AN ABSTRACT OF THE THESIS OF

Michael Eugene Millard for the degree of Master of Science in Hospital Pharmacy presented on July 25, 1977

Title: Analysis of Gentamicin Blood Levels for the Purpose of Establishing the Potential of Pharmacist Assisted Gentamicin Dosing

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Freyá Hermann, B.S., M.S.

A random sample of 60 patients receiving gentamicin at a small community hospital was studied. The gentamicin blood levels resulting from the actual doses given and those resulting from doses determined by a method of dose adjustment designed by a pharmacist were predicted and compared. The study shows that 79 percent of the doses given by physicians in this community hospital were within generally accepted guidelines. About 21 percent of the doses given patients were either too high or too low, with these errors made with about equal frequency. By the use of an objective method based on the kinetic parameters of gentamicin, these dosage errors can be eliminated. The pharmacist can eliminate these errors by first calculating creatinine clearance by the method of Siersbak-Nielsen, then using the dosage chart to make dosing recommendations. In selecting patients on gentamicin for monitoring, the creatinine clearance appeared to be the best predictor of inappropriate dosage. If the creatinine clearance was between 20 ml/min and 70 ml/min, the
patient was less likely to be dosed inappropriately. A lean body mass less than 60 kg and a serum creatinine over 2.2mg/100ml also indicate the need for closer scrutiny of the prescribed dose.

The use of the pharmacokinetic model and its drug utilization context allows for the quantification of the pharmacist's potential for change in the clinical setting.
Analysis of Gentamicin Blood Levels for the Purpose of Establishing the Potential of Pharmacist Assisted Gentamicin Dosing

by

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Typed by Karen Stover for Michael Eugene Millard
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I. INTRODUCTION

Literature Review

Gentamicin first became commercially available in April, 1969. Clinical evaluation up to that time was reviewed by Jao and Jackson. Gentamicin's usefulness was described as that of an aminoglycoside antibiotic with a wide antibacterial spectrum. High activity against gram negative bacteria, specifically pseudomonas species, as well as some gram positive organisms has been documented in clinical experience. Gentamicin has since been widely accepted as the drug of choice for serious gram negative infections.

Since the first clinical investigations, gentamicin has been studied for nephrotoxicity and ototoxicity similar to its aminoglycoside congeners. In 1969 Falco reported a low incidence of toxicity, less than 2 percent, due to gentamicin with doses of 1.2 mg/kg to 3 mg/kg per day and based this assessment on rises in blood urea nitrogen (BUN). Hewitt later studied the same patients, using elevations in serum creatinine of 0.3 mg/100 ml as criteria, and found this early incidence of nephrotoxicity during investigational studies to be 7.7 percent. In 1971, Wilfert discussed a higher incidence of elevated serum creatinines in patients receiving gentamicin and he reported an increase in serum creatinine in 32 of 77 patients (44 percent), however, renal failure was thought to be caused by gentamicin in only five of these cases (6.5 percent). But the drug had now been used more widely and in
larger doses of 3 mg/kg to 5 mg/kg a day. Wilfert described the toxicity with gentamicin in these five patients as rises in BUN and serum creatinine with acute tubular necrosis on autopsy.

Similar characteristics of nephrotoxicity became a widely described phenomenon in the literature. Hewitt\(^4\) reviewed the clinical experience accumulated from the manufacturer and concluded that the recognition of high risk patients, careful monitoring of serum creatinine, performance of serum gentamicin assays, and the adjustment of gentamicin dosage had reduced the incidence of nephrotoxicity to 2.2 percent during 1970 to 1973.

Hewitt described two types of nephrotoxicity related to each other pathophysiologically. The first type of toxicity was a transient rise in serum creatinine which is promptly reversible upon discontinuance of the drug. This was seen in 5 percent to 10 percent of the patients receiving gentamicin and Hewitt suggests that this toxicity was responsible for a large number of the rises in serum creatinines previously seen by Wilfert. The second type of toxicity was an acute renal failure characterized by a drastic decrease in renal function that lasted 10 to 12 days after gentamicin is discontinued, followed by a return of renal function to 50 percent of pre-morbid state. Wilfert\(^5\) and McHenry\(^6\) found that gentamicin toxicity was manifested clinically by proteinuria and cylinduria with rising blood urea nitrogen and serum crea-
tinine. Appel and Neu\textsuperscript{7} summarized the literature on the nephrotoxicity of gentamicin and stated:

Renal failure may be oliguric or non-oliguric, but has often presented as acute tubular necrosis. In general, changes are reversible after the drug is discontinued, but substantial damage may require dialysis.

In 1973, Kleinknecht\textsuperscript{8} reported a uremic death due to gentamicin induced acute renal failure.

In view of the potential morbidity and mortality of gentamicin nephrotoxicity, some investigators began to study ways in which to anticipate the toxicity by the use of serum levels. In early 1975, Dahlgren\textsuperscript{9} reported that trough serum gentamicin levels above 2 mcg/ml may indicate accumulation of gentamicin, which in turn may be correlated with early renal impairment. Dahlgren found that 21 of 86 patients had trough gentamicin levels above 2 mcg/ml. Of these 21 patients, 7 (33 percent) had elevations of serum creatinine. None of the patients with trough serum gentamicin levels below 2 mcg/ml had elevations of serum creatinine. Seven of eighty-six patients constitutes an incidence of nephrotoxicity of 8 percent. Dahlgren concluded that 33 percent of patients with trough gentamicin levels greater than 2 mcg/ml have a chance of experiencing nephrotoxicity and that this would define a high-risk subgroup for development of this adverse reaction. At about the same time, Goodman\textsuperscript{10} reported similar findings regarding trough serum levels of gentamicin. He found that trough serum levels of greater than 4 mcg/ml were the only
variable that correlated significantly with development or progression of renal insufficiency.

