

Comparative Nephrotoxicity of Gentamicin and Tobramycin: Pharmacokinetic and Clinical Studies in 201 Patients

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A total of 201 critically ill patients were studied during 267 courses of gentamicin or tobramycin treatment (139 gentamicin courses and 128 tobramycin courses). Of these 267 courses, pharmacokinetic and clinical data were obtained for 240 (120 gentamicin and 120 tobramycin). The data collected for pharmacokinetic analysis included measurements of serial blood and urine levels, urinary excretion of β_2 -microglobulin, protein levels, and granular casts. A two-compartment model was used to assess tissue accumulation, and in 89 courses the predicted accumulation was confirmed by cumulative urine collection or postmortem tissue analysis. As groups, the patients given gentamicin and tobramycin did not differ in age, weight, creatinine clearance, total dose given, duration of treatment, initial aminoglycoside trough serum levels, number of dosage adjustments, concurrent use of furosemide, or concurrent cephalosporins. Previous aminoglycoside treatment (usually gentamicin) had occurred more frequently in the tobramycin-treated patients ($P < 0.01$), and more males than females received tobramycin ($P < 0.05$). Pharmacokinetic assessments of renal damage were based on both changes in glomerular filtration rate (serum creatinine levels, creatinine clearance) and renal tubular damage (β_2 -microglobulin, casts), but only patients with elevated aminoglycoside tissue levels leading to renal tubular damage and subsequent creatinine clearance decreases were considered to have experienced aminoglycoside nephrotoxicity. In the pharmacokinetic analysis of nephrotoxicity, 29 gentamicin courses (24%) and 12 tobramycin courses (10%) were complicated by nephrotoxicity ($P < 0.01$). The 201 study patients were also evaluated independently for clinical nephrotoxicity (defined as a serum creatinine level increase of 0.5 mg/dl or more). Clinical nephrotoxicity occurred at rates of 37% in the gentamicin-treated group and 22% in the tobramycin-treated group ($P < 0.02$). In these similar groups of critically ill patients, tobramycin was less nephrotoxic than gentamicin.

Aminoglycoside antibiotics are potentially nephrotoxic substances which may cause specific damage to the lining cells of renal proximal tubules. The incidence of reported nephrotoxic damage in aminoglycoside-treated patients has increased from 5 to almost 40% recently (2, 4, 7, 8, 19); the occurrence rate is apparently a function of the type of patients studied, variations in the methods used to define nephrotoxicity, and intensity of renal monitoring by investigators.

The incidence of nephrotoxicity may also vary with the aminoglycoside used. Animal studies readily differentiate these compounds. Gentamicin is more nephrotoxic than tobramycin, netilmicin, or amikacin in animals (3, 5, 6). In animal studies elevated aminoglycoside doses are used, which result in blood levels that markedly exceed the levels employed to treat human infections. Also, at least one compound will

produce nephrotoxicity in most study animals, so that these animals can serve as a reference population for comparing aminoglycosides. In human trials, nephrotoxicity is much less common, and it may occur for different reasons than overdoses.

The widespread clinical use of dosing nomograms and the monitoring of serum concentrations mean that both overdoses and elevated blood concentrations are avoided, yet nephrotoxicity still occurs (1, 2, 7, 16, 18, 19). Thus, animals are overdosed until renal failure occurs, whereas patients may experience renal damage despite the use of recommended doses and therapeutic serum concentrations (1, 2, 15, 16, 18). In view of the differences between the nephrotoxic damage produced by overdoses in animals and clinical aminoglycoside nephrotoxicity, comparative studies in animals may not provide

relevant models for characterization of comparative clinical nephrotoxicity. Furthermore, the belief that aminoglycoside nephrotoxicity is always dose related might also be challenged, since clinical nephrotoxicity has not been abolished by the use of proper doses.

Our pharmacokinetic studies in patients have provided some insight into the pathogenesis of renal damage when appropriate doses are used. An early finding of these studies was that abnormally high aminoglycoside accumulations in renal tissue lead to proximal tubular damage, even though aminoglycoside blood levels remain normal (9, 15). A characteristic pattern of renal tubular damage precedes an eventual increase in serum creatinine levels by 5 to 10 days (15). In the patients experiencing aminoglycoside nephrotoxicity, increases in serum creatinine levels occur late in the sequence of events, after evidence of abnormally rapid tissue accumulation and proximal damage, as measured by urine sediment changes and excretion of β_2 -microglobulin (14). Thus, an increase in the serum creatinine level may reflect damage to the proximal tubules which actually began 5 to 7 days before changes in glomerular filtration.

