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**Prediction of Future Serum Concentrations with Bayesian
Fitted Pharmacokinetic Models: Results with Data
Collected by Nurses versus Trained Pharmacy Residents**

by

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Prediction of Future Serum Concentrations with Bayesian Fitted Pharmacokinetic Models: Results with Data Collected by Nurses versus Trained Pharmacy Residents

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ABSTRACT

Recording the times of dosage administration and serum sampling by trained personnel resulted in significantly greater adherence to the protocol of therapeutic drug monitoring and in significantly greater precision in the achievement of desired serum concentration goals of aminoglycoside therapy than when relatively untrained personnel recorded it as a relatively unemphasized part of their job. This was true even when only data of peak and trough serum concentrations was used. This study demonstrates that thoughtful data collection by appropriately trained nursing, pharmacy, or other clinical personnel is an essential part of therapeutic drug monitoring and plays a significant role in the optimal individualization of drug dosage regimens for patient care.

INTRODUCTION

Despite the introduction of several new classes of antimicrobial agents, the aminoglycoside antibiotics are still recognized as first line therapeutic agents in the management of severe Gram-negative sepsis [1]. It has been shown in several studies that the peak serum concentrations achieved with aminoglycoside therapy correlate with therapeutic response and outcome [2,3]. Toxicity of these agents is determined primarily by the accumulation of the drug in the body [4]. Wide intra- and inter-individual variability of the pharmacokinetic parameter values of these antibiotics make the design of optimal dosage regimens difficult for patients with normal or impaired renal function [5-7]. Aminoglycoside use has been limited by its potential ototoxicity and nephrotoxicity [8]. Results of studies whose goal was to predict toxicity have either been equivocal, not reproduced, or not widely accepted [9-14].

Individualized drug dosage for aminoglycoside therapy now enables one to reduce toxicity [15]. Furthermore, it has been shown that if used with the appropriate methodology, therapeutic drug monitoring is effective in keeping serum concentrations of aminoglycosides within desired ranges, increasing the proportion of patients having effective peak serum concentrations [4,16,17], and in reducing length of hospital stay with a potential cost-saving per patient [18-22].

Monitoring of aminoglycoside therapy can be performed with several different methodologies:

1. Measuring Serum Drug Concentrations: When used without appropriate expertise or software for drug concentration interpretation and modeling, therapeutic drug monitoring based only on raw data of serum concentrations is often ineffective [17].
2. Predictive nomograms [23,24].
3. Linear least squares regression [25].
4. Nonlinear least squares regression [26].
5. Maximum a posteriori probability (MAP) Bayesian fitting [27,28].

For aminoglycoside therapy, the MAP Bayesian method is a rapid and accurate mean of individualizing dosage requirements for patients with diverse pharmacokinetic profiles

[29]. Prediction (and therefore control) of subsequent aminoglycoside serum levels is more precise with Bayesian than with the other methods above [28,30-32]. Moreover, the Bayesian technique has the advantage of requiring fewer (as few as one) serum concentration measurements [33].

Bayesian Fitting for designing individualized dosage regimens to achieve desired therapeutic goals requires the following:

1. Information from clinical descriptors of patient physiology such as body weight, renal function, or cardiac index, data of the administered doses, the starting and stopping infusion times, and the times that serum samples were obtained.

2. Population pharmacokinetic parameter values and their associated errors.

3. Results of the measured drug concentrations and their associated errors.

4. The clinical decision concerning the selection of the appropriate individualized therapeutic goals to be achieved for each patient [34].

It has been shown by Monte-Carlo methods [35], during experimental studies [36], by population pharmacokinetic studies [37], or during routine clinical drug monitoring [38,39] that nonpharmacokinetic and nonclinical factors in the patient's therapeutic environment can affect both the precision of the patient's estimated pharmacokinetic parameter values and the precision with which the desired serum drug levels can be achieved.

The goal of the present study was to compare the predictions of future amikacin serum levels made during two separate studies whose major difference was the method and care with which the clinical data were collected. In one study the clinical data was collected by a trained pharmacy resident; in the other, by pharmacokinetically untrained nurses.

METHODS

We performed a nonrandomized retrospective comparison of predicted serum amikacin concentrations based on Bayesian fitted pharmacokinetic models where the data collection was obtained under two different sets of circumstances.

STUDY 1: RESIDENT COLLECTED DATA (RCD) GROUP: In this group, prospective data collection was done by a trained pharmacy resident specially assigned to this work. Data for the prospective study arose from a multicenter trial of the clinical efficacy and safety of amikacin in elderly patients. The predictive performance of this study has been previously presented [40].