The literature also discusses the ototoxicity of gentamicin as another adverse reaction shared by gentamicin with the aminoglycoside group of antibiotics. These ototoxicities include both auditory impairment and decreased vestibular function. In 1964, Jao and Jackson\textsuperscript{1} noted an incidence of ototoxicity of 9 percent in their study of 53 patients. In 1971, Jackson and Arceri\textsuperscript{11} reviewed the case summaries submitted to the manufacturer through 1965 and reported that the incidence of ototoxicity was 2.8 percent in the patients. They noted that the recognition of predisposing factors to ototoxicity was responsible for the reduction in the incidence. These factors were: a total dose larger than 1 gram, a serum concentration of greater than 12 mcg/ml, age of over 60 years, previous administration of other ototoxic agents, and renal insufficiency. Jackson and Arceri found a very clear relationship between ototoxicity and renal function, because two thirds of the patients with ototoxicity also had renal impairment. Their analysis showed that the vestibular function was involved alone in 66 percent of the affected patients, that auditory impairment alone was found in 16 percent, and co-existent vestibular and auditory toxicity was observed in the remainder of the patients. Jackson and Arceri found that both types of ototoxicity are usually irreversible.
In 1974, Hewitt\textsuperscript{4} reviewed the reports of the manufacturer through 1973 and concluded that the incidence of ototoxicity was 1 percent. He suggested that this decrease from 2.8 percent found by Jackson and Arceri was related to the adjustment of dosage in renal impairment that had become common practice since 1971.

While toxicity had been a major concern of clinicians in the first years of gentamicin use, another problem, that of low serum levels resulting from overcorrection of dosage for renal insufficiency, was soon recognized by Jackson and Riff\textsuperscript{12} in 1971. They documented in a small number of patients that regimens in which peak serum concentrations were below 4 mcg/ml were generally ineffective, while doses ensuring 4 mcg/ml peak concentrations eliminated pseudomonas bacteremias in all patients except those who had poor immune mechanisms.

In 1972 Chan\textsuperscript{13} stated:

Many physicians, when confronted by a patient with sepsis who also has an element of renal failure, have a great fear of toxicity because gentamicin is eliminated by the kidney. Reduced doses and prolongation of the time between doses are two methods used to avoid toxicity, but the result is also inadequate gentamicin activity.

Chan then described a nomogram for dosing according to creatinine clearance that assured effective gentamicin serum levels.

Klastersky\textsuperscript{14} found in 1974 that the clinical success rate was 67 percent if the peak serum concentration was four times the MIC. However, if the peak serum concentration was
eight times the MIC, the clinical success rate was over 80 percent. This study gave support to the concern of Chan that adequate doses must be given patients with renal impairment.

The first attempt made to study gentamicin dosage in renal impairment was made in 1972 when Cutler\textsuperscript{15} studied 21 patients with varying degrees of renal function. He concluded that the gentamicin half-life was equal to four times the serum creatinine. He suggested that patients with renal impairment be given 2 mg/kg loading dose, and 1 mg/kg every other half-life. This recommendation of Cutler became the "rule of eights", in which dosage interval could be determined by multiplying the serum creatinine by eight. O'Grady\textsuperscript{16} noted that long periods of subinhibitory activities occurred in this regimen.

Also in 1972, Chan\textsuperscript{13} published a method that used the pharmacokinetic properties of gentamicin to adjust dosage. When elimination rate constant was determined for 20 patients with various degrees of renal impairment and plotted against creatinine clearance, a linear relationship was found. The maintenance dose in mg/kg/8 hours was calculated for each elimination rate constant and plotted against creatinine clearance. This plot was used as a nomogram to calculate doses adjusted for renal function. The serum levels of 17 patients dosed by the nomogram were analyzed and found to be therapeutic and non-toxic.

In 1975, Schumacher,\textsuperscript{17} a pharmacist and pharmacokinetic-
cist, reviewed eight regimens for gentamicin dosage adjustment. He used prototype hypothetical patients and calculated gentamicin blood level vs. time profiles for each of the eight recommended doses. He concluded that methods such as Cutler's based on serum creatinine produced levels that were below 4 mcg/ml during much of the dosing interval. He further concluded that the use of serum creatinine was less accurate than creatinine clearance as an indication of renal function and gentamicin excretion. Schumacher reported that methods such as Chan's, that dosed on a frequent schedule, were more likely to produce serum levels that remained over 4 mcg/ml for most of the dosing interval.

In 1976, Heward Hull, another pharmacist-pharmacokineticist, published a study on gentamicin pharmacokinetics and developed his own nomogram for dosage. Hull predicted gentamicin serum levels and then measured the actual levels in 40 patients. His predictions were highly correlated with measured levels ($r = 0.9$). He showed that the use of lean body weight in the computation of predicted serum gentamicin levels contributed significantly to the accuracy of the prediction.

Hull stated that his dosing chart (see page 12) had several practical advantages over previous methods for gentamicin dosing. His chart offered a range of loading doses to allow for the treatment of mild to severe infection. Also, the maintenance dose which reflects the patient's creatinine clearance is computed as a percentage of the loading dose and
administered at commonly used dosage intervals. Extension of the dosing interval allows the administration of larger doses and would provide greater peak and valley effect. Hull noted that "Unnecessarily elevated trough levels that have been associated with toxicity can also be minimized by widening the dosage interval." He described the use of a dosing chart to adjust the dose of gentamicin in sixteen patients. Thirty-two peak gentamicin levels were drawn and all thirty-two were in the range of 4 mcg/ml to 10 mcg/ml.

