



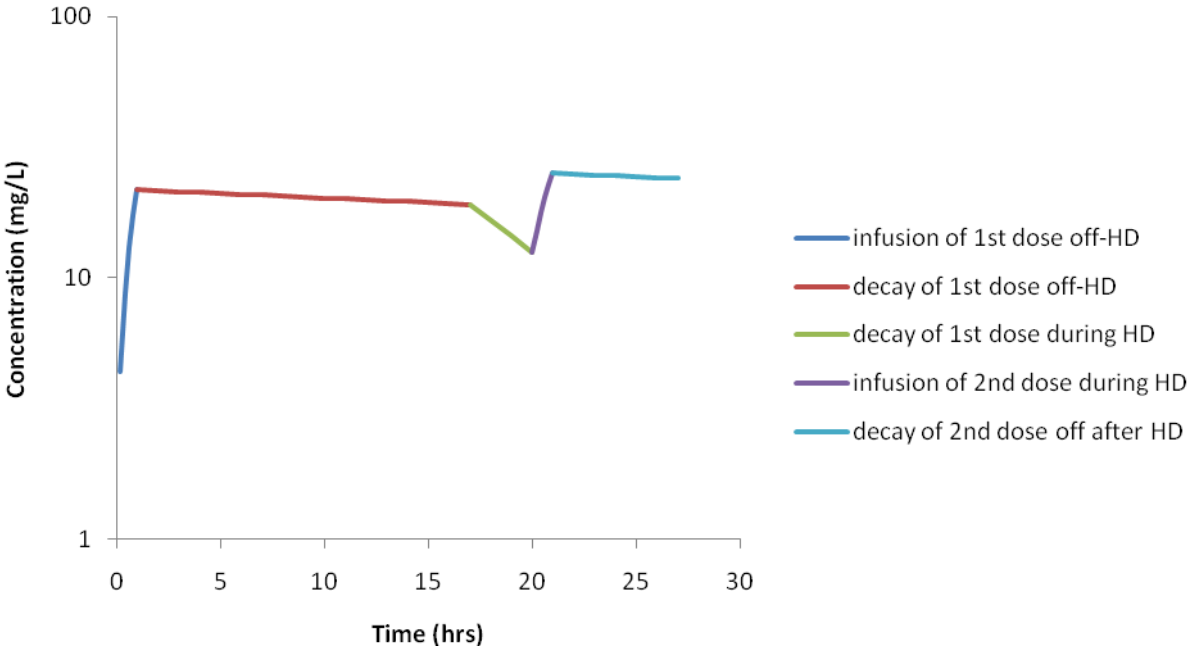
2.20 GRAPH TWO-COMPARTMENT SIMULATION, PATIENT 10



2.10 APPENDIX

2.10.1 ONE-COMPARTMENT EQUATIONS USED FOR SIMULATION

A1 GRAPH ONE-COMPARTMENT SIMULATION



Drug concentration during infusion off-dialysis

$$C = \frac{(D/ti)(1-e^{-ke(ti)})}{(V)(ke)}$$

C = concentration

D = dose

ti = infusion time

V= volume of distribution

ke = elimination rate constant (interdialytic)

Drug concentration after infusion is equal to the concentration immediately following the completion of dialysis and/or dosing multiplied by the percent remaining

$$C = C_0 \cdot e^{-ke(t)}$$

When simultaneous infusion of a dose and decay of drug concentration from prior dosing occur, the two above equations are combined to represent the summed drug concentration

$$C = \frac{(D/ti)(1-e^{-ke(ti)})}{(V)(ke)} + C_0 e^{-ke(t)}$$

In this case,

C_o = drug concentration immediately prior to the start of dialysis

C = concentration

D = dose

ti = infusion time

V= volume of distribution

ke = elimination rate constant (intradialytic)

2.10.2 TWO-COMPARTMENT EQUATIONS USED FOR SIMULATION

During infusion:

$$C_p = \frac{k_0(k_{21}-\alpha)(1-e^{-\alpha t})}{\alpha(\beta-\alpha)V_c} + \frac{k_0(k_{21}-\beta)(1-e^{-\beta t})}{\beta(\alpha-\beta)V_c}$$

Post-infusion:

$$C_p = \frac{k_0(k_{21}-\alpha)(e^{\alpha t_{in}}-1)e^{-\alpha t}}{\alpha(\beta-\alpha)V_c} + \frac{k_0(k_{21}-\beta)(e^{\beta t_{in}}-1)e^{-\alpha t}}{\beta(\alpha-\beta)V_c}$$

$$\alpha = \frac{1}{2}\left[(k_{12}+k_{21}+k_{el}) + \sqrt{(k_{12}+k_{21}+k_{el})^2 - 4k_{21}k_{el}}\right]$$

$$\beta = \frac{1}{2}\left[(k_{12}+k_{21}+k_{el}) - \sqrt{(k_{12}+k_{21}+k_{el})^2 - 4k_{21}k_{el}}\right]$$

k_0 = zero order infusion rate constant

V_c = central compartment volume

k_{12} = first order rate constant for transfer of drug from the central compartment to the peripheral compartment

k_{21} = first order rate constant for transfer of drug from the peripheral compartment to the central compartment

k_{el} = first order rate constant for elimination of drug from the central compartment

α = first order rate constant for distribution phase

β = first order rate constant for elimination phase

2.10.3 STATISTICS

Kolmogorov-Smirnov Test of Composite Normality for one-compartment simulation residuals

One sample Kolmogorov-Smirnov Test of Composite Normality

data: one.c.res in SDF21
ks = 0.1639, p-value = 0.0703
alternative hypothesis:
True cdf is not the normal distn. with estimated parameters
sample estimates:
mean of x standard deviation of x
-0.04423077 4.380408

Summary statistics for one-compartment simulations residuals

*** Summary Statistics for data in:
SDF21 ***

	one.c.res
Min:	-7.95000000
1st Qu.:	-2.35250000
Mean:	-0.04423077
Median:	0.70500000
3rd Qu.:	2.64500000
Max:	6.35000000
Total N:	26.00000000
NA's :	0.00000000
Std Dev.:	4.38040836

Kolmogorov-Smirnov Test of Composite Normality for one-compartment simulations |residuals|

One sample Kolmogorov-Smirnov Test of Composite Normality

data: one.c.abs.res in SDF21
ks = 0.1812, p-value = 0.0278
alternative hypothesis:
True cdf is not the normal distn. with estimated parameters
sample estimates:
mean of x standard

deviation of x
3.558846
2.453163

Summary statistics for one-compartment simulations |residuals|

*** Summary Statistics for data in: SDF21 ***

	one.c.abs.res
Min:	0.490000
1st Qu.:	1.467500
Mean:	3.558846
Median:	2.620000
3rd Qu.:	5.822500
Max:	7.950000
Total N:	26.000000
NA's :	0.000000
Std Dev.:	2.453163

Kolmogorov-Smirnov Test of Composite Normality for two-compartment simulations residuals

One sample Kolmogorov Smirnov Test of Composite Normality
2comp minuspt4

data: res in SDF16
ks = 0.1583, p-value = 0.5
alternative hypothesis:
True cdf is not the normal
distn. with estimated
parameters
sample estimates:
mean of x standard deviation
of x
9.114286 12.04355

Summary statistics for two-compartment simulations residuals

2comp minuspt4

	res
Min:	-4.260000
1st Qu.:	-0.235000
Mean:	9.114286
Median:	6.120000
3rd Qu.:	18.857500
Max:	31.910000

Total N: 14.000000
NA's : 0.000000
Std Dev.: 12.043547

Kolmogorov-Smirnov Test of Composite Normality for two-compartment simulations |residuals|

One sample Kolmogorov-Smirnov Test of Composite Normality

2comp
minuspt4
data: abs.res in SDF16
ks = 0.2307, p-value = 0.0419
alternative hypothesis:
True cdf is not the normal distn. with estimated parameters
sample estimates:
mean of x standard deviation
of x
10.76857 10.47019

Summary statistics for two-compartment simulations |residuals|

2comp minuspt4
abs.res
Min: 0.59000
1st Qu.: 3.37000
Mean: 10.76857
Median: 6.12000
3rd Qu.: 18.85750
Max: 31.91000
Total N: 14.00000
NA's : 0.00000
Std Dev.: 10.47019

Kolmogorov-Smirnov Test of Composite Normality for all prehemodialysis troughs

One sample Kolmogorov-Smirnov Test of Composite Normality

data: preHD.troughs in
SDF6
ks = 0.1183, p-value = 0.5
alternative hypothesis: True cdf is not the normal distn. with estimated
parameters
sample estimates:

mean of x standard deviation of x
18.34611
3.889414

Summary statistics for all prehemodialysis troughs

*** Summary Statistics for data in: SDF18 ***

	all.troughs
Min:	11.800000
1st Qu.:	14.902500
Mean:	18.346111
Median:	18.410000
3rd Qu.:	20.490000
Max:	24.700000
Total N:	18.000000
NA's :	0.000000
Std Dev.:	3.889414

Kolmogorov-Smirnov Test of Composite Normality for weight-based regimen troughs

One sample Kolmogorov-Smirnov Test of Composite Normality

data: regimen.troughs in SDF17
ks = 0.1396, p-value = 0.5
alternative hypothesis:
True cdf is not the normal distn. with estimated parameters
sample estimates:
mean of x standard deviation of x
17.58923
2.61607

Summary statistics for weight-based regimen troughs

*** Summary Statistics for data in: SDF17 ***

	regimen.troughs
Min:	13.60000
1st Qu.:	16.20000
Mean:	17.58923
Median:	18.00000
3rd Qu.:	19.32000

Max:	22.10000
Total N:	18.00000
NA's :	5.00000
Std Dev.:	2.61607

3 APREPITANT PHARMACOKINETICS IN CANCER PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION

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3.1 ABSTRACT

Delayed nausea and vomiting contribute significantly to morbidity and malnutrition in patients undergoing autologous and allogeneic hematopoietic stem cell transplantation (HSCT). Aprepitant, a neurokinin (NK_1) receptor antagonist which inhibits receptor activation by Substance P, suppresses emesis caused by various stimuli, including chemotherapy. The purpose of this study is to answer the question: How are aprepitant pharmacokinetic parameters affected by concurrent administration of selected other medications and the patient's clinical condition during hematopoietic stem cell transplantation. Standard antiemetic therapy for patients undergoing chemotherapy with high potential acute chemotherapy-induced nausea and vomiting (CINV) includes a $5HT_3$ antagonist, dexamethasone, a D_2 receptor antagonist, plus possibly a benzodiazepine. In this study, aprepitant was given orally daily, in addition to the standard antiemetics for each conditioning regimen, from the first day of conditioning chemotherapy or radiation. The aprepitant dosage was 125 mg orally on day 1 of conditioning and 80 mg orally on each consecutive day through day +4 post HSCT infusion. The dose of aprepitant was given 1 hour before the dose of chemotherapy or radiation —and at 0900 daily once chemotherapy or radiation was completed. Although there was interpatient variability in pharmacokinetic disposition secondary to drug interactions, aprepitant concentrations remained therapeutic. No dosage adjustment was necessary. Administration of aprepitant for CINV in HSCT at the prescribed dose of 125 mg PO on day 1 and 80 mg PO on each consecutive day through day +4 post HSCT was well tolerated with no significant changes in PK parameters.

3.2 INTRODUCTION

Standard antiemetic therapy for patients undergoing chemotherapy with high potential acute chemotherapy-induced nausea and vomiting (CINV) includes a $5HT_3$ antagonist, dexamethasone, a D_2 receptor antagonist, plus possibly a benzodiazepine. Control of CINV is poor in myeloablative hematopoietic stem cell transplantation recipients with $5HT_3$ antagonists, even with benzodiazepines and corticosteroids.[1, 2] Aprepitant makes a contribution to antiemetic therapy by functioning as a neurokinin (NK_1) receptor antagonist which inhibits receptor activation by Substance P and suppresses emesis caused by various stimuli, including chemotherapy.[3] No literature references were found for protocols suggesting aprepitant use in radiation induced nausea and vomiting (RINV) which is usually treated with $5HT_3$ antagonists, antihistamines, anticholinergics, dopamine antagonists, and corticosteroids.[4] The therapeutic range for aprepitant in CINV is between 500 and 1500 ng/ml.[5] Concentrations falling in this range provide antiemesis due to > 90% NK_1 receptor occupancy.[5] Thus, aprepitant provides a significant benefit in regimens for highly emetogenic chemotherapy-induced nausea and vomiting. In a study by Hesketh et al., 72.7% of patients given ondansetron, dexamethasone, and aprepitant responded with no emesis and no rescue therapy versus 52.3% of patients who were given ondansetron and dexamethasone.[6]

Treatment of leukemia and lymphoma includes high-dose chemotherapy followed by stem cell transplantation.[7,8] For autologous and allogeneic hematopoietic stem cell transplantation, patients received high dose chemotherapy conditioning regimens with or without total body irradiation for up to eight days. Nausea and vomiting frequently occur during this time and may continue after the conditioning therapy ends. Therefore, a medication regimen involving aprepitant along with a $5HT_3$ antagonist and

dexamethasone to address chemotherapy-induced nausea and vomiting is used.[1] During this time, patients are administered a wide array of medications, some of which have the potential for drug-drug interactions with aprepitant. These include medications such as opiates for pain management, phenytoin as prophylaxis for busulfan-induced seizures[9], Cyclosporine A for immunosuppression, azole antifungal(s) prophylaxis for the immunocompromised state of the patients, and other adjunctive antiemetics. Drug interactions with aprepitant can involve competitive or noncompetitive inhibition of CYP3A4. Also, interactions with inducers of CYP3A4 are to be considered. Table 3.1 shows known drug-drug interactions affecting aprepitant concentrations. Table 3.2 shows the effect of aprepitant on CYP450 substrates and transporters.

Aprepitant is cleared hepatically and not renally excreted.[10] Aprepitant is metabolized by CYP450 enzymes 1A2, 2C19, and 3A4, producing N- and O-dealkylation products. Aprepitant is also a moderate inhibitor of CYP3A4 in vitro and a very weak inhibitor of CYP2C19 and CYP2C9.[11] Aprepitant is a moderate inhibitor of orally administered CYP3A4 substrate metabolism.[12] However, aprepitant is a weak inhibitor of intravenously administered CYP3A4 substrate metabolism. This suggests that aprepitant has a more profound CYP3A4 inhibitory effect in the gastrointestinal tract than in the liver.[13] Aprepitant produces a transient induction of CYP3A4, appearing after eight days from the start of a 3-day dosing regimen and disappearing by Day 15 (p-value = 0.646).[14] Aprepitant also produces a transient induction of CYP2C9, appearing after four days from the start of a 3-day dosing regimen. This induction of CYP2C9 decreases to a modest level by Day 15 (p-value = 0.050).[14]

Metabolized aprepitant is eliminated approximately 50% in urine and 50% in feces.[15] Aprepitant is not likely to interact with drugs that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of aprepitant with digoxin in a drug interaction study.[16] Comparison of this study's data with this information would show how much of an impact the patient's condition and medication regimen would affect aprepitant pharmacokinetics.

3.3 METHODS

3.3.1 SUBJECTS

Fifteen hematopoietic stem cell transplantation patients began and fourteen, nine men and five women with a mean age of 45 years (ranging from 19-60), completed the study. Patients were scheduled for an autologous or allogeneic bone marrow or peripheral stem cell transplant, had performance status (ECOG ≤ 2), were able to swallow tablets and capsules, and receiving a cyclophosphamide containing conditioning regimen. Exclusion criteria included known sensitivity to aprepitant, ondansetron, or dexamethasone, receiving another investigational drug within the past 30 days, emesis or required antiemetic agents in the 48 hours prior to beginning conditioning therapy, taking neurokinin-1 antagonists for 14 days prior to enrollment, pregnancy, a positive serum hCG, or lactation, serum creatinine level ≥ 2 x upper limit of normal, severe hepatic insufficiency (Child-Pugh score > 9), drinking > 5 drinks/day for the last year, or concurrent illness requiring systemic corticosteroid use other than planned dexamethasone during conditioning therapy. The study protocol was approved by the Institutional Review Board at Oregon Health and Science University. Every patient gave written informed consent before participation. The study was conducted at Oregon Health and Science University, Portland, Oregon.

3.3.2 STUDY DESIGN

This was a double-blinded study to assess the potential for aprepitant to interact with concurrent medications during conditioning therapy for autologous or allogeneic hematopoietic stem cell transplantation. Twenty patients were randomized to placebo and twenty patients to aprepitant. Fifteen of the twenty patients receiving aprepitant consented to participating in the pharmacokinetic aspect of the study. Aprepitant or placebo was given orally daily, in addition to the standard antiemetics for each conditioning regimen, from the first day of conditioning chemotherapy or radiation. If aprepitant was given, the dosage was 125 mg orally on day 1 of conditioning and 80 mg orally on each consecutive day through day +4 post hematopoietic stem cell transplantation infusion. Each dose of aprepitant was given 1 hour before the dose of chemotherapy or radiation —and at 0900 daily once chemotherapy or radiation was completed.

3.3.3 SAFETY ASSESSMENT

At screening, all patients underwent a physical examination, including resting vital signs (temperature, pulse, respiration rate, and blood pressure), height and weight. Performance status (ECOG) was included in the physical exam. Complete blood count with differential, platelets and primary transplant set (chemistry set) were drawn. Patients were monitored throughout the study for adverse events. Hepatic function was also monitored (Child Pugh Score). See Appendix I.

3.3.4 BIOANALYTICAL METHODS

Sample Collection and Analytical Methods:

Each aprepitant blood sample (as described below) consisted of 3 mL collected directly into EDTA-containing tubes (0.05 mL of 15% EDTA solution per 5-mL

VACUTAINER™ tube) at 1, 2, 4, 7, 9, 12, and 24, hours post the first dose and then daily prior to the AM dose, (at 0900 if no dose) through day +7 or at least 3 days post the last aprepitant dose. Aprepitant and the internal standard, (2*R*)-[(3,5-bis-trifluoromethylphenyl)ethoxy]-3(*S*)-(phenyl)morpholin-4-ylmethyl]-5-oxo-(4,5-dihydro-[1,2,4]triazol)morpholine, compound **II** from [17], were obtained from the Merck Research Laboratories (Rahway, NJ). HPLC solvents were obtained from Burdick and Jackson and other solvents and chemicals were from Aldrich and were analytical grade. Greiner polypropylene 2.4 ml 96 well plates and Teflon coated silicone Micromat covers were obtained from Sun-Sri (Wilmington, NC).

Aprepitant concentrations were determined by LC/MS/MS using an adaptation of the method of Constanzer et al.[17] using a 96 well plate format. Plasma samples were thawed and a 0.25 ml aliquot was added to a well of a 96 well plate. The IS was added to a final concentration of 250 ng/ml followed by 0.25 ml of 0.2 M carbonate buffer, pH 9.8, and extracted with 1.2 ml of methyl-*t*-butyl ether by rotating mixing for 20 min after sealing the plate. A 0.75 ml aliquot of the organic phase was transferred to a clean 96-well plate and dried in a SC250EXP Speedvac Concentrator (ThermoFisher). The dried residue was dissolved in 500 µl of HPLC solvent. A series of standards from 10 to 5000 ng/ml aprepitant were prepared from stock solutions with control plasma for each plate. Linear least-square regression of the plasma concentrations and measured peak area ratios were used for the quantification. The interday coefficient of variation at 25 ng/ml was 8%.

Samples were analyzed using a Thermo TSQ Quantum Discovery triple-quadrupole mass spectrometer (San Jose, CA) equipped with an electrospray ionization

source. All mass analyzers were operated at unit mass resolution. The ionization interface was operated in the positive mode using the following settings: spray voltage, 2,500 V, sheath and aux gas flow rates, 50 and 40 ml/min, respectively; tube lens offset, 138 V; and capillary temperature, 240 °C. Aprepitant and the IS were monitored by MRM with a Q2 argon gas pressure of 1.0 and collision energy of 20 monitoring the transitions of *m/z* 535.15→277.00 for aprepitant and *m/z* 503.15→259.05 for the IS.

The LC-MS system was composed of an in-line Surveyor auto-sampler and HPLC pump (ThermoFisher, San Jose, CA). Aprepitant and IS were resolved from other plasma components using a 100x2.1 mm, 5 μm BetaBasic C_{18} column with 10x2.1 mm guard column (ThermoHypersil, Waltham, MA) maintained at 25 °C. The isocratic HPLC mobile phase consisted of 50% acetonitrile and 50% water containing 10 mM ammonium acetate and 0.1% formic acid delivered at a flow rate of 0.4 ml/min. The injection volume was 25 μl. Aprepitant and the IS eluted at 3.0 and 3.4 min, respectively. Data acquisition and quantitative processing were accomplished with Xcalibur software.

3.3.5 PHARMACOKINETIC METHODS

Aprepitant plasma concentrations were used to estimate aprepitant pharmacokinetic parameters by noncompartmental analysis (WinNonlin, Version 4.1; Pharsight Corporation, Mountain View, CA). Parameters inspected for the 125mg dose data included $AUC_{0-\infty}$, $AUC_{0-\infty}$/dose, C_{max}, $Cl_{observed}$, $T_{½}$, T_{max}, and V_{ss}. Maximum serum concentrations (C_{max}) and the corresponding time of occurrence (T_{max}) were inspected from the experimental data. The linear trapezoidal rule was used to calculate the area under the concentration time curve from time 0 to the last measurable concentration (AUC_{last}) for the 125mg dose. $AUC_{0-\infty}$ was calculated from ($AUC_{last} + C_{last}/\lambda_z$). A

uniform weighting was used for fitting the terminal log-linear portion of the plasma concentration time curve to estimate the terminal first-order elimination rate constant (λ_z). The terminal half-life ($T_{½}$), was calculated as $\ln(2)/\lambda_z$. Because blood samples were collected only every 24 hours for the 80mg dosing data, the only quantifiable pharmacokinetic parameter was $T_{½}$. Following the generation of pharmacokinetic parameters from both the first 125mg dose and last 80mg dose, pharmacokinetic parameters were compared with pharmacokinetic values reported in the literature for 125mg and 80mg doses given to healthy volunteers in the fasting state[18], respectively.

3.3.6 STATISTICAL ANALYSIS

For the 125mg dose, the harmonic mean and jackknife 95% confidence interval[19] were calculated for $T_{½}$. The harmonic mean was used to summarize this parameter since the variable for this pharmacokinetic parameter, the terminal elimination rate constant is in the denominator position. Also, the geometric means and 95% confidence intervals were calculated for C_{max}, $AUC_{0-\infty}$, $AUC_{0-\infty}$/dose, $Cl_{observed}$, and V_{ss}, given an expected log-normal distribution. The median was calculated for T_{max}, given a non-normal distribution. For the last 80mg dose, the harmonic mean and jackknife 95% confidence interval were calculated for $T_{½}$. Linear regression was performed to assess the following relationships: clearance of the 125mg aprepitant dose versus corresponding ALT on that day, clearance of the 125mg aprepitant dose versus corresponding AST on that day, terminal half-life for the 125mg aprepitant dose versus corresponding ALT on that day, terminal half-life for the 125mg aprepitant dose versus AST on that day, terminal half-life for the final 80mg dose versus ALT on that day, and the terminal half-life for the final

80mg dose versus AST on that day. V_{ss} estimated from the 125mg dose versus weight was also regressed.

3.4 RESULTS

Fourteen of the fifteen enrolled patients in the pharmacokinetic arm given aprepitant completed the study. Table 3.3 shows the demographic data describing the study cohort. Tables 3.4 and 3.5 summarize the pharmacokinetic results. Figure 3.1 shows the first dose drug plasma concentration versus time curve for the 14 patients. Patients 117 and 130 exhibited peak concentrations above the reported therapeutic range 500 and 1500 ng/ml.[5] With the exception of patients 115, 117, and 137, it was observed that patients had drug concentrations within the therapeutic range for at least half of the dosing interval. Patients 127 and 130 had positive slopes in the terminal phase. Patient 127 had unusually high alanine transaminase (ALT) (135 U/L) as well as high aspartate transaminase AST (49 U/L) on Day 1 of dosing. The normal range of values for ALT is (13-48 U/L), and the normal range for AST is (15-41 U/L) at Oregon Health and Science University. This could have led to decreased clearance of the drug. If the drug was not being cleared, then an accumulation would have occurred. Patient 130 had an ALT of 21 U/L and an AST of 27 U/L listed 1 day prior to the 125mg aprepitant dose. Except for the last sample, which had an elevated concentration, Patient 130 had a normal drug concentration versus time curve for that day. This may have been due to assay error for the last sample.

Figure 3.2 shows the trough concentrations for the doses preceding the last 80mg oral aprepitant dose. The 80mg dosage produced a trend of troughs that were decreasing following the first 125mg dose, as expected since dose is decreased. However, patients

121, 127, 128, 130, and 139 had an increase in trough concentrations before showing a subsequent decrease in troughs. By day 6 of the regimen, trough concentrations are increasing. This is consistent with the onset of CYP3A4 inhibition by concomitant drugs which results in an increased $T_{1/2}$ (decreased clearance) of aprepitant. Figure 3.3 shows trough concentrations following the last 80mg oral dose. Because of the presence of CYP3A4 inhibition and thus decreased aprepitant clearance, 7 of the patients shown continue to have an increase in trough concentration for 1-2 days afterwards. These trough concentrations after one day are still in the reported therapeutic concentration range for six patients.

