COMPARISON OF THE PREDICTIVE UTILITY OF TWO METHODS OF DOSING TOBRAMYCIN IN CYSTIC FIBROSIS PATIENTS

by

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY:

I have read the clinical research project report of Mary Y. Relling in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables, and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

Mary V. Relling

We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

5/28/85
Date

Chairman, Supervisory Committee

5-23-85
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Date

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INTRODUCTION

Aminoglycosides are often used to treat severe gram negative infections. It is desirable to achieve adequate peak concentrations for successful eradication of the infection, while minimizing the trough concentration, in order to decrease the amount of drug presented to the renal proximal tubule and thus theoretically decrease the risk of nephrotoxicity. For these reasons, serum aminoglycoside concentrations are monitored.

Cystic fibrosis (CF) patients are frequently hospitalized for treatment of pseudomonal pulmonary infections. An aminoglycoside is usually combined with an extended-spectrum penicillin to treat the infection. High peak serum aminoglycoside concentrations are generally desired, with 8 mg/l (for tobramycin and gentamicin) being necessary to effectively treat gram negative pulmonary infections.[1,2] In addition, there is some evidence that maintaining peak serum tobramycin concentrations (STC's) between 8 and 12 mg/l results in at least temporary eradication of Pseudomonas aeruginosa from sputum of CF patients.[3] In order to keep STC's greater than the minimum inhibitory concentration of the organism in CF for most of the dosing interval, there is evidence that peak concentrations as high as 10 to 12 mg/l are necessary.[4] High peak STC's are probably necessary in CF patients because of their enhanced elimination of aminoglycosides.

CF patients have been shown to have altered pharmacokinetic characterisitcs in handling gentamicin,[5,6] tobramycin,[6,7] and amikacin.[8,9] More specifically, they generally have an increased volume of distribution (Vd) and an increased total body clearance. The mechanism responsible for these altered pharmacokinetic characteristics is not clear. A

complication is the fact that Vd has not consistently been shown to be elevated, [10] and Kelly et. al. reported a wide inter and intrapatient variability of Vd in the CF population.[11] MacDonald et. al. studied CF patients who were not in pulmonary exacerbation and found no increase in Vd above that of the non-CF population[12], nor did Finkelstein and Hall.[9] Also, there is wide interpatient variability in the dose required to produce the desired serum concentrations, ranging from 7.5 to 26 mg/kg/day for tobramycin[6,7] and 6.9 to 15.0 mg/kg/day for gentamicin.[6] The need for high aminoglycoside concentrations, the altered pharmacokinetics, and the wide interpatient variability, make monitoring of serum aminoglycoside concentrations an important component of the management of CF.

One widely used method of dosing aminoglycosides is that proposed by Sawchuk and Zaske.[13,14] This method has been studied in CF patients and has been reported to be "adequate"[5,7] and to have "worked well"[6] in its ability to predict serum aminoglycoside concentrations, although it has not been compared to other methods in this population. Bauer et. al. found that projected peak and trough aminoglycoside concentrations were not statistically significantly different than actual measurements.[6] Kelly et. al. reported that 85% of the measured peak concentrations fell within 1.4 mg/l of the predicted value.[7] The predictive error of the Sawchuk-Zaske (SZ) method has not been previously reported in CF patients.

Another method of dosing aminoglycosides can be termed simplified pharmacokinetics (SP). This method uses simple algebraic principles in adjusting the dose of aminoglycoside to achieve the desired serum concentrations. The SP method is often used clinically, but has not been subjected to structured clinical evaluation.

The purpose of this study was to compare the predictive utility of the SZ method to that of the much simpler method of dosing aminoglycosides, the SP method. The SZ method differs in that it takes into account elimination of drug during infusion time in calculating Vd and the serum concentration at the end of an infusion. Many clinicians do not use programs or equations that take into account infusion time in their normal course of determining aminoglycoside dosage regimens. Thus, we compared the two methods to see if they were sufficiently different in their predictive utility to recommend the use of one instead of the other in CF patients. The SP method would be preferable to the SZ method if it is as good a predictor of STC's in CF as is the SZ method (or perhaps superior), because it can easily be explained to clinicians and allows for a rapid and simple method of dosing aminoglycosides in CF.

CF patients tend to have short elimination half-lives ($t_{1/2}$). The SP method is applicable only when trough concentrations are sufficiently low so that the dose may be increased without having to lengthen the dosing interval (τ). Patients with short $t_{1/2}$'s have low trough STC's because of their rapid elimination. Thus, CF patients are a good group in which to examine the SP method. In addition, if it is important to take into account infusion time, it is more likely to manifest itself in a population with short $t_{1/2}$'s,[14,15] in whom an overestimation in prediction of the peak serum concentration is likely if elimination during infusion is ignored.

The primary objective of this study was to determine whether there was a difference in the predictive utility of the two methods in CF patients. A secondary objective was to

determine if either method more frequently resulted in predicted or actual trough STC's of greater than 2.0 mg/l.

METHODS

Sixteen patients were consecutively enrolled as subjects in the study from the group of CF patients who were admitted to the University Hospital between July, 1984 and February, 1985 for treatment of pulmonary exacerbation. Patients of any age, without evidence of renal dysfunction (serum creatinine greater than 1.2 mg/dl), were accepted. Patients who had had blood drawn for STC determination within the last month were excluded.