While the literature contains a clear definition of the problem with gentamicin toxicity and presents dosage adjustment methods effective in clinical practice, it does not offer any guidelines regarding which member of the health care team should perform dosage adjustment of gentamicin. The physician has the legal and moral responsibility to the patient for the drugs he prescribes and most of the data concerning gentamicin dosing has appeared in the medical literature. However the pharmacist also has a responsibility to the patient for efficacious therapy and pharmacists such as Schumacher and Hull have made significant contributions to the literature regarding the rational dosing of gentamicin. To date, whether the physician or the pharmacist is more effective in appropriately dosing gentamicin has not been studied. Also, the extent to which gentamicin is being inappropriately dosed by physicians is unknown.
Statement of Problem

The problem existing in the clinical environment as reflected in the clinical literature is the problem of determining an optimal dosage regimen for an individual patient who is a candidate for gentamicin therapy. Determination of optimal dosage regimens is critical because of gentamicin's narrow therapeutic range and serious toxicities. Dose adjustment can be accomplished after consideration of pharmacokinetic principles. The pharmaceutical literature shows that pharmacists are extremely interested in this problem and have ability, as well as concern, to contribute toward the solution of the problem. The purpose of this study is to examine the null hypothesis that there is no difference in the blood levels calculated from actual doses received by patients in the normal course of practice, and the blood levels calculated from the doses that had been adjusted to account for the specific patient's renal function.

This study will be carried out by comparing predicted serum levels of gentamicin from dosage regimens determined by physicians with those from dosage regimens adjusted by a method that could be employed by pharmacists.

Failure to reject the null hypothesis would mean that pharmacist involvement is unnecessary and therefore unjustifiable in this hospital practice. If on the other hand, the
null hypothesis is rejected, pharmacists receive a clear indication that participation in dosage decisions can be regarded as a viable role in this hospital practice.
II. METHOD

Data Collection

Pharmacy patient profiles were reviewed for all patients admitted to the hospital studied during 1975 and 1976. For those patients who received gentamicin, medical record number, name, age and sex were recorded on a card designed for hand sorting of data. Patients under 12 years of age were not included since the pharmacokinetic model used does not apply in pediatric patients. From these cards, a random sample of 60 patients was selected for study. Using the medical chart number, medical records on these 60 patients were pulled from the files of the medical record department. From these medical records, the following information was obtained for each patient: from the admission sheet completed by the nurses' aide, height and weight; from the medication administration record, dosage date and interval for all doses of gentamicin received; from the laboratory examination section of the chart, serum creatinine values and date of determination.

Data Development

For the purpose of determining renally adjusted doses and predicting gentamicin blood levels, the following values were calculated from the data collected from the chart.
Weight

The weight found on the admission sheet was the actual weight in pounds. However, Hull\textsuperscript{18} demonstrated that lean body mass in kilograms is the most appropriate weight used in the calculation of creatinine clearance and the volume of distribution for gentamicin. The use of lean body mass is essential, as gentamicin is not distributed across lipid membranes and remains largely in the extracellular volume.\textsuperscript{13} The use of lean body mass also reduces the prediction error when used to compute the serum level. According to Hull,\textsuperscript{18} lean body mass may be derived from the actuarial tables\textsuperscript{20} for average body weight based on age, sex and height. The weight term in all calculations in this study is lean body mass in kilograms from those tables. Only when the actual weight was less than the value in the tables, was actual weight used instead of lean body mass.

Creatinine Clearance

A programmable hand held calculator was used to calculate the creatinine clearances from patients' lean body mass, age, sex and serum creatinine, using a recently developed program by Foster and Bourne,\textsuperscript{22} based on the method of Siersbak-Nielsen.\textsuperscript{23} The method of Siersbak-Nielsen uses age, weight and sex to estimate daily creatinine output and uses serum creatinine to estimate clearance. This method was chosen because it is well accepted by clinicians as a bedside
estimate of renal function. It takes into account weight, as well as age. Further, it is the method used by Hull to estimate renal function for the prediction of gentamicin serum levels and the method recommended for use with his nomogram to determine the renally adjusted gentamicin dose.

The parameters of age, lean body weight, sex and serum creatinine were entered into the program and creatinine clearance read in ml/minute. If serum creatinines were stable (not varying any more than plus or minus 0.4 mg/100 ml) then one creatinine clearance was used for the entire hospital stay. However, if serum creatinines were unstable, then creatinine clearances were calculated for a specific period until another serum creatinine determination. This was done to parallel the actual situation in which dosage adjustments were made according to the changing renal function. Thus, for each patient, a chronological creatinine clearance profile was generated.

Dose

From the creatinine clearance as derived above and lean body mass, dose adjusted for renal function was chosen, using the dosage chart of Hull\textsuperscript{18} reproduced on the following page. This method was chosen for the following reasons: 1) it is based on pharmacokinetic principles; 2) these principles have been verified by Hull in actual clinical practice; 3) it is practical to use in the patient care situation, it provides flexibility of changing dosage
1. Select Loading Dose in mg/kg LEAN WEIGHT to provide peak serum level desired. Approximate peak levels from commonly used loading doses are indicated below:

<table>
<thead>
<tr>
<th>LOADING DOSE</th>
<th>EXPECTED PEAK SERUM LEVEL BASED UPON ONE-HALF HOUR IV INFUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 mg/kg</td>
<td>6 - 8 μg/ml</td>
</tr>
<tr>
<td>1.75 mg/kg*</td>
<td>5 - 7 μg/ml</td>
</tr>
<tr>
<td>1.5 mg/kg</td>
<td>4 - 6 μg/ml</td>
</tr>
<tr>
<td>1.25 mg/kg</td>
<td>3 - 5 μg/ml</td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>2 - 4 μg/ml</td>
</tr>
</tbody>
</table>

*(Recommended for most moderate to severe systemic infections.)*

2. Select Maintenance Dose (as percentage of chosen loading dose) to continue peak serum levels indicated above according to patient's creatinine clearance and desired dosing interval.