We applied these criteria to a study of the comparative nephrotoxicities of gentamicin and tobramycin. Our study involved two groups from a homogeneous population of acutely ill older patients having similar base-line risks for nephrotoxicity and similar clinical complications during hospitalization.

MATERIALS AND METHODS

Patients. A total of 201 acutely ill patients were given 267 courses of aminoglycoside therapy (139 gentamicin courses, 128 tobramycin courses). These patients were older adults (average age, 66 years) with serious infections complicating either major medical or surgical disorders. All but a few of these patients had abdominal infections, pneumonia, septicemia, or a combination of these diseases. Each was entered prospectively into the study at the time of request for therapy and pharmacokinetic monitoring, after gentamicin or tobramycin was selected for use by the attending physician. The rates of patient accession were similar for the gentamicin-treated and tobramycin-treated groups over the 2-year study period.

Doses and sample collection. Rates of aminoglycoside administration were determined individually for all patients according to nomograms and measured peak and trough serum concentrations. Blood for assays was obtained throughout treatment and in most patients for 10 to 20 days after aminoglycoside treatment was stopped (to quantitate the terminal half-life), as previously described (9, 10, 11-13, 15). Desired therapeutic peak concentrations were between 4 and 10 $\mu\text{g}/\text{ml}$, and desired trough concentrations were 0.5 to 2.0 $\mu\text{g}/\text{ml}$ for both aminoglycosides. Most patients had been catheterized during their illness, and daily

24-h urine samples were collected to verify tissue accumulation and to measure indices of renal tubular damage. Pretreatment renal and pharmacokinetic parameters were obtained on the day before aminoglycoside administration was begun, or the value on treatment day 1 was used as the base-line value if a prior value was not available.

Assays. Serum, urine, and postmortem tissue aminoglycoside concentrations were measured by both a microbiological assay and a radioimmunoassay, as previously described (12, 13). The lower limit of sensitivity for the radioimmunoassay was 0.03 $\mu\text{g}/\text{ml}$; thus, this assay allowed measurement of both serum and urine concentrations for 10 to 30 days after the last dose. Serum creatinine levels and 24-h creatinine clearance values were determined by autoanalyzer methods; 24-h urinary excretion of β_2 -microglobulin was determined by the radioimmunoassay, and values of more than 50 mg/24 h were associated with nephrotoxicity (4). Quantitative cast counts were performed daily on random urine samples, and values of more than 500 casts per ml on 3 consecutive days were associated with nephrotoxicity (10).

Pharmacokinetic analysis. Serum concentrations (C_p) in the washout phase were fitted to a biexponential equation ($C_p = Ae^{-at} + Be^{-bt}$) by using the NONLIN least-squares regression computer program. The A and B intercepts were adjusted for the amount of residual drug present from previous doses to yield intercept values reflecting a single dose. The slopes and adjusted intercept values were used to calculate the rate constants and distribution volumes of the two-compartment model. These included the central and steady-state volumes of distribution, the intercompartment distribution rate constants, the elimination rate constant, and the body clearance. The values of these parameters were used in another digital computer program (NUMINT), which numerically integrated the differential equations for the model to simulate serum concentrations from the first dose through the final dose and for the washout period. When all computer-simulated serum concentration values agreed within 20% with the measured concentrations throughout treatment and in the washout period, the calculated parameters of the model were considered to be reliable. The NUMINT program provided the amount of drug in the central and tissue compartments of the two-component model during therapy and after therapy ended (11-13).

Nephrotoxicity. Nephrotoxicity was determined in each course of treatment by using two sets of criteria. A clinical assessment of nephrotoxicity was performed independently of a pharmacokinetic assessment in a blind fashion. The clinical criterion for nephrotoxicity was an increase in the serum creatinine level of 0.5 mg/dl or more during therapy or within 7 days of the last dose. Unless another cause of the increase was clearly apparent, the change was always attributed to aminoglycoside treatment.