The study's initial oral 125mg dose pharmacokinetic data yielded values for comparison with healthy adults. The study harmonic mean aprepitant half-life of 10.47 hours following the first dose was comparable to that of healthy adults, (11.1 hours).[18] This study cohort receiving the 125mg dose had a median time to maximum plasma concentration of 7.00 hours, showing a difference when compared with healthy adults (4.0 hours).[18] The geometric mean of the $AUC_{0-\infty}$ for this study cohort's 125mg dose was 27189.88 ng·h/mL, a +25.7% difference from the value listed for a group of healthy volunteers receiving a 125mg dose (21633.2 ng·h/mL).[18] The geometric mean of the C_{max} was 977.24 ng/mL, a -2.6% difference from the value listed for a group of healthy volunteers (1003.3 ng/mL).[18] The dose-standardized geometric mean $AUC_{0-\infty}$ of 201.18 ng·h/mL per mg was a +16.2% difference from what was listed for the healthy volunteers (173.1 ng·h/mL per mg).[18] All except one of the patients had a volume of distribution at steady state > 70L.[15]

The last dose of the aprepitant regimen was an 80mg oral dose. Following the first day of dosing, plasma concentrations were taken once daily only. Therefore, the only quantifiable pharmacokinetic parameter after the last 80mg dose was the terminal half-life. The harmonic mean terminal half-life of this study cohort's last 80mg dose was 29.71 hours, significantly different than the value for healthy adults (11.6 hours).[18]

3.5 SAFETY

There were no grade 4 adverse events. There were incidences of grade 3 anorexia, diarrhea, mucositis, gastrointestinal pain, and vomiting. See Appendix II. 17 of 20 patients who received aprepitant in combination with the $5HT_3$ antagonist and steroid had no emesis and mild-to-moderate nausea, or no emesis with severe nausea, or 1-2 emeses on 1 day only.

3.6 DISCUSSION

Aprepitant is a low extraction drug cleared by hepatic metabolism with minimal renal excretion of parent drug.[15] Aprepitant is metabolized by CYP450 enzymes 1A2, 2C19, and 3A4.[11] This raises the concern about drug-drug interactions with substrates and inhibitors of these isozymes. These metabolites, which are not active, are excreted in equal amounts via the urine and feces.[15] CYP3A4- related competitive inhibition, noncompetitive inhibition, and induction interactions involving concomitant drugs with aprepitant are to be considered.

Aprepitant concentrations in the therapeutic range are reported to be necessary[5] for prevention of CINV. The pharmacokinetic disposition of aprepitant, as described by measured pharmacokinetic parameters and plasma concentrations in the study cohort demonstrates the effect of simultaneously given drugs which inhibit metabolizing

CYP450 enzymes. These concurrent drugs can affect aprepitant clearance and whether aprepitant concentrations will fall in the therapeutic range or not. They did, in fact, result in pharmacokinetic parameters in the study cohort differing from those of healthy volunteers. Although there was noticeable individual variability, for the most part, the pharmacokinetics of aprepitant could be reasonably explained.

In this study, the median time to maximum plasma concentration (T_{max}) following a 125 mg oral dose was 7.00 hours in hematopoietic stem cell transplantation patients compared to a T_{max} of 4 hours reported in healthy adults.[18] Patients were concomitantly ordered intravenous (IV) and oral (PO) opioid pain medications such as IV morphine and PO oxycodone as needed for pain, as well as PO loperamide for loose stools, starting one day prior to beginning the aprepitant regimen. Slowing of the gastrointestinal tract due to opioids could have slowed transit time.

Aprepitant has a mean apparent volume of distribution at steady state of approximately 70 liters. It has 95% plasma protein binding.[15] It crosses the placenta and blood-brain barrier.[15] All except one of the patients had a volume of distribution at steady state greater than the reported value of 70 liters found in the literature.[15] The V_{ss} estimated from the 125 mg dose data ranged from 66 to 315 L.

An increased fraction of unbound drug in the plasma could have led to a larger V_{ss}. A decreased fraction of unbound drug in the tissues could have also contributed to the larger V_{ss}. Competition for plasma protein binding with other highly plasma protein bound drugs in the regimen, (phenytoin[20]) could have led to increased fraction unbound aprepitant in the plasma. On the day of the first aprepitant dose, serum albumin concentrations ranged between 2.8 and 4.3 g/dL and total serum protein concentrations

ranged from 5.4 to 6.5 g/dL. However, the fraction of unbound drug in the plasma and tissue could not be determined.

The increased V_{ss} is responsible for a decreased Cp compared to healthy volunteers.[18] A relationship (directly related) was found between weight and V_{ss} (R^2 = 0.5356, $P < 0.01$). Given aprepitant's lipophilicity, patients with increasing weight would be expected to have more drug binding in the tissues, thus resulting in increased V_{ss}.

Linear regression showed another statistically significant result: a direct relationship between terminal half-life for the 125mg dose versus ALT (R^2=0.7857, $P < 0.01$). This relationship is reasonable, given that aprepitant is hepatically cleared. AST ranged from 8 – 135 U/L and ALT ranged from 7 – 188 U/L throughout the course of aprepitant therapy. These are sensitive indicators of liver cell injury.[21] Elevated levels of either AST or ALT could indicate liver damage and potentially decreased aprepitant clearance. In general, elevated liver function tests did not correlate with elevated aprepitant plasma concentrations.

The reported elimination half-life for a fasting 125mg aprepitant oral dose in healthy adult patients is 11.1 hours.[18] Patients 114, 115, 118, and 121 were administered phenytoin as prophylaxis for busulfan-induced seizures for 6 days, starting one day before the aprepitant regimen began. Phenytoin is well characterized as an inducer of CYP 3A4 metabolism[22,23] which can be expected to decrease aprepitant half-life. Of the four patients receiving phenytoin, only patient 115 had a short aprepitant terminal half-life after the 125mg dose of 4.47 hours. Patient 114 had a normal half-life of 9.97 hours and patients 118 and 121 had elevated half-lives of 18.39 hours and 16.06 hours, respectively. Since, the onset of action for phenytoin's CYP3A inductive effect is

approximately 48 hours[24], it is possible that the phenytoin-related CYP3A4 induction did not have sufficient time to manifest in patients 114, 118, and 121.

Cyclosporine A was administered to patients starting 3-5 days into the aprepitant regimen. As a CYP3A substrate, Cyclosporine A competes with aprepitant for metabolism, leading to increased aprepitant trough concentrations.[25] This phenomenon was observed in one-half of the study patients (114, 115, 117, 118, 121, 132, and 134, see Table 3.6). Patients were also started on azole antifungals 5-8 days into the aprepitant regimen. Azole antifungals are known to inhibit CYP3A4, which in turn can increase aprepitant plasma concentrations. One patient was administered voriconazole. Ten patients were administered itraconazole. One patient was administered fluconazole. One patient was administered both voriconazole and itraconazole. Voriconazole exhibits competitive and noncompetitive inhibition of CYP3A4. Itraconazole exhibits competitive inhibition of CYP3A4. Fluconazole exhibits weak mixed, noncompetitive inhibition of CYP3A4.[26] As expected, the daily trough concentrations of aprepitant increased as a result of the azole antifungal(s) administration. Patients 128 and 134 had just stopped taking the azole antifungal voriconazole 1 and 2 days respectively, before starting aprepitant. The CYP3A4 inhibition from this azole antifungal led to an increased aprepitant terminal half-life measured for the first dose in these two patients. Patients 128 and 134 had terminal half-lives equaling 89 and 18 hours for the 125mg dose of aprepitant, respectively. As the concentration of the azole antifungal increased in the bloodstream, the resulting CYP3A4 inhibition is reflected in another significant rise in aprepitant trough concentrations thereafter. After the last dose of aprepitant was given, the daily concentrations of aprepitant decrease to values ranging from 0 – 2069 ng/ml.

The effect of the CYP3A4 inhibition is still prominent as the harmonic mean terminal half-life for the last 80mg dose is 29.71 hours. Although a wide range of values for terminal aprepitant half-life were found in this study (4.5 hours to 508.2 hours), the harmonic mean value was comparable to values reported in healthy adults (10.47 hours versus 11.1 hours).

A decreased clearance of aprepitant was indicated by the cohort's geometric mean Cl compared with the healthy volunteers (82.85 ml/min versus 96.30 ml/min).[18] With the exception of patient 114, the half-life of aprepitant was prolonged in patients with decreased clearance. Phenytoin CYP3A4 induction did not affect aprepitant clearance or half-life as expected it would. Cyclosporine A CYP3A4 competitive inhibition decreased aprepitant clearance in half of the cohort. Azole antifungal administration decreased aprepitant clearance and increased half-life as indicated by the resulting rise in aprepitant concentrations. Due to the magnitude of the CYP3A4 inhibition by azole antifungals, the induction of CYP3A4 by aprepitant was not seen.[14]

With therapeutic aprepitant concentrations, inhibition of NK_1 receptors leads to prevention of CINV. In 2 studies, inclusion of aprepitant in the regimen resulted in greater than 62% of patients achieving complete response, defined as no emesis and no use of rescue therapy.[27,6] This pharmacokinetic study demonstrates the possible CYP3A4 drug interactions affected aprepitant plasma concentrations. The effect was seen with raising aprepitant concentrations due to azole antifungal inhibition of CYP3A4. However, another possible interaction, the CYP3A4 inductive effect of phenytoin was not seen in the study cohort. Aprepitant's own CYP3A4 inductive effect was also not seen. The competitive inhibition of CYP3A4 by Cyclosporine A, which was

administered to patients resulted in elevated aprepitant concentrations. Although there was interpatient variability in pharmacokinetic disposition, including drug interactions, aprepitant concentrations remained therapeutic. Therefore no dosage adjustment was necessary and administration of aprepitant for CINV in hematopoietic stem cell transplantation at the prescribed dosage of 125 mg orally on day 1 and 80 mg orally on each consecutive day through day +4 post hematopoietic stem cell transplantation infusion was acceptable.

3.7 CONCLUSION

Although there was interpatient variability in pharmacokinetic disposition secondary to drug interactions, aprepitant concentrations remained therapeutic. No dosage adjustment was necessary. Administration of aprepitant for CINV in HSCT at the prescribed dose of 125 mg orally on day 1 and 80 mg orally on each consecutive day through day +4 post HSCT was well tolerated with no significant changes in pharmacokinetic parameters.

3.8 REFERENCES

1. Hesketh PJ. Chemotherapy-induced nausea and vomiting. *N Engl J Med* 2008; **358:** 2482-2494.

2. Lohr L. Chemotherapy-induced nausea and vomiting. *Cancer J* 2008; **14:** 85-93.

3. Smith AR, Repka TL, Weigel BJ. Aprepitant for the control of chemotherapy induced nausea and vomiting in adolescents. *Pediatr Blood Cancer* 2005; **45:** 857-860.

4. Abdelsayed GG. Management of radiation-induced nausea and vomiting. *Exp Hematol* 2007; **35:** 34-36.

5. Bergstrom M, Hargreaves RJ, Burns HD et al. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. *Biol Psychiatry* 2004; **55:** 1007-1012.

6. Hesketh PJ, Grunberg SM, Gralla RJ et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin--the Aprepitant Protocol 052 Study Group.[see comment]. *J Clin Oncol* 2003; **21:** 4112-4119.

7. Yusuf RZ, Dey B, Yeap BY et al. Autologous SCT with a dose-reduced BU and CY regimen in older patients with non-Hodgkin's lymphoma. *Bone Marrow Transplant* 2009; **43:** 37-42.

8. Cahu X, Mohty M, Faucher C et al. Outcome after reduced-intensity conditioning allogeneic SCT for AML in first complete remission: comparison of two regimens. *Bone Marrow Transplant* 2008; **42:** 689-691.

9. Chan KW, Mullen CA, Worth LL et al. Lorazepam for seizure prophylaxis during high-dose busulfan administration. *Bone Marrow Transplant* 2002; **29:** 963-965.

10. Bergman AJ, Marbury T, Fosbinder T et al. Effect of impaired renal function and haemodialysis on the pharmacokinetics of aprepitant. *Clin Pharmacokinet* 2005; **44:** 637-647.

11. Loos WJ, de Wit R, Freedman SJ et al. Aprepitant when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone does not affect vinorelbine pharmacokinetics in cancer patients. *Cancer Chemother Pharmacol* 2007; **59:** 407-412.

12. Majumdar AK, McCrea JB, Panebianco DL et al. Effects of aprepitant on cytochrome P450 3A4 activity using midazolam as a probe. *Clin Pharmacol Ther* 2003; **74:** 150-156.

13. Majumdar AK, Yan KX, Selverian DV et al. Effect of aprepitant on the pharmacokinetics of intravenous midazolam. *J Clin Pharmacol 2007;* **47:** 744-750.

14. Shadle CR, Lee Y, Majumdar AK et al. Evaluation of potential inductive effects of aprepitant on cytochrome P450 3A4 and 2C9 activity. *J Clin Pharmacol* 2004; **44:** 215-223.

15. Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. *Ann Pharmacother* 2005; **39:** 77-85.

16. Feuring M, Lee Y, Orlowski LH et al. Lack of effect of aprepitant on digoxin pharmacokinetics in healthy subjects. *J Clin Pharmacol* 2003; **43:** 912-917.

17. Constanzer ML, Chavez-Eng CM, Dru J et al. Determination of a novel substance P inhibitor in human plasma by high-performance liquid chromatography with atmospheric pressure chemical ionization mass spectrometric detection using single and triple quadrupole detectors. *J Chromatogr B Analyt Technol Biomed Life Sci* 2004; **807:** 243-250.

18. Majumdar AK, Howard L, Goldberg MR et al. Pharmacokinetics of aprepitant after single and multiple oral doses in healthy volunteers. *J Clin Pharmacol* 2006; **46:** 291-300.

19. Lam FC, Hung CT, Perrier DG. Estimation of variance for harmonic mean half-lives. *J Pharm Sci* 1985; **74:** 229-231.

20. von Winckelmann SL, Spriet I, Willems L. Therapeutic drug monitoring of phenytoin in critically ill patients. *Pharmacotherapy* 2008; **28:** 1391-1400.

21. Knight JA. Liver function tests: their role in the diagnosis of hepatobiliary diseases. *J Infus Nurs* 2005; **28:** 108-117.

22. Ripp SL, Mills JB, Fahmi OA et al. Use of immortalized human hepatocytes to predict the magnitude of clinical drug-drug interactions caused by CYP3A4 induction. *Drug Metabolism & Disposition* 2006; **34:** 1742-1748.

23. Villikka K, Kivisto KT, Maenpaa H et al. Cytochrome P450-inducing antiepileptics increase the clearance of vincristine in patients with brain tumors. *Clin Pharmacol Ther* 1999; **66:** 589-593.

24. Fleishaker JC, Pearson LK, Peters GR. Phenytoin causes a rapid increase in 6 beta-hydroxycortisol urinary excretion in humans--a putative measure of CYP3A induction. *J Pharm Sci* 1995; **84:** 292-294.

25. Picard N, Djebli N, Sauvage FL et al. Metabolism of sirolimus in the presence or absence of cyclosporine by genotyped human liver microsomes and recombinant cytochromes P450 3A4 and 3A5. *Drug Metabolism & Disposition* 2007; **35:** 350-355.

26. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. *Pharmacotherapy* 2006; **26:** 1730-1744.

27. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003; **97:** 3090-3098.

28. EMEND capsules (aprepitant). Whitehouse Station, NJ: Merck; 2006. Available at :http://www.emend.com/emend/shared/documents/pi.pdf. Accessed May 27, 2008.

29. de Jonge ME, Huitema AD, Holtkamp MJ et al. Aprepitant inhibits cyclophosphamide bioactivation and thiotepa metabolism. *Cancer Chemother Pharmacol* 2005; **56:** 370-378.

30. Durand JP, Gourmel B, Mir O et al. Antiemetic neurokinin-1 antagonist aprepitant and ifosfamide-induced encephalopathy. *Ann Oncol* 2007; **18:** 808-809.

31. Nygren P, Hande K, Petty KJ et al. Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients. *Cancer Chemother Pharmacol* 2005; **55:** 609-616.

32. Blum RA, Majumdar A, McCrea J et al. Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. *Clin Ther* 2003; **25:** 1407-1419.

33. Li SX, Pequignot E, Panebianco D et al. Lack of effect of aprepitant on hydrodolasetron pharmacokinetics in CYP2D6 extensive and poor metabolizers. *J Clin Pharmacol* 2006; **46:** 792-801.

34. Shah AK, Hunt TL, Gallagher SC et al. Pharmacokinetics of palonosetron in combination with aprepitant in healthy volunteers. *Curr Med Res Opin* 2005; **21:** 595-601.

35. McCrea JB, Majumdar AK, Goldberg MR et al. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther* 2003; **74:** 17-24.

36. Depre M, Van Hecken A, Oeyen M et al. Effect of aprepitant on the pharmacokinetics and pharmacodynamics of warfarin. *Eur J Clin Pharmacol* 2005; **61:** 341-346.

3.9 TABLES

3.1 DRUGS AFFECTING APREPITANT CONCENTRATIONS

Drug	ratio of aprepitant AUC With drug/without drug	ratio of aprepitant C_{max} With drug/without drug	Mean ratio of aprepitant $t_{1/2}$ With drug/without drug
Ketoconazole (potent 3A4 inhibitor)[28]	4.8		3
Diltiazem (moderate 3A4 inhibitor)[28]	2.0		
Rifampin (potent 3A4 inducer)[28]	0.09		0.33
Paroxetine[28]	0.75	0.8	

These are drugs reported to have an effect on aprepitant pharmacokinetics.

3.2 OBSERVED EFFECT OF APREPITANT ON CYP450 SUBSTRATES/TRANSPORTERS

Drug	CYP450 Isoenzyme/Transporter	Mean Ratio of AUC	Mean Ratio of C_{max}	Effect	Reference
Chemotherapy					
Cyclophosphamide (IV) (prodrug)	Activation by CYP2B6 to active 4-hydroxy metabolite			Rate of autoinduction 23% ↓. Exposure to active metabolite 5% ↓.	[29]
Ifosfamide (IV)	CYP3A4			Induction*	[30]
Thiotepa (IV) (active)	Activation by CYP2B6 and CYP3A4 to tepa (active metabolite)			Formation clearance of tepa 33% ↓. Exposure to tepa 20% ↓.	[29]
Docetaxel (IV)	CYP3A4	No effect.	No effect.	No effect.	[31]
Vinorelbine (IV)	CYP3A4	No effect.	No effect.	No effect.	[11]
Antiemetics					
Ondansetron (IV)	CYP3A4	No effect.	No effect.	No effect.	[32]
Granisetron (po)	CYP3A4	No effect.	No effect.	No effect.	[32]
Dolasetron (po) (prodrug)	Rapidly converted to hydrodolasetron (active metabolite) Hydrodolasetron largely metabolized by CYP2D6 and less than 1% metabolized by CYP3A4.	No effect.	No effect.	No effect.	[33]
Palonosetron (IV)	CYP2D6, CYP3A, CYP1A2	No effect.	No effect.	No effect.	[34]
Dexamethasone (po)	CYP3A4	2.2 ↑	1.5 ↑	Moderate inhibition. Reduce dose by 50% for oral dosing.	[28, 35]

Methylprednisolone (po)	CYP3A4	2.5 ↑	1.5 ↑	Moderate inhibition. Reduce dose by 50% for oral dosing.	[28, 35]
Methylprednisolone (IV)	CYP3A4	1.3 ↑		Moderate inhibition. Reduce dose by 25% for IV dosing.	[28, 35]
Miscellaneous					
Midazolam (IV)	CYP3A4 (probe)	1.25 ↑ (day 4) 0.81 ↓ (day 8) 0.96 ↔ (day 15)		Weak inhibition on day 4, induction on day 8, and no effect on day 15.	[14, 28]
Tolbutamide (po)	CYP2C9 (probe)	0.77 ↓ (day 4) 0.72 ↓ (day 8) 0.85 ↔ (day 15, $P = 0.05$)		Modest induction.	[14, 28]
Warfarin (po)	CYP2C9	0.89 ↓ INR (day 8)		Induction of S(-) warfarin metabolism. S(-) warfarin levels declined significantly beginning the 5^{th} day after initiation of aprepitant dosing with maximum decrease in INR observed on day 8	[28, 36]
Digoxin (po)	P-glycoprotein	No effect	No effect	No effect	[16, 28]
Diltiazem (po)	CYP3A4	1.7 ↑	1.5 ↑	Inhibition.	[28]
Ethinyl estradiol (po) (w/14 days aprepitant)	CYP3A4	0.59 ↓	0.64 ↓	Induction.	[28]
Norethindrone (po) (w/14 days aprepitant)	CYP3A4	0.91 ↓	0.81 ↓	Induction.	[28]
Paroxetine (po)	CYP2D6	0.75 ↓		Induction.	[28]

* Case report in a single patient; not validated in a clinical trial

3.3 PATIENT DEMOGRAPHICS

Patient #[a]	Sex[b]	Age yrs	Ht cm	Wt kg	BSA m^2	Disease under treatment[c]	Type of transplant[d]
114	M	54	182.0	82.8	2.05	AML	Allo
115	F	48	173.0	98.9	2.18	Myelodysplastic syndrome	MUD
117	F	36	155.0	56.8	1.56	AML	Allo
118	M	59	182.0	111.3	2.37	Diffuse Large B-cell Lymphoma	MUD
121	M	29	182.0	87.5	2.10	AML	MUD
123	M	25	180.3	102.6	2.27	CML	MUD
127	F	19	167.6	81.9	1.90	ALL	MUD
128	M	59	185.4	108.5	2.36	AML	Allo
130	F	43	162.0	89.3	2.00	AML	Allo
132	M	43	180.4	88.5	2.10	ALL	Allo
134	M	58	178.0	70.0	1.86	MDS	Allo
135	M	60	186.0	87.5	2.00	NHL	Auto
137	M	58	203.2	108.0	2.48	CML	MUD
139	F	50	175.0	85.3	2.00	AML	Allo

a. Opioid pain medications and loperamide were ordered one day prior to starting the aprepitant regimen

b. M = male; F = female

c. AML = Acute Myelogenous Leukemia; ALL = Acute Lymphoblastic Leukemia; NHL = Non-Hodgkin's Lymphoma; CML = Chronic Myeloid Leukemia; MDS = Myelodysplasia

d. Allo = Allogeneic stem cell transplant; Auto = Autologous stem cell transplant; MUD = matched unrelated donor transplant

3.4 INDIVIDUAL PK PARAMETERS FOR APREPITANT FOLLOWING ORAL 125MG DOSE

patient	Half-life, h	Tmax, h	Cmax, ng/mL	$AUC_{0-\infty}$, ng·h/mL	Dose-standardized $AUC_{0-\infty}$, ng·h/mL per mg	Cl, ml/min	V_{ss}, L
114	9.97	12.25	1168.00	27886.19	185.91	89.65	99.82
115	4.47	7.00	586.00	6803.82	45.36	367.44	205.07
117	4.80	4.00	2478.70	20584.20	137.23	121.45	66.24
118	18.39	4.00	728.70	22770.32	151.80	109.79	190.53
121	16.06	2.00	696.80	18405.65	122.70	135.83	192.04
123	19.37	2.00	1447.50	23456.79	156.38	106.58	163.37
127	508.20	8.97	1173.50	745998.46	5967.99	2.79	124.01
128	89.42	12.37	631.80	87760.48	702.08	23.74	187.72
130	16.97	7.08	2006.20	44307.81	354.46	47.02	82.17
132	7.01	2.17	921.30	15546.67	124.37	134.01	97.10
134	18.10	7.00	1028.90	31569.88	252.56	65.99	114.17
135	10.09	4.00	1052.50	16712.88	133.70	124.65	129.14
137	5.95	12.25	416.36	6096.26	48.77	341.74	315.41
139	10.10	10.13	940.33	21681.58	173.45	96.09	115.22
Mean[a]	10.47	7.00	977.21	27189.88	201.18	82.85	136.83
95% CI	5.99, 14.95		740.65, 1289.33	13878.24, 53269.69	100.82, 401.45	41.52, 165.32	107.35, 174.41

a. Geometric Mean and 95% confidence intervals estimated for C_{max}, $AUC_{0-\infty}$, $AUC_{0-\infty}/D$, apparent plasma clearance, and V_{ss}; Median estimated for T_{max}; Harmonic mean and jackknife 95% confidence intervals estimated for $T_{½}$

3.5 APREPITANT HALF-LIFE FOLLOWING FINAL ORAL 80MG DOSE

patient	Half-life, h
114	25.52
115	41.85
117	87.98
118	24.14
121	110.91
123	27.82
127	71.58
128	43.36
130	54.53
132	24.11
134	22.33
135	12.03
137	13.96
139	71.87
Mean[a]	29.71
95% CI	17.68, 41.75

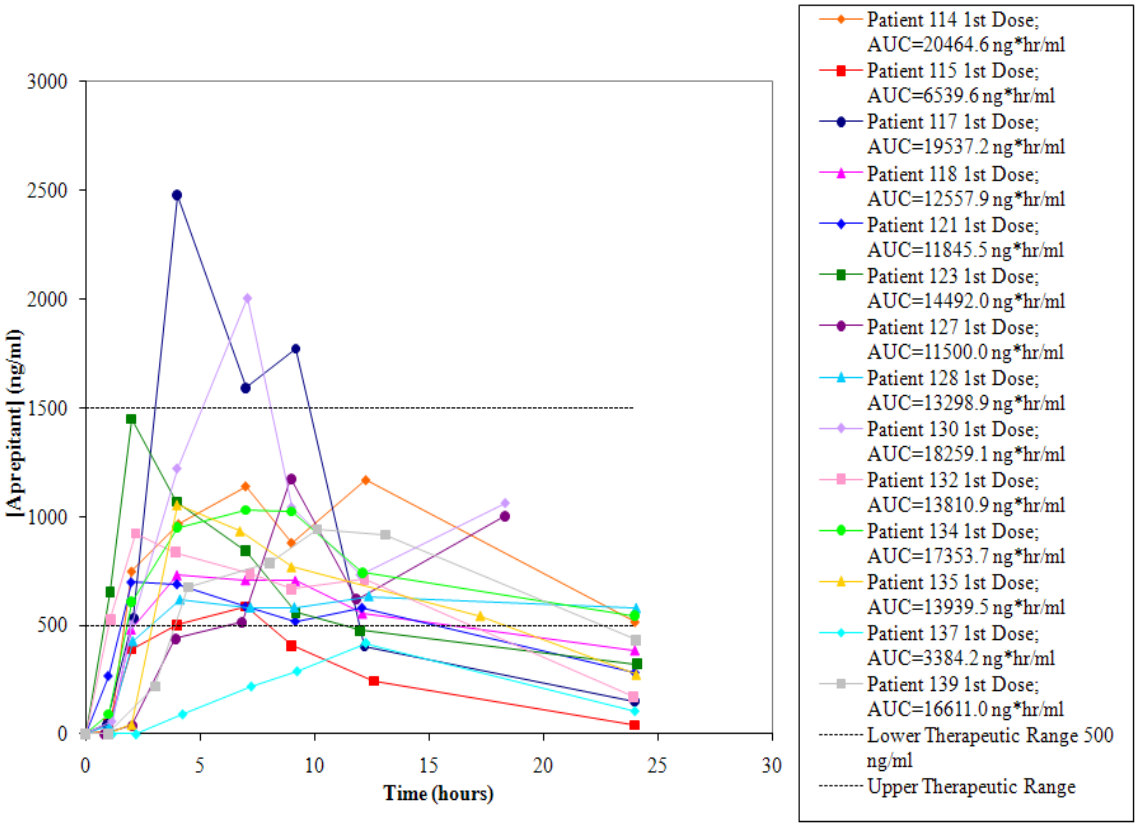
a. Harmonic mean and jackknife 95% confidence interval estimated for $T_{½}$