The initial dose of tobramycin was determined by house officer preference. Upon admission, patients were randomized, with the use of a random numbers table, to be dosed with either the SZ or the SP method. One of the investigators contacted the house officer and ensured that orders were written for peak and trough STC's between the first 24-48 hours of treatment, at which time steady-state serum concentrations should have been reached. Selection of the exact timing of blood sampling STC's was based on the need to keep venipunctures during the daytime hours (to avoid awakening patients). Blood samples for determination of peak concentrations were drawn 30 minutes after the infusion of the n^{th} (third to sixth) dose; trough concentrations were drawn immediately prior to the $n^{th} + 1$ dose. Blood for both STC's was obtained within the same dosing interval in order to ensure greater reliability in determination of elimination rate constant (k_{el}). The exact time of the start and end of the tobramycin infusion and times of venipuncture were recorded on a form developed for this study and kept on the patient's bedside chart.

The blood samples were transported to the laboratory on ice, centrifuged, and the serum was either assayed immediately or frozen and assayed within 48 hours. Assays were performed with the TD_X^R system (Abbott Laboratories; Chicago, Ill.), a fluorescence polarization immunoassay with a lower limit of sensitivity at our institution of 0.2 mg/l (95% confidence). The coefficient of variation ($\pm$ standard deviation) between batches was 3.58 $\pm$ 0.035% at 1.0 mg/l and 3.37 $\pm$ 0.258% at 8.0 mg/l.[16] The coefficient of variation within batches was 3.11 $\pm$ 0.03% at 1.0 mg/l and 2.88 $\pm$ 0.221% at 8.0 mg/l.

Both dosing methods were used to obtain a desired peak serum concentration of 8.0 mg/l, at exactly 30 minutes after the end of the infusion. Acceptable trough concentrations were less than 2.0 mg/l, since there is evidence to suggest an increased incidence of nephrotoxicity in patients with trough concentrations greater than 2.0 mg/l.[17,18]

The SZ program designed for use with TI-59 calculators, available from St. Paul-Ramsey Medical Center in St. Paul, MN, was used to calculate pharmacokinetic parameters. The program is based on equations which assume first-order elimination of drug in a one-compartment open model. The operative equations for this method have been published and are presented below.[14] Although optimal use of the SZ method involves obtaining a pre-dose and three post-infusion concentrations, only two post-infusion STC's were determined in keeping with the normal practice at our institution. A third post-infusion concentration would have theoretically added more reliability in calculation of k_{el} (elimination rate constant). A pre-dose trough would have resulted in more accuracy in calculation of Vd, because it would have represented the true pre-infusion concentration (Cp minimum), which is used in calculation of Vd. Instead, we assumed that the trough obtained

after a dose was equal to the trough obtained before a dose, because steady state conditions were assumed. Based on serum concentration versus time data, the program is used to calculate k_{el} and $t_{1/2}$ using the equation:

$$Cp\ post = Cp\ max\ e^{-kel(t-t')} \qquad (1)$$

where Cp post is the serum concentration at some time during the post infusion phase, Cp max is the serum concentration at the end of the infusion, t is the time corresponding to Cp post, and t' is the duration of the infusion. Vd is calculated using t' and the zero order infusion rate (k_0):

$$Vd = \frac{ko\ (1 - e^{-kel\ t'})}{k_{el}\ (Cp\ max - Cp_0\ e^{-kel\ t'})} \qquad (2)$$

where Cp_0 is the concentration in serum remaining from a previously administered dose (Cp minimum). Based on the above calculated parameters, the desired Cp min_{∞} (the steady state Cp_0) and Cp max_{∞} (the steady state Cp max), the dosing interval, τ, can be calculated:

$$\tau - t' = \frac{-1}{k_{el}} \ln\left[\frac{Cp\ min_{\infty}}{Cp\ max_{\infty}}\right] \qquad (3)$$

τ is rounded to give a practical dosing interval. The following two equations are used to calculate the infusion rate necessary to achieve the desired Cp max_{∞} and the actual Cp min_{∞} to expect based on the rounded τ.

$$k_0 = k_{el}\ Vd\ Cp\ max_{\infty}\ \frac{(1 - e^{-kel\,\tau})}{(1 - e^{-kel\ t'})} \qquad (4)$$

$$Cp\ min = \frac{k_0 (e^{kel\ t'} - 1)}{k_{el}\ Vd\ (e^{kel\ \tau} - 1)} \qquad (5)$$

Calculations for the SP method are as follows. Elimination occuring during the infusion was assumed to be relatively constant for each administration. Steady state conditions were assumed, because all concentrations were drawn after the patient had been on the same dosage regimen for at least 24 hours. This is much greater than four times the mean half life for tobramycin in CF patients, which has been reported to be 1.2[7] and 1.73 hours[10]. Because of this short $t_{1/2}$, it was anticipated that it would be possible to achieve adequate peak concentrations, while maintaining predicted trough concentrations less than 2.0 mg/l, without having to lengthen τ. Thus, in the following equation, (at steady state), kd, Vd, and τ may all be considered to be constant for each patient:

$$Cpmax_{\infty} = \frac{D}{Vd\ (1 - e^{-kel\ \tau})} \qquad (6)$$

and

$$Cpmin_{\infty} = Cpmax_{\infty}\ e^{-kel\ \tau} \qquad (7)$$

where D = dose. These relationships suggest that serum concentrations, at any given time, are directly proportional to dose. Thus, given a certain measured $Cpmax_{\infty}$,

