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Predicted and Measured Aminoglycoside Pharmacokinetic Parameters in Critically Ill Patients

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We conducted a prospective study to determine whether predicted aminoglycoside pharmacokinetic parameters (based on population averages) correlate with measured values in critically ill patients. There was wide interpatient variability for all pharmacokinetic parameters. Only predicted and measured volumes of distribution (18.7 ± 6.5 versus 22.9 ± 7.7 liters [mean ± standard deviation], respectively), with a mean of 0.32 ± 0.09 liter/kg of dosing body weight, were significantly different. There were no relationships between pharmacokinetic parameters and documented infection, death, or intubation status. The results indicate that volume of distribution is commonly underestimated in intensive care unit patients, whereas elimination rates may be adequately predicted based on population averages. We therefore recommend that aminoglycoside volume of distribution estimates for intensive care unit patients take fluid and adipose excess into account and be based on 0.32 liter/kg rather than the usual 0.25 liter/kg.

Successful medical therapy of infections caused by gram-negative organisms within the intensive care unit (ICU) commonly requires the use of aminoglycosides. To rapidly attain the desired serum aminoglycoside concentrations, several dosing nomograms and approaches have been advocated (1, 2). These dosing guidelines rely on pharmacokinetic parameters derived from population averages. Several patient populations (i.e., burn patients, intravenous drug abusers, patients with ascites, patients with cystic fibrosis, etc.) require aminoglycoside doses greater than those derived from these guidelines (4, 5, 16, 17).

The limited studies evaluating aminoglycoside dosing predictions in critically ill patients demonstrated low concentrations in serum and increased volumes of distribution (8, 11, 15). The increases in aminoglycoside volume of distribution may have been at least partially the result of fluid accumulation. The extensive use of aminoglycosides in seriously ill patients and lack of data accounting for fluid accumulation in the characterization of aminoglycoside disposition prompted us to prospectively study the accuracy of predicting aminoglycoside pharmacokinetic parameters in this patient population.

We prospectively evaluated 20 patients with suspected or documented infections within the medical or surgical ICU who were receiving any aminoglycoside either alone or in combination. Patients were excluded if they had fewer than three timed serum aminoglycoside concentrations obtained around the dose being studied or fewer than two concentrations obtained after dose 1. Data necessary to estimate aminoglycoside disposition and factors which may alter aminoglycoside pharmacokinetic parameters were collected. Information collected included age, sex, height, usual and current weight, maximum temperature, intubation status, serum creatinine, blood urea nitrogen, 24-h fluid balance, positive or negative bacteriologic cultures, and whether the patient was discharged alive from the ICU.

One serum sample for aminoglycoside assay was obtained before the beginning of the infusion unless the dose being studied was dose 1. Two samples were obtained in the postdistributive phase. Postdistributive sample 1 was obtained approximately 30 min after an approximately 30-min timed infusion. Postdistributive sample 2 was obtained approximately one predicted half-life after the end of the drug infusion. Actual sample times and infusion periods were used in all calculations. All samples were refrigerated and assayed within 24 h of collection or within 4 h if the patient was concomitantly receiving a semisynthetic penicillin. Aminoglycoside serum concentrations were determined by radioimmunoassay (ranges of sensitivity: gentamicin-tobramycin, 0.25 to 16.0 μg/ml; amikacin, 2.5 to 40 μg/ml; coefficients of variation: gentamicin-tobramycin, 4 to 5.5%; amikacin, 7 to 8%; American Biochemical, Portland, Oreg.).

The predicted aminoglycoside pharmacokinetic parameters were the volume of distribution in the central compartment (V_{1p}), elimination rate constant (k_{elp}), and clearance (CL_p). The V_{1p} was determined based on the weight of the patient adjusted for excess adipose tissue and fluid excess, if necessary. The usual dry weight for each patient was determined by either history or chart review. If the dry weight was less than the ideal body weight of the patient, 25% of the dry weight was used as the V_{1p} (12). Signs and symptoms of fluid excess, along with fluid input-output records and trends in documented weights, were assessed to determine whether the patient was fluid overloaded. Each kilogram of fluid gain was added as 1 liter to the dry-weight V_{1p}. If fluid accumulation could not be documented, and the weight of the patient was greater than the ideal body weight, the excess weight was assumed to be adipose tissue. The total amount of adipose tissue was multiplied by 0.125 and added to the dry-weight V_{1p} (12).