3.6 PATIENTS WITH INCREASED APREPITANT TROUGH CONCENTRATIONS; DUE TO CYCLOSPORINE A COMPETITIVE INHIBITION OF CYP3A

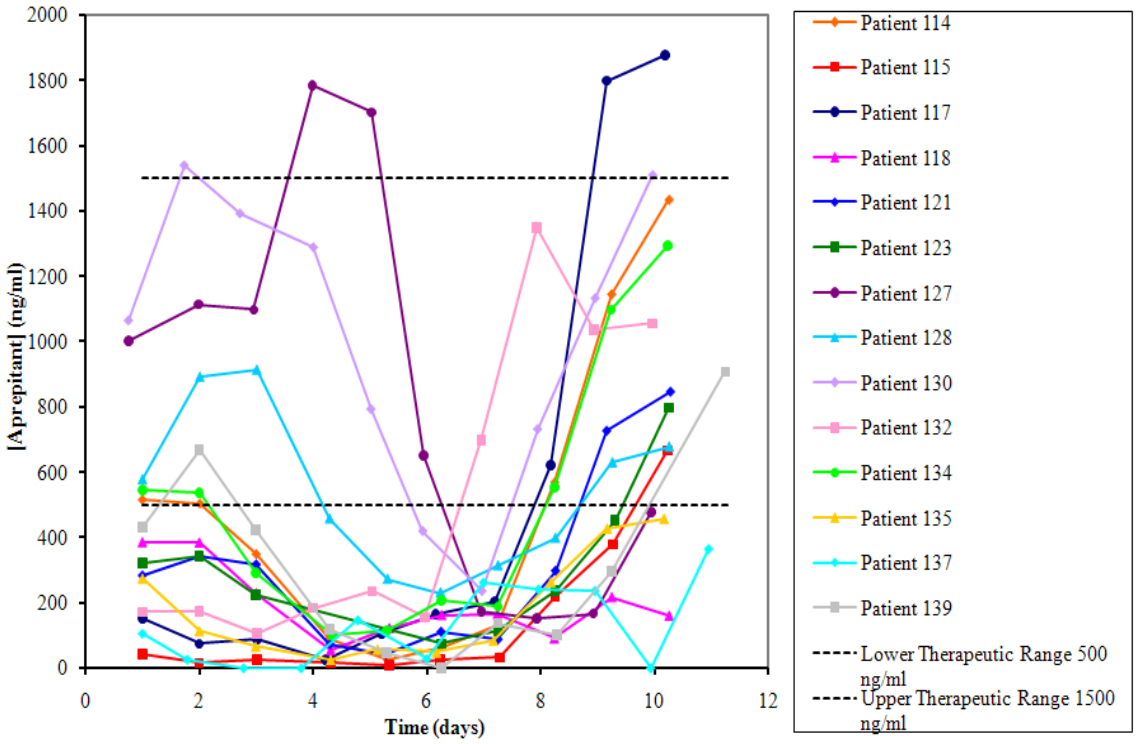
114
115
117
118
121
132
134

3.10 FIGURES

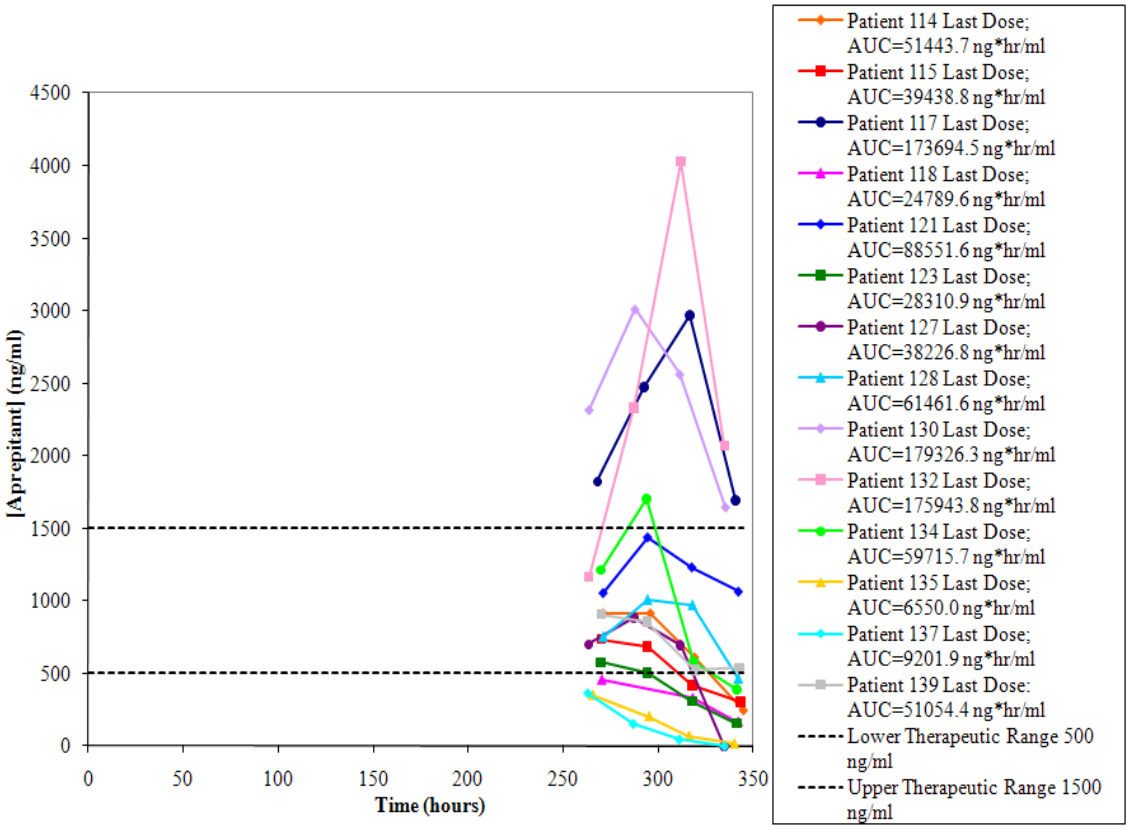
3.1 GRAPH PLASMA CP VS TIME AFTER 125MG DOSE



3.2 GRAPH PLASMA CP VS TIME OF TROUGHS; FOR DOSES PRECEDING LAST DOSE



3.3 GRAPH DAILY PLASMA CP VS TIME FOLLOWING LAST 80MG DOSE



3.11 APPENDIX

3.11.1 APPENDIX I: CHILD-PUGH CLASSIFICATION

Parameter	Points assigned 1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	≤ 2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds over control	1-3	4-6	>6
INR	<1.7	1.8-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Child-Pugh classification of severity of liver disease Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival: grade A – 100 and 85 percent; grade B – 80 and 60 percent; and grade C – 45 and 35 percent.

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3.11.2 APPENDIX II: TOXICITY CRITERIA

Toxicities and adverse events were assessed using the NCI Common Toxicity Criteria (CTC) Version 3.0. Since CTEP has standardized the CRCAE, the NCI does not require the inclusion of the CTC within the protocol document. A copy can be downloaded from the CTEP home page http://ctep.info.nih.gov.

4 VANCOMYCIN PHARMACOKINETICS IN PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA

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4.1 ABSTRACT

The purposes of this study were three-fold: 1) Evaluate the ability of a standard bedside clinical protocol approach to vancomycin dosing in patients with Acute Myelogenous Leukemia (AML) to produce desired target drug peak and trough concentrations, 2) Estimate vancomycin pharmacokinetic (PK) parameters in patients with AML for comparison to accepted general population PK parameter estimates, and 3) assess the impact of the findings on vancomycin dosage recommendations in AML patients. A three year retrospective study was conducted involving medical record review for inpatients at least 18 years of age with a diagnosis of AML or AML remission and one or more vancomycin concentrations. The primary endpoint was to compare PK parameters of patients with AML to general population estimates using a one-compartment PK model. Also considered were the effectiveness of a standard protocol clinical approach to vancomycin dosing based on general population PK estimates, time elapsed since AML diagnosis on PK predictions, and initial vancomycin dose requirements for patients with AML.

A total of 102 vancomycin concentrations from 27 ill AML patients were analyzed. All but two patients were neutropenic. The standard protocol clinical approach utilized in vancomycin dosing was suboptimal, producing vancomycin concentrations significantly below those desired clinically. Patients with AML had a faster average vancomycin elimination rate constant 0.157 (0.137-0.178) hr^{-1} [mean (95% CI)] than the general population 0.082 (0.065-0.099) hr^{-1}, and shorter average vancomycin half-life 5.92 (4.68-7.16) hrs compared with general population estimates of 9.1 (7.2-11) hrs. Patients received an average of 35mg/kg/day of vancomycin based on the standard protocol utilized, but PK estimates show an average of 54 mg/kg/day was

required to achieve recommended vancomycin concentrations. A relationship was tentatively noted between time elapsed since AML diagnosis and vancomycin dose requirements.

Patients with AML demonstrate altered vancomycin pharmacokinetics as compared with the general population including a shorter vancomycin half-life, and therefore require increased vancomycin dosing to achieve recognized therapeutically effective drug concentrations, particularly in younger patients with a recent diagnosis of AML. The standard bedside clinical approach protocol investigated for dosing vancomycin is suboptimal for patients with AML, typically underdosing the AML population. Vancomycin serum concentrations in the study population of AML patients dosed by standard protocol averaged only 72.88% of that expected due to one-compartment vancomycin predictions, suggesting patients with AML require increased vancomycin doses.

4.2 INTRODUCTION

Vancomycin is an antibiotic commonly used against gram-positive bacteria species.[1] Due to the increase in drug resistant infectious organisms, there is an increase in the use of vancomycin therapy.[2] Organisms of concern include Methicillin-resistant S. aureus (MRSA) (both nosicomial and community acquired), Methicillin-resistant S. epidermidis (MRSE), and Penicillin-resistant S. pneumoniae.[3, 4] With these infections, it is especially important to initiate dose regimens that obtain therapeutic vancomycin serum concentrations (15-20 mg/L).[5, 6] With infected patients who also have hematologic malignancy, this is even more important, as these patients have compromised immunity

due to chemotherapy.[7] Without rapidly achieving therapeutic antibiotic concentrations, these patients are vulnerable to life-threatening bacterial infections.[8]

Acute Myelogenous Leukemia is described as a hematopoietic stem cell disorder with a block in differentiation of the myeloid cell line.[9, 10] The standard approaches to treating this condition are autologous or allogeneic hematopoietic stem cell transplantation (HSCT).[11] Myeloablative conditioning regimens for HSCT involve cyclophosphamide and total body irradiation or busulfan.[12] These treatment options leave patients vulnerable to infections due to immunosuppression caused by the treatment.[12-14] IV vancomycin is used to treat such infections.

In order to estimate proper drug doses, pharmacokinetic parameters must be known. Although vancomycin pharmacokinetic parameters are known for the general population, they are not well known for patients with hematologic malignancies, who appear to have an increased clearance of vancomycin, compared with the general population. Fernandez de Gatta et al. and Santos Buelga et al. have the definitive articles describing this phenomenon.[15, 16] Santos Buelga et al. estimated one-compartment PK vancomycin parameters using NONMEM analysis for 215 patients with hematological malignancies and concluded that vancomycin clearance is increased by a factor of 1.66 in this patient population compared to the overall general population.[16, 17] In a subpopulation of 79 AML patients, the drug clearance was increased, with a higher coefficient of 1.8 (Clearance = 1.17*ClCr)[16] versus (Clearance = 0.65*ClCr) in the general population.[17] These investigators concluded that a typical patient with a hematological malignancy would require a mean vancomycin dosage of 45mg/kg/day (50% higher than that conventionally used) to be optimally effective. The Santos Buelga

et al. findings are consistent with an earlier report that clearance of vancomycin is by double or more in a group of patients with malignancies versus patients that do not have malignancies.[15]

In addition to, and consistent with the above reports, pharmacy experience in the current study hospital has shown that AML patients need to be dosed twice as often as non-AML patients in order to maintain therapeutic vancomycin concentrations. In other words, average general population pharmacokinetic parameters did not effectively apply to the AML population. This retrospective study aimed to estimate vancomycin pharmacokinetic parameters for AML patients using simple one-compartment clinical pharmacokinetic assumptions with AML patient drug concentration data. This information is then used to suggest appropriate dosing amounts for AML patients.

4.3 METHODS

4.3.1 PATIENTS

A retrospective chart review involving admissions from 2003-2006 was performed for Providence St. Vincent Medical Center in Portland, Oregon. The study was approved by the Institutional Review Board. Inclusion criteria were as follows: patients of at least 18 years of age, diagnosed with AML, received vancomycin, and had at least one vancomycin serum concentration measured. Data from vancomycin courses during which a change in SCr $\geq$ 0.5 mg/dl occurred during vancomycin therapy were excluded unless the change in SCr occurred > 5 days after the last vancomycin serum concentration obtained, because vancomycin PK clearance parameters vary during kidney function changes. Dialysis patients were excluded as well.

4.3.2 DATA COLLECTION

The subjects' medical records were reviewed for demographics, medical history, and laboratory data. Data needed for pharmacokinetic analysis included sex, height, age, patient weight, serum creatinine concentration, vancomycin dosing information and resultant serum vancomycin concentrations, including sample collection times. One-compartment pharmacokinetic parameters are expressed as mean, 95% CI. Statistical calculations were performed using Microsoft Excel.

4.3.3 ONE-COMPARTMENT PHARMACOKINETIC MODELING

Typical clinical one-compartment vancomycin pharmacokinetics assumptions[17-22] (Appendix 1) were used throughout because this is the standard approach in the study hospital, and because insufficient patient drug concentration data are collected in clinical practice to evaluate a two-compartment model. The Cockcroft and Gault equation[23] was used for creatinine clearance (ClCr) estimation. Because the equation can poorly overestimate creatinine clearance if the serum creatinine (SCr) is low,[24] the SCr was rounded up to 0.7 mg/dl for values < 0.7mg/dl.[25] ClCr estimation results were capped at a maximum of 140ml/min[26, 27] because impossibly high estimates for ClCr can produce unreasonably high estimates for vancomycin clearance. This would lead to unusually low estimates for serum vancomycin concentrations which are not realistic and which would be below the actual drug concentrations. Since the Cockcroft and Gault equation considers only stable renal function in estimating ClCr[28], data following a change in serum creatinine $\geq$ 0.5 mg/dl[29-31] were excluded from the one-compartment analysis. Steps involved in conducting analysis for this research are as follows:

1. Calculate initial vancomycin dose for each AML patient using general population PK parameters.

2. Simulate the expected Cmax and Cmin with the calculated dose for non-steady state and steady-state conditions.

3. Compare the simulated values to the available laboratory measured drug concentrations.

4. Calculate the patient specific PK parameters of each AML patient.

5. Compare the AML patient specific PK values with the general population PK values.

6. Calculate the desired vancomycin dose for AML patients using the calculated AML patient specific PK parameters.

7. Present additional observations such as relationship between time since disease diagnosis and drug clearance, and therefore necessary dose.

Over the three retrospective study years at the study site, standard protocol doses were calculated for vancomycin using a general one-compartment vancomycin population pharmacokinetic model,[17-22] and parameters. Estimation of vancomycin concentrations using one-compartment clinical equations and population PK parameter values is described with an example in Appendix I. The general population PK values utilized for a typical dose were input = 1200 mg vancomycin infused in a zero-order manner over 1.5 hours, Vd=68.32L, ke=0.071hr^{-1}, and drug Cl=4.85L/hr.

If more than one dose was to be administered, patient blood samples were collected, drug concentrations determined, and the drug dose adjusted if necessary, and the process repeated if more drug doses were administered. As this process occurred, it was observed that initial dose calculations typically resulted in underdosing of AML patients and subtherapeutic drug concentrations for the initial doses, even though repeated dosing with higher doses or at shorter dosing intervals, or both, eventually resulted in effective peak and trough drug concentrations in the blood.

In the current study, the standard protocol one-compartment PK calculated doses were independently and separately re-calculated by two investigators for each course of vancomycin therapy in each patient, and resultant predicted drug concentrations then compared with actual measured serum concentrations reported in the files, including both steady-state and pre-steady state values. These values were compared to known therapeutically effective vancomycin concentrations to evaluate the effectiveness of the standard protocol bedside clinical approach to vancomycin dosing in AML patients. Estimation of the vancomycin elimination rate constant (ke) and half-life ($t_{1/2}$) values and estimated vancomycin dose requirements for each patient in the AML cohort were also performed based on steady-state drug trough concentrations and a general population volume of distribution of 0.8L/kg[18], which is reported to be appropriate for this population.[15] A primary goal of the study was comparison of vancomycin pharmacokinetic parameters for AML patients to general population pharmacokinetic parameters. See Appendix I for all equations, definitions of terms, and calculation examples.

4.4 RESULTS

4.4.1 PATIENT DATA COLLECTED

The average age of patients was 51 years (range 18-81yrs), 62% of patients were male, 38% were female, the average patient weight was 84 kg (range 54-113 kg), and the average baseline SCr value (defined as SCr obtained within 48 hours of vancomycin start time) was 0.8 mg/dl (range 0.4-1.5 mg/dl).

One patient had the first SCr drawn 4 days after starting vancomycin, and SCr fell within this range. All but two patients were neutropenic while receiving vancomycin therapy.

Review of patient records resulted in data from 30 patients, involving 121 vancomycin serum concentrations which were considered. There were six courses of vancomycin including 14 vancomycin serum concentrations omitted from the analysis due to a change in patient Scr of at least 0.5mg/dl during vancomycin therapy which indicated changing renal function and drug clearance over time. An additional five vancomycin serum concentrations were excluded due to the measured concentrations falling below the laboratory reportable assay reference range and inability to quantify the concentration. Therefore, 102 serum concentrations (64 at steady state, 38 pre-steady state) from 27 patients with AML were included in the analysis.

4.4.2 NEEDED VANCOMYCIN DOSE IN AML PATIENTS

During the time period of this study, patients with AML received only an average vancomycin dose of 35 mg/kg/day because standard dosing protocols using standard population parameters for vancomycin underestimate the drug clearance. Vancomycin exhibits time-dependent killing. Therefore, increasing the concentration beyond the minimal inhibitory concentration has no apparent effect in the rate of killing.[18] Peak concentrations are important only when considering ototoxicity, which is rare.[32] Therefore, peak concentrations are not routinely ordered. See Table 4.1 for listing of patient doses and resultant measured serum concentrations. The average trough concentration was 8.9 mg/L. The average peak concentration was 22.2mg/L. Measured vancomycin concentrations in patients were on average 72.88% of predicted drug concentrations which is a result of vancomycin clearance being faster in AML patients than in the general population. The PK parameters for the AML patient population indicated a shorter half-life and faster clearance than the general population.

Choosing a desired one-compartment target Cmax of 35mg/L and a target Cmin of 15mg/L[6] to provide a therapeutic vancomycin plasma concentration range, and a dose interval no more frequent than 8 hours for convenience of administration reveals an average dose requirement in the study AML patients of 54 mg/kg/day of vancomycin to achieve target drug concentrations. Therefore, on average, patients with AML received only 64.8% of the dose necessary to achieve therapeutic vancomycin serum concentrations. Seven of 74 (9.5%) vancomycin trough concentrations were within the therapeutic trough concentration range of 15-20mg/L. Five patients specifically achieved a trough concentration of 15-20mg/L. These data include those cases where dose was increased during therapy because Cp measurements indicated the initial dose was too low. Therefore initial doses were an even smaller fraction of the required dose.

Time since AML diagnosis was available for only 18 patients but involved 74 vancomycin serum concentrations. These data were evaluated for a possible trend of time since diagnosis on vancomycin PK predictions. Results in Table 4.2 show underprediction of serum vancomycin concentrations in AML patients using general population PK for patients for whom time since diagnosis was known. Figure 4.1 summarizes estimated vancomycin dose requirements divided into patient age groups for those 15 patients with data known to have been collected within six months of AML diagnosis. As expected, it is a result that dosage requirements decrease as patient age increases. Figure 4.2 shows the actual dose administered compared to the dose that was needed for all patients. Results in Figure 4.2 also show a substantial increase in required dose for AML patients over what was actually administered to these AML patients with the largest increases needed in the youngest patients.

It was an observation that when time since diagnosis of AML was relatively short, the vancomycin half-life was also quite short. When time since diagnosis became relatively long, then drug half-life also became relatively longer. In other words, it was a tentative result that the largest percent underprediction of serum concentrations using general population pharmacokinetic values occurred in newly diagnosed patients (Table 4.2). The concern regarding underdosing vancomycin is greatest with newly diagnosed patients.

The one-compartment patient specific PK parameters for the study patients are shown in Table 4.3. On average, vancomycin clearance results in these AML patients could be calculated as Cl = (1.52)(ClCr).

4.5 DISCUSSION

This study confirms earlier reports[15, 16] that patients with hematological malignancies, and even more specifically with AML, have a faster average vancomycin elimination rate constant, higher clearance, and shorter vancomycin half-life than the general population receiving vancomycin therapy.[22] Thus, dosing vancomycin using a general population elimination rate constant or clearance is suboptimal for patients with AML, with typical dosing regimens underdosing the AML population. Because of this, vancomycin serum concentrations in this population of AML patients were only 72.88% of that predicted by protocol bedside one-compartment vancomycin predictions described herein, suggesting patients with AML require increased vancomycin doses. Confirmation of the earlier studies did not require a complicated NONMEM approach[16] and was achieved assuming only a standard population Vd and a one-compartment model with limited data points for each patient.

The average administered dose was 35 mg/kg/day and the average needed dose was 54 mg/kg/day, reflecting an increased clearance in this population.[15, 16] Clinically, vancomycin dosing is often capped at ~50-60 mg/kg/day[33], but Figure 4.2 shows, based on 102 measured vancomycin concentrations, that 13 of 22 patients in this study needed a vancomycin dose greater than 50 mg/kg/day. This now makes three studies all using different methodologies and different study sites but reaching the same conclusion: vancomycin doses must be increased in AML patients.[15, 16] No patients (0%) with doses in the range of 14-16mg/kg resulted in trough concentrations between 15-20mg/L. While more study is needed before vancomycin doses even greater than 60 mg/kg/day can be routinely recommended, these three studies suggest that some patients with AML may require more than 60 mg/kg/day.[33]

4.6 LIMITATIONS

Limitations of this study include, but are not limited to: a small patient population of 27 AML patients and limited data. This study was designed to evaluate a standard protocol bedside clinical approach to vancomycin dosing, which at the study institution involved equations listed in Appendix 1. In accordance with the standard approach to monitoring vancomycin, serum concentration data consisted predominantly of vancomycin trough concentrations and only limited vancomycin peak serum concentrations were obtained. Thus, specific data available to assess volume of distribution (Vd) in this patient population were not available and Vd was assumed to be (0.8 L/kg*total body weight)[18] (see Appendix 1), because it has previously been suggested that alterations in vancomycin pharmacokinetics in patients with hematologic malignancy involve predominant changes in vancomycin clearance, rather than volume

of distribution.[15] This may be a limitation, since Santos Buelga et al. report Vd in AML patients as (0.98 L/kg*total body weight)[16]. It should be noted however that using the simple analysis herein with 102 measured vancomycin drug concentrations independently results in essentially the same clinical conclusions as from the more complicated NONMEM analysis and multiple linear regression reported earlier.[16]

All but two patients included in the study were neutropenic during the time of receiving vancomycin therapy. Unfortunately, the effect of degree of neutropenia on vancomycin clearance in AML patients could not be evaluated since the vast majority of absolute neutrophil count values were zero or very near zero, i.e., no range of data were available. Data for dose estimates in Figure 4.1 when subdivided by age and time since diagnosis were based on very small numbers of patients and additional data are needed to identify optimal vancomycin doses. Further study needs to be performed to assess factors such as age, time since diagnosis, and neutropenia on the vancomycin dose requirements in patients with AML.

4.7 CONCLUSIONS

Patients with AML demonstrate altered vancomycin PK parameters compared with the general population. Results indicate patients with AML have an average increased vancomycin elimination rate constant and shortened vancomycin half-life compared with general population estimates. Patients with AML require increased vancomycin dosages to achieve therapeutic serum concentrations. A well designed prospective study is warranted to define all vancomycin PK parameters in patients with AML and to differentiate the impact of neutropenia, patient age, and time elapsed since AML diagnosis on pharmacokinetic estimates and dosage requirements.

4.8 REFERENCES

1. Cohen E, Dadashev A, Drucker M et al. Once-daily versus twice-daily intravenous administration of vancomycin for infections in hospitalized patients. *J Antimicrob Chemother* 2002; **49:** 155-160.

2. Yoshida M, Yasuda N, Nishikata M et al. New recommendations for vancomycin dosage for patients with MRSA pneumonia with various degrees of renal function impairment. *J Infect Chemother* 2005; **11:** 182-188.