Ten patients in that study were from our center. Dosage adjustments were performed during therapy using the MAP Bayesian method [41]. For this group of patients, from Monday to Friday from 8:30AM to 6:30PM, and on Saturday from 8:30AM until 12:00 noon, information about drug therapy, administered doses, start and stop infusion times and serum sampling times were ordered and collected by a resident specially trained in and assigned to this work. No serum levels were obtained during the week-end. During the night shift and on the week-end, the administered doses and the start and stop infusion times were recorded by nurses.

STUDY 2: NURSE COLLECTED DATA (NCD) GROUP: In this group, prospective data collection was done by the nurses as part of their usual nursing duties. They had no special pharmacokinetic training. This group of subjects consisted of 23 elderly patients treated with amikacin after the end of the RCD study described above. Information about drug therapy was collected by the nurses, and data was transmitted to the pharmacy along with the blood samples. Dosage adjustments were performed using the same MAP Bayesian method. No serum levels were obtained during the week-end. The results of this study have also been presented elsewhere [42].

For both groups, either the resident or the nurses were asked to collect four serum levels for the first set, one just before the infusion, one at 1/2 hour after the end of the 1/2 hour infusion (or at 1 hour after the dose if the dose was given intramuscularly), and one each at 3 and at 6 hours after the end of the 1/2 hour infusion. Preparation of Amikacin doses by nurses, and their administration by minibag via gravity flow, both were done under the same conditions in both studies. For both study groups, each patient had two sets of serum levels obtained. For both groups, the nurses and the residents each were asked to collect four serum levels for the first set as described above. For the second set, four serum levels were also to be obtained, usually 2 to 8 days after the first set, and at the same times as for the first set. For all patients, there was at least one sample in each set obtained 30 minutes after the end of the infusion or one hour after intra-muscular injection (the “peak” value), and one sample just before the next infusion (the “trough” value).

The MAP Bayesian method was used to fit either a one compartment model (B1) or a two compartment model (B2) to the data of the doses and the first set of serum concentrations. The fitted, patient-specific parameter values were found. Each patient’s fitted model was then used to predict prospectively the subsequent serum concentrations which later were achieved on the subsequent dosage regimen he or she received. The relationship between predicted (P) and measured (M) serum concentrations was then examined using a scattergram of the data, by evaluating their correlation coefficient, by calculating the bias or mean weighted error (MWE), and by computing the precision or mean weighted squared error (MWSE), respectively as follows:

$$MWE = \frac{1}{n} \times \sum_{i=1}^n \frac{(P - M)}{SD_i}$$

$$MWSE = \frac{1}{n} \times \sum_{i=1}^n \frac{(P - M)^2}{SD_i^2}$$

where N is the number of serum levels and SD_i is the standard deviation (SD) of each (the ith) observed serum concentration.

In addition, the percentage of serum levels accurately predicted (%SLAP), defined as being centered on the predicted concentration $\pm 20\%$, was determined.

Determination of Amikacin Plasma Concentrations:

Amikacin plasma concentration determinations were performed by the same laboratory for both studies by fluorescence polarization immunoassay (the Abbott TDx System). The error pattern of this assay was described by the following polynomial equation:

$$SD = 0.040987 + 0.021181 C + 0.000087 C^2 + 0.000004 C^3$$

where SD represents the standard deviation of a measurement, C represents the measured serum concentration, and C² and C³ represent the square and the cube of C.

Data Analysis:

In each study, the frequency distribution of the individual weighted errors, (P-M) containing their sign, was found to have a Gaussian distribution. The t-test for differences between the means of two populations was used to evaluate their differences.

However, the weighted squared errors (P-M)² are not normally distributed. The mean weighted squared error (MWSE) for the two groups was therefore compared using the Mann-Whitney U test. In addition, the percent of serum levels accurately predicted, within ± 20 percent, (%SLAP) for each group were compared by Chi-squared analysis. When the expected number in a cell was less than five, the Yates modified Chi-squared test was performed. A p value of 0.05 was chosen to represent a significant difference between groups.

RESULTS

As shown in Table 1, we did not observe any significant difference between the two study groups with respect to sex, age, height, or initial estimated creatinine clearance. However, there was a significant difference between the two groups in the number of serum levels obtained for the first set of serum levels. The RCD group had 4 ± 0 samples obtained in the first cluster, while the NCD group had 3.26 ± 0.45 samples drawn, a significant difference. Even if one were to assume that the SD in the RCD group were to be as high as 0.5, then, using the T Test comparing the means of two populations and the method for small samples, $T = 4.2$, $DF = 31$, and $P < 0.001$ [43]. Further, for the same data, but using the X^2 test instead, as shown in Table I, $X^2 = 12.7$, and also $P < 0.001$.

Table II shows the correlation coefficient (R) between predicted and measured serum levels and the Bayesian predictive performance with the one compartment fitted model for the RCD and the NCD groups. The MWSE was significantly less in the RCD group (64 versus 271 units), and the %SLAP was significantly greater (58% versus 30%).