Estimates of creatinine clearance were generated by using the method of Jelliffe and Jelliffe (3). Aminoglycoside k_{elp} was determined as follows: k_{elp} = (0.003 × creatinine clearance) + 0.01. Aminoglycoside CL_p was calculated as the product of V_{1p} and k_{elp}.

Specific patient aminoglycoside pharmacokinetic parameters were determined from the measured serum aminoglyco-

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TABLE 1. Patient characteristics

Parameter	Value
V_1 adjustments (no. of patients)	
Fluid	8
Adipose	1
Both	4
Neither	7
Bacteriologic culture positive (no. of patients)	9
Intubated and mechanically ventilated (no. of patients)	14
ICU survivors (no.)	8
Time aminoglycoside concn obtained (min; mean ± SD)	
Before infusion	6.2 ± 12.7
Drug infusion period	31.1 ± 10.8
Peak after end of infusion	45.5 ± 39.1
Concn 3 obtained:	
After at least 1 measured $t_{1/2}$[a] elapsed (no. of patients)	13
Before 1 measured $t_{1/2}$ elapsed (no. of patients)	7
Mean $t_{1/2}$ (h; mean ± SD)	11.3 ± 7.2
Mean time level obtained (h; mean ± SD)	5.8 ± 4.8
Mean calculated creatinine clearance (ml/min per 1.73 m^2; mean ± SD)	47.3 ± 26.8

[a] $t_{1/2}$, Half-life.

side concentrations. Each patient's measured volume of distribution in the central compartment (V_{1m}) and measured elimination rate constant (k_{elm}) were calculated using non-steady-state-dependent equations assuming a one-compartment, first-order elimination model (13, 14). Pre- and postdose concentrations were extrapolated to actual trough and peak concentrations. The measured aminoglycoside clearance (CL_m) was determined by the product of V_{1m} and k_{elm}.

All results are expressed as the mean ± standard deviation. Statistical analysis was conducted using a two-tailed paired Student t test and stepwise multiple linear regression analysis.

The study group consisted of 20 patients (11 of them men; 12 of them medical ICU patients) with a mean age of 68.0 ± 15.1 years. Seventeen patients received gentamicin, two patients received amikacin, and one patient received tobramycin. Additional patient demographic information is shown in Table 1.

Wide interpatient variability occurred with each measured and predicted pharmacokinetic parameter (Table 2). The only significant difference observed was between V_{1p} and V_{1m}. The mean V_{1m} as a function of dosing body weight, accounting for adipose tissue and fluid accumulation, was 0.32 ± 0.09 liter/kg.

The correlation between predicted and measured V_1 values was $r^2 = 0.43$ (Fig. 1), with the regression line being far removed from the line of identity. The relationship between V_{1m} and V_{1p} was very good in 5 patients (V_{1m} and V_{1p} difference, <20%) and poor in 15 patients (in 13 patients, V_{1m} was ≥120% of V_{1p}; in 2 patients, V_{1p} was ≥120% of V_{1m}).

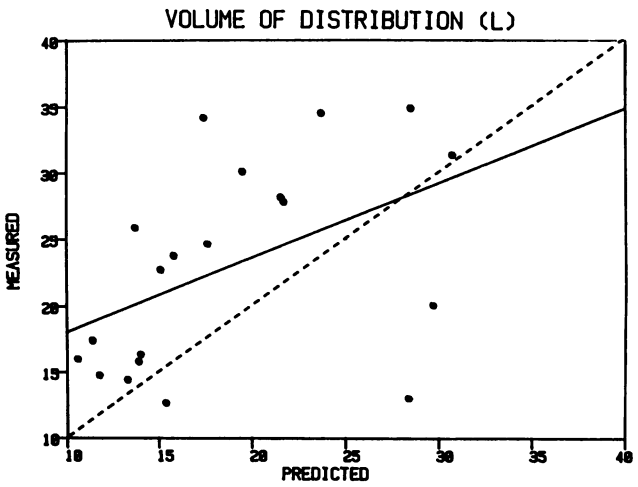

FIG. 1. Measured and predicted V_1 values ($r^2 = 0.43$). - - - - -, Line of identity; ——, linear regression.