In the pharmacokinetic assessment of nephrotoxicity, two essential criteria were used to define nephrotoxicity. The first was an abnormally high aminoglycoside tissue accumulation, which was defined as an amount more than two standard deviations above the mean value for treated patients who did not show an

increase in the creatinine level. These abnormal values were more than 200 mg for gentamicin and more than 175 mg for tobramycin (15). The second criterion of the pharmacokinetic assessment was an increase in urine β_2 -microglobulin levels and casts occurring before the serum creatinine level increase in a specific pattern, as previously described (15). In the pharmacokinetic definition of nephrotoxicity, serum creatinine level increases of more than 0.5 mg/dl not preceded by indices of renal tubular damage or abnormal tissue accumulation were considered to be caused by something other than aminoglycoside nephrotoxicity (15).

Analysis. Each course of aminoglycoside therapy was examined separately even in the same patient, since clinical status and risk factors could change course by course. About 25% of the patients were studied during more than one course of therapy. A separate analysis of only those single-course patients who had not received aminoglycosides previously examined the influence of previous aminoglycoside treatments on our findings. Differences between aminoglycosides were analyzed by using the Student *t* test and the chi-square test with the Yates correction. A *P* value of <0.05 was considered significant.

RESULTS

Of the 267 courses of treatment examined, 9 were excluded from the clinical analysis, either because of failure to determine serum creatinine levels after therapy or because hemodialysis invalidated serial creatinine level measurements. The remaining 258 courses were analyzed by using clinical criteria.

Of the 267 courses, 27 were excluded from the pharmacokinetic analysis because there were inadequate data to employ the pharmacokinetic criteria for nephrotoxicity. Of the remaining 240 courses, 120 patients were given gentamicin and 120 received tobramycin. This report summarizes our findings after an analysis of these 240 courses of treatment by using the pharmacokinetic criteria for nephrotoxicity and compares the incidence of nephrotoxicity as determined by pharmacokinetic assessment with the incidence as determined by clinical criteria.

Analysis of course eliminated due to insufficient pharmacokinetic data. A total of 27 courses had inadequate data for analysis by the pharmacokinetic criteria, but all 27 could be evaluated for creatinine level increases. Of these 27 courses, 19 involved gentamicin and 8 involved tobramycin. Creatinine level increases occurred in 3 of 19 gentamicin courses and in 3 of 8 tobramycin courses. If all six of these creatinine level increases had been caused by the aminoglycosides, the outcome of this study regarding gentamicin and tobramycin nephrotoxicities would not have changed ($\chi^2 = 5.2$; *P* < 0.02).

Nephrotoxicity in 240 courses as determined by pharmacokinetic analysis. The

120 gentamicin and 120 tobramycin courses of treatment were administered to patients of similar age, weight, initial creatinine clearance level and incidence of proven infection (Table 1). One-fourth of each group had positive blood cultures. Previous aminoglycoside treatments (usually with gentamicin) were given twice as frequently to the tobramycin group (*P* < 0.001), and more men than women were given tobramycin (*P* < 0.05).

During treatment, the two groups had similar initial trough concentrations, received the same average doses and durations of treatment, and required an average of 1.1 dosage changes (usually decreases) to maintain blood levels within the therapeutic range. Cephalosporins were given concurrently in slightly more tobramycin courses, and diuretics (chiefly furosemide) were given in more gentamicin courses (Table 1). Neither of these differences was significant.

About 75% of the infections in each group either were cured or improved by the treatment (Table 2). Approximately 25% of the patients in each group died, usually as a consequence of an underlying disease. However, in 11 of the patients (4.5%) who died aminoglycoside-induced renal failure was a major contributing factor.

By the end of therapy, the gentamicin-treated group had a greater mean decrease in creatinine clearance (*P* < 0.02), a higher final trough concentration (*P* < 0.05), and a greater average tissue accumulation (*P* < 0.01) than the tobramycin-treated group (Table 2). Figure 1 shows the measured tissue accumulation values and the values predicted in the patients for whom we obtained consent for autopsy. This figure shows that the pharmacokinetic model was accurate for both gentamicin and tobramycin over the entire range of the observed tissue accumulation values. Consistent with differences between gentamicin and tobramycin in tissue accumulation, nephrotoxicity occurred in 24% of the gentamicin courses and in 10% of the tobramycin courses, a significant difference (*P* < 0.01).

