Correlation of Aminoglycoside Dosages with Serum Concentrations During Therapy of Serious Gram-Negative Bacillary Disease

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Received for publication 23 February 1979

We prospectively evaluated serum aminoglycoside (AMG) concentrations in 120 patients who received gentamicin or tobramycin for serious gram-negative bacillary disease. AMG serum concentrations were assayed by microbiological and radioimmunoassay techniques. Correlation between the two assay methods was good. When AMG doses were based on total body weight, there was no significant correlation between AMG dosage administered and serum concentrations in patients with either normal or abnormal renal function. The use of ideal body weight for calculation of AMG dosage improved this correlation significantly except in hemodialysis patients. AMG-induced nephrotoxicity occurred in 13 patients. No significant association was noted between the occurrence of toxicity and the specific AMG given or with other commonly recognized risk factors. Among study groups, peak AMG serum concentrations failed to exceed the minimal inhibitory concentration of the infecting organism in 17 to 33% of the cases. Serum inhibitory levels of $\geq 1:8$ were not associated with improved survival. There was no significant difference in mortality between the gentamicin- and tobramycin-treated groups. We advise base-line serum AMG levels in seriously ill patients with gram-negative bacillary disease and additional bacteriological studies in selected situations.

A major factor limiting the use of aminoglycoside (AMG) antibiotics is their narrow therapeutic-toxic ratio, particularly as it relates to the occurrence of nephro- and ototoxicity. A number of studies have suggested a relationship between toxicity and elevated AMG serum concentrations (9, 10, 12, 14, 20). In addition, attempts have been made to correlate "therapeutic" AMG serum concentrations with clinical efficacy (16, 24). However, many commonly used AMG dosage schedules do not give predictable AMG serum concentrations. Moreover, there is no general consensus on the optimal dosage in milligrams per kilogram per day and the most precise method for adjustment of dosage interval based on the variation in the renal function of a patient. Serum creatinine, measured creatinine clearance, "calculated" creatinine clearance, and computer-assisted techniques have been utilized in the development of formulas and/or nomograms for dosage regimens which vary either (i) the dosage interval (variable frequency regimen) or (ii) the dose which is given at the standard interval of every 8 h (variable dosage regimen).

We performed a prospective clinical study to evaluate two commonly used AMGs, gentamicin

and tobramycin, in patients with serious gram-negative bacillary disease. Our objectives were: (i) to assess the relationship between AMG dosage and achieved serum concentrations with several currently used dosage regimens in patients with normal and impaired renal function, (ii) to compare serum concentrations obtained with the minimal inhibitory concentration (MIC) of antibiotic against the infecting organism, and (iii) to determine the effect of carefully controlled serum concentrations on efficacy and toxicity.

(These results were presented in part at the 10th International Congress of Chemotherapy, Zurich, Switzerland, 18-24 September 1977.)

MATERIALS AND METHODS

Clinical material. A total of 120 patients were enrolled in the study; these patients were hospitalized at the University of Alabama Medical Center between September 1976 and July 1977. Requirements for admission to the study were: (i) age of >16 years and (ii) documented or suspected gram-negative bacillary disease (i.e., bacteremia, peritonitis, pneumonia, meningitis, or soft tissue infection) for which an AMG appeared appropriate for initial therapy. Of the 120 patients 104 (87%) were treated with at least one other

antibiotic in addition to the AMG during the period of treatment. No patients with urinary tract infection alone were studied.

Patients were identified for study by two methods: (i) daily surveillance of all positive blood and cerebrospinal fluid cultures in the clinical laboratories and (ii) daily review of pharmacy records of patients begun on AMGs during each preceding 24-h period. Patients receiving an AMG for <24 h were placed into the study group appropriate for their renal function (see below). The remaining patients (i.e., those not previously begun on AMG treatment) were assigned by pair randomization to gentamicin or tobramycin within the appropriate study group based on renal function. Informed consent was obtained in each instance.

