0090-3493/87/1512-1143$02.00/0
CRITICAL CARE MEDICINE
Copyright © 1987 by The Williams & Wilkins Co.
Vol. 15, No. 12
Printed in U.S.A.

brief report

Inadequacy of standard aminoglycoside loading doses in acutely ill patients

LAKSHMIPATHI CHELLURI, MD; MICHAEL S. JASTREMSKI, MD

The outcome from Gram-negative sepsis is clearly dependent on the adequacy of the initial antibiotic therapy. Even the appropriate antibiotics begun expeditiously will not be effective unless adequate doses are administered. For example, in 89 patients with Gram-negative bacteremia reported by Moore et al. (1), mortality was only 2.4% in patients with peak aminoglycoside concentrations >5 μg/ml one hour after a maintenance dose, but rose to 20.9% in patients with peak concentrations <5 μg/ml. Since aminoglycosides penetrate the lung poorly, even higher concentrations, in the 6 to 10-μg/ml range, are necessary for the successful treatment of Gram-negative pneumonia (2–4).

Summer et al. (5) have shown that a 2-mg/kg loading dose of gentamicin or tobramycin gave unpredictable and usually low early concentrations in a group of critically ill septic subjects; however, they did not determine if there was a cumulative effect from subsequent maintenance doses that eliminated this problem. This study was undertaken to determine if an early peak aminoglycoside concentration after the loading dose could be used to predict peak concentrations after several maintenance doses, the time when concentrations are traditionally first determined.

PATIENTS AND METHODS

The study population consisted of 13 critically ill patients in our medical-surgical ICU, with 14 presumed episodes of Gram-negative sepsis. The diagnosis of sepsis was based on the clinical findings of fever or hypothermia, tachycardia, tachypnea, hypoperfusion, and an identifiable infectious focus. In all cases, antibiotic therapy was begun empirically before the culture results became available.

All patients received gentamicin or tobramycin using the method of Hull and Sarubbi (6). Their technique recommends a 2-mg/kg of lean body weight loading dose given as a half-hour iv infusion. For obese subjects, weight was corrected for height to obtain ideal body weight (7). Maintenance doses and dosing intervals were then calculated based on the patient's measured serum creatinine level using the nomogram of Hull and Sarubbi (6). All aminoglycoside doses were administered iv by gravity over 30 min. In patients receiving additional antibiotics, those antibiotics were administered at different times so as to avoid interaction between aminoglycosides and other antibiotics. Serum was drawn 30 min after the end of the loading dose and 30 min after the end of the third maintenance dose for measurement of peak aminoglycoside concentrations by the fluorescent immunoassay technique (Optimate, Ames Division, Miles Laboratories, Elkhart, IN). The coefficient of variation was 4% for a control value of 6 μg/ml. Deterioration in renal function was defined as an increase in creatinine of 0.5 mg/dl if the initial value was less than 3 mg/dl or an increase of 1 mg/dl if the initial value was 3 mg/dl or greater (4). Volume of distribution was calculated based on trough and peak aminoglycoside concentrations drawn around the third maintenance dose (8).

The results were expressed as mean ± SD. The Pearson correlation coefficient was used to analyze the data, with $p < .05$ considered significant.

RESULTS

The mean total loading dose given to these patients was 136 ± 19.6 or 1.94 ± 0.22 mg/kg of lean body weight. Figure 1 shows the regression line comparing the total loading dose with the peak aminoglycoside concentration obtained 30 min after the loading infusion. The total loading dose did not correlate with the early 30-min aminoglycoside concentration ($r = .34$, $p > .05$). Ten of the 14 patients had early peak concentrations <6 μg/ml, and three patients had concentrations <5 μg/ml. The loading dose adjusted to lean body weight also did not correlate with the peak concentration one half-hour after the loading dose ($r = .03$, $p > .05$).

There was a good correlation between the early postinfusion peak concentration and the peak concentration after the third maintenance dose in the ten patients who received the third maintenance dose ($r = .76$, $p < .01$; Fig. 2). It should be noted that eight of

From the Department of Critical Care and Emergency Medicine, SUNY Health Science Center at Syracuse, Syracuse, NY.