<table>
<thead>
<tr>
<th>PERCENTAGE OF LOADING DOSE REQUIRED FOR DOSAGE INTERVAL SELECTED:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr. Clear</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>70</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>40</td>
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<td>30</td>
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<td>25</td>
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<td>20</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>
intervals, as well as dose, 4) it reflects the current thought
and practice in the clinical setting.

The patient's lean body mass is multiplied by 1.75 mg/kg
to obtain the loading dose necessary to achieve a peak serum
level of 5 mcg/ml to 7 mcg/ml. This level is recommended for
most moderate to severe systemic infections (see dosing chart). The maintenance dose was then calculated considering
the patient's creatinine clearance and the dosage interval
recommended on the chart.

Determining the Calculated Gentamicin Blood Level

For calculation of predicted blood levels to compare
gentamicin doses empirically derived and doses determined by
the use of the dosing chart, a pharmacokinetic model was con-
structed which would allow prediction of gentamicin serum
levels that would result from each dosage regimen. A program
was written for a Hewlett-Packard HP 65 programmable calcu-
lator and was used to calculate the predicted gentamicin
levels (Appendix 2). As stated in the literature, gentamicin
was assumed to be adequately described by a one compartment
open linear pharmacokinetic model. Constant values were
accepted from the literature of 260 ml/kg lean body mass for
the volume of distribution. A variable excretion rate
constant was assumed to be linearly related to creatinine
clearance and based on normal and anuric half-lives of 2.06
hours and 56.5 hours respectively.
The relationship of $K_{e1}$ to creatinine clearance can be described by the equation, $K_{e1} = 0.003367 \times$ creatinine clearance $+ 0.01227$. Using this equation, $K_{e1}$ was calculated from creatinine clearance. Elimination rate constant may then be used to calculate the fraction of drug remaining in the body at the end of dosage interval ($t$), $P_{\text{min}} = \frac{D \left( e^{-K_{e1} t} \right)}{V_d \left( 1 - e^{-K_{e1} t} \right)}$.

The fraction remaining can then be divided by the volume of distribution to obtain serum concentration at the end of dosage interval ($t$) or $P_{\text{min}}$.

By dividing the dose by volume of distribution and adding to $P_{\text{min}}$, the expected peak can be obtained.

$$P_{\text{max}} = P_{\text{min}} + \frac{D}{V_d}$$

The use of these methods programmed on a calculator allows the prediction of peak and trough gentamicin levels for each dose which the patient actually received ($D$) and for each dose which the patient would have received if the pharmacist had adjusted the dose for renal function (PAD).

**Statistical Methods**

The 60 patients in the study received 77 doses ($D$) of gentamicin from their physicians and for the same 60 patients, 77 pharmacist adjusted doses (PAD) were determined, as stated above. These data were compared for difference in distribution by the sign test.

The difference in predicted blood levels for the two
populations (D) and (PAD) were compared. The test statistic for this comparison was the percentage of levels which was not inside a specified range. The peak blood levels were studied for the percentage falling outside the range of 4 mcg/ml to 10 mcg/ml. This range is the suggested range for gentamicin levels. A level of 4 mcg/ml is necessary for clinical cure, and the higher serum level was chosen to reflect the highest serum level which did not result in toxicity. The trough gentamicin serum levels were studied for the percentage of levels above 2 mcg/ml. This limit is based on recent studies that indicate that elevated trough serum levels predict toxicity in renal insufficiency. In the study of Dahlgren et al., patients with a rise in serum creatinine had trough levels of greater than 2 mcg/ml and patients with trough serum levels below 2 mcg/ml did not experience a deterioration in renal function. These percentages of levels not within the specified range were analyzed using the Z test for two proportions. The mean serum troughs and peaks were compared using a t' statistic. Several factors were examined to find any characteristic that might be used to identify patients at risk for either being underdosed or overdosed. The factors examined were age, sex, ideal weight, highest serum creatinine and lowest creatinine clearance during hospitalization. The difference in daily dose of gentamicin between the two regimens PAD and D was calculated for each patient and compared to that patient's creatinine
clearance by linear regression to examine the difference in the doses per se between them.
III. RESULTS

The results are presented in Tables I and II with the appropriate statistical analyses. When the variations between the two populations were significantly different, the students' t' statistic was used to test the difference of the means.

The mean peak concentration for actual doses administered was 6.20 mcg/ml with a standard deviation of 3.73 mcg/ml. The mean peak gentamicin serum levels for pharmacist adjusted doses was 6.17 mcg/ml with a standard deviation of 0.54 mcg/ml. There was no statistically significant difference between the mean peak concentrations.

The mean trough serum concentrations for actual doses received was 1.82 mcg/ml with a standard deviation of 2.80 mcg/ml. The mean trough serum concentrations for pharmacist adjusted doses was 1.16 mcg/ml with a standard deviation of 0.56 mcg/ml. There was no statistically significant difference between the mean trough serum concentrations.