Patients were grouped according to pretreatment renal function; a normal serum creatinine was defined as ≤ 1.3 mg/100 ml. Equal numbers of patients within each group received gentamicin and tobramycin. The patient groups and AMG dosage regimens are given in Table 1.

All dosages of AMG were based on total body weight. AMG dosage in group IA was determined by the attending physician (within the range noted in Table 1), and dosage alterations in this group were made solely for peak levels of >10 μ g/ml. These 30 patients are considered a control group in our data analysis. In all other groups, we determined AMG dosage, and doses were changed in an attempt to (i) maintain peak concentrations in the therapeutic range of 4 to 10 μ g/ml, (ii) optimize peak levels with respect to the MIC of the infecting pathogen and the inhibitory capacity of the serum of the patient when these data were readily available, and (iii) maintain trough concentrations of <2.0 μ g/ml.

Serum aminoglycoside concentration determinations. Peak and trough serum gentamicin or tobramycin levels were obtained for each patient. Peak levels were obtained 15 min after an intravenous infusion or 1 h after an intramuscular injection. Trough levels were obtained 1 h before the next dose of AMG.

The number of levels determined for each patient was based on the duration of AMG therapy. Levels were obtained during the first study day and subsequently every 2 to 3 days while the patient remained on AMG therapy. Each serum specimen was assayed by two methods: (i) a microbiological assay utilizing the agar well diffusion technique and *Bacillus globigii* as the test organism (33), and (ii) a radioimmunoassay using a commercially marketed assay kit with 125 I as the radioactive label (Monitor Science). The microbiological assay was performed daily, and the appropriate beta-lactamase was added to serum specimens from patients receiving concurrent therapy with pen-

icillins or cephalosporins. Sera were run in triplicate, and plates were read after an overnight incubation. The assay value used in data analysis represents the mean of the three assay results per specimen. The radioimmunoassay was performed every 2 to 3 weeks on specimens which had been refrigerated at -40°C . Samples were run in duplicate, and a standard curve was constructed for each group of sera.

Bacteriology. Disk susceptibility testing was performed on all isolates by the standardized Kirby-Bauer technique (4). The MIC and the minimum bactericidal concentration of the appropriate AMG were determined by the broth dilution technique, using brain-heart infusion broth (32). Sera from specimens containing peak AMG concentrations were used to perform serum inhibitory and serum bactericidal assays by a modification of the method of Schlichter, utilizing brain-heart infusion broth (2), in those patients from whom a gram-negative bacillus was isolated. These serum assays were performed during the first few days of treatment and at approximately 4 to 5-day intervals for patients who received prolonged AMG therapy.

Monitoring of toxicity. Base-line blood urea nitrogen, creatinine, and urinalysis were obtained for all patients before the initiation of antibiotic therapy. During the treatment period, these tests were repeated every 2 to 3 days. These values were used in the adjustment of dosage intervals in patients with abnormal renal function. Nephrotoxicity was defined as an increase in serum creatinine of ≥ 0.5 mg/100 ml over the pretreatment value during or immediately after AMG therapy. Nephrotoxicity was judged to be AMG induced if there was no other clinically evident cause, such as significant hypotension, septic shock, hepatorenal syndrome, etc. Nephrotoxicity risk factors assessed for each patient included the following: (i) peak serum concentrations of >10 μ g/ml, (ii) trough serum concentrations of >2 μ g/ml, (iii) volume depletion determined either by clinical parameters (i.e., gastrointestinal bleeding, excessive diuresis, etc.) or by measurement of cardiovascular pressure or pulmonary artery pressures, (iv) concurrent therapy with cephalosporins or furosemide, (v) prior AMG therapy of >3 days, and (vi) underlying renal disease with pretreatment serum creatinine of >1.3 mg/100 ml.

Ototoxicity was monitored clinically by inquiring about symptoms of auditory or vestibular dysfunction. Whenever feasible, base-line and posttreatment audiometry were performed. However, because of logistical problems and the critical nature of the illnesses of many patients, pre- and posttreatment audiograms were obtained on only 12 patients. Therefore, we have excluded an assessment of ototoxicity from the discussion which follows.