the ratio of 8.0 mg/l to $Cpmax_{\infty}$ was computed. This ratio was multiplied by the initial dose, yielding the dose required to produce peak concentrations of 8.0 mcg/ml at the initial τ. This same ratio was multiplied by the initial measured trough concentration ($Cpmin_{\infty}$) to calculate the predicted trough. Calculations for k_{el} and Vd were made using the following formulae:

$$k_{el} = \frac{\ln Cp\ max_{\infty} - \ln Cp\ min_{\infty}}{t_{peak} - t_{trough}} \quad (8)$$

$$Vd = \frac{Dose}{Cp\ max_{\infty}(1 - e^{-kel\tau})} \quad (9)$$

One method or the other was used to determine dosage recommendations (depending on randomization schedule). Calculations for the concentrations each method would predict (given the dose that was actually used), were made for both methods. The predictive utility of each method was thus calculated based on the same set of STC data.

Data were tabulated and analyzed for statistical and clinical significance as follows. In order to determine the predictive utility of the two methods, the mean prediction error (ME) and mean squared prediction error (MSE) were calculated as described by Sheiner and Beal.[19] Ninety-five percent confidence intervals (CI's) were calculated for the differences between the two MSE's (Δ MSE) and the two ME's (ΔME). Our chosen level of

significance was 0.05. If the CI for Δ MSE includes zero, then there is no statistically significant difference in the precision of the two methods. If the CI does not include zero, the method with the smaller MSE is considered more precise. If the CI for ΔME includes zero, then there is no difference in the bias of the two methods. We considered a ΔME of greater than 1.0 mg/l to represent a clinically significant difference.

The second objective was to determine if the two methods differed in the frequency of producing trough concentrations greater than 2.0 mg/l. This frequency was calculated for both methods, and analyzed descriptively by calculating the percentage of patients with elevated troughs at the second set of serum concentrations. A difference between the two methods in the frequency of trough concentrations greater than 2.0 mg/l would need to be weighed, along with any differences in predictive utility, to decide which, if either, of the two methods is preferable for dosing aminoglycosides in CF patients with normal renal function.

RESULTS

Data were collected from July 1, 1984 to February 1, 1985. Sixteen patients successfully completed two sets of peak and trough determinations. Subjects ranged in age from 1 to 30 years (median 19 years). Ten were female and six were male. All had serum creatinine concentrations less than 1.2 mg/dl (mean 0.8 mg/dl). All subjects were treated with standard medications used in CF including pancreatic enzymes, an antipseudomonal penicillin, and frequently theophylline and vitamins E and K.

The predicted and measured tobramycin concentrations are shown in Figures 1-4. The values for predictive error (PE, the predicted tobramycin serum concentration minus the measured concentration) for peaks and troughs, calculated for both the SZ and SP methods, are reported in Tables 1 and 2. All peak STC's (predicted and measured) are extrapolated to the concentration achieved at thirty minutes after the end of the infusion. All trough concentrations (predicted and measured) are extrapolated to one minute prior to the next dose.

The difference in the mean squared error (ΔMSE) of the methods was 0.49 for peaks and 0.04 for troughs. The 95% confidence interval (CI) for peaks was -0.68 to 1.42 and the 95% CI for troughs was -0.04 to 0.12. Both CI's included zero, indicating that there was no statistically significant difference in the capacity of the two methods to accurately predict serum concentrations.

The difference in the mean error between the two methods (ΔME) was equal to 0.12 mg/l for peaks and -0.06 mg/l for troughs. The 95% CI for peaks was -0.02 to 0.26 and

for troughs was -0.14 to 0.02 mg/l. Since both CI's included zero, there was no statistically significant difference between the two methods in their mean bias in predicting STC's.

The β error in this study was 18%, based on the standard deviation (S.D.) in predictive error that we obtained ($\pm$4.6 mg/l). Thus, there is an 18% chance that there was a difference between the two methods that we failed to detect. Based on the previously published S.D. of differences in predicted versus measured STC's for the SZ method (1.4 mg/l),[20,21] the predicted β error for this study was expected to be 4.8%.

It should be noted that although the two methods were quite similar in their degree of predictive utility and the mean bias was small (less that 1.0 mg/l), neither method was very reliable in predicting STC's for any given patient. Thus, although the ME for peaks is only -1.01 mg/l (SZ) and -1.13 mg/l (SP), the range was from -10.0 to 4.7 mg/l (SZ) and from -9.7 to 4.8 mg/l (SP). The S.D. was 4.64 mg/l (SZ) and 4.60 mg/l (SP). For troughs, the range for PE was from -1.0 to 1.0 mg/l (SZ) (S.D. 0.50) and from -0.8 to 0.8 mg/l (SP) (S.D. 0.45).

Neither method resulted in predicted or measured troughs greater than 2.0 mg/l.

We calculated Vd and k_{el} based on STC's obtained one to two days after admission and again three to four days after admission. The results are listed in Tables 3 and 4. There is large variability in the Vd calculated for patients with both methods. The mean Vd decreased from 0.539 l/kg to 0.391 l/kg (SZ) and from 0.664 l/kg to 0.506 l/kg (SP). The mean k_{el} increased from 0.349 hr^{-1} to 0.371 hr^{-1} (same for both SZ and SP methods).