The percentage of serum levels falling outside the range of 4 mcg/ml to 10 mcg/ml in the actual doses received was 21 percent, while none of the predicted gentamicin levels for the pharmacist adjusted doses fell outside this range. This is highly significant (P less than 0.001). The percentage of predicted trough gentamicin levels greater than 2 mcg/ml was 21 percent for the actual doses administered and 8 percent
### TABLE I. STATISTICAL ANALYSIS OF DATA.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>ACTUAL DOSES</th>
<th>PHARMACIST ADJUSTED DOSES</th>
<th>STATISTIC</th>
<th>SIGNIFICANCE (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEAN PEAK</td>
<td>6.20 mcg/ml</td>
<td>6.17 mcg/ml</td>
<td>t'</td>
<td>not significant</td>
</tr>
<tr>
<td>STANDARD DEVIATION (PEAKS)</td>
<td>3.73 mcg/ml</td>
<td>0.54 mcg/ml</td>
<td>F</td>
<td>p less than .01</td>
</tr>
<tr>
<td>MEAN TROUGH</td>
<td>1.82 mcg/ml</td>
<td>1.16 mcg/ml</td>
<td>t'</td>
<td>not significant</td>
</tr>
<tr>
<td>STANDARD DEVIATION (TROUGHS)</td>
<td>2.80 mcg/ml</td>
<td>0.56 mcg/ml</td>
<td>F</td>
<td>p less than .01</td>
</tr>
<tr>
<td>PERCENT NOT 4-10 mcg/ml (PEAKS)</td>
<td>21 %</td>
<td>0 %</td>
<td>Z</td>
<td>p less than .001</td>
</tr>
<tr>
<td>PERCENT GREATER THAN 2 mcg/ml (TROUGHS)</td>
<td>21 %</td>
<td>8 %</td>
<td>Z</td>
<td>p less than 0.025</td>
</tr>
<tr>
<td>RANGE (PEAKS)</td>
<td>26.65 mcg/ml</td>
<td>6.96 mcg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RANGE (TROUGHS)</td>
<td>17.30 mcg/ml</td>
<td>3.57 mcg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHARACTERISTIC</td>
<td>PEAKS MORE THAN 4 mcg/ml</td>
<td>PEAKS LESS THAN 4 mcg/ml</td>
<td>STATISTIC</td>
<td>SIGNIFICANCE (P)</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>AGE</td>
<td>57.58±20.65 yrs</td>
<td>56.56±19.69 yrs</td>
<td>t</td>
<td>not significant</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>67.07±10.29 kg</td>
<td>75.89±15.88 kg</td>
<td>t'</td>
<td>not significant</td>
</tr>
<tr>
<td>SERUM CREAT.</td>
<td>1.26± 0.476 mg/100 ml</td>
<td>1.13± 0.470 mg/100 ml</td>
<td>t</td>
<td>not significant</td>
</tr>
<tr>
<td>CREAT. CLEAR</td>
<td>64.6 ±25.79 ml/minute</td>
<td>91.63±25.64 ml/minute</td>
<td>t</td>
<td>p less than .01</td>
</tr>
<tr>
<td>CHARACTERISTIC</td>
<td>TROUGHS LESS THAN 2 mcg/ml</td>
<td>TROUGHS MORE THAN 2 mcg/ml</td>
<td>STATISTIC</td>
<td>SIGNIFICANCE (P)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------</td>
<td>----------------------------</td>
<td>-----------</td>
<td>------------------</td>
</tr>
<tr>
<td>AGE</td>
<td>57.58±20.65 yrs</td>
<td>69.50±27.80 yrs</td>
<td>t</td>
<td>not significant</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>67.07±10.29 kg</td>
<td>55.17±13.41 kg</td>
<td>t</td>
<td>p less than .02</td>
</tr>
<tr>
<td>SERUM CREAT.</td>
<td>1.26± 0.476 mg/100 ml</td>
<td>3.60± 2.56 mg/100 ml</td>
<td>t'</td>
<td>not significant</td>
</tr>
<tr>
<td>CREAT. CLEAR</td>
<td>64.60±25.79 ml/minute</td>
<td>16.83±12.23 ml/minute</td>
<td>t'</td>
<td>p less than .001</td>
</tr>
</tbody>
</table>
for the pharmacist adjusted doses. These were also significantly different (P less than 0.025).

The differences in distribution were examined by the use of the sign test and were found to be significantly different (P less than 0.05). There were sixteen patients who fell outside the range of 4 mcg/ml to 10 mcg/ml for actual doses received. Nine of these patients were underdosed or had peak serum concentrations below 4 mcg/ml. Seven of these patients had peak serum concentrations above 10 mcg/ml.

For all patients who received peak concentrations less than 4 mcg/ml five parameters were studied and compared with the same parameters for patients whose peak concentration fell within the 4 mcg/ml to 10 mcg/ml range. This was done to determine whether any of these parameters could serve as predictors for the need to monitor dosage. These factors were age, sex, weight, serum creatinine and creatinine clearance. The mean age for patients with peaks between 4 mcg/ml and 10 mcg/ml was 57.58 years of age. Their mean weight was 67.07 kg. Their mean serum creatinine was 1.26 mg/100 ml. Their mean creatinine clearance was 64.6 ml/minute. For the group of patients who had peak serum concentrations less than 4 mcg/ml, the mean age was 65.6 years, which was not significantly different from the group with levels between 4 mcg/ml and 10 mcg/ml. The weight was 75.89 kg, which was not significantly different from the appropriately dosed group. Serum creatinine was 1.13 mg/100 ml, which was not signifi-
cantly different from the appropriately dosed group. The mean creatinine clearance for patients with less than 4 mcg/ml however, was 91.63 ml/minute, which was significantly higher than that of patients who exceeded the 4 mcg/ml peak blood level (P less than 0.01). In examining those patients who had trough serum concentrations of over 2 mcg/ml, it was found that their mean age was 69.5 years of age and their mean weight was 55.17 kg. The weight was significantly less than that of the appropriately dosed group. The mean serum creatinine of patients with trough serum concentrations above 2 mcg/ml was 3.6 mg/100 ml which is not significantly different than the standard group, and their creatinine clearance was 16.83, which was significantly less than the standard group (P less than 0.001).
IV. DISCUSSION AND CONCLUSIONS

Gentamicin's relatively uncomplicated pharmacokinetics and widely documented nephrotoxicity and ototoxicity stimulated the development of techniques for dose adjustment in patients with renal impairment. To date, at least 10 of these techniques have reached some degree of use.13,15,18,19,24-28