TABLE 1. Patient groups and dosages

Group	No. of patients	Renal function	Aminoglycoside dose ^a
IA	30	Creatinine ≤ 1.3 mg/100 mg	1.0–1.5 mg/kg q8h
IB	30	Creatinine ≤ 1.3 mg/100 mg	1.5 mg/kg q8h
IIA	20	Creatinine > 1.3 mg/100 mg	1.5 mg/kg q(10 $\times$ Cr)
IIB	20	Creatinine > 1.3 mg/100 mg	0.75 mg/kg 1(5 $\times$ Cr)
III	20	Hemodialysis	1.0 mg/kg after dialysis

^a q8h, Every 8 h; q(10 $\times$ Cr), 10 times the serum creatinine; q(5 $\times$ Cr), 5 times the serum creatinine.

Comparisons of assay values in groups IA, IB, IIA, IIB, and III was by a standard one-way analysis of variance. Individual comparisons between means were by Duncan's new multiple-range test (29). Average responses for each patient were calculated and subjected to analysis. Comparisons between the two AMGs were carried out by using Student's two-sample *t* test. Associations between assay methods were tested by calculating correlation coefficients. Associations between factors represented in two-way contingency tables were tested by calculating chi-square statistics. All computations were performed by using the statistical analysis system (1).

RESULTS

Comparison of assay methods. Figure 1 illustrates the relationship between the values obtained for peak AMG serum levels by the two assay methods employed, bioassay and radioimmunoassay. Each point on the graph represents the mean peak gentamicin or tobramycin concentration for one patient. Correlation between the two methods was good ($r = 0.770$). A like comparison of trough concentrations by the two assay methods showed a very good correlation ($r = 0.885$).

Relationship of dosage to serum concentration. A mean of 4.0 peak and 3.6 trough AMG levels was obtained for all study patients. In evaluating the relationship of AMG dosage to achieved serum concentrations no significant difference was noted between the results obtained for gentamicin and those obtained for tobramycin. For this reason, no distinction is made with regard to the specific AMG administered in the figures and discussion below.

Figure 2 shows the relationship between AMG dosage and achieved peak serum concentrations in groups IA, IB, IIA, IIB, and III. Each point

on the graphs represents the mean peak concentration for a single patient. In no group is there a significant positive correlation between dosage of antibiotic and serum level (P values range from 0.172 to 0.811). From groups IA and IB, we evaluated 54 patients who had at least one set of consecutive trough and peak serum levels which allowed the determination of an absolute increase in AMG serum concentration (i.e., a peak minus trough difference). Comparing AMG dosage (in milligrams per kilogram) with the peak minus trough difference, an improved correlation was found; for group IA $r = 0.44$ and for group IB $r = 0.46$.

Because of recent data regarding the distribution characteristics of the AMGs and the study of antibiotic dosage based on ideal body weight (15), we retrospectively analyzed the effect of this variable in the 34 patients from groups IA and IB whose heights were available. (All lean body weights utilized in our retrospective analysis were derived from actuarial tables for average body weight based upon age, sex, and height.) Figure 3 illustrates the relationship between AMG dose in milligrams per kilogram of ideal body weight and achieved peak serum concentration in patients with normal renal function (groups IA and IB). When analyzed in this fashion, there is an improvement in the correlation of these two variables ($r = 0.625$, $P = 0.0001$) as compared with that found in this group of 34 patients when actual body weight was used for the calculation of AMG dosage ($r = 0.42$, $P = 0.015$). In contrast, when a similar analysis was made of the 16 hemodialysis patients from group III for whom an ideal body weight was available, no improvement was noted ($r = 0.05$, $P = 0.84$) when compared with results obtained when actual body weight was used to calculate AMG dosage ($r = 0.147$, $P = 0.535$).