DISCUSSION

The CF patients involved in this study routinely have peak and trough STC's measured to aid in determining their dose of tobramycin. Usually, peak and trough concentrations are obtained the day after admission, dosage is altered (either by housestaff or pharmacy residents or staff) according to the SP method, and frequently, no further STC's are drawn for that admission. The SZ method has been used to aid in dosing of aminoglycosides in CF.[4-7] To date, the SZ method has not been compared to the SP method to determine if there is a difference in their predictive utility. Because the SP method requires no detailed calculations, it can be used easily and quickly by housestaff or pharmacy staff to make dosage changes. We found no statistically significant difference between the two methods. Thus, there appears to be no advantage to using calculator or computer programs using the SZ method to aid in making dosage changes in CF patients with normal renal function.

However, the use of the SP method was not as simple as it first appeared. The major reason for this is that the SP method requires that the peak concentration be reflective of the thirty minute post-infusion peak and that the trough concentration be reflective of the one minute pre-infusion trough. In actuality, peaks and troughs were infrequently drawn at exactly these times. Thus, almost all measured peaks and troughs had to be extrapolated to the true peaks (thirty minute post-infusion) and troughs (one minute per-infusion), a procedure which is simple enough for the clinician with skills in pharmacokinetics, but which is generally foreign to the house officer. Thus, even the recommendations based

upon the SP method required interpretation by a clinical pharmacist and were not readily apparent to the housestaff. Nonetheless, such calculations are more easily done than those required by the SZ method, and can be quickly performed in the patient care areas without having to use programmable calculators or computer programs.

The effects of a peak STC being drawn late were sometimes remarkable. In one instance, the measured peak was drawn approximately one-half hour late and was 8.3 mg/l. When it was extrapolated back to a thirty minute post-infusion peak, the value was 10.4 mg/l. In this case, the house officer would probably have been satisfied with a peak of 8.3 mg/l and would not have changed the dose. When it was pointed out that the "true" peak was 10.4 mg/l, we made recommendations to decrease the dose. The house officer did so, in a case where he would not have, if it were not for clinical pharmacy intervention. The effect of clinical pharmacy interpretation in these types of cases had impact on the dosage adjustments that were made.

DeVito and Cross address the problem of trough aminoglycoside concentrations being drawn one-half hour late, thus altering the timing of the next dose and subsequent measured peak concentration.[15] In patients with a $t_{1/2}$ of only one hour, they reported a 13.6% increase in the calculated k_{el} and a 2.4% decrease in the calculated Vd, with almost a 1.0 mg/l error in measured Cp max. Their data, and the results obtained in this study, illustrate the impact that even minor errors in timing of blood draws in relationship to dose can have on calculated pharmacokinetic parameters and thus on the dosage changes made. Realistically, one cannot guarantee that the timing of dosing and blood draws will always be as scheduled; thus, pharmacokinetic interpretation of the results is frequently

necessary.

The β error is this study was 18%. This is less than the arbitrarily acceptable error of 20%. However, we had anticipated that the β error would be even less than 18% because we did not expect that there would be such wide variability in the predicitve utility of the two methods.

All predicted and measured troughs were less than 2.0 mg/l. This is not an unexpected result, because all subjects were young, had normal renal function, and had the short $t_{1/2}$'s (mean 1.99 hours, first draw and 1.87 hours, second draw), that have been described in CF patients previously.[1-3,5,15,16] Since most patients were dosed on an every eight hour schedule, it was unlikely that their trough STC would be elevated.

A variety of problems occurred in the study which prevented data collection on some patients. We attempted to collect STC's on over 30 courses of therapy, but could only completely collect data for 16 patients. A discussion of some of these problems will illustrate the difficulty in obtaining reliable STC's in the clinical setting, which is where pharmacokinetics ultimately must be applied.

Occasionally the laboratory personnel drew peak STC's less than 30 minutes after the infusion of the dose. This resulted in peak concentrations that were very high, probably because the drug was still in its distributive phase. Early in the study, nurses sometimes forgot to record the time of doses, resulting in unusable data or delays in checking STC's. To prevent this, the nurse was contacted shortly before a dose was due and reminded to record times. This was necessary throughout the study. Occasionally, the phlebotomist forgot to write down the time of venipuncture; again, through constant

reminders, the implementation of the data collection sheet, and use of a central laboratory sign out sheet for blood draws, times of draws were finally consistently recorded. Sometimes patients would leave the ward and not be available for blood collection or dose administration. Some patients adamantly refused to have their blood drawn. More frequently, their reluctance caused the housestaff considerable distress, and thus the physicians refused to order STC's. Finally, STC's were occasionally obtained that were not believable (i.e. trough concentrations being greater than peak concentrations), possibly due to inadvertent mislabelling of patients' serum samples.

In all of the above instances, either we could not obtain data or we did not use it in the reported results. In some of the above cases, without the interpretation and intervention of a clinical pharmacist, unreliable STC's may have been used for making dosage change decisions by the physicians. Careful analysis of the way in which doses are given and venipunctures are done is necessary to prevent the use of unreliable laboratory values.

An unexpected finding of this study was the lack of utility of both methods in predicting STC's. Because of the variability and lack of precision in predictive utility that was found, parameters that could account for changes observed in both Vd and k_{el}, (maximum temperature and weight changes from the first STC to the second STC a few days later), were examined. These are listed in Table 5. When those patients whose STC's that were underpredicted are compared to those that are overpredicted, visual inspection of the data shows that a positive or negative change in either weight or temperature was not associated with either event. That is, positive and negative changes in weight and

temperature were about equally distributed among patients whose STC's were underpredicted and among those that were overpredicted. Additionally, serum creatinine, albumin, age, sex, or concurrent use of theophylline were not associated with either overprediction or underprediction of STC's.