3. Akins RL, Haase KK. Gram-positive resistance: pathogens, implications, and treatment options: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy* 2005; **25:** 1001-1010.

4. Wilcox MH, Tack KJ, Bouza E et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study.[see comment]. *Clin Infect Dis* 2009; **48:** 203-212.

5. Tunkel AR, Hartman BJ, Kaplan SL et al. Practice guidelines for the management of bacterial meningitis.[see comment]. *Clin Infect Dis* 2004; **39:** 1267-1284.

6. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia.[see comment]. *Am J Respir Crit Care Med* 2005; **171:** 388-416.

7. Salazar R, Sola C, Maroto P et al. Infectious complications in 126 patients treated with high-dose chemotherapy and autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999; **23:** 27-33.

8. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. *Clin Pharmacokinet* 2006; **45:** 755-773.

9. Shipley JL, Butera JN. Acute myelogenous leukemia. *Exp Hematol* 2009; **37:** 649-658.

10. Stegmaier K, Corsello SM, Ross KN et al. Gefitinib induces myeloid differentiation of acute myeloid leukemia. *Blood* 2005; **106:** 2841-2848.

11. Hegenbart U, Niederwieser D, Sandmaier BM et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol* 2006; **24:** 444-453.

12. Valcarcel D, Martino R. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in myelodysplastic syndromes and acute myelogenous leukemia. *Curr Opin Oncol* 2007; **19:** 660-666.

13. Le Normand Y, Milpied N, Kergueris MF et al. Pharmacokinetic parameters of vancomycin for therapeutic regimens in neutropenic adult patients. *Int J Biomed Comput* 1994; **36:** 121-125.

14. Syed MI, Clark LJ, Sturrock RD. Unintended benefits of immunosupression on autoimmune disease due to chemoradiation therapy for head and neck cancer. *Am J Otolaryngol* 2008; **29:** 63-65.

15. Fernandez de Gatta MM, Fruns I, Hernandez JM et al. Vancomycin pharmacokinetics and dosage requirements in hematologic malignancies. *Clin Pharm* 1993; **12:** 515-520.

16. Buelga DS, del Mar Fernandez de Gatta M, Herrera EV et al. Population pharmacokinetic analysis of vancomycin in patients with hematological malignancies. *Antimicrob Agents Chemother* 2005; **49:** 4934-4941.

17. Winter ME. (3rd edition). *Basic Clinical Pharmacokinetics*. Applied Therapeutics, Inc.: WA, 1994.

18. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis* 2006; **42 Suppl 1:** S35-39.

19. Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. *Ann Pharmacother* 2000; **34:** 1066-1069.

20. Demirovic JA, Pai AB, Pai MP. Estimation of creatinine clearance in morbidly obese patients. *Am J Health-Syst Pharm* 2009; **66:** 642-648.

21. Smilde TD, van Veldhuisen DJ, Navis G et al. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction.[see comment]. *Circulation* 2006; **114:** 1572-1580.

22. Matzke GR, McGory RW, Halstenson CE et al. Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrob Agents Chemother* 1984; **25:** 433-437.

23. Herget-Rosenthal S, Bokenkamp A, Hofmann W. How to estimate GFR-serum creatinine, serum cystatin C or equations? *Clin Biochem* 2007; **40:** 153-161.

24. Hermida J, Tutor JC. Serum cystatin C for the prediction of glomerular filtration rate with regard to the dose adjustment of amikacin, gentamicin, tobramycin, and vancomycin. *Ther Drug Monit* 2006; **28:** 326-331.

25. Kirkpatrick CM, Duffull SB, Begg EJ. Pharmacokinetics of gentamicin in 957 patients with varying renal function dosed once daily. *Br J Clin Pharmacol* 1999; **47:** 637-643.

26. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: physiological principles. *Intensive Care Med* 2004; **30:** 33-37.

27. Lamb EJ, Tomson CR, Roderick PJ et al. Estimating kidney function in adults using formulae.[see comment]. *Ann Clin Biochem* 2005; **42:** 321-345.

28. Jelliffe R. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. *Am J Nephrol* 2002; **22:** 320-324.

29. Sym D, Smith C, Meenan G et al. Fluorescence polarization immunoassay: can it result in an overestimation of vancomycin in patients not suffering from renal failure? *Ther Drug Monit* 2001; **23:** 441-444.

30. Staatz CE, Byrne C, Thomson AH. Population pharmacokinetic modelling of gentamicin and vancomycin in patients with unstable renal function following cardiothoracic surgery. *Br J Clin Pharmacol* 2006; **61:** 164-176.

31. Hu KT, Matayoshi A, Stevenson FT. Calculation of the estimated creatinine clearance in avoiding drug dosing errors in the older patient. *Am J Med Sci* 2001; **322:** 133-136.

32. Barth RH, DeVincenzo N. Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy. *Kidney Int* 1996; **50:** 929-936.

33. Rybak MJ, Lomaestro BM, Rotscahfer JC et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis* 2009; **49:** 325-327.

4.9 TABLES

4.1 PATIENT DOSES AND RESULTANT SERUM CONCENTRATIONS

patient	admission	dose (mg)	dose/kg	Conc (mg/L)	peak(p) trough(t) random(r)
1	1	1200	14.1	13.9	t
1	1	1200	14.1	14.6	t
2	1	1000	19.8	3.9	t
2	1	1500	29.2	5.1	t
2	1	1000	19.5	11.7	t

3	1	1000	8.7	13.5	t
3	2	1250	10.9	11.3	t
3	2	1400	12.5	18	t
3	2	1400	13.1	20.3	t
3	2	1200	11.4	15.1	t
3	2	1250	12.1	21.4	r
4	1	1400	17.0	12.7	t
4	1	1250	15.2	5	t
4	2	1000	13.6	5.1	t
4	2	1000	13.6	7.3	r
4	2	1750	23.8	9.1	t
4	2	1250	17.0	5.3	t
5	1	1000	15.1	4.1	t
5	1	1500	22.8	8.2	t
5	1	1250	19.1	15.2	t
6	1	1000	10.4	1.8	t
6	1	1000	10.4	17	p
6	2	1000	9.5	1.8	t
6	2	1000	9.5	18.1	p
7	1	1000	11.2	6.6	t
7	1	1000	11.2	23.6	p
8	1	1500	14.1	10.9	r
8	1	1500	15.2	10.1	t
9	1	1250	15.6	7	t
10	1	1000	12.9	5.1	t
11	1	1500	15.9	1.7	t
11	1	1500	15.9	7.3	r
11	2	2000	21.4	25.6	r
11	2	2000	21.4	9.6	r
11	2	2000	21.4	9.7	t
12	1	1500	22.7	7.2	t
12	1	1000	15.2	12.1	t
13	1	1250	13.6	8	r
13	1	1250	13.6	0.7	t
13	1	1250	13.6	18.4	t
14	1	1250	14.0	6.1	t
14	1	1250	15.1	2.4	t
14	1	1500	18.3	2.9	t
15	1	1400	15.3	9.9	t
15	1	1400	15.7	12.5	t
15	1	1400	15.7	33.7	p
15	1	1250	14.1	19	p
16	1	1250	16.4	6.2	t
16	1	1400	18.3	9.8	t
16	1	1500	20.9	8.5	t

16	1	1600	22.1	15.8	r
16	1	1500	20.5	11.1	t
17	1	1000	18.7	13.6	r
18	1	1000	12.9	6.2	r
18	1	1000	12.9	4.7	t
18	2	1250	15.4	4.8	t
19	1	1650	15.4	9.4	t
20	1	1250	15.0	8.7	t
20	1	1250	15.0	9.5	t
20	1	1250	15.0	9.6	t
20	2	1250	15.0	10.7	t
20	2	1000	12.0	6.7	t
20	3	1000	11.4	4.8	t
20	3	1000	11.4	19.9	p
20	4	1000	11.1	6.2	t
20	4	1000	11.1	8.5	r
20	4	1000	11.1	21.1	p
20	5	1000	10.1	5.6	t
21	1	1000	13.5	9.4	t
21	1	1000	13.5	28.3	p
22	1	1000	15.8	19.2	p
22	2	1250	20.3	7.6	t
22	3	1250	17.5	7.1	t
22	3	1500	21.0	11	t
22	4	1500	20.3	8.4	t
23	1	900	12.9	7.9	t
23	1	1250	18.9	16.2	t
23	1	1000	15.6	12.1	t
23	1	1000	15.5	19.3	r
23	1	1000	15.5	13.3	t
23	1	750	10.8	5	t
23	1	1250	18.7	12.1	t
24	1	1500	18.5	10.3	r
24	2	1500	18.2	5.5	r
24	3	1000	12.2	19.1	p
24	3	1000	12.2	5.2	t
25	1	1500	18.0	11.6	t
25	2	1500	19.3	16.8	t
25	2	1250	16.1	12.7	t
25	2	1250	15.8	5.7	t
26	1	1500	15.6	10.5	t
26	1	1000	10.4	6.5	t
26	1	1000	10.4	22.2	p
26	2	1500	15.9	13	t
26	2	1250	12.9	13.7	t

26	2	1400	14.8	6.9	t
26	2	1400	14.8	20.4	p
26	2	1500	15.9	7.8	t
26	2	1500	15.9	26.5	p
27	1	1250	15.5	4.9	t
27	1	1250	14.9	9.8	r
27	2	1250	16.0	9	t

4.2 PREDICTIVE PERFORMANCE OF CLINICAL PK

Time Since Diagnosis	Average Actual Vancomycin Serum Concentration as Percent of Predicted	# Serum Concentrations	Total number of patients in each group
All patients	72.88	102	33
< 6 months	61.88	55	16
6-22 months	71.67	13	4
> 22 months	108.24	6	2

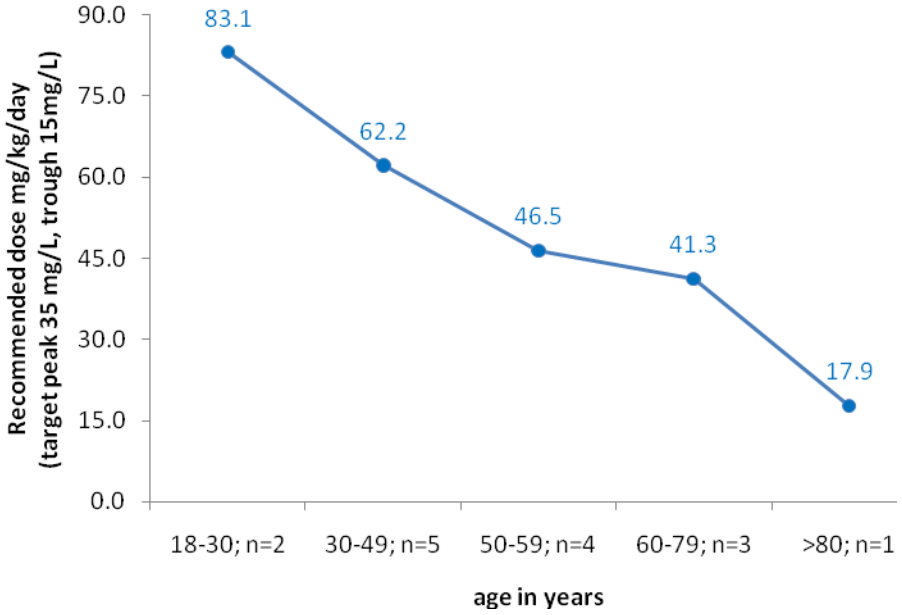
Time since diagnosis unknown for 28 serum concentrations involving 11 patients. Some patients had multiple admissions. These patients fall into multiple Time Since Diagnosis categories. This is the reason the total 33 patients listed in Table 4.2 is greater than the 27 individual patients used for the study.

4.3 ONE-COMPARTMENT VANCOMYCIN PK PARAMETERS

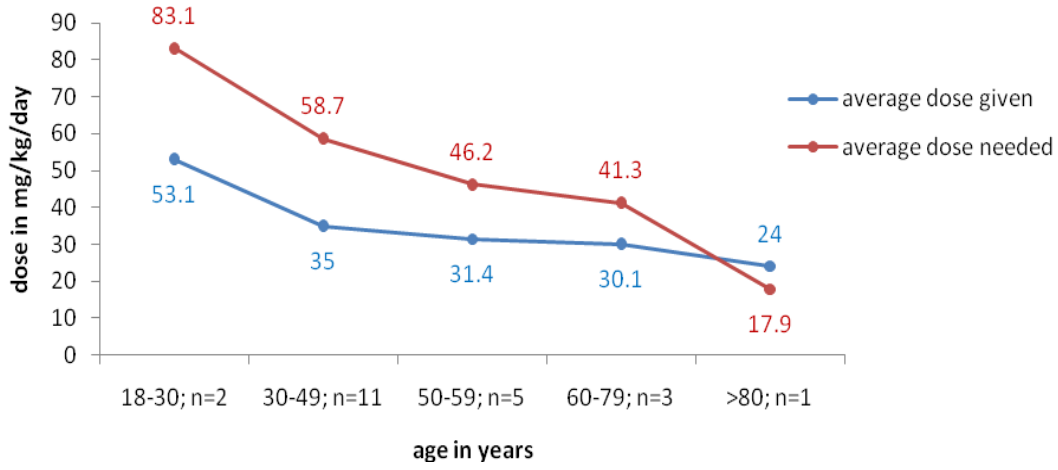
	General Population[22] Mean (95% CI)	AML Population Mean (95% CI)	Patients with Hematologic Malignancies[16] Mean (95% CI)
Average Ke	0.082 (0.065-0.099) hr^{-1}	0.157 (0.137-0.178) hr^{-1}	
Average $t_{1/2}$	9.1 (7.2-11) hrs	5.92 (4.68-7.16) hrs	
Average Clearance	3.76 (2.74-4.78) L/hr	9.9 (8.4-11.3) L/hr	5.79 (5.57-6.01) L/hrs

4.10 FIGURES

4.1 GRAPH VANCOMYCIN DOSAGE NEEDED ESTIMATES; AML PATIENTS WITH TIME SINCE DIAGNOSIS LESS THAN SIX MONTHS; PATIENT STEADY STATE CONCENTRATION DATA USED FOR ESTIMATION



4.2 GRAPH COMPARING DOSE GIVEN VS DOSE NEEDED; ALL PATIENTS WITH STEADY STATE CONCENTRATION DATA



4.11 APPENDIX

4.11.1 ONE-COMPARTMENT MODEL VANCOMYCIN PK EQUATIONS

DEFINITIONS

ClCr (ml/min) = Creatinine Clearance
ke (hr^{-1}) = vancomycin elimination rate constant
AdjBW (kg) = Adjusted body weight
$t_{1/2}$ (hrs) = vancomycin half-life
Vd (L) = vancomycin volume of distribution
TBW (kg) = total body weight
IBW (kg) = ideal body weight
Cmax (mg/L) = peak vancomycin serum concentration
Cmin (mg/L) = trough vancomycin serum concentration
D (mg) = dose given
ti (hrs) = infusion time
t= time after completion of infusion
n= number doses given

EQUATIONS AND BODY WEIGHTS USED IN THE STUDY[17-22]

IBW female (kg): 2.3 (inches over 5 feet) + 45.5
IBW male (kg): 2.3 (inches over 5 feet) + 50

ClCr (ml/min) = $\frac{(140-age)(IBW)}{(72)(Scr)}$ x 0.85 for females

*AdjBW = IBW + 0.4(TBW – IBW); used if TBW $\geq$ 130% IBW; TBW used if TBW< IBW
SCr rounded to 0.7 mg/dl if reported value < 0.7 mg/dl (clinical assumption-see text)
ClCr estimate capped at 140ml/min (clinical assumption-see text)

ke (hr^{-1}) = 0.00083 x ClCr (ml/min) + 0.0044
$t_{1/2}$ (hrs) = 0.693/ke
Vd (L) = 0.8 L/kg (TBW; AdjBW if TBW $\geq$130% of IBW)

PRE-STEADY-STATE INFUSION EQUATIONS

Cmax (mg/L) = $\frac{(D/ti)(1-e^{-ke(ti)})(1-e^{-nke(\tau)})}{(Vd)(ke)(1-e^{-ke(\tau)})}$

Cmin (mg/L) = (Non-Css Cmax)($e^{-ke(t)}$)

STEADY-STATE INFUSION EQUATIONS

Steady-state Cmax (mg/L) = $\frac{D/ti\ \ (1-e^{-ke(ti)})}{Vd\ \ (ke)(1-e^{-ke(\tau)})}$

Steady-state Cmin (mg/L) = (Css Cmax)($e^{-ke(t)}$)

$$\tau = \frac{-\ln(C\min/C\max)}{ke} + ti$$

$$Dose(mg) = \frac{(Vd)(ke)(ti)(C\max)(1-e^{-ke(\tau-ti)})}{(1-e^{-ke(ti)})}$$

4.11.2 EXAMPLES OF ESTIMATION OF VANCOMYCIN CONCENTRATIONS; ONE-COMPARTMENT CLINICAL EQUATIONS AND POPULATION PK PARAMETER VALUES

The population PK parameter values involved with the estimations included Vd, which used the most recent recorded total body weight prior to the time of dose administration.

Vd = 0.8L/kg * 85.4kg (total body weight) = 68.32L

If the patient had a total body weight > 130% of their ideal body weight, then adjusted body weight was used for estimation of Vd.

Total body weight = 114.5kg
Ideal body weight = 77.6kg
Total body weight/ideal body weight = 114.5/77.6 = 1.48

Adjusted body weight = ideal body weight + 0.4(total body weight – ideal body weight)
= 77.6 + 0.4(114.5 – 77.6) = 92.36kg

The Cockcroft and Gault (CG) equation was used to estimate creatinine clearance to be entered into the Matzke equation. Ideal body weight was used for the CG equation. If the patient's total weight was > 130% of their ideal body weight, then adjusted body weight was used for the CG equation. If the patient's total body weight was < ideal body weight, then total body weight was used for the CG equation. The serum creatinine value used in the CG equation was the most recent recorded value prior to the time of dose administration. If the serum creatinine value was < 0.7mg/dL, then the serum creatinine value for the CG equation was rounded up to 0.7mg/dl. The estimated ClCr value was capped at 140ml/min.

$$ClCr = (0.85)\frac{(140-age)(IBW)}{(72)(Scr)} = (0.85)\frac{(140-47)(79.9)}{(72)(1.1)} = 79.75ml/\min$$

The Matzke equation which included ClCr, was used to estimate the vancomycin elimination rate constant.

Ke (hr^{-1}) = 0.00083 x ClCr (ml/min) + 0.0044 = 0.00083 x 79.75 + 0.0044 = 0.071

The dose, infusion time, dosing interval, and sampling time were taken from patient records.

Dose = 1200mg
Infusion time = ti = 1.5hrs
τ = dosing interval = 12hrs
t = time between end of infusion and blood sampling time = 10.83hrs
For doses given for a period of at least 4 terminal half-lives, the steady state equations were used to estimate the resulting drug concentration.

Steady-state Cmax (mg/L) =

$$\frac{D/ti\ \ (1-e^{-ke(ti)})}{Vd\ \ (ke)(1-e^{-ke(\tau)})} = \frac{(1200mg/1.5hrs)(1-e^{-0.071(1.5)})}{(68.32L)(0.071)(1-e^{-0.071(12)})} = 29.06mg/L$$

Steady-state Cmin (mg/L) = (Css Cmax)($e^{-ke(t)}$)

Resulting concentration =

$$\frac{D/ti\ \ (1-e^{-ke(ti)})}{Vd\ \ (ke)(1-e^{-ke(\tau)})}(e^{-ke(t)}) = \frac{(1200mg/1.5hrs)(1-e^{-0.071(1.5)})}{(68.32L)(0.071)(1-e^{-0.071(12)})}(e^{-0.071(10.83)}) = 13.47mg/L$$

For drug plasma samples taken during a regimen that was dosed for a period of less than 4 terminal half-lives, that is prior to steady-state, the non-steady state equation was used to estimate the resulting drug concentration. This included listing the number of doses given under this regimen.

$$\frac{(D/ti)(1-e^{-ke(ti)})(1-e^{-nke(\tau)})}{(Vd)(ke)(1-e^{-ke(\tau)})}(e^{-ke(t)}) = \frac{(1200mg/1.5hr)(1-e^{-0.071(1.5)})(1-e^{-2\bullet 0.071(12)})}{(68.3L)(0.071)(1-e^{-0.071(12)})}(e^{-0.071(10.5)})$$

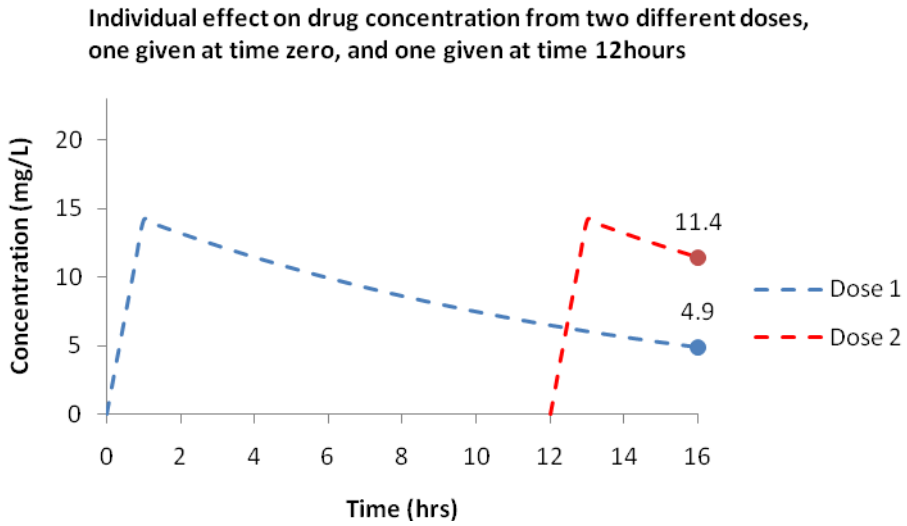
=11.28 mg/L

EFFECT OF MULTIPLE DOSES

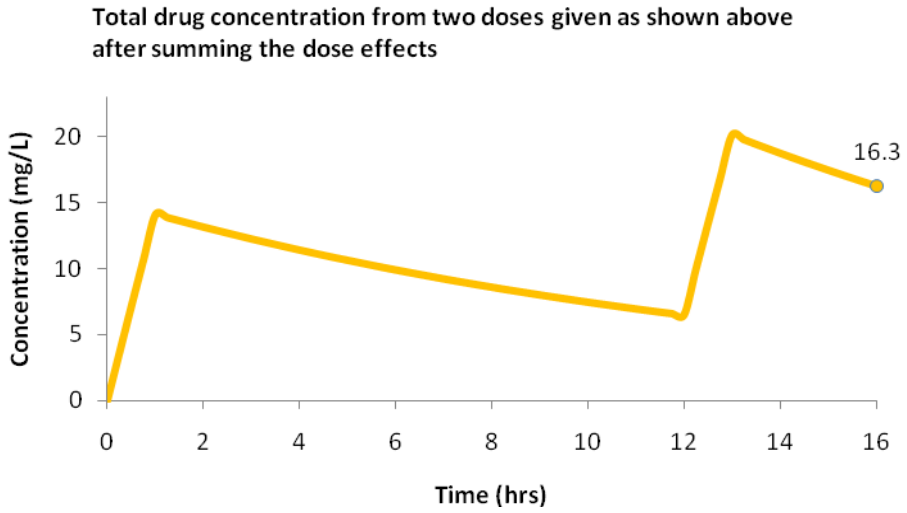
For successive doses, the residual drug concentrations from each previous dose regimen for a patient were summed to produce the estimate for the total drug concentration at the time of interest. The sequence of Figures A2 and A3 show the Superposition Principle.

EXAMPLE

A2 GRAPH DRUG CP VERSUS TIME CURVES FROM INDIVIDUAL DOSES



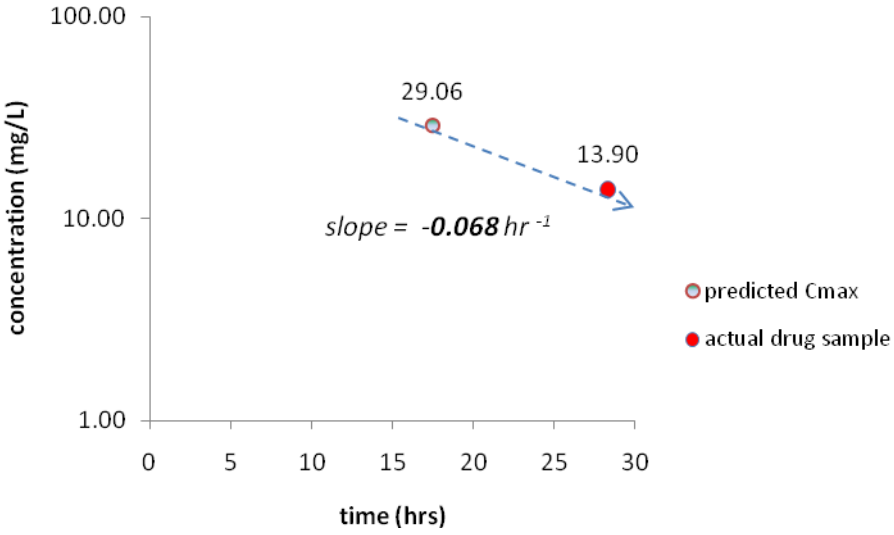
A3 GRAPH SUPERPOSITION PRINCIPLE EXAMPLE



ESTIMATION OF AML COHORT ELIMINATION RATE CONSTANT

PK parameters are typically estimated from steady state concentrations. Therefore, a peak concentration estimated using population PK parameters from a regimen at steady state and an actual steady state concentration trough or near trough resulting from the regimen were used to determine the slope of the elimination rate constant.