The purpose of this study was to assess the potential for improvement of dosing by involving the pharmacist in the selection of doses. This assessment was based on the predicted incidence of excessive or subtherapeutic doses in the population of patients receiving gentamicin in a specific hospital. In this manner, it was possible to estimate the problems with gentamicin dosing occurring in this specific practice setting. It was then also possible to evaluate the effect of pharmacist assisted dosing and to determine whether this monitoring and dosage recommendation could be a viable role for the clinical pharmacist. The pharmacokinetic model of Hull for gentamicin dosing, using certain parameters, was found to have good reliability in predicting gentamicin serum levels. Hull first predicted levels, then made corresponding serum level determinations and found the correlation coefficient of 0.9 between the predicted and measured levels. Therefore, his model was used to predict the serum gentamicin levels in specific patients, using data found in the medical record. This prediction allowed the comparison of different
dosage regimens with respect to serum levels. Serum levels were chosen for the comparison because serum level is the parameter most applicable to clinical outcome, and is most meaningful as a guide for actual practice.

This assessment is practical for anyone wishing to study gentamicin use in a specific institutional setting, if the necessary medical data is available. This study does not require informed consent, nor add any physical or financial burden on the patients studied. It is easily carried out by the pharmacist, requiring only that the patients receiving gentamicin during the period in question can be identified, and that a random sample of approximately 60 of these patients' medical records can be examined. This study can be done as an ongoing project in the course of normal routine, utilizing spare hours, with a minimum impact on Pharmacy Service function.

The null hypothesis was that there is no difference in the blood levels calculated from actual doses received by patients and blood levels calculated from doses adjusted to account for the specific patients' renal functions. The data indicate that the null hypothesis should be rejected. The data suggest that there is a role for the pharmacist monitoring of gentamicin dosage in this community hospital setting. The pharmacist adjusted dose proved significantly better than actual doses in respect to producing consistently appropriate blood levels. Sixteen (21 percent) of the
patients given doses of gentamicin without pharmacy monitoring were exposed to serum levels outside the 4 mcg/ml to 10 mcg/ml range. Nine patients had a peak concentration below 4 mcg/ml and were underdosed. Sixteen patients (21 percent) had trough concentrations over 2 mcg/ml which should place them at risk for toxicity.

The standard deviation of peak serum levels for D was about seven times as large as for PAD, 3.73 mcg/ml and 0.54 mcg/ml respectively. The range of peak gentamicin levels for PAD was 6.96 mcg/ml to 4.23 mcg/ml, a difference of 2.73 mcg/ml between the lowest peak and the highest peak. The peak serum levels from actual doses range from 26.65 mcg/ml to 1.45 mcg/ml, a difference of 25.18 mcg/ml or a nine times greater range than the values for pharmacist adjusted doses. Of the 77 doses administered, 22 percent resulted in peak gentamicin concentrations outside the 4 mcg/ml to 10 mcg/ml range. None of the pharmacist adjusted doses resulted in levels outside this range. Figure 1 and Figure 2 graphically present this difference of the frequency distribution of serum levels resulting from PAD and D. PAD was less variable and reliably produced levels within the optimal range. The role of the pharmacist monitoring would be to detect these inappropriately dosed patients and correct their doses by consultation with the physician.

Therefore it was important to analyze the data for patients' characteristics that could serve as indicators
Figure 1. Frequency Distribution of Calculated Peak Serum Levels For Actual Doses and Pharmacist Adjusted Doses.
Figure 2. Frequency Distribution of Calculated Trough Levels For Actual Doses and Pharmacist Adjusted Doses.
for the need for the pharmacist to analyze and adjust a patient's gentamicin dosage. The patients who had been dosed appropriately and patients underdosed and overdosed were compared for four characteristics--age, weight, serum creatinine and creatinine clearance. The results are listed in Table II.

The nine patients who were underdosed had a mean creatinine clearance of 91.63 ml/minute, which was significantly greater (P less than 0.01) than the appropriately dosed patients. None of the patients who were underdosed had a creatinine clearance less than 70 ml/minute. These patients were also slightly heavier in lean body mass, but the difference was not significant. These data suggest that inadequate doses of gentamicin are more likely to occur in patients with creatinine clearances above 70 ml/minute. Mean age, mean weight and mean serum creatinine did not differ from underdosed patients and those appropriately dosed. These criteria may not be used as indicators for underdosing.