To determine if any factor could be associated with Vd, Vd values were arranged in descending order, both for the values based on the first set of STC's and the second set of STC's. The corresponding serum albumin concentration, weight change and temperature change were plotted against these values for Vd. Visual inspection of the plots showed no relationship between Vd and these three factors. When patients whose Vd increased over time are compared to those whose Vd decreased over time, and the presence of an increase or decrease in temperature and weight are examined, there is no association between changes in Vd and positve or negative changes in temperature and weight (see Table 5).

In addition, when patients whose k_{el} increased over time are compared to those whose k_{el} decreased over time, and the presence of an increase in temperature or a decrease in temperature is examined, there is no relationship between the change in temperature over time and the change in k_{el}. That is, positive and negative changes in temperature were about equally distributed among patients whose k_{el} increased and among those whose k_{el} decreased.

It was not the objective of this study to examine the reasons for discrepancies between predicted and measured STC's, but the issue will be addressed here. There are several possible explanations for why the STC's obtained may not have been reflective of

the true peak and trough. First, the dose may not have been accurately measured by the pharmacy or completely infused by the nurse. Second, the dose may not have been given at the time recorded by the nurse. Third, perhaps the phlebotomists did not accurately record times of venipunctures. The samples may not have been promptly placed on ice and centrifuged. Variability in the assay itself could account for some variability in the STC's, although not enough (only 3-4%) to account for the large variances from expected that were observed in STC's. Possibly, one-half hour after the infusion still constitutes the distributive phase for some patients,(resulting in elevated STC's), although most of the peak STC's were drawn more than one-half hour after the infusion. Inactivation of tobramycin by the concurrently administered antipseudomonal penicillin is a potential problem, although this is generally a clinically relevant problem only in patients with renal failure.[22] In addition, the TD_x^R assay is probably capable of distinguishing between active and inactive tobramycin,[23] and if any inactivation occurred, it should have been a constant from the first STC set to the second one, as dosing schedules for neither the penicillin nor the tobramycin were changed during the hospital stay.

All of the above factors were possible reasons for the variations seen between predicted versus actual STC's. However, considerable effort was made to decrease the possibility of errors in all of the above factors. Another possible explanation, as to why measured STC's were not as predicted, is that there is a genuine change over time in the pharmacokinetic handling of tobramycin in CF patients over the course of their pulmonary exacerbation. Most subjects showed a striking change in their Vd from about day 2 to day 4 or 5 (SZ method: decrease in mean Vd from 0.54 $\pm$ 0.546 to 0.39 $\pm$ 0.279 l/kg).

Many patients had a change in their k_{el}, although it was less striking than the change in Vd (increase in mean k_{el} from 0.349 $\pm$ 0.098 to 0.371 $\pm$ 0.071 hr^{-1}). Other authors have observed a change in Vd for aminoglycosides in CF patients over time, [11] and wide interpatient variability in Vd.[6,7,9] Kelly states that some patients demonstrated a decrease in Vd with improvement of their exacerbation.[11] Most investigators who have studied aminoglycoside pharmacokinetics in CF have not calculated a second value for Vd from their second set of serum drug concentrations (SDC's)[4-9] and thus it is not known whether Vd changes occurred. However, several authors reported that the SZ method worked fairly well in predicting SDC's, [5-7] thus making it unlikely that changes in Vd occurred unless compensatory changes in k_{el} occurred. MacDonald et. al. studied pharmacokinetics of gentamicin in CF patients who were not in pulmonary exacerabation, and found no increase in Vd over non-CF populations (0.205 l/kg $\pm$ 0.065).[12] They found that Vd did not correlate with weight, percent body fat, severity of CF, age, or plasma clearance. They did find, however, that total plasma clearance did increase as severity of disease increased (as measured by decreases in forced expiratory volume in one second). These were not intrapatient changes over time, but interpatient changes that were plotted against one another. Unfortunately, it's not known if these relatively healthy CF patients had a change in their Vd over time.

If there is a change in CF patients' pharmacokinetic parameters over the course of an exacerbation, what factors could account for this? A change in weight could change the

Vd,[24] but we found no overall significant change in weight (mean decrease of 0.14 kg). An increase in temperature can decrease serum aminoglycoside concentrations,[24] but we found an overall decrease in oral temperature of only 0.13 degrees Centigrade. A decrease in intravascular volume, due to improvement of cor pulmonale during treatment, is a possible explanation, so that Vd could fluctuate with the degree of right sided heart failure.[25] Although Vogelstein et. al. found an increased renal clearance of amikacin in CF,[8] other investigators have not been able to show an increased renal clearance.[5,10] There may be an increased penetration of aminoglycoside into sputum during inflammation of the pulmonary tissues; this penetration may decrease as antibiotic and chest physiotherapy continue.[11] Sputum production may also decrease as the exacerbation lessens. Thus, perhaps nonrenal routes of elimination and nonvascular body compartments of distribution are more important early in the exacerbation than later. Protein binding may be different in CF patients; however, Levy et. al. found no difference in percent of drug bound between patients with CF and controls.[10] They did not state if albumin concentrations were similar in both groups. Albumin concentration was just slightly less than normal in our patients at 3.8 g/dl ($\pm$ 0.46). It is unlikely that albumin concentration would change over a short time, although perhaps other factors affecting protein binding might change over the course of an exacerbation. Another factor which could influence aminoglycoside pharmacokinetics is a change in red blood cell count over time.[24] Finally, an increase in physical activity during the course of the hospitalization may play some as yet undetermined role on the STC. For instance, the effect of posture on plasma volume is often ignored when examining drug concentrations. Warren reports an

increase in theophylline levels in upright subjects, possibly due to the 12-15 % reduction in plasma volume that occurs with standing. [26]