A4 GRAPH ELIMINATION RATE CONSTANT ESTIMATION



0.693/(the estimated elimination rate constant) = the elimination half-life
0.693/**0.068** = 10.2 hrs

ESTIMATION OF THE APPROPRIATE DOSE

Estimation of the dosing interval (τ) involves the following:
Cmax = target Cmax set to equal 35mg/L
Cmin = target Cmin set to equal 15mg/L
ti = infusion time assumed to be 1 hour
ke = semi patient-specific ke estimated using population PK parameter estimated Cmax and patient measured drug plasma concentration

This resulting τ is rounded up or down to the nearest clinically used dose interval of the following: 8, 12, 18, 24 hours. Any τ less than 8 hours was rounded up to equal 8 hours.

$$\tau = \frac{-\ln(C\min/C\max)}{ke} + ti = \frac{-\ln(15/35)}{0.068} + 1 = 13.5 hrs$$

13.5 hrs was rounded down to 12 hrs for convenience of administration.

Dose Estimation (mg every 12 hours):

$$Dose(mg) = \frac{(Vd)(ke)(ti)(C\max)(1-e^{-ke(\tau-ti)})}{(1-e^{-ke(ti)})} = \frac{(68.3L)(0.068)(1.5)(35)(1-e^{-0.068(12-1.5)})}{(1-e^{-0.068(1.5)})} = 1283mg$$

Cmax = target Cmax set to equal 35

ti = assumed to be 1.5 hour
Note: Increased dosing needs were suspected in this population, so a longer infusion time was selected, but this was kept constant at 1.5 hours for dose calculations.
τ = rounded τ from above
Vd = population Vd
ke = semi pt-specific ke estimated using population PK-based Cmax and measured drug plasma concentration

Estimated dose in mg/day = estimated dose * (24 hrs/estimated τ)
=1283mg * (24/12) = 2566mg
Divide dose (mg/day) by total body weight for estimated dose in mg/kg/day

=2566/85.4 = 30mg/kg/24hrs

5 POPULATION PHARMACOKINETIC MODELING OF VANCOMYCIN IN LIMITED ACUTE MYELOGENOUS LEUKEMIA PATIENTS

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5.1 ABSTRACT

Retrospective pharmacokinetic (PK) analysis of 94 clinically available vancomycin drug concentrations using the population PK software MM-USC*PACK resulted in detection of increased drug clearance in patients with Acute Myelogenous Leukemia (AML). Use of the program to estimate dosage needs in AML patients indicated the study population was underdosed by 47.4%. Results and error were similar when any of four different creatinine clearance methods were used. A typical root mean squared prediction error (RMSE) was about 5 mg/L which is considered clinically significant, given that the therapeutic range for trough concentrations is between 15 to 20mg/L. The fitting was as good as could be expected considering that only minimal data were available for each patient and the included population database had limited support points.

5.2 INTRODUCTION

VANCOMYCIN USE IN ACUTE MYELOGENOUS LEUKEMIA

Vancomycin is an antibiotic commonly used against gram-positive bacteria species.[1] Organisms of concern include Methicillin-resistant S. *aureus* (MRSA) (both nosicomial and community acquired), Methicillin-resistant S. *epidermidis* (MRSE), and Penicillin-resistant S. *pneumoniae*.[2, 3] With these infections, it is especially important to initiate dose regimens that obtain therapeutic vancomycin serum concentrations.[4, 5] With infected patients who also have hematologic malignancy, this is even more important, as these patients have compromised immunity due to chemotherapy.[6] Without rapidly achieving therapeutic antibiotic concentrations, these patients are vulnerable to life-threatening bacterial infections.[7]

Acute Myelogenous Leukemia (AML) is described as a hematopoietic stem cell disorder with a block in differentiation of the myeloid cell line.[8, 9] Standard approaches to treating this condition are autologous or allogeneic hematopoietic stem cell transplantation (HSCT).[10] Myeloablative conditioning regimens for HSCT involve cyclophosphamide and total body irradiation or busulfan.[11] These treatment options leave patients vulnerable to infections due to immunosuppression caused by the treatment.[11-13] IV vancomycin is used to treat such infections.

There are literature reports[14, 15] and Chapter 4 of this thesis supports that clearance of vancomycin is accelerated in many AML patients compared to the general population. If AML patients are dosed using general population PK parameters, then it is estimated that the patients receive only about 65% of the amount required to be an effective drug dose. Even so, typical clinical care feedback processes involve dosing vancomycin in AML patients based on general non-AML population PK parameters, waiting until after a few doses to achieve drug steady-state concentrations, collecting a blood sample to assay for drug, assuming the drug is following one-compartment pharmacokinetics, and then adjusting the dose.

5.3 DESCRIPTION OF THE USC SOFTWARE

5.3.1 OVERVIEW

The University of Southern California Lab of Applied Pharmacokinetics has produced a population pharmacokinetic software suite including MM-USC*PACK[16] to be used for therapeutic drug monitoring. A subpopulation database was developed and made available to assist physicians and pharmacists in vancomycin dosage adjustments.[17] It is intended to be especially helpful in a typical clinical setting where very little drug concentration versus time data are available for a patient.[18]

The goal of this research was determination of whether or not application of MM-USC*PACK could use minimally available clinical drug concentration data to predict vancomycin drug concentrations with sufficient accuracy to be clinically useful in adjusting AML patient drug doses. A related question was whether or not using MM-USC*PACK would detect an increased vancomycin clearance in AML patients in spite of the limited data required by the software. Another goal involved determination of effect of creatinine clearance calculation method on predictive accuracy of using the MM-USC*PACK in AML patients.

There are two main elements of this software suite. The first element is the population modeling software, BigWinPops. MM-USC*PACK (second element) then takes the generated population model for a given drug and uses it to fit the data and run simulations for a given subject. The simulations are intended to provide clinical dose estimation.

5.3.2 POPULATION MODELING WITH BIGWINPOPS

PASTRx is a software package used to collect individual patient data to produce files which are used to generate the population model. Drug doses, infusion times, patient weights, and resultant serum drug concentrations are required. Serum creatinine may be entered for each dosing interval in order to estimate creatinine clearance throughout the patient's regimen using the Jelliffe equation[19], or users may independently enter in creatinine clearance estimates.[20] BigWinPops takes the collection of PASTRx generated individual patient data files to produce a population distribution. BigWinPops can generate a PK population database exhibiting a normal distribution and can also generate a PK population database that exhibits a non-normal distribution.[16]

5.3.3 FITTING OF DRUG CP VERSUS TIME DATA USING MM-USC*PACK

MM-USC*PACK uses a population model generated by BigWinPops to fit given drug concentration versus time data for a specific patient. The population model database was generated using outpatients with prosthetic valves needing vancomycin as prophylaxis prior to dental work by Hurst et al.[18] The version of MM-USC*PACK utilized for the retrospective study involved a population database of 18 population database members, called "support points", each with two-compartment PK parameters (Figure 5.1). This database was used in the fitting of the retrospective AML patient data.

The support points were implemented in a series of simulations for the AML cohort. Each member of the population database is given the patient's weights, varying renal function, and dosing regimen. These individual members of the population database are then weighted by their Bayesian probability, or their potential of being equal to the AML subject that is being inspected, given the actual drug concentration versus time data on file for the patient in question.[17, 21] Appendix 1 provides examples of output from the program.

It is important to note that as little as one drug concentration at a determined time (one data point) is enough for the program to apply Bayesian probability to estimate the set of Bayesian posterior PK parameters for a specific patient which allows a suggested dosing regimen. The software package will fit the pharmacokinetic model to the available data point(s) given by the user, whether it be one or more. A composite simulation is produced which involves all of the population database members, each weighed by their Bayesian probability which attempts to regress the line of the simulation through the subject's drug concentration versus time points, minimizing error.[17]

Given the Bayesian probability of each support point, MM-USC*PACK can simulate subsequent drug concentration versus time data for dose estimation purposes to achieve target peak and trough concentrations.[17] The traditional clinical pharmacokinetic approach uses one set of PK parameters for dose estimation.[21] The multiple model design of dosage regimens with MM-USC*PACK uses a population model of PK parameters for dosage regimen design, and therefore can isolate the best fitting set(s) of PK parameters.[17]

5.4 METHODS

A retrospective chart review involving admissions from 2003-2006 was performed for Providence St. Vincent Medical Center in Portland, Oregon. The study was approved by the Institutional Review Board. Inclusion criteria were as follows: patients of at least 18 years of age, diagnosed with AML, received vancomycin, and had at least one vancomycin serum concentration measured. Data from vancomycin courses during which a change in SCr $\geq$ 0.5 mg/dl occurred during vancomycin therapy were excluded unless the change in SCr occurred > 5 days after the last vancomycin serum concentration obtained, because vancomycin PK clearance parameters vary during kidney function changes. Dialysis patients were excluded as well.

Four versions of the patient file sets, each utilizing a different creatinine clearance estimation scheme were input into MM-USC*PACK and the drug concentration versus time data were fitted. Comparisons were made between the fitted and actual drug concentration values and statistics describing the accuracy were reported. For purposes of fitting the four sets of data using MM-USC*PACK, and the original vancomycin population database included with the software were used.

PASTRx, the patient data entry interface, had the ability to estimate creatinine clearance (CrCl) for each patient's dosing interval using the Jelliffe CrCl estimation equation.[19] Three additional sets of patient data were created for the analysis. A replicate set of patient files utilized the Cockcroft and Gault creatinine clearance estimation equation using ideal body weight because this method is more often used clinically than the Jelliffe method. A second replicate set of patient files included creatinine clearance estimated using the Cockcroft and Gault equation using ideal body weight and rounding of serum creatinine values < 0.7mg/dl to 0.7.[22] A third replicate set of patient files was created involving the Cockcroft and Gault creatinine clearance estimation scheme used in the second set. However, for the third replicate set, estimated creatinine clearance values were capped at a maximum of 140ml/min, as impossibly high estimates for creatinine clearance can produce unreasonably high estimates for vancomycin clearance.[23, 24] The equations and calculation process for each creatinine clearance calculation method can be found in Appendix 1 of Chapter 4. Each support point is assigned a Bayesian probability, with the sum of the probabilities equaling one. Each of the PK parameters for a given support point is multiplied by the Bayesian probability. The sum of these (support point Bayesian probability)*(PK parameter value) for a given PK parameter (e.g. volume of distribution/weight in kg) is expressed as the mean for the PK parameter values.

5.5 RESULTS/DISCUSSION

A total of 94 drug concentration versus time points were surveyed. The line of identity plots (Figures 5.2-5.5) show the Bayesian weighted predicted serum concentrations versus the actual concentrations for each of the patient data file sets

utilizing a different CrCl estimation scheme. The line of identity has a slope of 1 and the intercept is at the origin. Line of identity is shown rather than a regression line making it easy to see that points above the line show over-predictions while points below the line show under-predictions. Points lying directly on the line show accurate predictions.

Data fitting results for the patient files that utilized the Jelliffe creatinine clearance estimation[19] had a RMSE of 4.83mg/L (95% CI: 2.67, 6.29) (Figure 5.2). The data fitting for the patient files that utilized the Cockcroft and Gault equation using ideal body weight[22] had a RMSE of 5.22mg/L (95% CI: 2.69, 6.88) (Figure 5.3). Data fitting for the patient files that utilized the Cockcroft and Gault equation using the ideal body weight and rounding serum creatinine values < 0.7mg/dl to 0.7 as recommended by Kirkpatrick et al.[22] had a RMSE of 4.61mg/L (95% CI: 1.50, 6.34) (Figure 5.4). Using the Cockcroft and Gault equation with the ideal body weight, rounding of serum creatinine values < 0.7mg/dl to 0.7, and capping the maximum estimated CrCl at 140ml/min[22-24] produced a RMSE of 4.84mg/L (95% CI: 1.97, 6.56) (Figure 5.5). The four different creatinine clearance options had similar error. The option using the Cockcroft and Gault equation using ideal body weight with rounding of serum creatinine values < 0.7mg/dl to 0.7 produced the least error. (Table 5.1) A RMSE between 4.83 to 5.22mg/L is clinically significant, given that the therapeutic range for trough concentrations is between 15 to 20mg/L.[5] The fitting was as good as could be expected considering that only minimal data were available for each patient and the included population database had limited support points. Such fitting was useful for determining the PK parameters and an appropriate dose after blood concentration(s) of drug were obtained.

Figures 5.6-5.9 show simulated drug concentration versus time curves for a single selected patient and the measured drug concentrations for that patient. The patient age, weight, height, gender, serum creatinine, first drug dose, infusion time, and determined drug concentration in the plasma were input into MM-USC*PACK. MM-USC*PACK then compared the patient information to the population PK database and selected sets of most likely PK parameters and associated Bayesian probability of each set for this individual patient, based on the measured drug concentration and other individual patient data. The program then used a two-compartment open pharmacokinetic model for vancomycin and simulated an expected drug concentration versus time curve for this patient as shown in the small insert at the top of Figure 5.6, using the composite set of PK parameters from the population PK database.[17]

In the next step, additional drug concentration versus time data previously measured and known for the selected patient of Figure 5.6 were compared to the simulated drug concentrations. These measured drug concentrations are shown as red circles in the small insert of Figure 5.6. It can be seen that the first, second, and fifth drug concentrations collected were higher than predicted using the MM-USC*PACK, while the third and fourth drug concentrations were lower than predicted. The R-squared, mean error, mean squared error, line of identity and regression equation for measured drug concentrations regressed on simulated drug concentrations are all shown in the larger portion of Figure 5.6. Creatinine clearance calculations used in Figure 5.6 were based on the Jelliffe equation.[19]

Figures 5.7-5.9 are for the same patient and were generated in the same way

as Figure 5.6 except that the method of calculating creatinine clearance was varied (see text and figure legends). The 4 different CrCl estimation methods[19, 22] resulted in differences in the mean squared prediction error for the patient in Figures 5.6-5.9. The lowest mean squared prediction errors were seen with the patient files where the latter 2 of the 3 Cockcroft and Gault creatinine clearance estimation schemes were used (Figures 5.8 and 5.9).

Figures 5.10-5.15 show more selected patient examples, with each file using the Jelliffe creatinine clearance estimation[19] as a covariate in the simulation. Figures 5.10-5.12 show examples of very good fit of the measured drug concentration data with the simulation points falling close to the line of identity. For these examples, the software is able to select a dose that is expected to be therapeutically effective in these patients.

Figures 5.13-5.15 show examples of poor fit of the measured drug concentration data. In these patients, most of the measured drug concentration points are far from the line of identity. It is not expected that the software would produce a therapeutically effective dose in these patients. In cases of poor fit, simulated concentrations are mostly over-predictions of actual drug concentrations. This is most likely due to increased clearance in these patients.[15]

Table 5.2 shows the average of the mean Bayesian weighted PK parameters for the cohort. PK parameters for the AML cohort estimated using MM-USC*PACK are as follows: The average volume of distribution at steady state was 0.87 L/kg. The estimated elimination half-life for a 70kg subject was 5.83 hrs. The vancomycin clearance of the AML cohort estimated using MM-USC*PACK was 7.235 ± 4.199 L/hr. For comparison, the estimated volume of distribution in the article by Fernandez de Gatta et al. for the

entire malignancy group (n = 40) was 1.00 ± 0.41 L/kg.[15] The elimination half-life was 6.1 ± 2.6 hrs.[15] The total body clearance was 0.122 L/kg/hr.[15] The recommended dose to achieve serum trough concentrations of 15 mg/L was 76mg/kg/day.[15] The volume of distribution for the cohort (n = 215) in the article by Santos Buelga et al. was 0.98 ± 0.36 L/kg.[14] The estimated elimination half-life for a 70kg subject was 8.21 hrs. The clearance was 5.79 ± 1.63 L/hr.[14] Santos Buelga recommends a mean dosage of 45mg/kg/day to achieve an area under the curve of 500mg/liter·L.[14] Chapter 4 of this thesis assumes a volume of distribution of 0.8L/kg in AML patients. The elimination half-life is estimated at 5.92 ± 4.03 hrs. Chapter 4 of this thesis estimates an average clearance of vancomycin in AML patients to be 9.9 ± 4.7 L/hr. The corresponding dosage recommendation was 54mg/kg/day. For comparison with the general population, in the article by Matzke et al.[25], there were 7 patients with a CrCl of >60ml/min. The volume of distribution was 0.72 ± 0.35 L/kg.[25] The elimination half-life was 9.1 ± 2.8 hrs.[25] Clearance was 3.76 ± 1.52 L/hr.[25] MM-USC*PACK was able to detect an increased vancomycin clearance relative to the general population. The average dose per patient admission to generate troughs of 15mg/L was estimated to be 36mg/kg/24hrs, given that the creatinine clearance covariate was estimated using the Jelliffe equation.[19] This dose estimate was approximately half of what was presented by Fernandez de Gatta et al. to generate troughs of 15mg/L.[15]

The simulations may or may not be able to predict the actual drug concentrations depending on the specific patient. It is suggested that such dosing could be initiated using Cl and V_d consistent with Chapter 4 findings and then MM-USC*PACK be employed to modify dosing when vancomycin drug concentrations become available.

5.6 CONCLUSION

Even though the vancomycin PK population database was not produced using the patient data from the cohort with AML, it was reasonable to evaluate the MM-USC*PACK in AML patients. This software is easy to use and is a feasible option to help pharmacists dose vancomycin. It is easier to implement than the traditional clinical approach that involves manual calculations. As expected, the mg/kg doses produced by the software are dependent on the desired dosing interval and desired therapeutic range. Various creatinine clearance estimation variations had little effect on the ability of MM-USC*PACK to fit the individual drug concentration versus time data. Vancomycin is probably underdosed in AML patients using MM-USC*PACK alone but the results will be better than using only non-AML population PK values. Given these findings, it is expected that a PK population database generated using a given patient cohort for that patient subpopulation would have excellent predictive performance after incorporation into MM-USC*PACK. Thus a population database using AML patients is suggested as being needed, especially given the finding in Chapter 4 of this thesis that vancomycin clearance is often increased substantially in AML patients.

5.7 REFERENCES

1. Cohen E, Dadashev A, Drucker M et al. Once-daily versus twice-daily intravenous administration of vancomycin for infections in hospitalized patients. *J Antimicrob Chemother* 2002; **49:** 155-160.

2. Akins RL, Haase KK. Gram-positive resistance: pathogens, implications, and treatment options: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy* 2005; **25:** 1001-1010.

3. Wilcox MH, Tack KJ, Bouza E et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study.[see comment]. *Clin Infect Dis* 2009; **48:** 203-212.

4. Tunkel AR, Hartman BJ, Kaplan SL et al. Practice guidelines for the management of bacterial meningitis.[see comment]. *Clin Infect Dis* 2004; **39:** 1267-1284.

5. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia.[see comment]. *Am J Respir Crit Care Med* 2005; **171:** 388-416.

6. Salazar R, Sola C, Maroto P et al. Infectious complications in 126 patients treated with high-dose chemotherapy and autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999; **23:** 27-33.

7. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. *Clin Pharmacokinet* 2006; **45:** 755-773.

8. Shipley JL, Butera JN. Acute myelogenous leukemia. *Exp Hematol* 2009; **37:** 649-658.

9. Stegmaier K, Corsello SM, Ross KN et al. Gefitinib induces myeloid differentiation of acute myeloid leukemia. *Blood* 2005; **106:** 2841-2848.

10. Hegenbart U, Niederwieser D, Sandmaier BM et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol* 2006; **24:** 444-453.

11. Valcarcel D, Martino R. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in myelodysplastic syndromes and acute myelogenous leukemia. *Curr Opin Oncol* 2007; **19:** 660-666.

12. Le Normand Y, Milpied N, Kergueris MF et al. Pharmacokinetic parameters of vancomycin for therapeutic regimens in neutropenic adult patients. *Int J Biomed Comput* 1994; **36:** 121-125.

13. Syed MI, Clark LJ, Sturrock RD. Unintended benefits of immunosupression on autoimmune disease due to chemoradiation therapy for head and neck cancer. *Am J Otolaryngol* 2008; **29:** 63-65.

14. Buelga DS, del Mar Fernandez de Gatta M, Herrera EV et al. Population pharmacokinetic analysis of vancomycin in patients with hematological malignancies. *Antimicrob Agents Chemother* 2005; **49:** 4934-4941.

15. Fernandez de Gatta MM, Fruns I, Hernandez JM et al. Vancomycin pharmacokinetics and dosage requirements in hematologic malignancies. *Clinical Pharmacy* 1993; **12:** 515-520.

16. Bustad A, Terziivanov D, Leary R et al. Parametric and nonparametric population methods: their comparative performance in analysing a clinical dataset and two Monte Carlo simulation studies.[see comment]. *Clin Pharmacokinet* 2006; **45:** 365-383.

17. Jelliffe R, Bayard D, Milman M et al. Achieving target goals most precisely using nonparametric compartmental models and "multiple model" design of dosage regimens. *Ther Drug Monit* 2000; **22:** 346-353.

18. Hurst AK, Yoshinaga MA, Mitani GH et al. Application of a Bayesian method to monitor and adjust vancomycin dosage regimens. *Antimicrob Agents Chemother* 1990; **34:** 1165-1171.

19. Jelliffe R. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. *American Journal of Nephrology* 2002; **22:** 320-324.

20. Jelliffe RW, Schumitzky A, Van Guilder M et al. Individualizing drug dosage regimens: roles of population pharmacokinetic and dynamic models, Bayesian fitting, and adaptive control. *Ther Drug Monit* 1993; **15:** 380-393.

21. Jelliffe RW, Schumitzky A, Bayard D et al. Model-based, goal-oriented, individualised drug therapy. Linkage of population modelling, new 'multiple model' dosage design, bayesian feedback and individualised target goals. *Clin Pharmacokinet* 1998; **34:** 57-77.

22. Kirkpatrick CM, Duffull SB, Begg EJ. Pharmacokinetics of gentamicin in 957 patients with varying renal function dosed once daily. *British Journal of Clinical Pharmacology* 1999; **47:** 637-643.

23. Lamb EJ, Tomson CR, Roderick PJ et al. Estimating kidney function in adults using formulae.[see comment]. *Annals of Clinical Biochemistry* 2005; **42:** 321-345.

24. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: physiological principles. *Intensive Care Medicine* 2004; **30:** 33-37.

25. Matzke GR, McGory RW, Halstenson CE et al. Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrob Agents Chemother* 1984; **25:** 433-437.