The seventeen patients who were overdosed with gentamicin (troughs greater than 2 mcg/ml) were lighter in lean body mass (P less than 0.02) and had a much lower creatinine clearance (P less than 0.01) (Table II), and the mean value of creatinine clearance was 16.83 ml/minute. Mean serum creatinine for these patients was 3.60 mg/100 ml, which was not significantly different from that of the appropriately dosed patients. The difference in serum creatinine between these
two groups is 2.34 mg/100 ml, which is certainly clinically significant if not statistically significant. The values for the underdosed patients were highly variable, which is due to some extent to the small number of observations. If more overdosed patients were studied, this parameter might become less variable and a truer statistical inference of its significance could be made. If one assumes that the patients that were appropriately dosed had normally distributed serum creatinines, then 95 percent of the expected values would be within plus or minus two standard deviations of the mean. This range would be 0.3 mg/100 ml to 2.21 mg/100 ml. If this guide were used, then a serum creatinine larger than 2.2 mg/100 ml could indicate that the patient is not in the appropriately dosed group. These data suggest that patients who are overdosed are likely to be less than 60 kg in lean body mass, have a serum creatinine greater than 2.2 mg/100 ml and are likely to have creatinine clearances less than 20 ml/minute. Age or sex cannot be used to differentiate the groups that will be overdosed and groups that will be appropriately dosed. Serum creatinine was not statistically different in this study. However it possibly may be a useful predictor or indicator of potential overdose. The PAD resulted in trough serum gentamicin levels above 2 mcg/ml for six doses in four patients (Table III). This points out the possibility that Hull's dosing chart does not always succeed at keeping the trough concentrations below 2 mcg/ml.
TABLE III. CREATININE CLEARANCE AND TROUGH CONCENTRATIONS FOR PATIENTS OVERDOSED BY PAD.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>CREATININE CLEARANCE</th>
<th>TROUGHS WITH D</th>
<th>TROUGHS WITH PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 ml/minute</td>
<td>17.30 mcg/ml</td>
<td>2.34 mcg/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.81 mcg/ml</td>
<td>2.34 mcg/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.89 mcg/ml</td>
<td>2.34 mcg/ml</td>
</tr>
<tr>
<td>2</td>
<td>12 ml/minute</td>
<td>10.99 mcg/ml</td>
<td>3.57 mcg/ml</td>
</tr>
<tr>
<td>3</td>
<td>16 ml/minute</td>
<td>2.18 mcg/ml</td>
<td>2.77 mcg/ml</td>
</tr>
<tr>
<td>4</td>
<td>19 ml/minute</td>
<td>6.13 mcg/ml</td>
<td>2.30 mcg/ml</td>
</tr>
</tbody>
</table>
An examination of Table III reveals that these patients have the lowest creatinine clearances among the patients studied. While there are not enough observations to allow statistical analysis, it would appear that at very low creatinine clearances, either a prediction or direct measurement of serum gentamicin level is required to assure appropriate dosing. Adjustment of Hull's dose by either decreasing the amounts or extending the interval, would be necessary in patients whose trough levels were greater than 2 mcg/ml. Further investigation is needed to determine how frequently the nomogram fails to keep the trough levels under 2 mcg/ml. The trough levels resulting from PAD ranged from 3.57 mcg/ml to 2.30 mcg/ml. However, the trough levels resulting from D ranged from 17.3 mcg/ml to 2.13 mcg/ml. The method of Hull, while not keeping the trough serum level under 2 mcg/ml in these four patients, resulted in much lower serum levels than actual doses.

These data indicate that there is a potential for pharmacists to improve therapy with gentamicin in the community hospital setting. The role of the pharmacist is to protect the patients who are inappropriately dosed and make dosage suggestions to correct the deficiency in therapy. This can be accomplished by the use of the dosing chart of Hull. Recommendations made from this chart will result in levels falling in the desired range of 4 mcg/ml to 10 mcg/ml.

The calculation of creatinine clearance is the single
most valuable monitoring parameter for pharmacists, with creatinine clearances below 20 ml/minute suggesting the possibility of overdosing, and creatinine clearances of greater than 70 ml/minute suggesting underdosing. Calculation of expected peak and trough blood levels and review of the patient's chart should be essential in these patients. To guard against overdosing, lean body mass below 60 kg and a serum creatinine above 2.2 mg/100 ml might also serve as valuable preliminary indicators of overdosing. Patients falling between these extremes could be monitored calculating a pharmacist adjusted dose, using the dosing chart, and comparing the dose with the prescribed dose to check for clinically significant differences.

The choice of these monitoring parameters appears entirely rational. A drug that is exclusively renally excreted would be expected to be monitored by a measure of renal function because the problem areas in adjustment of doses will be at the extremes of renal function.

The potential for this monitoring role of the pharmacist is related to the degree of empiricism which the practicing physician uses in establishing the dose adjustment for gentamicin. In this practice setting, it is interesting to note that the attending physician was not a factor in inappropriate dosing. There were fifteen different physicians prescribing gentamicin to these patients who were considered inappropriately dosed. One could assume therefore, that it
may not be a lack of expertise by individual practitioners, but inadequacy of the generally accepted approach in determining the dose of gentamicin that caused the inappropriate dose.

The daily dose of gentamicin recommended by the pharmacist was subtracted from the actual daily dose. This quantity, delta D, was correlated with the creatinine clearance by linear regression to study any relationship between possible input by the pharmacist (change in dose prescribed) and degree of renal impairment. The correlation coefficient was 0.69. While the correlation was not highly significant, the graph of delta D vs. creatinine clearance was interesting (Figure 3). As renal function decreased from about 60 ml/minute to 0 ml/minute, the PAD are usually smaller than D. As creatinine clearance increases from 60 ml/minute, PAD are larger than D. This correlation reflects the underdosing and overdosing by physicians already discussed, but does not have practical value.

The method for dose adjustment described in this study is an improvement over the empirical approach. However there is nothing inherently desirable in the pharmacist using techniques to adjust gentamicin dose. The desirability lies in the adjustment of the dose of gentamicin using parameters known to affect the pharmacokinetics. However, it is not necessary for the pharmacist to adjust the dose but whether the pharmacist or physician is responsible is a mute question.
Figure 3. Relation Between delta D and Creatinine Clearance from 60 Patients.
It is important that an assessment of the status quo be made and this study suggests one approach. The pharmacokinetic models are used frequently to individualize therapy of some drugs for specific patients. If the understanding of pharmacokinetics and drug use can enable the pharmacist to assess problems in therapy, and propose solutions through education, then there is a new role for pharmacists and a new goal for monitoring by pharmacists.

Pharmacists, like many others in health care, have always felt that they are positively affecting the quality of patient care. Such an impact is difficult to quantify. This study gives a baseline incidence of inappropriate dosing of gentamicin at a small community hospital. If the monitoring program was begun, the impact on care could be quantified using the same methodology by observing the change in percent of the blood levels outside the 4 mcg/ml to 10 mcg/ml range. This assessment of the pharmacist's effect on patient care would be helpful to the specific institution, the profession of pharmacy, and the patient. Specific institutions would gain by knowing the cost benefit of monitoring by the pharmacist, and then be able to proceed with programs that change the quality of care, while minimizing programs that do not change quality. The profession will gain a more definite idea of its role in the clinical setting, and enjoy enhanced credibility through the documentation of its effect on the quality of care. The patient will be treated more appropri-
ately, but will not have to pay for the duplication of physician efforts by the pharmacist.