Bacteriology. A gram-negative bacillus was identified as the responsible pathogen in 96 of the 120 study patients. During the period of study participation, each patient from whom a pathogen was isolated received an AMG to which his or her organism was susceptible. MICs and minimum bactericidal concentrations were determined for one of these isolates. These values were used to evaluate the adequacy of achieved serum concentrations. Table 2 compares the AMG dosage (in milligrams per kilogram) with the ratio of peak serum concentration to the MIC of AMG for the infecting organism; 17 to 33% of serum concentrations in the three dosage ranges did not exceed the MIC of the infecting organism. The cumulative percentage of peak levels which were more than four times the MIC was 72 to 77%. When this method of evaluation was used, there was no significant

FIG. 1. Comparison of microbiobioassay and radioimmunoassay (RIA) methods for AMG serum concentration determinations. Each point represents the mean peak gentamicin or tobramycin concentration for one patient. mcg, Microgram.

FIG. 2. Relationship between AMG dosage and serum AMG concentration in the five study groups. Each point represents the mean peak AMG concentration for one patient. mcg, Microgram.

improvement in the "adequacy" of peak serum concentrations as the dosage of AMG was increased. A comparison of group IA and the other study groups revealed no significant difference ($P > 0.40$) with regard to peak concentration-MIC ratio achieved at any given dosage.

Nephrotoxicity. We performed an analysis of nephrotoxicity by using the criteria enumer-

ated above. The 20 hemodialysis patients (group III) were excluded from this analysis. The overall incidence of nephrotoxicity occurring during AMG therapy was 34% (34 of 100). Table 3 defines the frequency with which identified nephrotoxicity risk factors occurred in both the 66 patients without evidence of renal impairment and the 34 patients who met our criteria

for renal toxicity. Volume depletion was found to be a more frequent characteristic of the nephrotoxic patients ($P < 0.005$). There was no significant difference in the two groups with regard to the occurrence of other specified risk factors ($P > 0.10$). In addition, there was no significant relationship between the specific AMG received and the development of nephrotoxicity ($P > 0.20$).

Of the 34 patients with renal toxicity, 13 were judged to have nephrotoxicity induced by AMG therapy. Nephrotoxicity in the remaining 21 patients was judged to be secondary to hypoten-

sion, volume depletion, sepsis, or underlying renal disease. With the exception of the more frequent occurrence of underlying renal disease in those patients with renal toxicity judged to be unrelated to AMG ($P < 0.05$), no significant difference in risk factors was found for the two groups of patients with nephrotoxicity shown in Table 3 ($P > 0.10$). Of the 13 patients with AMG-induced renal damage, 8 had received gentamicin and 5 had received tobramycin. Thus, in these two groups with nephrotoxicity, there was no significant relationship between the specific AMG received and development of toxicity ($P > 0.20$).

Trough serum concentrations of gentamicin and tobramycin were examined to determine their relationship to the occurrence of nephrotoxicity. Trough levels of $>2.0 \mu\text{g/ml}$ were just as common in patients not demonstrating evidence of nephrotoxicity as in those who did develop renal impairment. In the patients without evidence of nephrotoxicity, 18 of 66 (27%) had at least one trough level of $>2.0 \mu\text{g/ml}$, and among the 34 patients with nephrotoxicity due to all causes, trough levels of $>2.0 \mu\text{g/ml}$ occurred in 14 of 34 or 41% ($P > 0.10$). In addition, elevated trough levels occurred with equal frequency in patients judged to have AMG-induced nephrotoxicity (6 of 13 patients) and those with nephropathy due to other causes (8 of 12).

In group IIB patients who received their AMG by a schedule which has characteristics of both variable dosage regimens and variable frequency regimens, there was a higher frequency of trough levels of $>2.0 \mu\text{g/ml}$ (21 versus 10 to 15% for other groups; $P > 0.10$). However, the incidence of nephrotoxicity was not significantly greater in this study group.

Nephrotoxicity occurred in 7 of 30 (23%) group IA patients compared with 6 of 70 (8.6%) patients in the other study groups ($P < 0.10$). Assessment of risk factors revealed only a significantly higher incidence ($P < 0.05$) of prior

FIG. 3. Relationship between AMG dosage based on ideal body weight (IBW) and serum AMG concentration for groups IA and IB. Each point represents the mean peak AMG concentration for one patient. mcg, Microgram.