The reason for the change in tobramycin pharmacokinetics over time which we observed is not known. If tobramycin pharmacokinetics change over a period of 4-5 days, do they change significantly upon the patients's subsequent hospital admission one to six months later? The one patient whom we studied on a second hospitalization had completely different pharmacokinetic parameters determined during the second admission. Do CF patients' pharmacokinetic parameters change continually throughout the course of the hospitalization? Should we feel confident that checking one set of peak and trough values per admission (as has been done frequently in the past) can adequately describe and predict pharmacokinetic values for a given patient for their entire hospitalization? One set of STC's is probably not adequate to define a CF patient's pharmacokinetic profile. Is it necessary and cost-effective to frequently check peak and trough values to ensure adequate tobramycin concentrations at all times? This question could only be conclusively answered by a comparative trial of constantly individualized therapy versus high dose, only partly individually dosed aminoglycoside therapy.

CONCLUSIONS

We found no statistically significant difference between the SZ method and the SP method in their utility at predicting STC's in CF patients. The SP method is preferable, because of its ease of use, if one can be assured of accurately collected blood samples. The utility of either method, however, for any given patient with CF, is questionable, given the possible physiologic changes that occur in CF patients during a pulmonary exacerbation of their disease.

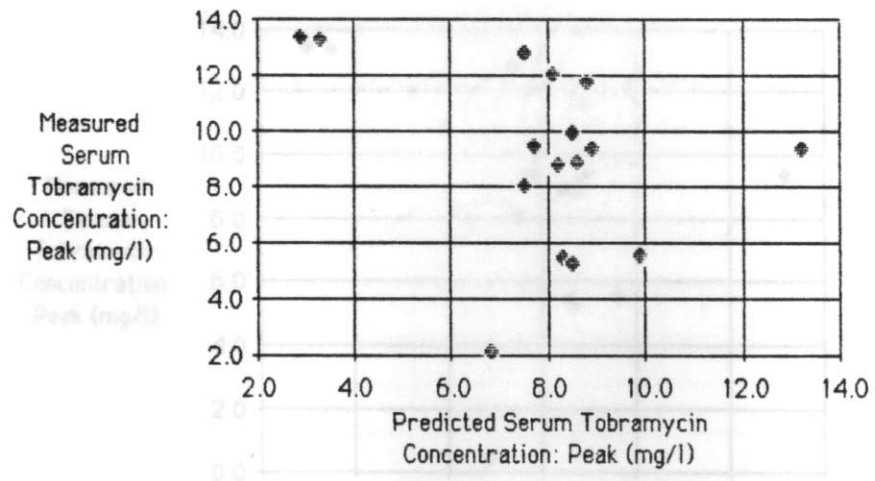

FIGURE 1

PREDICTED VERSUS MEASURED PEAK SERUM TOBRAMYCIN CONCENTRATIONS USING THE SAWCHUK-ZASKE METHOD

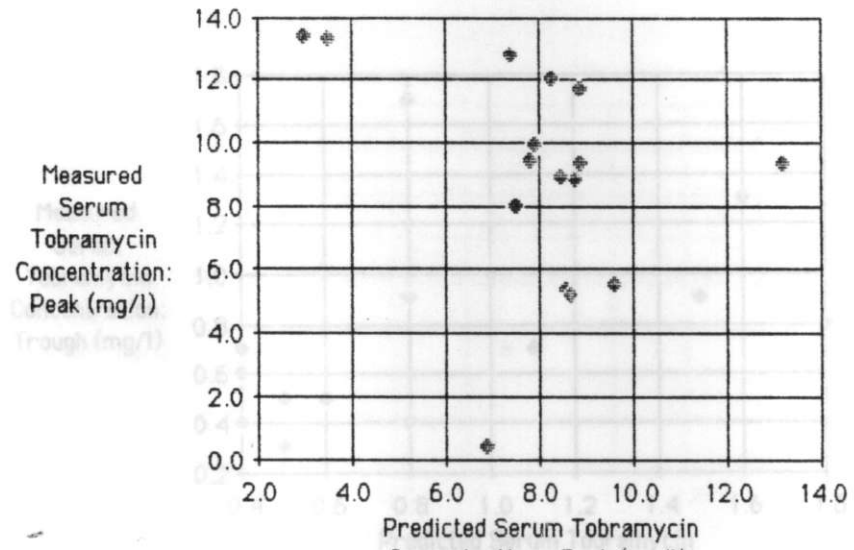