Table III shows the correlation coefficient (R) between predicted and measured serum levels and the Bayesian predictive performance with the two compartment fitted model for the RCD and the NCD groups. The MWSE here was also significantly less in the

RCD group (82 versus 329 units), and the %SLAP was also significantly greater (72% versus 40%).

Tables IV and V show for the RCD group and the NCD group the percentage of peak (PSLAP) and trough (TSLAP) serum levels accurately predicted in the interval centered on the predicted concentration $\pm 20\%$, obtained respectively with the one compartment (B1) and the two compartment (B2) models. Both PSLAP and TSLAP were greater in the RCD group, significantly so for PSLAP (80% versus 30%) for the B1 model. For the B2 model, both PSLAP and TSLAP again were greater in the RCD group, significantly so for TSLAP (80% versus 26%).

Because there was a significant difference between the two groups in the number of serum levels obtained for the first set of serum levels, the amount of information available for each group might be different. This fact might influence the Bayesian predictive performance and thus confound the comparison, as the group with more levels and information in the first cluster might be able to predict subsequent levels more accurately because of that fact. It was clear, however, as described above, that the NCD group obtained significantly fewer serum levels than did the RCD group, and thus adhered to the desired monitoring protocol significantly less well.

We therefore did another comparison, using only data of peak and trough levels for each patient in each group. The results of this second comparison are shown in tables VI, VII, VII, and IX.

Table VI shows the correlation coefficient (R) between predicted and measured serum levels and the Bayesian predictive performance MWE and MWSE, using the one compartment (B1) fitted model for the RCD and the NCD groups, now employing only data of the peak and trough concentrations in the first set of serum levels. As shown, the errors were all smaller in the RCD group, significantly so for the MWSE (96 versus 367 units), and for the %SLAP (55% accurately predicted versus 27%).

Table VII shows the correlation coefficient (R) between predicted and measured serum levels and the Bayesian predictive performance MWE and MSWE, using the two compartment fitted model for the RCD and the NCD groups, now employing only data of peak and trough concentrations in the first set of serum levels. Again, the errors were significantly smaller for MWSE (111 versus 343 units), and for the %SLAP (58% accurately predicted versus 36%).

Tables VIII and IX show, for the RCD group and the NCD group, using only data of peak and trough concentrations in the first set of serum levels, the percentage of peak (PSLAP) and trough (TSLAP) serum levels accurately predicted in the interval of the predicted concentration $\pm 20\%$, obtained respectively with the one compartment (B1) and the two compartment (B2) models. Both PSLAP and TSLAP were better predicted in the RCD group, although a significant difference was found only for TSLAP in the B2 group (60% accurately predicted versus 13%).

DISCUSSION

It has been customary to emphasize the importance of accurately recording when doses were given, when infusions started and stopped, and when serum levels were drawn. Indeed, the importance of these nonpharmacokinetic factors in permitting or preventing precise achievement of clinically selected serum aminoglycoside therapeutic concentration goals was carefully evaluated in a rigidly controlled study in which Monte-Carlo simulations of a typical clinical scenario with tobramycin therapy were analyzed. In that study, it was shown that the ward care setting, in which the recording of data of dosage administration timing was well or poorly done, was the single most important environmental factor in permitting or preventing precise control of serum aminoglycoside concentrations to achieve specifically selected therapeutic goals, having a greater effect on predictions than the pharmacy (in preparing the doses precisely or not) or the laboratory assay errors [35].

The results of that simulation study are now confirmed and extended by the results of the present clinical study, which show that when trained personnel are used to record the data of dosage administration times and serum sampling times, significantly greater therapeutic precision was obtained in the achievement of the desired therapeutic serum concentration goals associated with aminoglycoside therapy than when untrained nursing personnel recorded the data, and more of the serum levels which should have been obtained were actually drawn. Further, this was true even when only data of peak and trough serum concentrations was used, rather than the full data set.

CONCLUSION

Recording the times of dosage administration and serum sampling by trained personnel resulted in significantly greater adherence to the monitoring protocol and in significantly greater precision in the achievement of desired serum concentration goals of aminoglycoside therapy than when relatively untrained nurses recorded it as a relatively unemphasized part of their job. This was true even when only data of peak and trough serum concentrations was used. This study demonstrates that thoughtful data collection by trained nursing, pharmacy, or other trained clinical personnel is an essential part of therapeutic drug monitoring and plays a significant role in the optimal individualization of drug dosage regimens for patient care.

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Table 1: Patient demographic data for the RCD and NCD groups.