TABLE 2. Comparison of dosage administered with ratio of peak serum concentration to MIC

Dose (mg/kg)	% of patients with a ratio of peak serum concentration to MIC of:			
	≤ 1	$>1-4$	$>4-8$	>8
1.0	17	60	13	10
1.1-1.5	27	46	17	10
>1.5	33	39	14	14

TABLE 3. Frequency of occurrence of risk factors associated with nephrotoxicity

Patient group	No. of patients	No. with elevated AMG levels		No. with volume depletion	No. taking concurrent drugs		No. with prior AMG therapy	No. with underlying renal disease
		Peak of $>10 \mu\text{g/ml}$	Trough of $>2 \mu\text{g/ml}$		Furosemide	Cephalosporins		
No nephrotoxicity	66	5 (8) ^a	18 (27)	4 (6) ^b	17 (26)	38 (58)	3 (4)	17 (26)
Nephrotoxicity								
AMG induced	13	2 (15)	6 (46)	5 (38)	4 (30)	10 (77)	2 (15)	1 (8) ^c
Other causes	21	1 (5)	8 (38)	5 (24)	10 (48)	15 (71)	1 (5)	9 (43) ^c
Total	34	3 (9)	14 (41)	10 (29) ^b	14 (41)	25 (74)	3 (9)	10 (29)

^a Numbers in parentheses are percentages.

^b $P < 0.005$.

^c $P < 0.05$.

AMG therapy in the group IA patients.

Mortality. The overall mortality of patients in all groups was 37% (44 of 120 patients) (Table 4). Patients were recorded as deaths in this analysis if they died during or shortly after the course of antibiotic therapy, regardless of cause of death. Mortality was 32% (19 of 60) in gentamicin-treated patients and 42% (26 of 60) in tobramycin-treated patients. This difference was not significant ($P > 0.20$). By using the McCabe system for classifying patients into rapidly fatal, ultimately fatal, and nonfatal groups on the basis of underlying disease (22), there was no significant difference ($P > 0.20$) in the distribution of our study patients with regard to the specific AMG administered.

The overall mortality in group IA was 20% (6 to 30 patients) compared with 42% (38 of 90) in the other study groups ($P < 0.05$). However, within each McCabe category (rapidly fatal, ultimately fatal, and nonfatal) group IA mortality did not differ significantly from the other study patients. Evaluation revealed a skewed distribution of group IA patients into the nonfatal McCabe group ($P < 0.10$).

Evaluation of the 93 patients for whom serum bacteriostatic activity data were available revealed a mortality of 32% (16 of 50 patients) among those with a serum inhibitory level of $<1:8$ and a mortality of 37% (16 of 43) among those with an inhibitory level of $\geq 1:8$ ($P > 0.50$). When these patients were analyzed with regard to the severity of underlying disease according to the McCabe system, there was no significant difference between the group with inhibitory levels of $<1:8$ and the group with inhibitory levels of $\geq 1:8$.

DISCUSSION

We found good correlation between the serum concentration values obtained by the two assay methods employed (i.e., microbiological assay and radioimmunoassay). Comparative studies of microbiological assay and radioimmunoassay methods by other investigators have also shown no significant differences in the results obtained (30). It is within the capability of most hospital clinical laboratories to utilize one of the available AMG assay techniques.

TABLE 4. Mortality during AMG therapy

Agent	No. of deaths/total no.		
	Rapidly fatal	Ultimately fatal	Nonfatal
Gentamicin	10/15 (67) ^a	8/30 (27)	1/15 (7)
Tobramycin	16/19 (84)	8/27 (30)	1/14 (7)

^a Numbers in parentheses are percentages.

The pharmacokinetics of gentamicin and tobramycin are almost identical (21, 25). For this reason, we chose to make no distinction between the two antibiotics in our discussion of various dosage regimens.