5.8 TABLES

5.1 PREDICTIVE PERFORMANCE USING MM-USC*PACK

Predictive Performance
N=94
pei = (prediction – actual value)$_i$

Estimation method for CrCl covariate	RMSE	95% CI lower bound	95% CI upper bound
Jelliffe	4.83	2.67	6.29
C&Gvar1	5.22	2.69	6.88
C&Gvar2	4.61	1.50	6.34
C&Gvar3	4.84	1.97	6.56

Jelliffe = estimated creatinine clearance values using the Jelliffe equation

C&Gvar1= estimated creatinine clearance values using the Cockcroft and Gault equation and ideal body weight

C&Gvar2 = estimated creatinine clearance values using the Cockcroft and Gault equation, ideal body weight, and rounding of serum creatinine values < 0.7mg/dl to 0.7

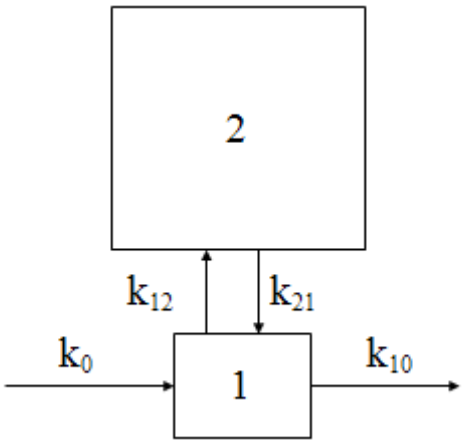
C&Gvar3 = estimated creatinine clearance values using the Cockcroft and Gault equation, ideal body weight, rounding of serum creatinine values < 0.7mg/dl to 0.7, and capping estimated creatinine clearance values at a maximum of 140ml/min

5.2 AVERAGE OF THE MEAN BAYESIAN WEIGHTED PK PARAMETERS FOR THE COHORT; COCKCROFT AND GAULT EQUATION USING IDEAL BODY WEIGHT AND ROUNDING OF SERUM CREATININE VALUES < 0.7MG/DL TO 0.7 FOR ESTIMATION OF CRCL

	Vc (L/kg)	K12 (1/hr)	K21 (1/hr)	Kel (1/hr)	Cl (L/hr/kg)	Cl (L/hr)
mean	0.272	0.962	0.440	0.002	0.101	7.235
SD	0.155	1.410	0.611	0.00047	0.082	4.199
cv	0.570	1.466	1.389	0.242	0.812	0.580
median	0.221	0.891	0.270	0.002	0.084	6.763

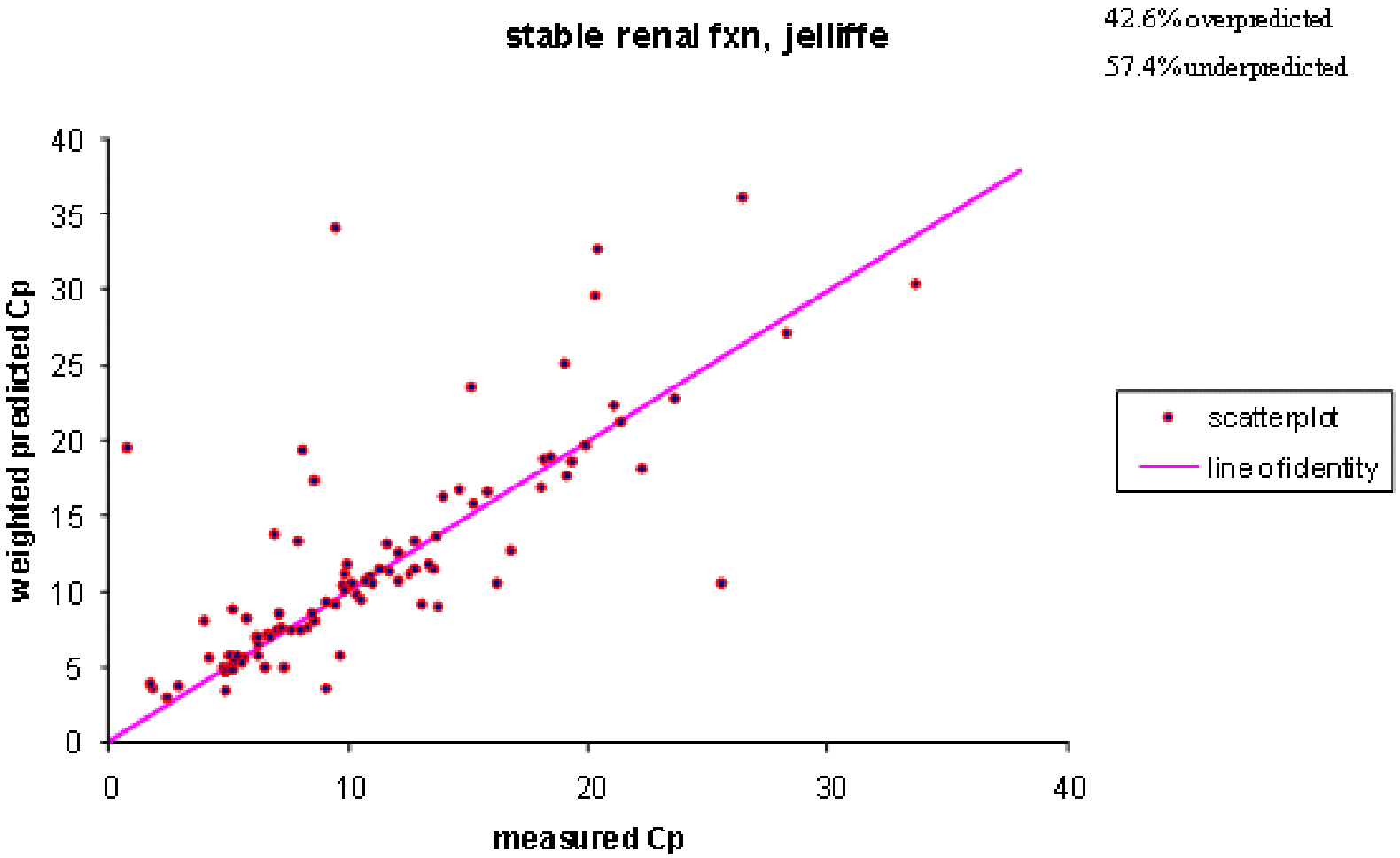
5.9 FIGURES

5.1 DIAGRAM TWO-COMPARTMENT OPEN MODEL; WITH ZERO ORDER INFUSION AND FIRST ORDER ELIMINATION FROM THE CENTRAL COMPARTMENT

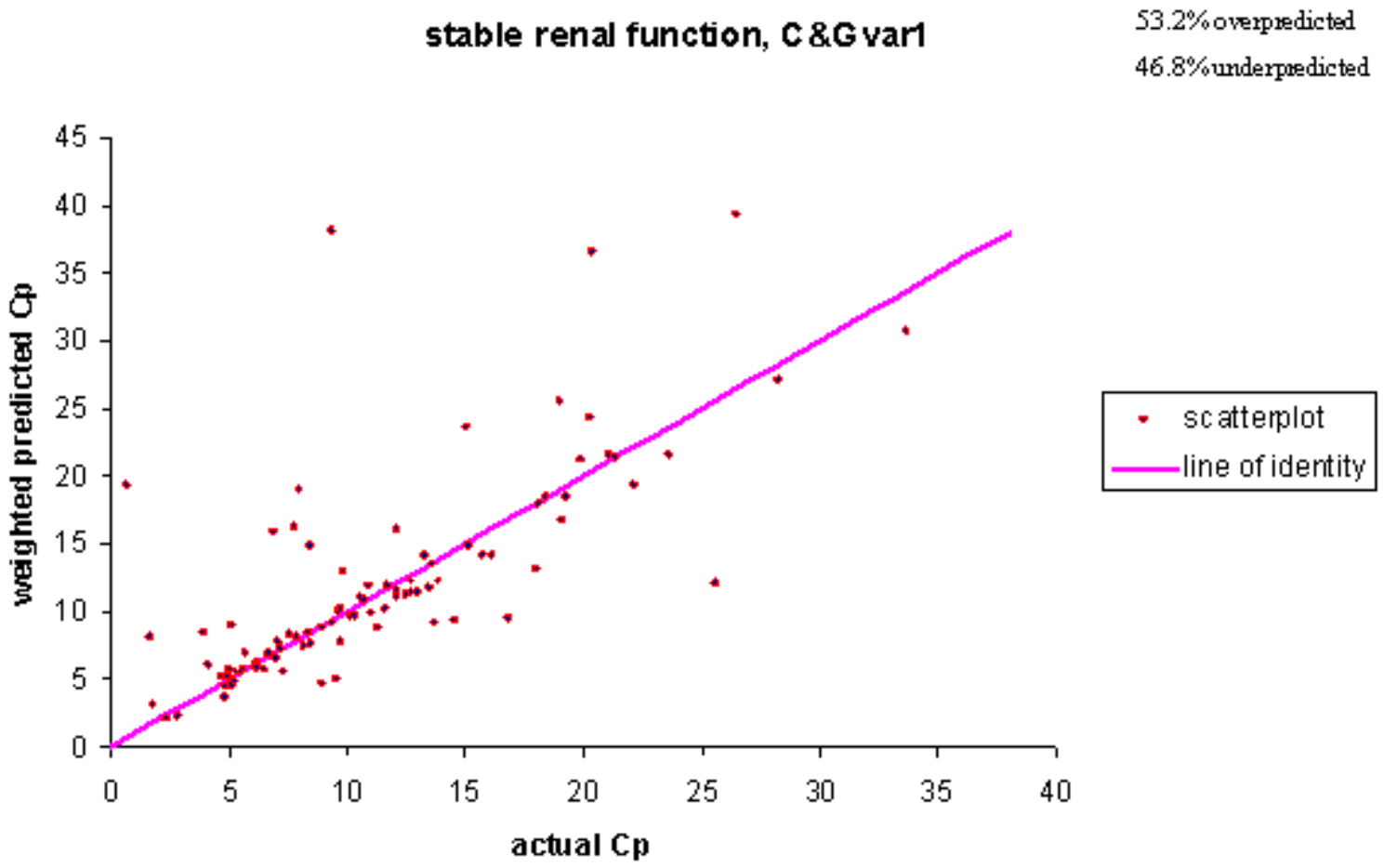


k_0 = zero order infusion rate constant
k_{12} = first order rate constant for transfer of drug from the central compartment to the peripheral compartment
k_{21} = first order rate constant for transfer of drug from the peripheral compartment to the central compartment
k_{10} = (CrCl)*(renal portion of elimination rate constant/unit CrCl) + (nonrenal elimination rate constant) = first order rate constant for elimination of drug from the central compartment

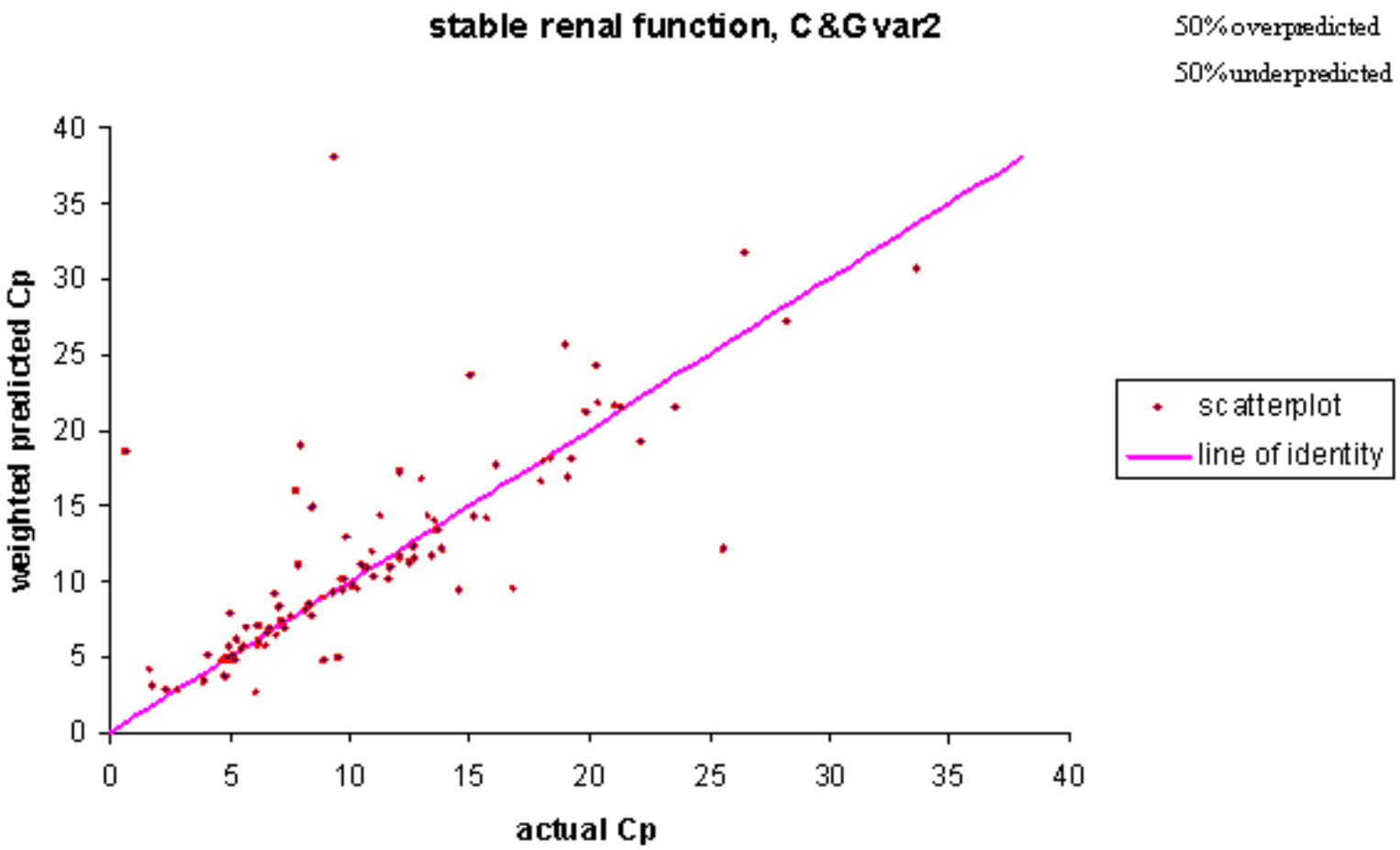
5.2 GRAPH PREDICTIVE PERFORMANCE OF MM-USC*PACK 1;
HAVING ESTIMATED CREATININE CLEARANCE VALUES USING THE JELLIFFE EQUATION



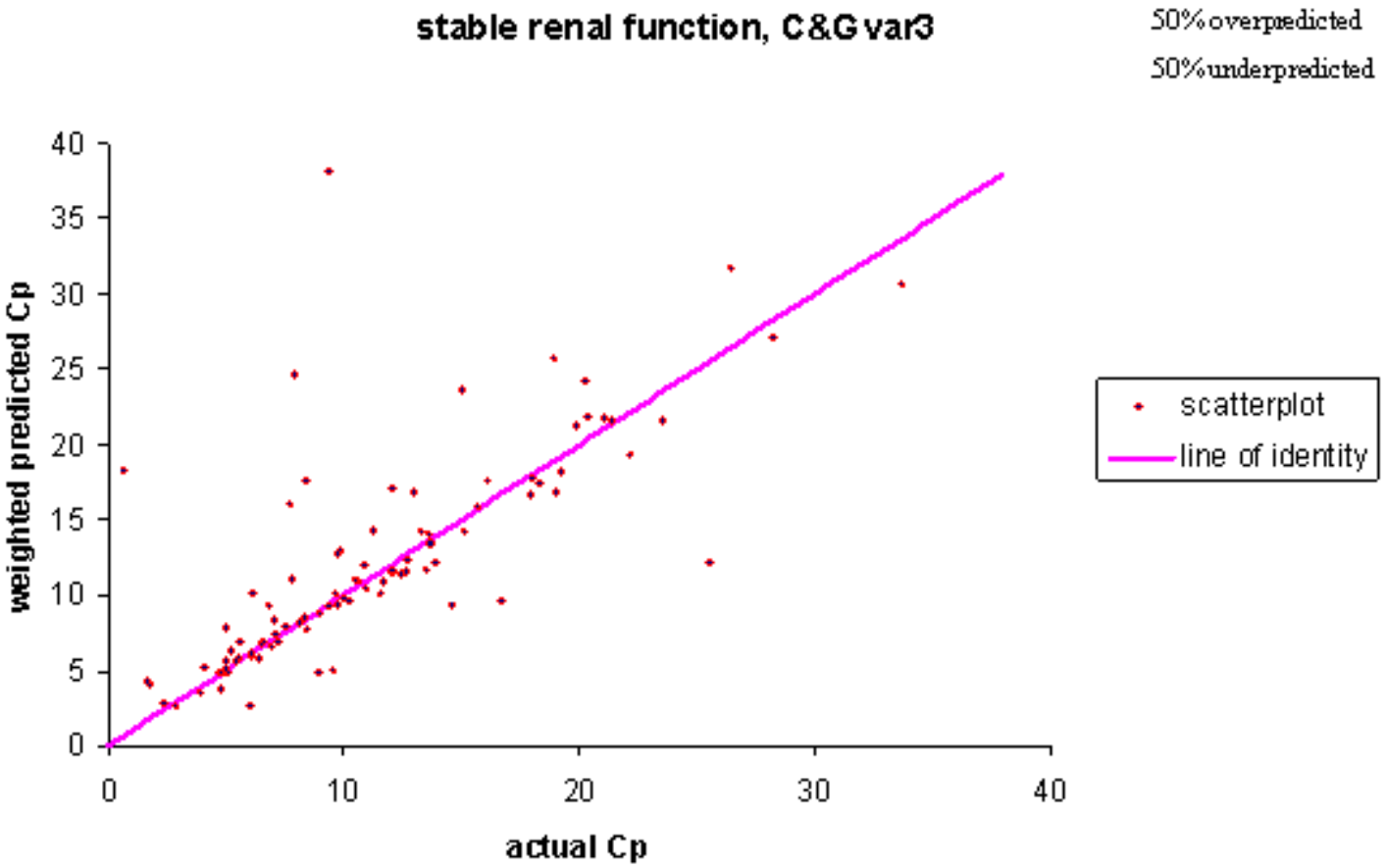
5.3 GRAPH PREDICTIVE PERFORMANCE OF MM-USC*PACK 2; HAVING ESTIMATED CREATININE CLEARANCE VALUES USING THE COCKCROFT AND GAULT EQUATION AND IDEAL BODY WEIGHT



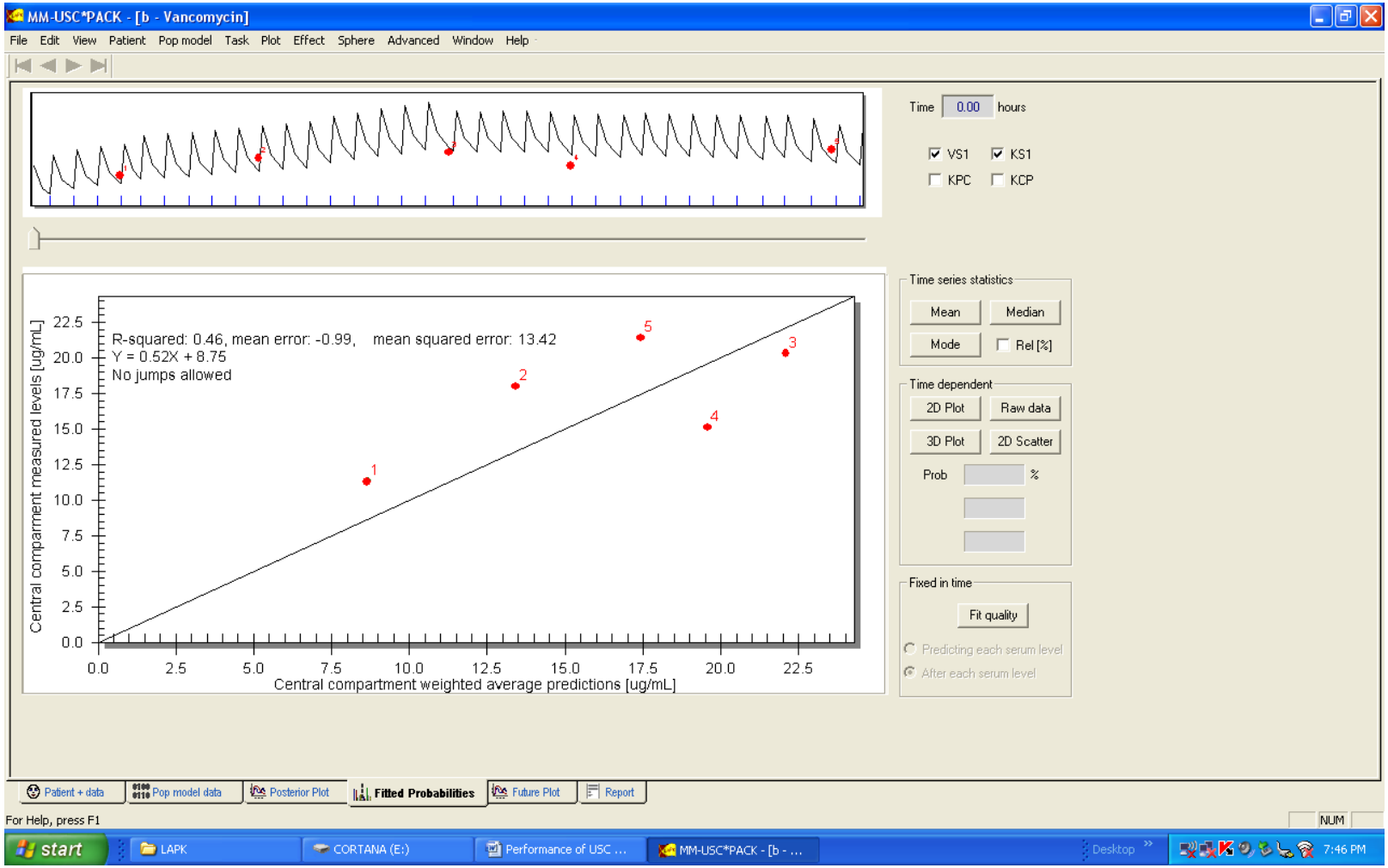
5.4 GRAPH PREDICTIVE PERFORMANCE OF MM-USC*PACK 3; HAVING ESTIMATED CREATININE CLEARANCE VALUES USING THE COCKCROFT AND GAULT EQUATION, IDEAL BODY WEIGHT, AND ROUNDING OF SERUM CREATININE VALUES < 0.7MG/DL TO 0.7



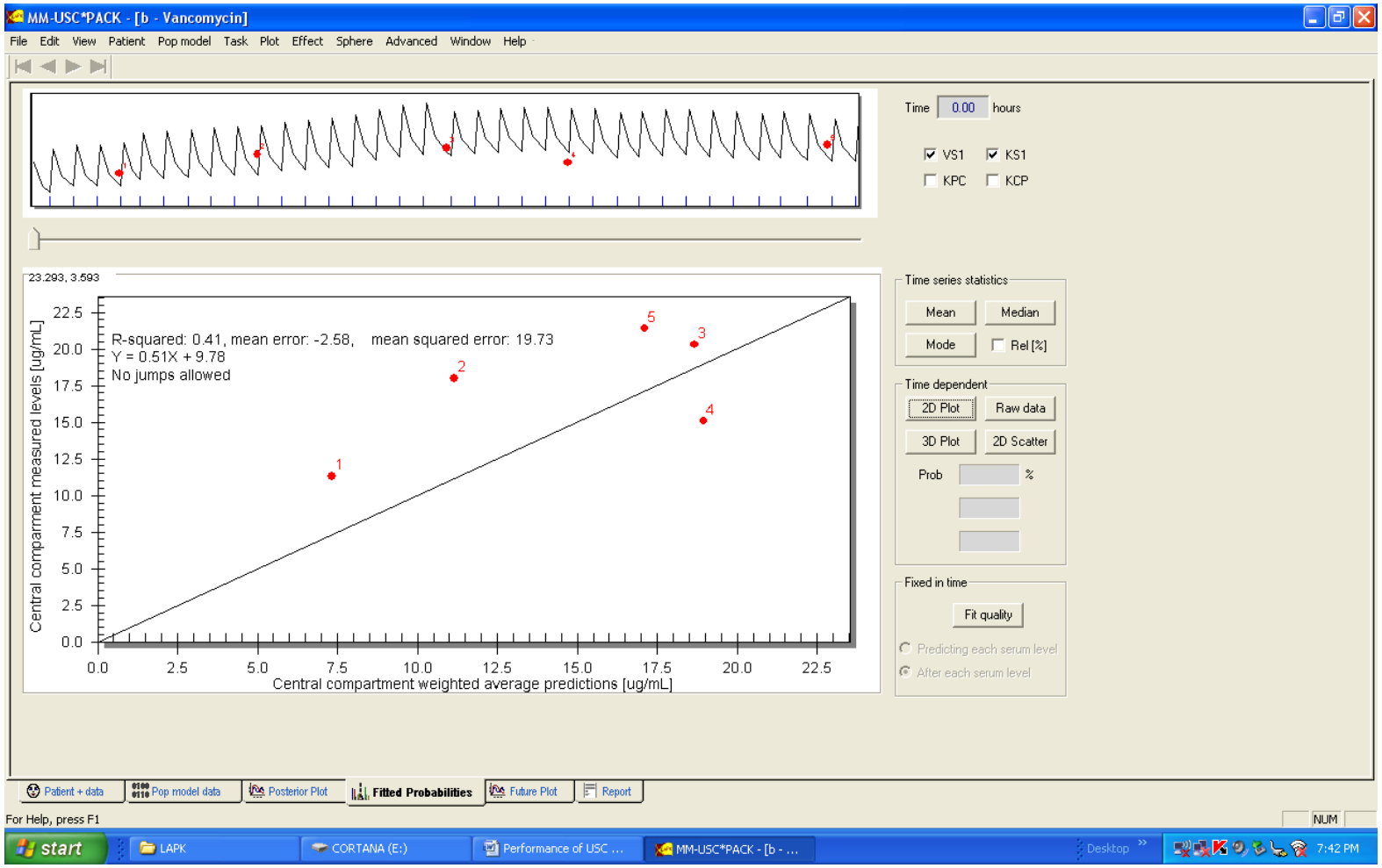
5.5 GRAPH PREDICTIVE PERFORMANCE OF MM-USC*PACK 4; HAVING ESTIMATED CREATININE CLEARANCE VALUES USING THE COCKCROFT AND GAULT EQUATION, IDEAL BODY WEIGHT, ROUNDING OF SERUM CREATININE VALUES < 0.7MG/DL TO 0.7, AND CAPPING ESTIMATED CREATININE CLEARANCE VALUES AT A MAXIMUM OF 140ML/MIN



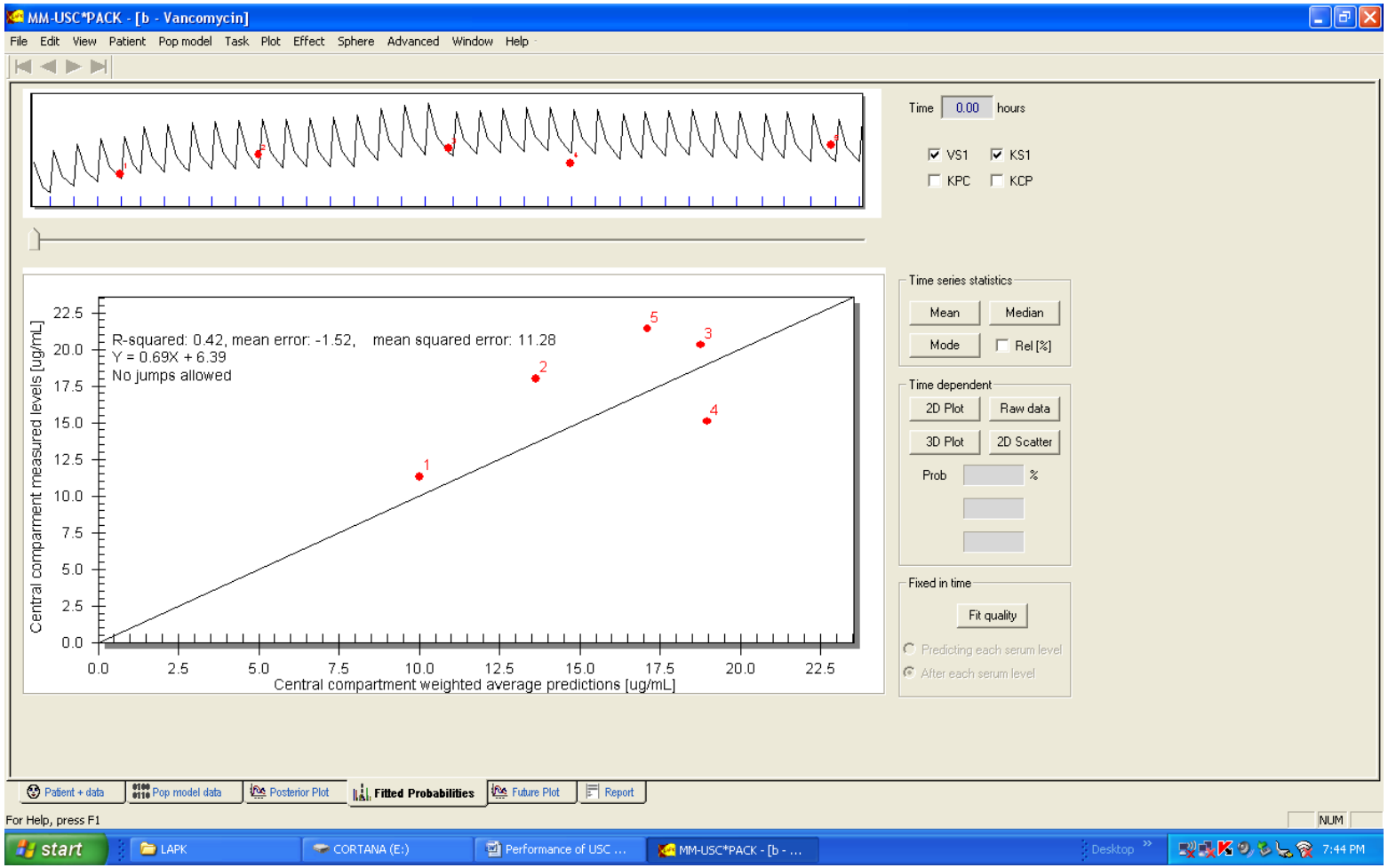
5.6 GRAPH PREDICTIVE PERFORMANCE OF MM-USC*PACK 5; WITH INDIVIDUAL PATIENT FILE HAVING ESTIMATED CREATININE CLEARANCE VALUES USING THE JELLIFFE EQUATION