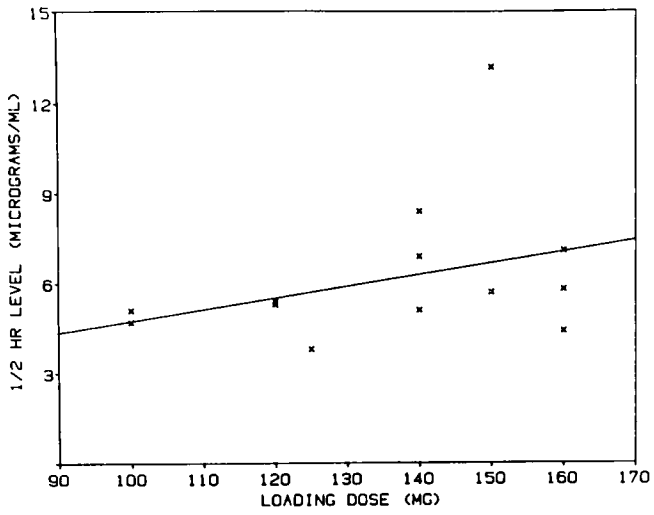

FIG. 1. Total loading dose of tobramycin/gentamicin vs. level one-half hour after administration of loading dose (r = .34, $p > .05$).

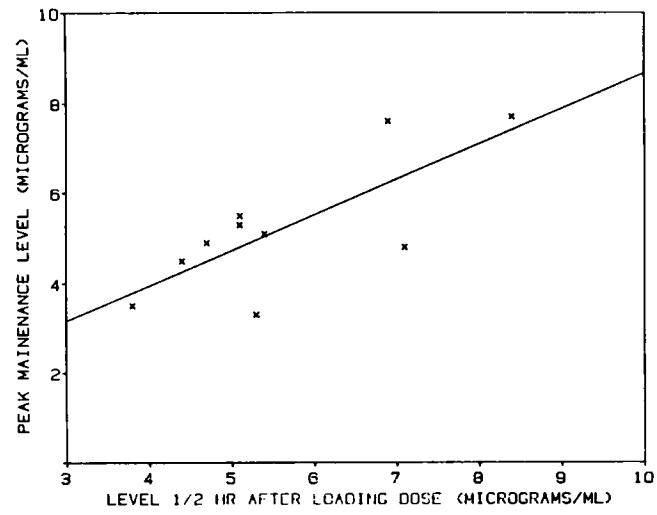

FIG. 2. Tobramicin/gentamicin concentration one-half hour after infusion of loading dose vs. maintenance peak level (r = .76, $p < .01$).

these ten patients had peak concentrations <6 μg/ml after the third maintenance dose. The volume of distribution of tobramycin/gentamycin was 0.37 ± 0.13 L/kg (range 0.2 to 0.6).

In patients 1 and 13, there was a significant change in serum creatinine during the 48 h after the loading dose. In patient 1, serum creatinine increased from 1.4 to 2.7 mg/dl, while in patient 13, it decreased from 3.4 to 1.3 mg/dl. In the other patients, there was no significant change in renal function as defined in *Patients and Methods* or based on daily urine output.

DISCUSSION

Gram-negative sepsis is a commonly encountered problem in the emergency department and ICU. Since approximately 50% of the fatalities from Gram-negative sepsis occur in the initial 24 h, early adequate antibiotic therapy is an important part of the initial management (1, 9). Previous studies have shown that survival correlates with the aminoglycoside concentrations in Gram-negative infections. Peak concentrations >5 μg/ml are associated with an improved survival in Gram-negative sepsis (1, 2). Peak concentrations of 8 to 10 μg/ml are necessary in Gram-negative pulmonary infections because of the poor penetration of aminoglycosides into the lungs (3, 4). This study confirms the finding of Summer and co-workers (5) that a 2-mg/kg of lean body weight loading dose of gentamicin or tobramycin cannot be expected to reliably produce adequate peak concentrations in acutely septic patients.

Previous work from several other authors (10–14) shows that the most likely explanation for the low peak serum concentrations of aminoglycosides in acutely septic patients relates to an expanded volume of distribution for aminoglycosides. Table 1 shows that most of our patients were in positive fluid balance over the study period, with increased volume of distribution. Only patients 6, 8, and 9 were in negative fluid balance during the study period, and two of these three patients had adequate peak aminoglycoside concentrations. Since serum creatinine and urine output did not change significantly in eight of our ten patients, it is unlikely that this was a factor. In addition, it is more likely that any changes in renal function that do occur in the critically ill will be deteriorations due to hypoperfusion of the kidneys, which would be expected to cause aminoglycoside concentrations to increase.