In a group of patients with variable degrees of renal dysfunction, Cutler et al. (8) determined that the gentamicin half-life was equal to approximately three to four times the serum creatinine in hours. McHenry et al. (23) found the same relationship between half-life and serum creatinine in their overall patient group; however, they noted that estimated and measured half-lives varied by 20 to 60% in 5 of their 29 patients. Because of a concern about prolonged subtherapeutic serum concentrations, Chan et al. (7) compared AMG elimination to creatinine clearance and constructed a nomogram for use in a variable dosage regimen. It was found that patients with creatinine clearance of >70 ml/min demonstrated normal elimination of gentamicin. In patients with creatinine clearance <70 ml/min, it was possible to calculate maintenance doses to be given every 8 h in order to achieve more therapeutic serum concentrations.

As an alternative to the use of urine collections in the calculation of creatinine clearance, Siersback-Nielsen et al. have provided a nomogram which incorporates the patient's age, serum creatinine, and weight in order to determine creatinine clearance (28). Similarly, Jelliffe has devised a formula for estimating creatinine clearance (17).

There is a question, however, about the adequacy of any of these methods in terms of broad applicability to patients who are receiving AMGs. Sawchuk et al. (26) found a significant patient-to-patient variability in gentamicin half-life even with normal renal function. They noted a marginal correlation between serum creatinine and half-life ($r = 0.50$) and only a slightly improved relationship between gentamicin clearance and creatinine clearance ($r = 0.69$). The predictability of serum concentrations was improved by the direct calculation of half-life and the volume of distribution for each patient. Such an approach, however, is unlikely to find wide use among clinicians since logistically difficult determinations are necessary in each patient. The unpredictability of AMG concentrations and half-lives has also been emphasized by other investigators (3, 18).

Our results substantiate the premise that serum AMG concentrations are unpredictable in the population at large regardless of the renal function of a patient. A wide range of peak AMG levels was seen in the group as a whole when identical doses (in milligrams per kilogram) were administered to individual patients within the

group. Although we found an improved correlation when we compared AMG dosage to peak minus trough differences in 54 patients from groups IA and IB, analysis of our data by this method still fails to show a level of correlation acceptable for optimal clinical results. In addition, our use of higher (1.5 to 2.0 mg/kg) loading or maintenance doses could not be relied on the assure therapeutic levels. Zaske et al. have recently emphasized this same point in a study of 14 burn patients receiving AMGs (34). However, Echeverria et al. (11) did note that individual patients tended to have predictable peak concentrations with repeated doses, once a dose-response base line had been established by monitoring serum levels.

Hull and Sarubbi have reported their experience with a computer-assisted program of AMG dosage by utilizing creatinine clearance and ideal body weight rather than total body weight for calculation of both dosage and dosage interval (15). These investigators found an excellent correlation between predicted and measured gentamicin serum levels ($r = 0.87$). A nomogram for calculation of dosage was developed and, when it was used in 16 study patients, no significant difference was found between measured and predicted serum levels.

In the analysis of our data, we found a significant improvement in the correlation between dose of AMG per kilogram of ideal body weight and serum concentration in patients with normal renal function. This approach seems theoretically sound based on the observed pharmacokinetics and volume of distribution of gentamicin and tobramycin. The explanation for why the use of ideal body weight in our hemodialysis patients failed to improve the correlation between dosage and serum level is unclear, but this failure suggests that even this method has limitations.

Nephrotoxicity has been recognized as a major factor in the limitation of AMG usage. The incidence of this occurrence with gentamicin has been variably reported as being from 9 to 50% (9, 14, 20) and is dependent, in part, upon the methodology and criteria for nephrotoxicity used in each study. For the most part, the azotemia associated with AMG therapy is reversible upon discontinuation of the antibiotic. Histological examination reveals primarily proximal tubular necrosis, manifested clinically by rising blood urea nitrogen and creatinine and decreased ability to concentrate urine (5, 13). Risk factors for development of nephrotoxicity are not fully agreed upon. Among those previously reported are preexisting renal disease, elevated AMG serum levels, concomitant use of other nephrotoxic agents, dehydration, advanced pa-

tient age, and prior courses of AMGs (6, 20). Among our 34 nephrotoxic patients, volume depletion was significantly more common. However, no identifiable risk factor was found to distinguish the patients with AMG-related toxicity from those with toxicity related to another cause.