The study that was carried out was designed to examine the whole practice environment rather than the individual patient therapy. Factors necessary for the determination of ideal therapy in infection in specific patients have not been included in this study--i.e. culture results and site of infection. For the purposes of this study, three assumptions were made--firstly that the organisms were susceptible to gentamicin, secondly that gentamicin was the agent of choice for the patient's infection. The third assumption was that all patients in this study had infections of wound, skin, soft tissue, or septicemia that required levels of 5 mcg/ml to 7 mcg/ml for clinical cure. This assumption was made because these sites of infection are the most common ones, and defining the desired serum level allowed objective selection of PAD to be used for comparison with actual doses. But the site of infection can drastically alter dosage required. Noone21 observed that pneumonia requires peak levels of 8 mcg/ml or more. Urinary tract infections can be treated with very small doses because gentamicin concentrates in the urine five to twenty-five times the peak serum concentration. If this method is used to assess the individual patient therapy for appropriateness, adjustments based on these factors must be considered in the few cases. Therefore, before an individual patient can be considered to
be underdosed or overdosed, these possibilities must be ruled out.

This technique of pharmacokinetic modeling to examine current prescribing habits is not limited to gentamicin. Any drug that has appropriate characteristics may be studied in this manner. 1) The drug must have a pharmacokinetic model that accurately and reliably describes the absorption, fate and excretion of the drug, 2) pharmacologic effect must be correlated with blood levels and the desired range of serum concentrations must be known, 3) the data necessary to use the model must be routinely available when the drug is in use, so that concurrent retrospective examination of charts will allow the prediction of blood levels. Some drugs for which these criteria may be met are digoxin, aminophyllin, some anticonvulsants and most antibiotics, especially aminoglycosides. In a similar fashion, data could be gathered on the value of pharmacist involvement in dosing of these drugs that have appropriate characteristics.

Summary

The study shows that 79 percent of the doses given by physicians in this community hospital were within generally accepted guidelines. About 21 percent of the doses given patients were either too high or too low, with these errors made with about equal frequency. By the use of an objective method based on the kinetic parameters of gentamicin, these
dosage errors can be significantly reduced. The pharmacist can eliminate these errors by first calculating creatinine clearance by the method of Siersbak-Nielsen, then using the dosage chart to make dosing recommendations. In selecting patients on gentamicin for monitoring, the creatinine clearance appeared to be the best predictor of inappropriate dosage. If the creatinine clearance was between 20 ml/minute and 70 ml/minute, the patient was less likely to be dosed inappropriately. A lean body mass less than 60 kg and a serum creatinine over 2.2 mg/100 ml also indicate the need for closer scrutiny of the prescribed dose. The use of the pharmacokinetic models and its drug utilization context allows for the quantification of the pharmacist's potential for change in the clinical setting.


APPENDIX 1: Program steps and instructions for estimating creatinine clearances for HP-65

KEY ENTRY

```
KEY ENTRY

     f  +  STO 4  STO 7
cl x  RCL 1  RTN  RCL 5
LBL A  X  LBL E  RCL 4
2.205 STO 3  STO 5  -
:  GTO D  RCL 4  RCL 2
STO 1  LBL C  +  X
RCL 1  .175  RCL 1  CHS
4  X  -  RCL 7
X  CHS  STO 6  +
STO 2  25.3  .03  100
RTN  +  X  X
LBL B  RCL 1  CHS  RCL 6
.203  X  1  :
X  STO 3  +  1440
CHS  RTN  RCL 3  :
29.3  LBL D  X  RTN
```

STEP INSTRUCTIONS

1. Calculator on
2. Turn to run
3. Enter weight (lbs.)
4. Enter age (years)
<table>
<thead>
<tr>
<th>STEP</th>
<th>INSTRUCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.</td>
<td>Enter serum creatinine (Day 1)</td>
</tr>
<tr>
<td>6.</td>
<td>Enter serum creatinine (Day 2)</td>
</tr>
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<td>7.</td>
<td>OUTPUT: Creatinine Clearance (ml/min)</td>
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</table>
APPENDIX 2: Program steps and instructions for the pharmacokinetic model of gentamicin

KEY ENTRY

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<tbody>
<tr>
<td>STO 1</td>
<td>1</td>
<td>STO 3</td>
<td>STO 6</td>
</tr>
<tr>
<td>LBL B</td>
<td>-</td>
<td>LBL D</td>
<td>RCL 5</td>
</tr>
<tr>
<td>RCL 1</td>
<td>RCL 2</td>
<td>STO 4</td>
<td>+</td>
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<tr>
<td>X</td>
<td>÷</td>
<td>RCL 4</td>
<td>STO 7</td>
</tr>
<tr>
<td>CHS g 1/x</td>
<td>RCL 3</td>
<td></td>
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<tr>
<td>f⁻¹ STO 2</td>
<td>÷</td>
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</tr>
<tr>
<td>ln LBL C</td>
<td>STO 5</td>
<td></td>
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<tr>
<td>STO 2</td>
<td>R/S RCL 2</td>
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<tr>
<td>RCL 2 .260</td>
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</tr>
</tbody>
</table>

STEPs INSTRUCTIONS

1. Calculator on
2. Turn to run
3. Enter dosing interval (hrs)
4. Enter elimination rate constant
5. Enter weight (kilos)
6. Enter dose of gentamicin (mg)
7. OUTPUT: trough gentamicin serum level (mcg/ml)
8. Press R/S
9. OUTPUT: peak gentamicin serum level (mcg/ml)