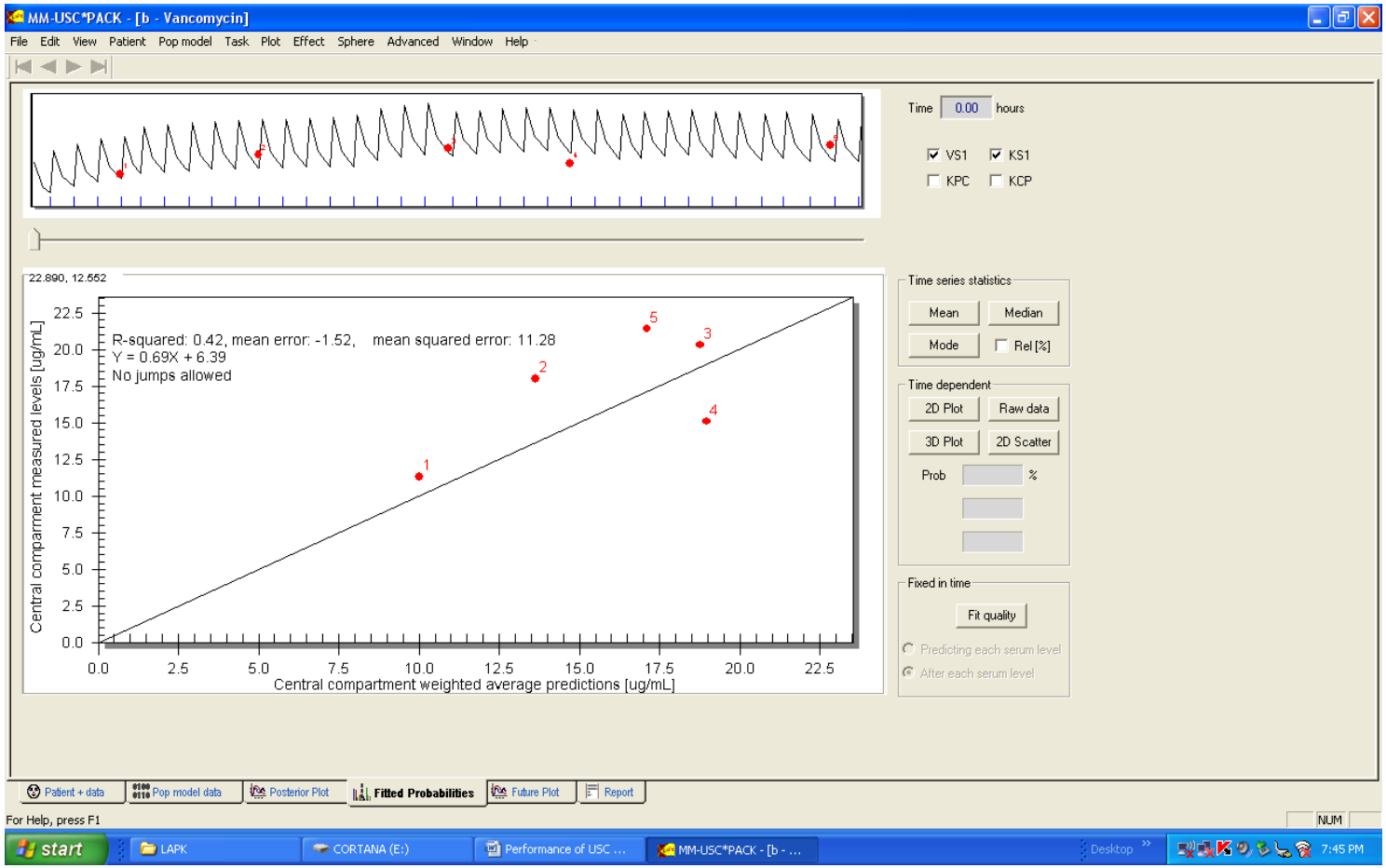
5.7 GRAPH PREDICTIVE PERFORMANCE OF MM-USC*PACK 6; WITH INDIVIDUAL PATIENT FILE HAVING ESTIMATED CREATININE CLEARANCE VALUES USING THE COCKCROFT AND GAULT EQUATION AND IDEAL BODY WEIGHT



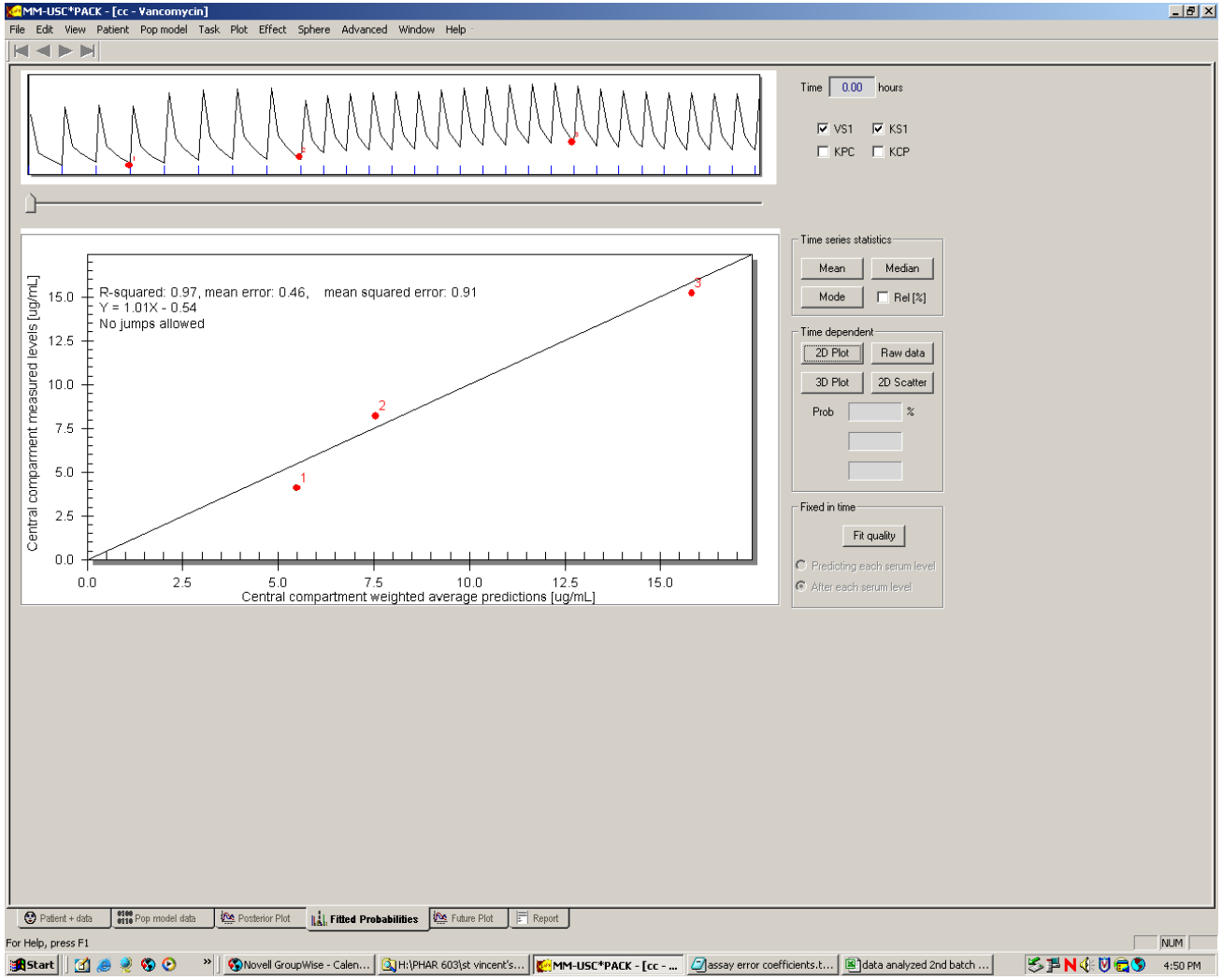
5.8 GRAPH PREDICTIVE PERFORMANCE OF MM-USC*PACK 7; WITH INDIVIDUAL PATIENT FILE HAVING ESTIMATED CREATININE CLEARANCE VALUES USING THE COCKCROFT AND GAULT EQUATION, IDEAL BODY WEIGHT, AND ROUNDING OF SERUM CREATININE VALUES < 0.7MG/DL TO 0.7



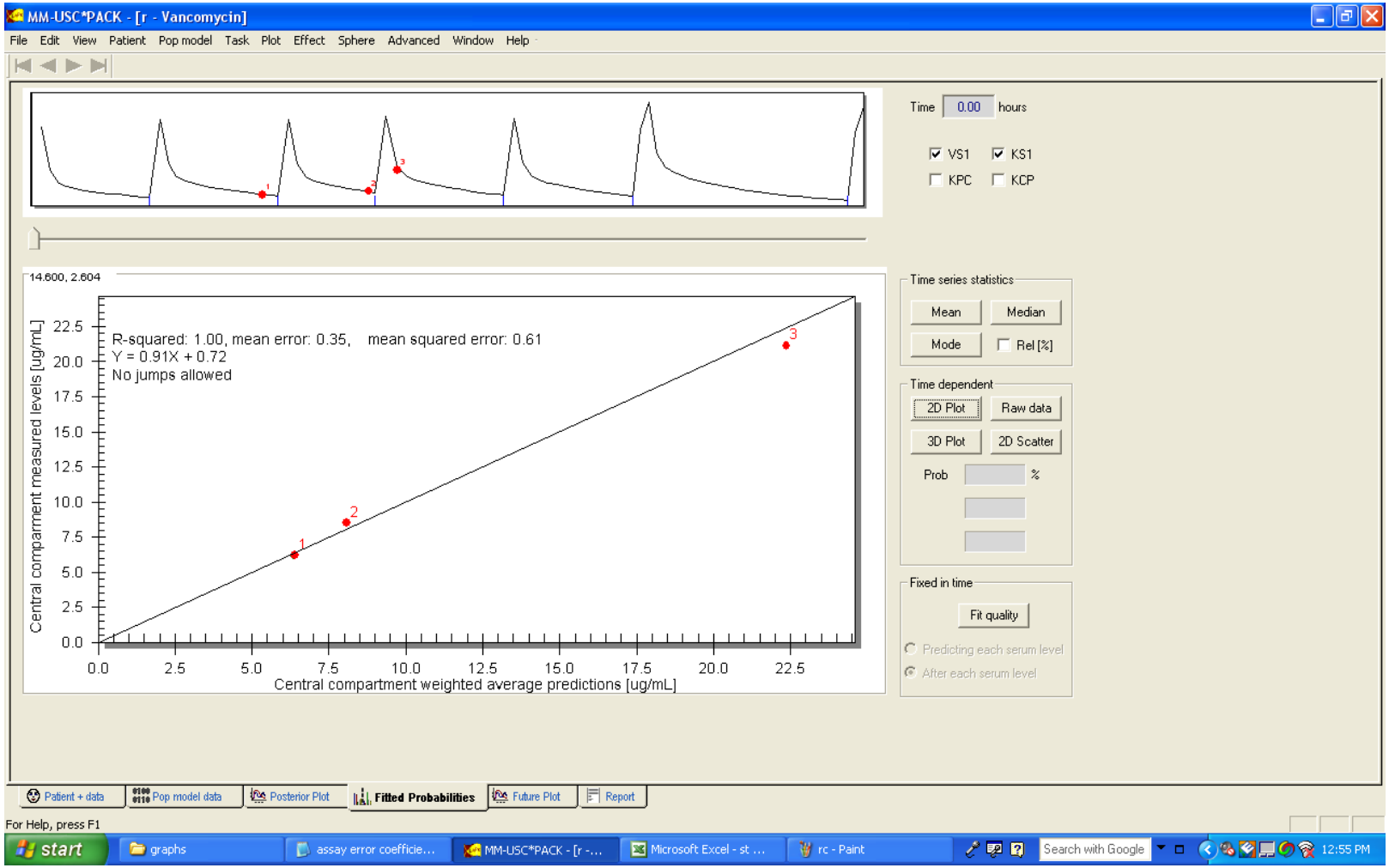
5.9 GRAPH PREDICTIVE PERFORMANCE OF MM-USC*PACK 8; WITH INDIVIDUAL PATIENT FILE HAVING ESTIMATED CREATININE CLEARANCE VALUES USING THE COCKCROFT AND GAULT EQUATION, IDEAL BODY WEIGHT, ROUNDING OF SERUM CREATININE VALUES < 0.7MG/DL TO 0.7, AND CAPPING ESTIMATED CREATININE CLEARANCE VALUES AT A MAXIMUM OF 140ML/MIN



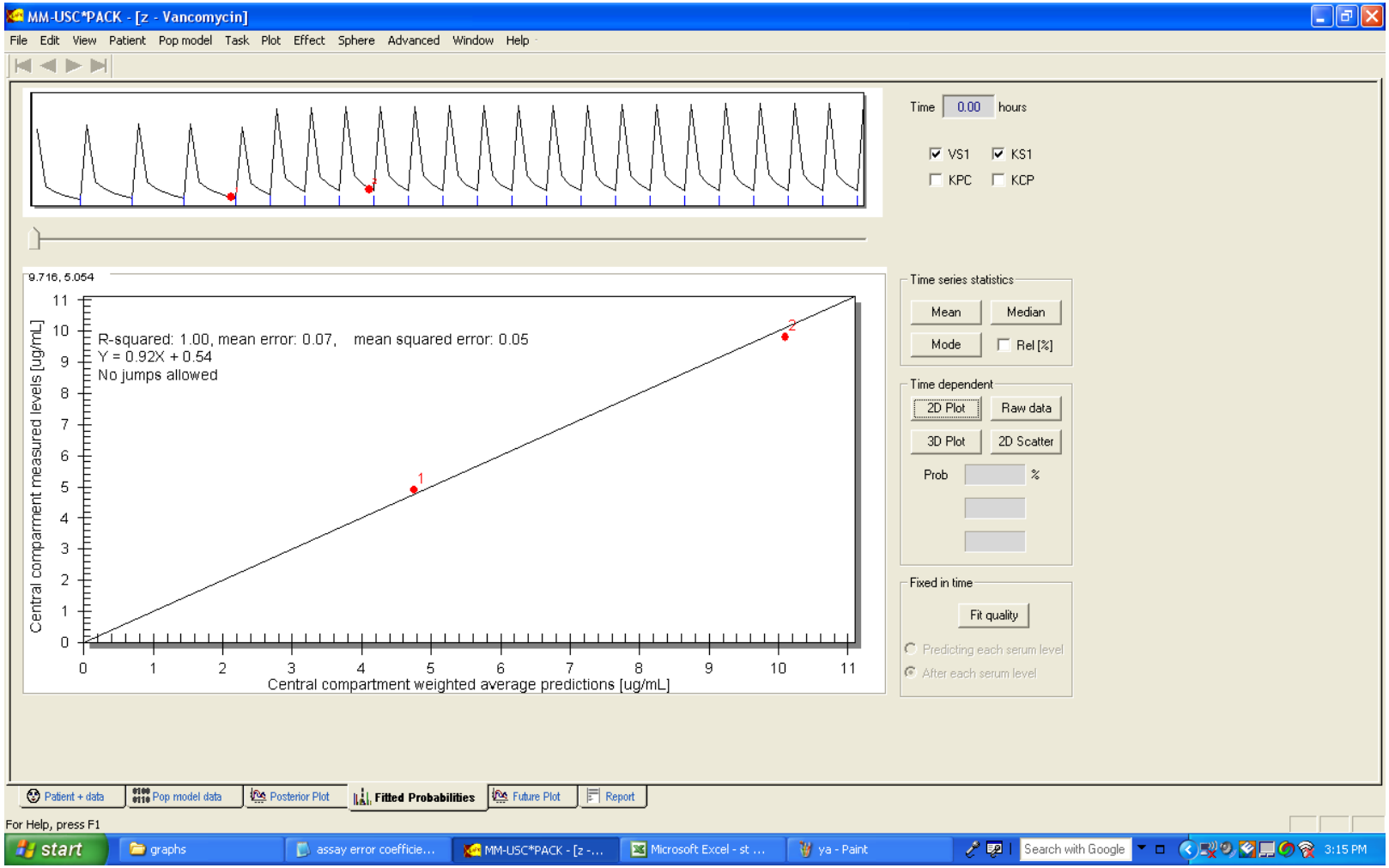
5.10 GRAPH EXAMPLE OF GOOD FIT 1



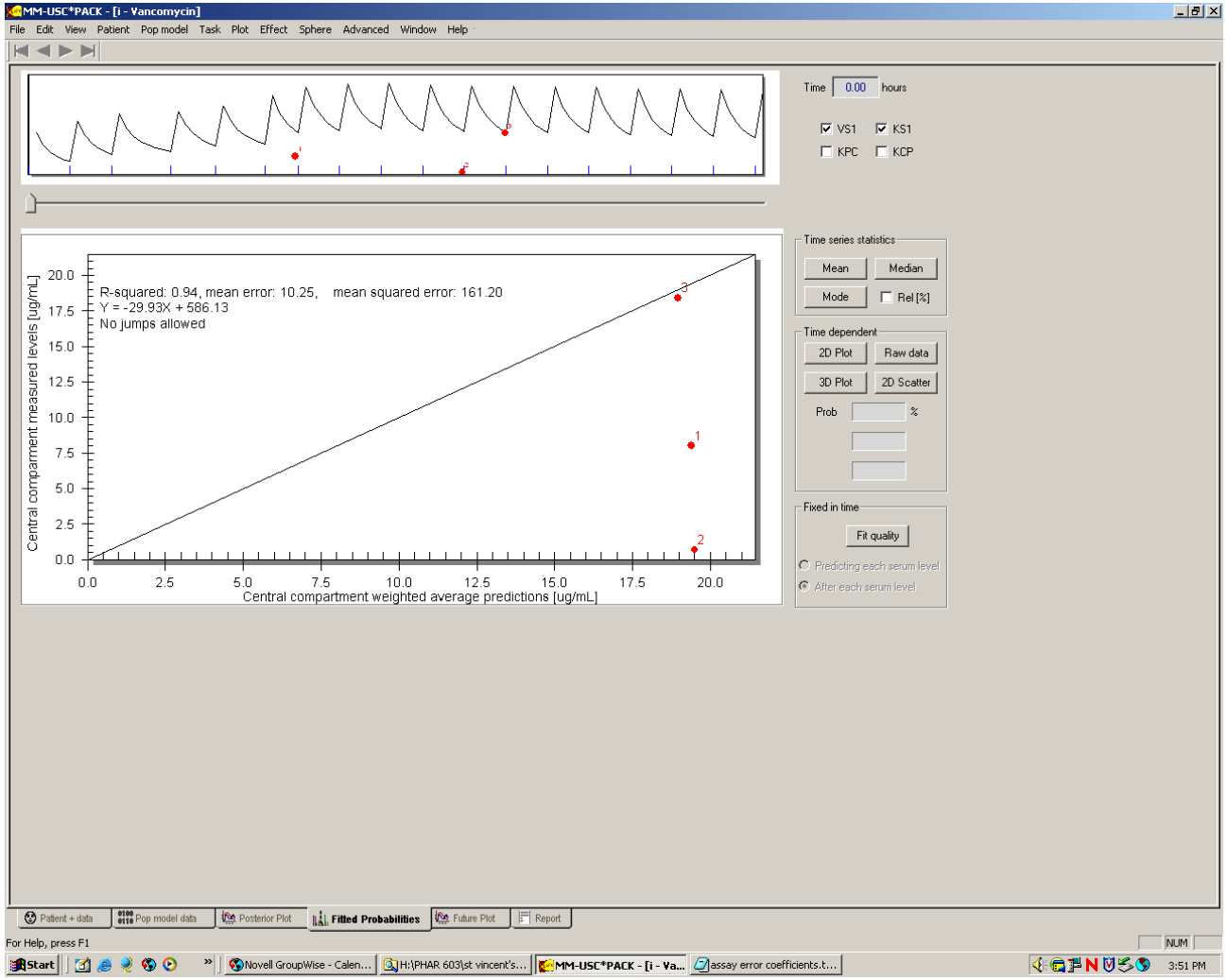
5.11 GRAPH EXAMPLE OF GOOD FIT 2



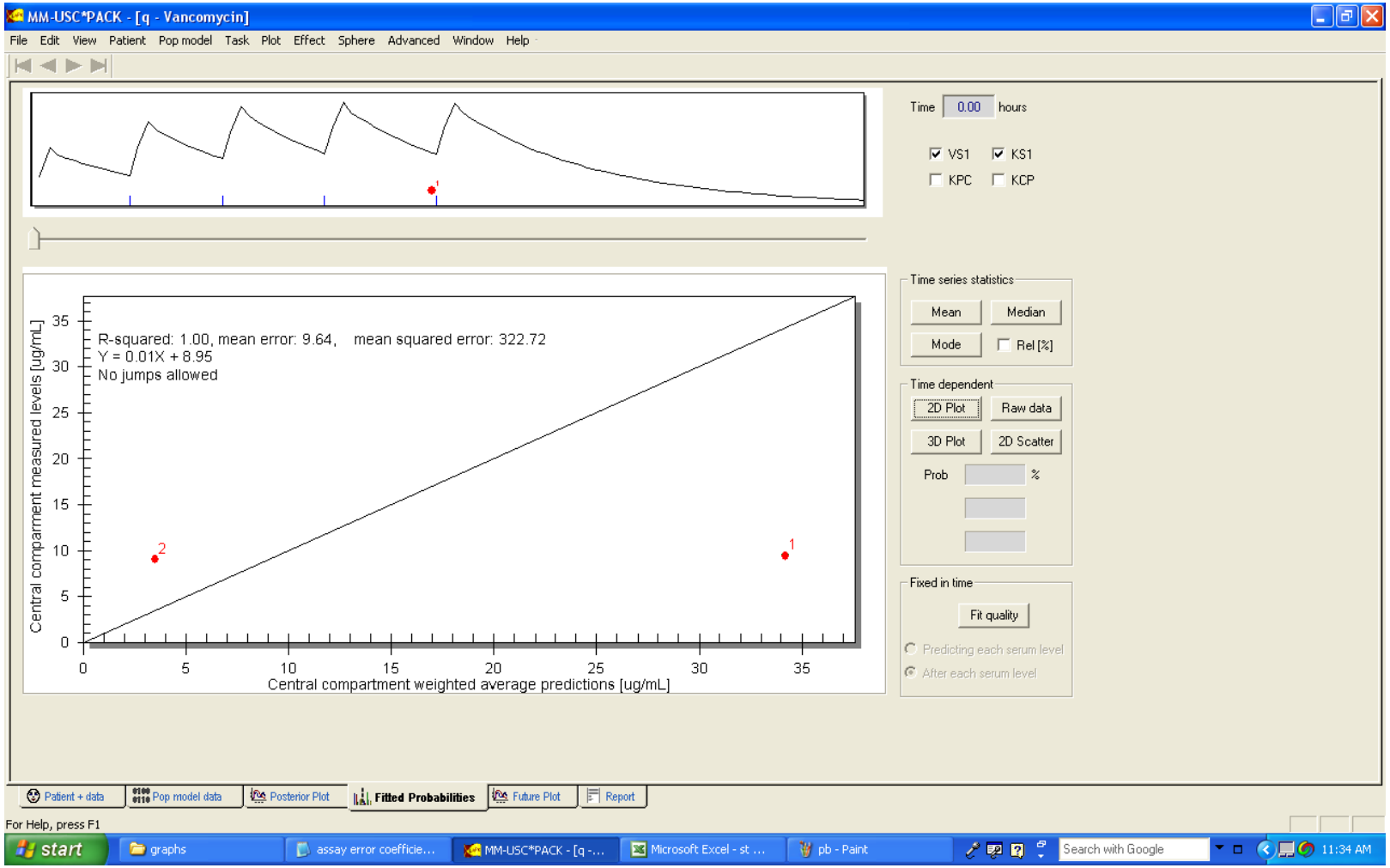
5.12 GRAPH EXAMPLE OF GOOD FIT 3



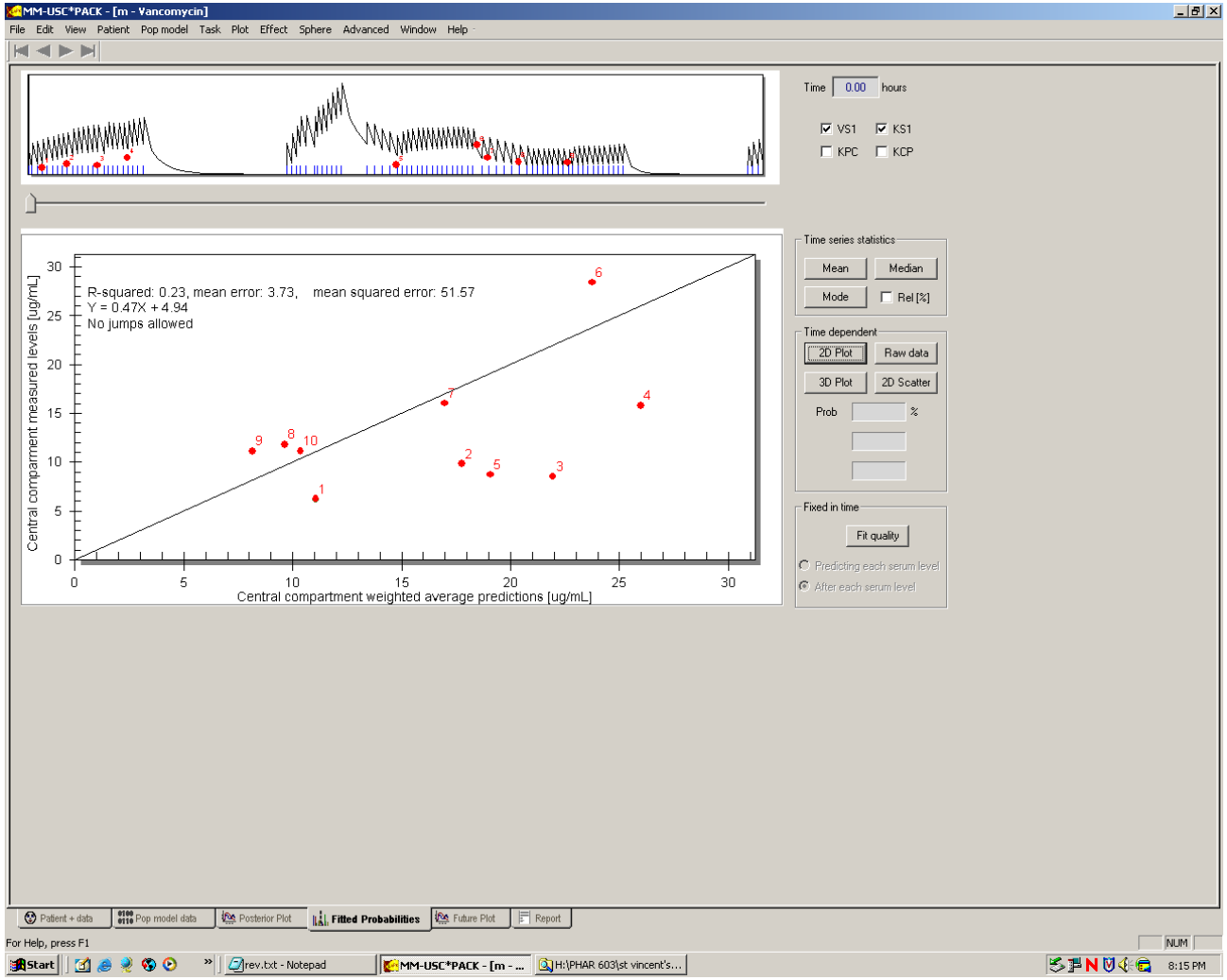
5.13 GRAPH EXAMPLE OF POOR FIT 1



5.14 GRAPH EXAMPLE OF POOR FIT 2



5.15 GRAPH EXAMPLE OF POOR FIT 3



6 GENERAL CONCLUSION

Sunny Tse

Pharmacokinetics has multiple roles in the clinical environment. Prospective simulations can serve as a general guide for dosing vancomycin during the last hour of hemodialysis. PK weight-based dosing of vancomycin during the last hour of hemodialysis is a more individualized method of dose estimation that can generate therapeutic drug concentrations in hemodialysis patients.