In view of the problems with presently available aminoglycoside dosing nomograms (1, 15), our finding that the early peak concentration after the loading infusion predicts subsequent peak concentrations after the maintenance doses has important therapeutic im-

TABLE 1. Pharmacokinetic data

Patient No.	Loading Dose (mg)	Intake and Output (ml)[a]	Peak Aminoglycoside Concentrations (μg/ml)[b]	Volume of Distribution (L/kg)
1	150	5,089/2,056	5.7/NA	NA
2	150	5,280/3,143	13.2/NA	NA
3	160	5,355/3,224	4.4/4.5	0.39
4	100	6,660/4,716	4.7/4.9	0.30
5	100	6,140/3,643	5.1/5.5	0.4
6	160	6,150/11,415	7.1/4.8	0.41
7	120	12,715/6,969	5.4/5.1	0.41
8	140	5,812/6,936	5.1/5.3	0.5
9	140	2,040/5,420	8.4/7.7	0.2
10	160	16,640/11,460	5.8/NA	NA
11	125	7,500/5,850	3.8/3.5	0.6
12	120	5,397/3,825	5.3/3.3	0.22
13	140	8,935/3,315	5.1/NA	NA
14	140	5,375/4,989	6.9/7.6	0.26

[a] Intake and output 24 h before administration of aminoglycosides to 24 h after loading dose.

[b] One-half hour after loading dose/maintenance peak concentration.

NA = not available.

plications. We would recommend that the first peak aminoglycoside concentration be obtained at this time, 30 min after the end of the loading dose, rather than after the third maintenance dose, with additional concentrations obtained before the second dose, so that other pharmacokinetic variables can be calculated and dosage adjustments can be made accordingly in these acutely septic patients. Additional studies need to be undertaken, using larger loading doses and maintenance doses, to develop a more accurate dosing approach in the acutely septic patient.

REFERENCES

1. Moore RD, Smith CR, Lietman PS: The association of aminoglycoside plasma levels with mortality in patients with Gram-negative bacteremia. *J Infect Dis* 1984; 149:443
2. Noone SP, Parsons TMC, Pattison JR, et al: Experience in monitoring gentamicin therapy during treatment of serious Gram-negative sepsis. *Br Med J* 1974; 1:477
3. Alexander MR, Shoell J, Hicklin G, et al: Bronchial secretion concentrations of tobramycin. *Am Rev Respir Dis* 1982; 125:208
4. Moore RD, Smith CR, Lietman PS: Association of aminoglycoside plasma levels with therapeutic outcome in Gram-negative pneumonia. *Am J Med* 1984; 77:657
5. Summer WR, Michael JR, Lipsky JJ: Initial aminoglycoside levels in the critically ill. *Crit Care Med* 1983; 11:948
6. Hull JH, Sarubbi FA: Gentamicin serum concentration: Pharmacokinetic predictions. *Ann Intern Med* 1976; 85:183
7. Schwartz SN, Pazin GJ, Lyon JA: A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. *J Infect Dis* 1978; 138:499
8. Ng PK: Determining aminoglycoside dosage and blood levels using a programmable calculator. *Am J Hosp Pharmacol* 1980; 37:225
9. Kreger BE, Craven DE, McCabe WR: Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. *Am J Med* 1980; 68:344
10. Zaske DE, Cipolle RJ, Strate RJ: Gentamicin dosage requirements: Wide interpatient variations in 242 surgery patients with normal renal function. *Surgery* 1980; 87:164
11. Kaye D, Levison ME, Labovitz ED: The unpredictability of serum concentrations of gentamicin: Pharmacokinetics of gentamicin in patients with normal and abnormal renal function. *J Infect Dis* 1974; 130:150
12. Zaske DE, Cipolle RJ, Strate RG: Increased gentamicin dosage requirements: Rapid elimination in 249 gynecology patients. *Am J Obstet Gynecol* 1981; 139:896
13. Dasta JF, Armstrong DK: Variability in aminoglycoside pharmacokinetics in critically ill surgical patients. Abstr. *Crit Care Med* 1986; 14:393
14. Hassan E, Ober J: Predicted and measured aminoglycoside pharmacokinetics parameters in critically ill patients. Abstr. *Crit Care Med* 1986; 14:394
15. Platt DR, Matthews SJ, Sevka MJ, et al: Comparison of four methods of predicting serum gentamicin concentrations in adult patients with impaired renal function. *Clin Pharacokinet* 1982; 1:361