	RCD group	NCD group
Sex male	3(30%)	7 (30.4%)

Female	7 (70%)	16 (69.6%)
Age (yr)	79.1±7.9	81.3 ± 7
Height (m)	1.6 ± 0.15	1.6 ± 0.08
Weight (kg)	58.8 ± 14.4	60.5 ± 12.6
Initial estimated creatinine clearance (ml/mm/1.73m ²)	41.9 ± 15.6	42.5 ± 15
Number of patients with 4 levels in first cluster	10*	6*
Number of patients with ≤ 3 levels in first cluster	0*	17*

All ± data are listed as mean values ± SD.

* $\chi^2 = 12.7$, $P < 0.001$

Table II: Comparison of Predicted Versus Measured Serum Levels in the RCD and NCD Groups Using the MAP Bayesian One-Compartment Fitted Model.

	RCD	NCD	p Value *
R	0.94	0.82	-
MWE	-3.6	-6.6	N.S. **
MWSE	63.9	270.6	<0.05
%SLAP	58%	30%	<0.01

*Comparing the groups

**N.S. = Not significant

R = correlation coefficient

MWE = Mean Weighted Error

MWSE = Mean Weighted Squared Error

%SLAP = percent of Serum Levels Accurately Predicted (within ± 20%).

Table III: Comparison of Predicted versus Measured Serum Levels in the RCD and NCD Groups, Using the MAP Bayesian Two-Compartment Fitted Model.

	RCD	NCD	p Value *
R	0.96	0.81	-
MWE	2.7	-2.3	N.S. **
MWSE	82.1	328.8	<0.05
%SLAP	72%	40%	<0.01

* Comparing the groups

** N.S. = Not Significant

R = correlation coefficient

MWE = Mean Weighted Error

MWSE = Mean Weighted Serum Error

%SLAP = percent of Serum Levels Accurately Predicted (within $\pm 20\%$).

Table IV: Percent of Serum Levels Accurately Predicted (within $\pm 20\%$) in the RCD and NCD Groups, Using the One-Compartment MAP Bayesian Fitted Model.

B1	RCD	NCD	p Value *
PSLAP	80%	30.4%	<0.05
TSLAP	30%	13%	N.S. **

* Comparing the Groups

** N.S. = Not Significant

PSLAP = Peak Levels Accurately Predicted

TSLAP = Trough Levels Accurately Predicted

Table V: Percent of Serum Levels Accurately Predicted (within $\pm 20\%$) in the RCD and NCD Groups, Using the Two-Compartment MAP Bayesian Fitted Model.

B2	RCD	NCD	p Value *
PSLAP	70%	43.5% N.S.	**
TSLAP	80%	26.1% <0.02	

* Comparing the groups

** N.S. = Not Significant

PSLAP = Peak Levels Accurately Predicted

TSLAP = Trough Levels Accurately Predicted

Table VI: New Comparison, Based on Only the Peak and Trough Serum Levels in the First Set, of the Predicted Versus Measured Serum Levels in the RCD and NCD Groups, Using the One-Compartment MAP Bayesian Fitted Model.

	RCD	NCD	p Value *
R	0.92	0.80	-
MWE	-1.49	-5.79	N.S. **
MWSE	96	367	<0.05
%SLAP	55.6%	27.4% <0.04	

*Comparing the groups

** N.S. = Not significant

PSLAP = Peak Levels Accurately Predicted

TSLAP = Trough Levels Accurately Predicted

Table VII: New Comparison, Based on Only the Peak and Trough Serum Levels in the First Set, of the Predicted Versus Measured Serum Levels in the RCD and NCD Groups, Using the Two-Compartment MAP Bayesian Fitted Model.

	RCD	NCD	p Value *
R	0.93	0.79	-
MWE	4.66	-1.7	N.S. **

MWSE	111	343	<0.05
%SLAP	58.3%	35.7%	<0.02

*Comparing the groups

** N.S. = Not significant

PSLAP = Peak Levels Accurately Predicted

TSLAP = Trough Levels Accurately Predicted

Table VIII: New Comparison, Based on Only the Peak and Trough Serum Levels in the First Data Set, of the Predicted Versus Measured Serum Levels in the RCD and NCD Groups, Using the One-Compartment MAP Bayesian Fitted Model.

B1	RCD	NCD	p Value *
PSLAP	60%	30.4%	N.S. **
TSLAP	40%	13%	N.S. **

*Comparing the groups

** N.S. = Not significant

PSLAP = Peak Levels Accurately Predicted

TSLAP = Trough Levels Accurately Predicted

Table IX: New Comparison, Based on Only the Peak and Trough Serum Levels in the First Data Set, of the Percent of Serum Levels Accurately Predicted (within $\pm 20\%$) in the RCD and NCD Groups, Using the Two-Compartment MAP Bayesian Fitted Model.

B2	RCD	NCD	p Value *
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PSLAP	70%	43.5% N.S.	**
TSLAP	60%	13%	0.01

*Comparing the groups

** N.S. = Not significant

PSLAP = Peak Levels Accurately Predicted

TSLAP = Trough Levels Accurately Predicted

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