These findings indicate a tendency to underpredict the V_1 in most ICU patients.

Although wide interpatient variability was observed between k_{elp} and k_{elm}, the regression line is very similar to the line of identity ($r^2 = 0.76$; Fig. 2). The relationship between measured and predicted k_{el} values was maintained regardless of the degree of renal insufficiency demonstrated by the patients studied. The regression line between CL_p and CL_m ($r^2 = 0.64$; Fig. 3) is similar to the line of identity. The relationship between CL_m and CL_p was very good in 6 patients (CL_m and CL_p difference, <20%) and poor in 14 patients (in 11 patients, CL_m was ≥120% of CL_p; in 3 patients, CL_p was ≥120% of CL_m). In most patients, CL was underpredicted. This was due to the underprediction of V_1, since the CL was the product of V_1 and k_{el}.

The presence of a documented infection, intubation with mechanical ventilation, or death in the ICU did not significantly correlate with the ability to accurately predict any pharmacokinetic parameter. A trend ($P < 0.08$) was found between intubated patients and V_1. Of the 13 patients whose V_{1m} was greater than 120% of the V_{1p}, 11 patients (85%) were intubated and 2 patients (15%) were not intubated.

Plasma aminoglycoside concentrations have been associated with efficacy in various disease states. Moore et al. (9, 10) recently evaluated all patients with gram-negative infections from four well-controlled trials of gentamicin, tobramycin, and amikacin. In addition to other factors, 1-h postinfusion peak concentrations of greater than 5 μg of gentamicin or tobramycin per ml and of greater than 20 μg of amikacin per ml produced significant decreases in mortality from gram-negative bacteremia. The association between aminoglycoside serum concentration and a beneficial outcome occurred with the initial aminoglycoside peak and was maintained throughout the course of therapy. A strong association between therapeutic outcome and a higher max-

TABLE 2. Measured and predicted pharmacokinetics[a]

Parameter	V_1 (liters)	k_{el} (h^{-1})	CL (ml/min)
Predicted	18.7 ± 6.5[b] (10.6–30.7)	0.148 ± 0.08 (0.052–0.385)	43 ± 22 (12–89)
Measured	22.9 ± 7.7[b] (12.7–34.9)	0.154 ± 0.1 (0.029–0.396)	54 ± 30 (10–109)

[a] Values are means ± standard deviation. Ranges are given in parentheses.
[b] $P < 0.05$.

imal peak concentration above the MIC was also found in a variety of gram-negative bacterial infections. These data document that the initial aminoglycoside concentration is a major determinant of clinical response. Clinicians need to rapidly attain acceptable aminoglycoside serum concentrations with dose 1.

Our results demonstrate that the regression relationship between V_{1p} and V_{1m} is poor. In the seriously ill medical or surgical ICU patient, estimation of V_1 is consistently underpredicted using standard population average parameters, even when fluid accumulation and adipose tissue are accounted for. The underestimation of V_1 may produce less-than-desired aminoglycoside serum concentrations and may result in suboptimal therapy and clinical failure (9, 10).

There is little data examining the predictability of aminoglycoside dosing in critically ill patients (8, 11, 15; J. F. Dasta and D. K. Armstrong, Abstr. Soc. Crit. Care Med. 15th Annu. Educ. Sci. Symp. Crit. Care Med. **14**:393, 1986; R. F. P. Cheung, J. M. Patrias, J. T. DiPiro, K. A. Michael, J. R. May, E. L. Hall, and R. C. Treat, Abstr. 7th Annu. Meet. Am. College Clin. Pharm., abstr. no. 4, 1986). The mean V_1 values in these studies were consistently greater (0.20 to 0.36 liter/kg) than population averages. All of the above-mentioned reports attributed the larger V_1 values at least partially to fluid accumulation. Unfortunately, it was not stated whether any of the researchers accounted for fluid excess in their calculations. In contrast, one group of investigators demonstrated a good correlation between measured and predicted peak (r^2 = 0.94) and trough (r^2 = 0.87) gentamicin serum concentrations in trauma patients (7).