FIGURE 2

PREDICTED VERSUS MEASURED PEAK SERUM TOBRAMYCIN CONCENTRATIONS USING THE SIMPLIFIED PHARMACOKINETICS METHOD

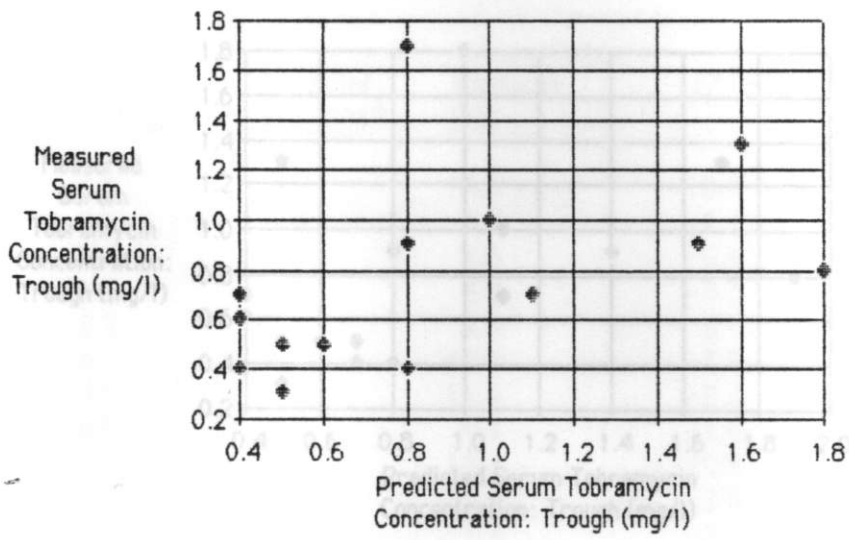

FIGURE 3

PREDICTED VERSUS MEASURED TROUGH SERUM TOBRAMYCIN CONCENTRATIONS USING THE SAWCHUK-ZASKE METHOD

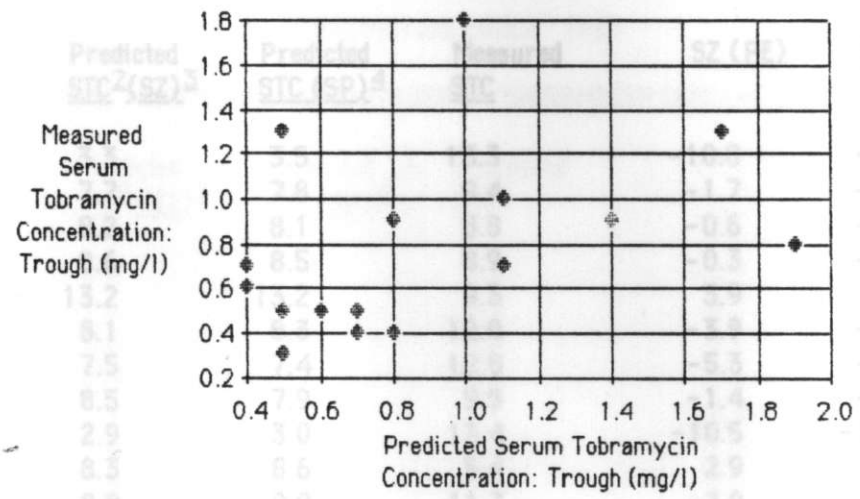

FIGURE 4

PREDICTED VERSUS MEASURED TROUGH SERUM TOBRAMYCIN CONCENTRATIONS USING THE SIMPLIFIED PHARMACOKINETICS METHOD

TABLE 1

PREDICTION ERROR [1] (PE)

THIRTY MINUTE POST-INFUSION SERUM TOBRAMYCIN CONCENTRATIONS

patient number	Predicted STC[2](SZ)[3]	Predicted STC (SP)[4]	Measured STC	SZ (PE)	SP (PE)
1	3.3	3.5	13.3	-10.0	-9.8
2	7.7	7.8	9.4	-1.7	-1.6
3	8.2	8.1	8.8	-0.6	-0.7
4	8.6	8.5	8.9	-0.3	-0.4
5	13.2	13.2	9.3	3.9	3.9
6	8.1	8.3	12.0	-3.9	-3.7
7	7.5	7.4	12.8	-5.3	-5.4
8	8.5	7.9	9.9	-1.4	-2.0
9	2.9	3.0	13.4	-10.5	-10.4
10	8.3	8.6	5.4	2.9	3.2
11	8.8	8.9	11.7	-2.9	-2.8
12	6.8	6.9	2.1	4.7	4.8
13	9.9	9.6	5.5	4.4	4.1
14	8.5	8.7	5.2	3.3	3.5
15	7.5	7.5	8.0	-0.5	-0.5
16	8.9	8.9	9.3	-0.4	-0.4
			Mean	-1.14	-1.13
			S.D.	±4.64	±4.60

1 predicted minus measured serum tobramycin concentrations in mg/l
2 STC = serum tobramycin concentration in mg/l
3 SZ = Sawchuk-Zaske method
4 SP = Simplified Pharmacokinetics method

TABLE 2

PREDICTION ERROR[1] (PE)

ONE MINUTE PRE-INFUSION SERUM TOBRAMYCIN CONCENTRATIONS

patient number	Predicted STC[2] (SZ)[3]	Predicted STC (SP)[4]	Measured STC		SZ (PE)	SP (PE)
1	0.8	1.0	1.7		-0.9	-0.7
2	1.6	1.7	1.3		0.3	0.4
3	0.6	0.6	0.5		0.1	0.1
4	0.4	0.7	0.4		0.0	0.3
5	1.1	1.1	0.7		0.4	0.4
6	1.8	1.9	0.8		1.0	1.1
7	1.5	1.4	0.9		0.6	0.5
8	0.4	0.4	0.7		-0.3	-0.3
9	0.4	0.5	1.4		-1.0	-0.9
10	0.6	0.7	0.5		0.1	0.5
11	0.4	0.4	0.6		-0.2	-0.2
12	0.8	0.8	0.4		0.4	0.4
13	0.5	0.5	0.5		0.0	0.0
14	0.5	0.5	0.3		0.2	0.2
15	0.8	0.8	0.9		-0.1	-0.1
16	1.0	1.1	1.0		0.0	0.1
				Mean	0.04	0.09
				S.D.	±0.50	±0.45