Comparative nephrotoxicities as determined by pharmacokinetic assessment and clinical criteria. Clinical criteria identified nephrotoxicity in 37% of the gentamicin courses and 22% of the tobramycin courses (*P* < 0.02). As nearly all patients with creatinine level increases were defined clinically as experiencing aminoglycoside nephrotoxicity, clinical nephrotoxicity occurred more often than pharmacokinetic nephrotoxicity, the latter requiring abnormal tissue accumulation and evidence of tubular damage before creatinine level increases. Pharmacokinetic assessments, which were based primarily on abnormal tissue accumulation, attrib-

TABLE 1. Pretherapy and concurrent therapy comparisons of 120 gentamicin courses and 120 tobramycin courses

Group	No.	Age (years) ^a	Sex ^b		Wt (kg) ^a	Initial creatinine clearance (ml/min) ^{b,c}	% With proven infections ^a	% With positive blood cultures ^a	% Receiving aminoglycosides previously ^d	First trough concn (μg/ml) ^a	Total dosage (g) ^e	Duration of therapy (days) ^a	No. of dosage changes ^a	% Receiving cephalosporins concurrently ^a	% Receiving diuretics concurrently ^a
			No. of males	No. of females											
Gentamicin	120	67 ± 12 ^r	61	59	66 ± 15 ^r	51 ± 27 ^r	84	22.5	18	1.6 ± 0.9 ^r	1.7 ± 1.2 ^r	9.7 ± 5.5 ^r	1.1 ± 1.4 ^r	30	63
Tobramycin	120	66 ± 12	81	39	68 ± 13	51 ± 31	91	23	44	1.4 ± 1.0	1.7 ± 1.8	11.3 ± 8.1	1.1 ± 1.5	40	54

^a Difference between gentamicin-treated group and tobramycin-treated group not statistically significant.

^b Difference between gentamicin-treated group and tobramycin-treated group significant at $P < 0.05$.

^c Values were determined for 24-h urine samples in most cases; the remainder were predicted by using nomograms.

^d Percent receiving aminoglycoside treatment within 1 month of the start of our study. The difference between the gentamicin-treated group and the tobramycin-treated group was significant at $P < 0.001$.

^e Mean ± standard deviation.

uted renal tubular damage to gentamicin in 24% of the courses and to tobramycin in 10% of the courses ($P < 0.01$). Only four patients (three treated with tobramycin, one treated with gentamicin) had abnormal tissue accumulations without subsequent increases in serum creatinine levels. Clinical and pharmacokinetic assessments agreed more than 75% of the time (Table 2) and did not differ significantly between gentamicin and tobramycin nephrotoxic courses.

Effects of treatment duration and total dosage on comparative nephrotoxicities. Because we thought that the duration of therapy had an important influence on the development of aminoglycoside nephrotoxicity, we analyzed the 240 courses of treatment in relation to treatment duration. As Table 3 shows, 48 patients received less than 5 days of treatment. Of these 48 short courses, the incidence of nephrotoxicity did not differ between gentamicin and tobramycin courses; it was below 10% in both cases.

When courses exceeded 5 days, a sharply higher incidence of renal damage was observed, especially in gentamicin courses. In the 135 courses lasting 6 to 12 days, gentamicin was significantly more nephrotoxic than tobramycin ($P < 0.01$). The same trends were observed in patients treated for more than 12 days, but there were not enough observations to measure statistical significance.

To explore further the relationship between doses and creatinine level increases, we plotted the total aminoglycoside dosage given versus the percent change in serum creatinine level. This relationship is shown for gentamicin and tobramycin in Fig. 2. Besides showing individual creatinine level increases for our 240 courses, this graph shows three interesting features of the patient population. First, there were no significant differences in the distribution of total dosages between the two aminoglycosides. Second, it appeared that the degree of creatinine level increase was similar for the two antibiotics, although several gentamicin-treated patients experienced severe nephrotoxicity. And third and perhaps most interesting, there was essentially no relationship between total dosage and nephrotoxicity; rather, there were seven patients who were given average to low dosages and experienced severe nephrotoxicity. All of these demonstrated both abnormally rapid tissue accumulation and normal trough levels until the day on which creatinine levels began to increase rapidly. A second group of seven patients appeared to demonstrate a similar pattern at total dosages ranging from 2,000 to 5,000 mg. These patients also had excessive tissue accumulation but they had a slower rate of tissue uptake than that observed in the first group.

TABLE 2. Nephrotoxicity assessments and responses to treatment in gentamicin and tobramycin courses

Group	No.	% In which infection responded ^{a,b}	Final creatinine clearance (ml/min) ^c	Last trough concn ($\mu\text{g/ml}$) ^d	Tissue accumulation (mg) ^{e,f}	% Showing clinical nephrotoxicity ^{e,g}	% Showing pharmacokinetic nephrotoxicity ^f	% Overall agreement ^a
Gentamicin	120	73	41 ± 27^h	2.8 ± 2.3^h	141 ± 133^h	37	24	76
Tobramycin	120	75	50 ± 34	2.2 ± 2.2	97 ± 64	22	10	83

^a Difference between gentamicin-treated group and tobramycin-treated group not statistically significant.