The exact cause of altered aminoglycoside distribution in the critically ill patient is not known. A number of physiologic alterations in these patients (i.e., activated complement cascade, polymorphonuclear leukocytes, prostaglandins, leukotrienes, etc.) may induce endothelial damage, promoting increased capillary permeability and interstitial edema formation throughout the microcirculation (6). Although these effects may not be clinically detectable, a change in the ratio between interstitial and total body fluid may occur, resulting in a larger observed V_1 than predicted.

The estimated k_{el}, and therefore half-life, appears to be adequately predicted in seriously ill patients using accepted population averages and equations. Therefore, aminoglycoside-dosing protocols are relatively reliable in determining the dosing interval in this patient population.

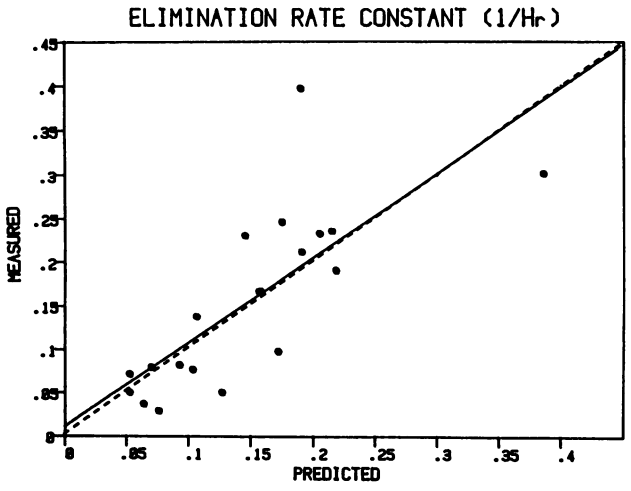

FIG. 2. Measured and predicted k_{el} values (r^2 = 0.76). - - - - -, Line of identity; ——, linear regression.

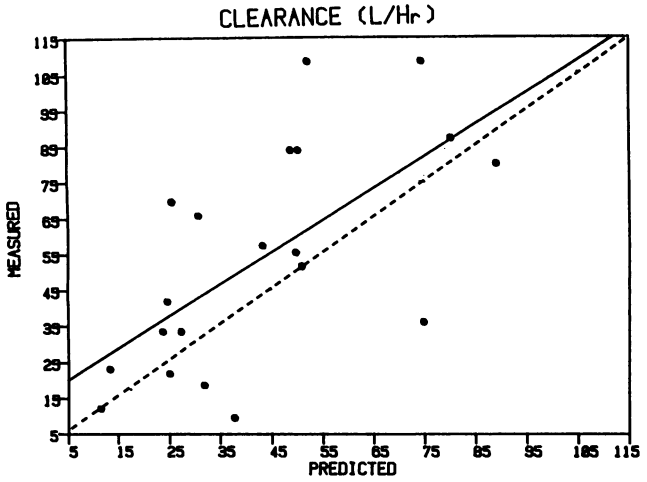

FIG. 3. Measured and predicted CL values (r^2 = 0.64). - - - - -, Line of identity; ——, linear regression.

On the basis of our findings, we recommend that initial aminoglycoside dosing predictions be calculated using a V_1 of 0.32 liter/kg of the dosing weight, taking fluid and adipose tissue into account as described above. The k_{el} may be calculated based on available population averages. Serum aminoglycoside concentrations should be obtained within the first 24 to 48 h to ensure that the desired concentrations are being attained. In the small number of patients in whom the V_{1m} is much less than the V_{1p} (10% in the present series), high serum aminoglycoside concentrations may occur. However, those patients will be identified by attaining serum aminoglycoside concentrations within the first 48 h of therapy. The dose may then be adjusted with little risk of toxicity (12).

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