1 predicted minus measured serum tobramycin concentrations in mg/l
2 STC = serum tobramycin concentrtion in mg/l
3 SZ = Sawchuk-Zaske method
4 SP = Simplified Pharmacokinetics method

TABLE 3

VOLUMES OF DISTRIBUTION (l/kg)

patient number		SZ Vd_1*	SZ Vd_2#	SP Vd_1*	SP Vd_2#
1		2.26	0.47	2.69	0.59
2		0.39	0.30	0.45	0.37
3		0.38	0.34	0.51	0.46
4		0.35	0.35	0.48	0.47
5		0.16	0.22	0.20	0.29
6		0.59	0.30	0.68	0.41
7		0.69	0.30	0.81	0.39
8		0.30	0.24	0.42	0.34
9		1.40	0.26	1.68	0.35
10		0.25	0.40	0.32	0.51
11		0.23	0.19	0.31	0.24
12		0.39	1.40	0.47	1.70
13		0.17	0.32	0.26	0.46
14		0.24	0.39	0.32	0.53
15		0.45	0.43	0.56	0.53
16		0.37	0.35	0.47	0.45
	mean	0.539	0.391	0.664	0.506
	S.D.	±0.546	±0.279	±0.641	±0.332

*Vd_1 is calculated based on the first set of STC's

#Vd_2 is calculated based on the second set of STC's

TABLE 4

ELIMINATION RATE CONSTANTS (k_{el}) in $hours^{-1}$

patient number		k_{el} 1*	k_{el} 2#
1		0.28	0.42
2		0.22	0.29
3		0.39	0.41
4		0.43	0.43
5		0.36	0.36
6		0.22	0.40
7		0.23	0.37
8		0.43	0.40
9		0.27	0.35
10		0.37	0.31
11		0.44	0.43
12		0.30	0.22
13		0.58	0.52
14		0.42	0.39
15		0.32	0.31
16		0.32	0.32
	Mean	0.349	0.371
	S.D.	±0.098	±0.071

*measured from first set of serum tobramycin concentrations
#measured from second set of serum tobramycin concentrations

TABLE 5

PREDICTION ERROR FOR PEAK SERUM TOBRAMYCIN CONCENTRATIONS AND CHANGES IN VOLUME OF DISTRIBUTION (Vd), ELIMINATION RATE CONSTANT (kel), WEIGHT, AND MAXIMUM TEMPERATURE

Pt no.	PE[1]	PE[2]	ΔVd[3]	ΔVd[4]	Δkel[5]	Δwt[6]	Δtemp[7]
1	-10.0	-9.7	-1.79	-2.10	0.14	-0.5	0.4
2	-1.7	-1.6	-0.09	-0.08	0.07	-2.7	-0.1
3	-0.6	-0.7	-0.04	-0.05	0.02	0.1	-1.0
4	-0.3	-0.4	0.0	-0.01	0.0	-0.5	-0.8
5	3.9	3.9	0.06	-0.09	0.0	0.0	0.2
6	-3.9	-3.7	-0.29	-0.27	0.18	-0.4	-0.5
7	-5.3	-5.4	-0.39	-0.42	0.14	1.0	-0.7
8	-1.4	-2.0	-0.06	-0.08	-0.03	0.0	-0.07
9	-10.5	-10.4	-1.14	-1.33	0.08	0.1	0.3
10	2.9	3.2	0.15	0.19	-0.06	1.2	-0.1
11	-2.9	-2.8	-0.04	-0.07	-0.01	-0.7	-0.8
12	4.7	4.8	1.01	1.23	-0.08	-0.1	1.4
13	4.4	4.1	0.15	0.20	-0.06	0.03	1.0
14	3.3	3.5	0.15	0.27	-0.03	-0.5	0.8
15	-0.5	-0.5	-0.02	-0.03	-0.01	0.0	-0.5
16	-0.4	-0.4	-0.02	-0.02	0.0	0.7	-0.4
Mean	-1.14	-1.13	-0.148	-0.166	0.022	-0.14	-0.13
S.D.	±4.64	±4.60	±0.605	±0.715	±0.078	±0.87	±0.71

1 PE = prediction error in mg/l for peak serum tobramycin concentrations (STC's) for Sawchuk-Zaske (SZ) method

2 PE = prediction error in mg/l for peak STC's for Simplified Pharmacokinetics (SP) method

3 ΔVd = Vd (in l/kg) calculated based on second set of STC's minus Vd calculated based on first set of STC's using the SZ method*

4 ΔVd = Vd (in l/kg) calculated based on second set of STC's minus Vd calculated based on first set of STC's using the SP method*

5 Δkel = kel (in hours - 1) calculated based on second set of STC's minus kel calculated based on first set of STC's (same for both methods)*

6 Δwt = weight (in kg) on day of second set of STC's minus the weight on day of first set of STC's*

7 Δtemp = maximum temperature in degrees Centigrade (oral) on day of second set of STC's minus maximum temperature on day of first set of STC's*

*second set of STC's were obtained a mean of 68 hours after the first set of STC's

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