Dahlgren et al. noted in a clinical study of 86 patients that trough serum gentamicin levels of $>2 \mu\text{g/ml}$ were associated with a higher risk of nephrotoxicity (9). Goodman et al. also reported a significant correlation between trough serum concentrations of $>4 \mu\text{g/ml}$ and the development or progression of renal insufficiency (14). In our patient groups, 10 to 21% of all trough levels exceeded $2 \mu\text{g/ml}$. Although there was a trend toward more frequent elevation of trough concentrations in group IIB patients, who received doses every half interval, this was not significant ($P > 0.10$). No significant difference in the occurrence of trough levels of $>2 \mu\text{g/ml}$ was found when the 66 patients without alterations of renal function were compared with the 34 patients who developed nephrotoxicity during AMG therapy ($P > 0.10$). Evaluation of these 34 patients who developed nephrotoxicity showed that elevated trough levels occurred with equal frequency in patients judged to have AMG-related renal injury (6 of 13 patients) and those with nephropathy due to other causes (8 of 21).

Although our data do not establish a significant difference between gentamicin and tobramycin with respect to the risk of nephrotoxicity, several recent studies have shown that tobramycin has significantly lower nephrotoxic potential in experimental animals (13, 31). This difference may be partially accounted for by the greater concentration of gentamicin in the renal cortex (27). Presently, there are no data gathered in a controlled comparative clinical study to support a difference in nephrotoxicity between gentamicin and tobramycin.

The importance of AMG serum determinations, in terms of improving efficacy of therapy, is not well established. In our study patients, 17 to 33% of all peak serum concentrations failed to exceed the MIC of the infecting organism. Our results are comparable to those of McHenry et al., who found that the MICs of their pathogens were not exceeded in 22 to 34% of their cases (23). Other investigators have reported that 32 to 60% of peak levels are $<4 \mu\text{g/ml}$, a proposed therapeutic minimum, after doses of 1.2 to 1.7 mg/kg (3, 18).

In our study, achievement of a serum inhibitory level of $\geq 1:8$ did not correlate with improved survival. In contrast, Klastersky et al., in a study of patients with gram-negative bacillary infections, observed that serum bacteriostatic

activity of $\geq 1:8$ dilution was associated with a "cure" rate of greater than 80% (19). Antibiotic synergism may cause discrepancies between the anticipated inhibition of bacteria growth based on MIC and that observed in a serum inhibitory assay. Pending additional confirmation of the findings of Klastersky et al., the assurance that the AMG serum concentration is adequate should also be a concern. An adequate AMG peak serum concentration can be arbitrarily defined as one which is in the generally accepted therapeutic range (4 to 10 $\mu\text{g/ml}$) or which inhibits growth of the pathogenic organism in a dilution of 1:8 or greater.

Based on the foregoing information, available from our study and others, we advise the determination of AMG dosage and dosage interval by using creatinine clearance in accordance with the nomogram and tables provided by Hull and Sarubbi (15). During AMG therapy of patients with serious gram-negative bacillary disease, we measure peak and trough serum AMG concentrations early in the course of therapy, to establish the base-line responsiveness of each patient. Additional bacteriological studies, such as MIC, minimum bactericidal concentration, and serum inhibition assays, should also be performed in selected situations (e.g., endocarditis, meningitis, and apparent treatment failures). These, in conjunction with AMG serum concentrations, should help to determine the optimal antibiotic dosage regimen.

ACKNOWLEDGMENTS

We are indebted to Dr. Edwin Bradley, Department of Biostatistics, University of Alabama School of Medicine, for his statistical assistance. We also thank Deborah Duke, Donna Reagin, Dale Schulz, and Janet Haldeman of the Division of Infectious Diseases and Ed Collins of the University Hospital Pharmacy for their assistance.

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