Differences between sets of pharmacokinetic parameters can indicate differences in drug disposition between treatment regimens. This is true when comparing a patient cohort receiving an experimental regimen versus healthy volunteers receiving a standard of care regimen. Although there was interpatient variability in pharmacokinetic disposition secondary to drug interactions, aprepitant concentrations remained therapeutic in an experimental regimen cohort under study. No dosage adjustment was necessary. Administration of aprepitant for CINV in HSCT at the prescribed dose of 125 mg orally on day 1 and 80 mg orally on each consecutive day through day +4 post HSCT was well tolerated with no significant changes in pharmacokinetic parameters.

Patients with AML demonstrate altered vancomycin PK parameters compared with the general population. Results indicate patients with AML have an average increased vancomycin elimination rate constant and shortened vancomycin half-life compared with general population estimates. Patients with AML require increased vancomycin dosages to achieve therapeutic serum concentrations. A well designed prospective study is warranted to define all vancomycin PK parameters in patients with AML and to differentiate the impact of neutropenia, patient age, and time elapsed since AML diagnosis on pharmacokinetic estimates and dosage requirements.

Because of the need to produce reasonably precise PK parameters for clinical applications, there is continual need to use state of the art software for PK analysis, such as the LAPK Suites. Even though the vancomycin PK population database was not produced using the patient data from the cohort with AML, it was reasonable to evaluate the MM-USC*PACK in AML patients. This software is easy to use and is a feasible option to help pharmacists dose vancomycin. It is easier to implement than the traditional clinical approach that involves manual calculations. As expected, the mg/kg doses produced by the software are dependent on the desired dosing interval and desired therapeutic range. Various creatinine clearance estimation variations had little effect on the ability of MM-USC*PACK to fit the individual drug concentration versus time data. Vancomycin is probably underdosed in AML patients using MM-USC*PACK alone but the results will be better than using only non-AML population PK values. Given these findings, it is expected that a PK population database generated using a given patient cohort for that patient subpopulation would have excellent predictive performance after incorporation into MM-USC*PACK. Thus a population database using AML patients is suggested as being needed, especially given the finding in Chapter 4 of this thesis that vancomycin clearance is often increased substantially in AML patients.

In conclusion, pharmacokinetics can be used to characterize the disposition of drugs in the body. Given this information, patients can be properly dosed to achieve therapeutic drug concentrations, while avoiding toxicities from overdosing.

COMMON BIBLIOGRAPHY

1. Abdelsayed GG. Management of radiation-induced nausea and vomiting. *Experimental Hematology* 2007; **35:** 34-36.

2. Akins RL, Haase KK. Gram-positive resistance: pathogens, implications, and treatment options: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy* 2005; **25:** 1001-1010.

3. Al Beihany A, Al Omar H, Sahovic E et al. Successful treatment of hepatic veno-occlusive disease after myeloablative allogeneic hematopoietic stem cell transplantation by early administration of a short course of methylprednisolone. *Bone Marrow Transplantation* 2008; **41:** 287-291.

4. Allon M. Dialysis catheter-related bacteremia: treatment and prophylaxis. *American Journal of Kidney Diseases* 2004; **44:** 779-791.

5. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia.[see comment]. *American Journal of Respiratory & Critical Care Medicine* 2005; **171:** 388-416.

6. Ariano RE, Fine A, Sitar DS et al. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. *American Journal of Kidney Diseases* 2005; **46:** 681-687.

7. Barth RH, DeVincenzo N. Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy. *Kidney International* 1996; **50:** 929-936.

8. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: physiological principles. *Intensive Care Medicine* 2004; **30:** 33-37.

9. Bergman AJ, Marbury T, Fosbinder T et al. Effect of impaired renal function and haemodialysis on the pharmacokinetics of aprepitant. *Clinical Pharmacokinetics* 2005; **44:** 637-647.

10. Bergstrom M, Hargreaves RJ, Burns HD et al. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. *Biological Psychiatry* 2004; **55:** 1007-1012.

11. Blum RA, Majumdar A, McCrea J et al. Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. *Clinical Therapeutics* 2003; **25:** 1407-1419.

12. Bouman CS, van Kan HJ, Koopmans RP et al. Discrepancies between observed and predicted continuous venovenous hemofiltration removal of antimicrobial agents in critically ill patients and the effects on dosing. *Intensive Care Medicine*

2006; **32:** 2013-2019.

13. Buelga DS, del Mar Fernandez de Gatta M, Herrera EV et al. Population pharmacokinetic analysis of vancomycin in patients with hematological malignancies. *Antimicrobial Agents & Chemotherapy* 2005; **49:** 4934-4941.

14. Bustad A, Terziivanov D, Leary R et al. Parametric and nonparametric population methods: their comparative performance in analysing a clinical dataset and two Monte Carlo simulation studies.[see comment]. *Clinical Pharmacokinetics* 2006; **45:** 365-383.

15. Cahu X, Mohty M, Faucher C et al. Outcome after reduced-intensity conditioning allogeneic SCT for AML in first complete remission: comparison of two regimens. *Bone Marrow Transplantation* 2008; **42:** 689-691.

16. Chan KW, Mullen CA, Worth LL et al. Lorazepam for seizure prophylaxis during high-dose busulfan administration. *Bone Marrow Transplantation* 2002; **29:** 963-965.

17. Cohen E, Dadashev A, Drucker M et al. Once-daily versus twice-daily intravenous administration of vancomycin for infections in hospitalized patients. *Journal of Antimicrobial Chemotherapy* 2002; **49:** 155-160.

18. Constanzer ML, Chavez-Eng CM, Dru J et al. Determination of a novel substance P inhibitor in human plasma by high-performance liquid chromatography with atmospheric pressure chemical ionization mass spectrometric detection using single and triple quadrupole detectors. *Journal of Chromatography B: Analytical Technologies in the Biomedical & Life Sciences* 2004; **807:** 243-250.

19. de Jonge ME, Huitema AD, Holtkamp MJ et al. Aprepitant inhibits cyclophosphamide bioactivation and thiotepa metabolism. *Cancer Chemotherapy & Pharmacology* 2005; **56:** 370-378.

20. Demirovic JA, Pai AB, Pai MP. Estimation of creatinine clearance in morbidly obese patients. *American Journal of Health-System Pharmacy* 2009; **66:** 642-648.

21. Depre M, Van Hecken A, Oeyen M et al. Effect of aprepitant on the pharmacokinetics and pharmacodynamics of warfarin. *European Journal of Clinical Pharmacology* 2005; **61:** 341-346.

22. Dressel D, Ritter CA, Sperker B et al. Busulfan induces activin A expression in vitro and in vivo: a possible link to venous occlusive disease. *Clinical Pharmacology & Therapeutics* 2003; **74:** 264-274.

23. Durand JP, Gourmel B, Mir O et al. Antiemetic neurokinin-1 antagonist aprepitant and ifosfamide-induced encephalopathy. *Annals of Oncology* 2007; **18:**

808-809.

24. Fernandez de Gatta MM, Fruns I, Calvo MV et al. Influence of pharmacokinetic model on vancomycin peak concentration targets. *Therapeutic Drug Monitoring* 1996; **18:** 145-148.

25. Fernandez de Gatta MM, Fruns I, Hernandez JM et al. Vancomycin pharmacokinetics and dosage requirements in hematologic malignancies. *Clinical Pharmacy* 1993; **12:** 515-520.

26. Feuring M, Lee Y, Orlowski LH et al. Lack of effect of aprepitant on digoxin pharmacokinetics in healthy subjects. *Journal of Clinical Pharmacology* 2003; **43:** 912-917.

27. Fleishaker JC, Pearson LK, Peters GR. Phenytoin causes a rapid increase in 6 beta-hydroxycortisol urinary excretion in humans--a putative measure of CYP3A induction. *Journal of Pharmaceutical Sciences* 1995; **84:** 292-294.

28. Foote EF, Dreitlein WB, Steward CA et al. Pharmacokinetics of vancomycin when administered during high flux hemodialysis. *Clinical Nephrology* 1998; **50:** 51-55.

29. Fridkin SK, Hageman J, McDougal LK et al. Epidemiological and microbiological characterization of infections caused by Staphylococcus aureus with reduced susceptibility to vancomycin, United States, 1997-2001. *Clinical Infectious Diseases* 2003; **36:** 429-439.

30. Girish C, Manikandan S. Aprepitant: a substance P antagonist for chemotherapy induced nausea and vomiting. *Indian Journal of Cancer* 2007; **44:** 25-30.

31. Harigaya Y, Bulitta JB, Forrest A et al. Pharmacodynamics of vancomycin at simulated epithelial lining fluid concentrations against methicillin-resistant Staphylococcus aureus (MRSA): implications for dosing in MRSA pneumonia. *Antimicrobial Agents & Chemotherapy* 2009; **53:** 3894-3901.

32. Hegenbart U, Niederwieser D, Sandmaier BM et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *Journal of Clinical Oncology* 2006; **24:** 444-453.

33. Herget-Rosenthal S, Bokenkamp A, Hofmann W. How to estimate GFR-serum creatinine, serum cystatin C or equations? *Clinical Biochemistry* 2007; **40:** 153-161.

34. Hermida J, Tutor JC. Serum cystatin C for the prediction of glomerular filtration rate with regard to the dose adjustment of amikacin, gentamicin, tobramycin, and

vancomycin. *Therapeutic Drug Monitoring* 2006; **28:** 326-331.

35. Hesketh PJ. Chemotherapy-induced nausea and vomiting. *New England Journal of Medicine* 2008; **358:** 2482-2494.

36. Hesketh PJ, Grunberg SM, Gralla RJ et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin--the Aprepitant Protocol 052 Study Group.[see comment]. *Journal of Clinical Oncology* 2003; **21:** 4112-4119.

37. Ho VT, Revta C, Richardson PG. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies. *Bone Marrow Transplantation* 2008; **41:** 229-237.

38. Hu KT, Matayoshi A, Stevenson FT. Calculation of the estimated creatinine clearance in avoiding drug dosing errors in the older patient. *American Journal of the Medical Sciences* 2001; **322:** 133-136.

39. Hurst AK, Yoshinaga MA, Mitani GH et al. Application of a Bayesian method to monitor and adjust vancomycin dosage regimens. *Antimicrobial Agents & Chemotherapy* 1990; **34:** 1165-1171.

40. Jelliffe R. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. *American Journal of Nephrology* 2002; **22:** 320-324.

41. Jelliffe R, Bayard D, Milman M et al. Achieving target goals most precisely using nonparametric compartmental models and "multiple model" design of dosage regimens. *Therapeutic Drug Monitoring* 2000; **22:** 346-353.

42. Jelliffe RW, Schumitzky A, Bayard D et al. Model-based, goal-oriented, individualised drug therapy. Linkage of population modelling, new 'multiple model' dosage design, bayesian feedback and individualised target goals. *Clinical Pharmacokinetics* 1998; **34:** 57-77.

43. Jelliffe RW, Schumitzky A, Van Guilder M et al. Individualizing drug dosage regimens: roles of population pharmacokinetic and dynamic models, Bayesian fitting, and adaptive control. *Therapeutic Drug Monitoring* 1993; **15:** 380-393.

44. Kirkpatrick CM, Duffull SB, Begg EJ. Pharmacokinetics of gentamicin in 957 patients with varying renal function dosed once daily. *British Journal of Clinical Pharmacology* 1999; **47:** 637-643.

45. Knight JA. Liver function tests: their role in the diagnosis of hepatobiliary diseases. *Journal of Infusion Nursing* 2005; **28:** 108-117.

46. Lam FC, Hung CT, Perrier DG. Estimation of variance for harmonic mean half-lives. *Journal of Pharmaceutical Sciences* 1985; **74:** 229-231.

47. Lamb EJ, Tomson CR, Roderick PJ et al. Estimating kidney function in adults using formulae.[see comment]. *Annals of Clinical Biochemistry* 2005; **42:** 321-345.

48. Le Normand Y, Milpied N, Kergueris MF et al. Pharmacokinetic parameters of vancomycin for therapeutic regimens in neutropenic adult patients. *International Journal of Bio-Medical Computing* 1994; **36:** 121-125.

49. Li SX, Pequignot E, Panebianco D et al. Lack of effect of aprepitant on hydrodolasetron pharmacokinetics in CYP2D6 extensive and poor metabolizers. *Journal of Clinical Pharmacology* 2006; **46:** 792-801.

50. Lohr L. Chemotherapy-induced nausea and vomiting. *Cancer Journal* 2008; **14:** 85-93.

51. Loos WJ, de Wit R, Freedman SJ et al. Aprepitant when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone does not affect vinorelbine pharmacokinetics in cancer patients. *Cancer Chemotherapy & Pharmacology* 2007; **59:** 407-412.

52. Lucksiri A, Scott MK, Mueller BA et al. CAHP-210 dialyzer influence on intra-dialytic vancomycin removal. *Nephrology Dialysis Transplantation* 2002; **17:** 1649-1654.

53. Majumdar AK, Howard L, Goldberg MR et al. Pharmacokinetics of aprepitant after single and multiple oral doses in healthy volunteers. *Journal of Clinical Pharmacology* 2006; **46:** 291-300.

54. Majumdar AK, McCrea JB, Panebianco DL et al. Effects of aprepitant on cytochrome P450 3A4 activity using midazolam as a probe. *Clinical Pharmacology & Therapeutics* 2003; **74:** 150-156.

55. Majumdar AK, Yan KX, Selverian DV et al. Effect of aprepitant on the pharmacokinetics of intravenous midazolam. *Journal of Clinical Pharmacology* 2007; **47:** 744-750.

56. Mason NA, Neudeck BL, Welage LS et al. Comparison of 3 vancomycin dosage regimens during hemodialysis with cellulose triacetate dialyzers: post-dialysis versus intradialytic administration. *Clinical Nephrology* 2003; **60:** 96-104.

57. Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. *Annals of Pharmacotherapy* 2005; **39:** 77-85.

58. Matzke GR, McGory RW, Halstenson CE et al. Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrobial Agents & Chemotherapy* 1984; **25:** 433-437.

59. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. *Clinical Pharmacokinetics* 1986; **11:** 257-282.

60. McCrea JB, Majumdar AK, Goldberg MR et al. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clinical Pharmacology & Therapeutics* 2003; **74:** 17-24.

61. Mendonza AE, Gohh RY, Akhlaghi F. Blood and plasma pharmacokinetics of ciclosporin in diabetic kidney transplant recipients. *Clinical Pharmacokinetics* 2008; **47:** 733-742.

62. Merck. EMEND capsules (aprepitant). Whitehouse Station, NJ: Merck; 2006. Available at :http://www.emend.com/emend/shared/documents/pi.pdf. Accessed May 27, 2008.

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63. Nygren P, Hande K, Petty KJ et al. Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients. *Cancer Chemotherapy & Pharmacology* 2005; **55:** 609-616.

64. Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. *Annals of Pharmacotherapy* 2000; **34:** 1066-1069.

65. Pea F, Viale P. Should the currently recommended twice-daily dosing still be considered the most appropriate regimen for treating MRSA ventilator-associated pneumonia with vancomycin? *Clinical Pharmacokinetics* 2008; **47:** 147-152.

66. Picard N, Djebli N, Sauvage FL et al. Metabolism of sirolimus in the presence or absence of cyclosporine by genotyped human liver microsomes and recombinant cytochromes P450 3A4 and 3A5. *Drug Metabolism & Disposition* 2007; **35:** 350-355.

67. Polard E, Le Bouquin V, Le Corre P et al. Non steady state and steady state PKS Bayesian forecasting and vancomycin pharmacokinetics in ICU adult patients. *Therapeutic Drug Monitoring* 1999; **21:** 395-403.

68. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003; **97:** 3090-3098.

69. Prentice AG, Glasmacher A. Making sense of itraconazole pharmacokinetics.

Journal of Antimicrobial Chemotherapy 2005; **56 Suppl 1:** i17-i22.

70. Quale JM, O'Halloran JJ, DeVincenzo N et al. Removal of vancomycin by high-flux hemodialysis membranes. *Antimicrobial Agents & Chemotherapy* 1992; **36:** 1424-1426.

71. Ripp SL, Mills JB, Fahmi OA et al. Use of immortalized human hepatocytes to predict the magnitude of clinical drug-drug interactions caused by CYP3A4 induction. *Drug Metabolism & Disposition* 2006; **34:** 1742-1748.

72. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. *Clinical Pharmacokinetics* 2006; **45:** 755-773.

73. Ronco C, Orlandini G, Brendolan A et al. Enhancement of convective transport by internal filtration in a modified experimental hemodialyzer: technical note. *Kidney International* 1998; **54:** 979-985.

74. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clinical Infectious Diseases* 2006; **42 Suppl 1:** S35-39.

75. Rybak MJ, Lomaestro BM, Rotscahfer JC et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clinical Infectious Diseases* 2009; **49:** 325-327.

76. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. *Pharmacotherapy* 2006; **26:** 1730-1744.

77. Salazar R, Sola C, Maroto P et al. Infectious complications in 126 patients treated with high-dose chemotherapy and autologous peripheral blood stem cell transplantation. *Bone Marrow Transplantation* 1999; **23:** 27-33.

78. Scott MK, Macias WL, Kraus MA et al. Effects of dialysis membrane on intradialytic vancomycin administration. *Pharmacotherapy* 1997; **17:** 256-262.

79. Shadle CR, Lee Y, Majumdar AK et al. Evaluation of potential inductive effects of aprepitant on cytochrome P450 3A4 and 2C9 activity. *Journal of Clinical Pharmacology* 2004; **44:** 215-223.

80. Shah AK, Hunt TL, Gallagher SC et al. Pharmacokinetics of palonosetron in combination with aprepitant in healthy volunteers. *Current Medical Research & Opinion* 2005; **21:** 595-601.

81. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *Journal of Pharmacokinetics & Biopharmaceutics* 1981; **9:** 503-512.

82. Shipley JL, Butera JN. Acute myelogenous leukemia. *Experimental Hematology* 2009; **37:** 649-658.

83. Smilde TD, van Veldhuisen DJ, Navis G et al. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction.[see comment]. *Circulation* 2006; **114:** 1572-1580.

84. Smith AR, Repka TL, Weigel BJ. Aprepitant for the control of chemotherapy induced nausea and vomiting in adolescents. *Pediatric Blood & Cancer* 2005; **45:** 857-860.

85. Smith RG. Vancomycin: an overview for the podiatric physician. *Journal of the American Podiatric Medical Association* 2004; **94:** 389-394.

86. Soto J, Alsar MJ, Chantal P et al. Correlation of vancomycin clearance and creatinine clearance: unreliability for predicting initial dosing in neutropenic haematological patients. *Journal of Antimicrobial Chemotherapy* 1993; **32:** 920-922.

87. Staatz CE, Byrne C, Thomson AH. Population pharmacokinetic modelling of gentamicin and vancomycin in patients with unstable renal function following cardiothoracic surgery. *British Journal of Clinical Pharmacology* 2006; **61:** 164-176.

88. Stegmaier K, Corsello SM, Ross KN et al. Gefitinib induces myeloid differentiation of acute myeloid leukemia. *Blood* 2005; **106:** 2841-2848.

89. Susla GM. The impact of continuous renal replacement therapy on drug therapy. *Clinical Pharmacology & Therapeutics* 2009; **86:** 562-565.

90. Syed MI, Clark LJ, Sturrock RD. Unintended benefits of immunosupression on autoimmune disease due to chemoradiation therapy for head and neck cancer. *American Journal of Otolaryngology* 2008; **29:** 63-65.

91. Sym D, Smith C, Meenan G et al. Fluorescence polarization immunoassay: can it result in an overestimation of vancomycin in patients not suffering from renal failure? *Therapeutic Drug Monitoring* 2001; **23:** 441-444.

92. Touchette MA, Patel RV, Anandan JV et al. Vancomycin removal by high-flux polysulfone hemodialysis membranes in critically ill patients with end-stage renal disease. *American Journal of Kidney Diseases* 1995; **26:** 469-474.

93. Traynor J, Mactier R, Geddes CC et al. How to measure renal function in clinical

practice.[see comment]. *BMJ* 2006; **333:** 733-737.

94. Trigg ME, Inverso DM. Nausea and vomiting with high-dose chemotherapy and stem cell rescue therapy: a review of antiemetic regimens. *Bone Marrow Transplantation* 2008; **42:** 501-506.

95. Tunkel AR, Hartman BJ, Kaplan SL et al. Practice guidelines for the management of bacterial meningitis.[see comment]. *Clinical Infectious Diseases* 2004; **39:** 1267-1284.

96. Valcarcel D, Martino R. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in myelodysplastic syndromes and acute myelogenous leukemia. *Current Opinion in Oncology* 2007; **19:** 660-666.

97. Villikka K, Kivisto KT, Maenpaa H et al. Cytochrome P450-inducing antiepileptics increase the clearance of vincristine in patients with brain tumors. *Clinical Pharmacology & Therapeutics* 1999; **66:** 589-593.

98. von Winckelmann SL, Spriet I, Willems L. Therapeutic drug monitoring of phenytoin in critically ill patients. *Pharmacotherapy* 2008; **28:** 1391-1400.

99. Wazny LD, Daghigh B. Desensitization protocols for vancomycin hypersensitivity. *Annals of Pharmacotherapy* 2001; **35:** 1458-1464.

100. Welage LS, Mason NA, Hoffman EJ et al. Influence of cellulose triacetate hemodialyzers on vancomycin pharmacokinetics. *Journal of the American Society of Nephrology* 1995; **6:** 1284-1290.

101. Wilcox MH, Tack KJ, Bouza E et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study.[see comment]. *Clinical Infectious Diseases* 2009; **48:** 203-212.

102. Wilhelm MP, Estes L. Symposium on antimicrobial agents--Part XII. Vancomycin. *Mayo Clinic Proceedings* 1999; **74:** 928-935.

103. Winter ME. (3rd edition). *Basic Clinical Pharmacokinetics*. Applied Therapeutics, Inc.: WA, 1994.

104. Yoshida M, Yasuda N, Nishikata M et al. New recommendations for vancomycin dosage for patients with MRSA pneumonia with various degrees of renal function impairment. *Journal of Infection & Chemotherapy* 2005; **11:** 182-188.

105. Yusuf RZ, Dey B, Yeap BY et al. Autologous SCT with a dose-reduced BU and CY regimen in older patients with non-Hodgkin's lymphoma. *Bone Marrow Transplantation* 2009; **43:** 37-42.

106. Zoer J, Schrander-van der Meer AM, van Dorp WT. Dosage recommendation of vancomycin during haemodialysis with highly permeable membranes. *Pharmacy World & Science* 1997; **19:** 191-196.