^b Response was defined as clinical cure or clinical improvement.

^c Difference between gentamicin-treated group and tobramycin-treated group significant at $P < 0.02$.

^d The value on the last day of treatment. The difference between the gentamicin-treated group and the tobramycin-treated group was significant at $P < 0.05$.

^e Calculations were based on a two-compartment pharmacokinetic model and were confirmed independently by urine or postmortem tissue measurements for 81 courses of treatment.

^f Difference between gentamicin-treated group and tobramycin-treated group significant at $P < 0.01$.

^g These values were based on 258 courses (137 gentamicin, 121 tobramycin) because serum creatinine levels were available for 18 more courses than complete pharmacokinetic assessments (120 gentamicin, 120 tobramycin).

^h Mean \pm standard deviation.

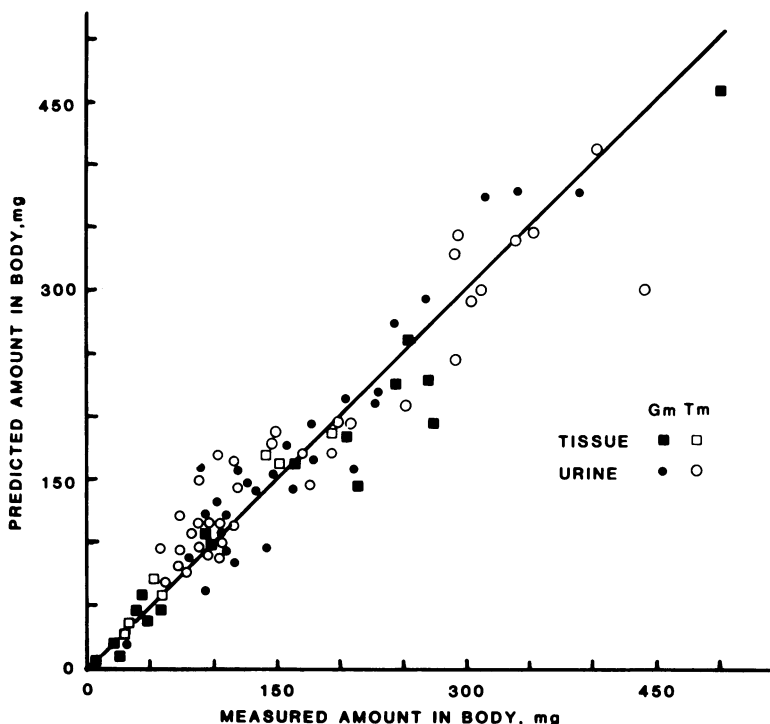


FIG. 1. Measured versus predicted tissue amounts in 89 aminoglycoside courses. Shown are amounts of gentamicin (Gm) (■) and tobramycin (Tm) (□) recovered in tissues and amounts of gentamicin (●) and tobramycin (○) recovered in urine. The identity line is shown. Regression analysis gave the following equation: predicted value = 0.93 (measured value) + 12.2 ($r = 0.95$).

Single-course analysis. Table 4 shows the results of a single-course analysis which was performed to examine the influence of both previous and multiple-course treatments. Beginning with the 240 courses, we excluded all patients who had more than one course of aminoglycoside treatment and all patients who had received

aminoglycosides previously, whether or not we had studied them during the previous course of treatment. Of the 136 patients remaining, 56 received tobramycin, and 80 were given gentamicin. In these patients, the population characteristics were similar to those shown in Table 1. By pharmacokinetic criteria, 4 of the 56 tobra-

TABLE 3. Comparative nephrotoxicities of gentamicin and tobramycin in relation to duration of treatment

Duration of treatment (days)	Total no. of courses		No. of nephrotoxic courses		% of nephrotoxic courses	
	Gentamicin	Tobramycin	Gentamicin	Tobramycin	Gentamicin	Tobramycin
1-5	30	18	2	1	7	6
6-12	61	74	18	7	29	9 ^a
13-52	29	28	9	4	31	14

^a Significantly different from the gentamicin value at $P < 0.01$ ($\chi^2 = 7.6$).

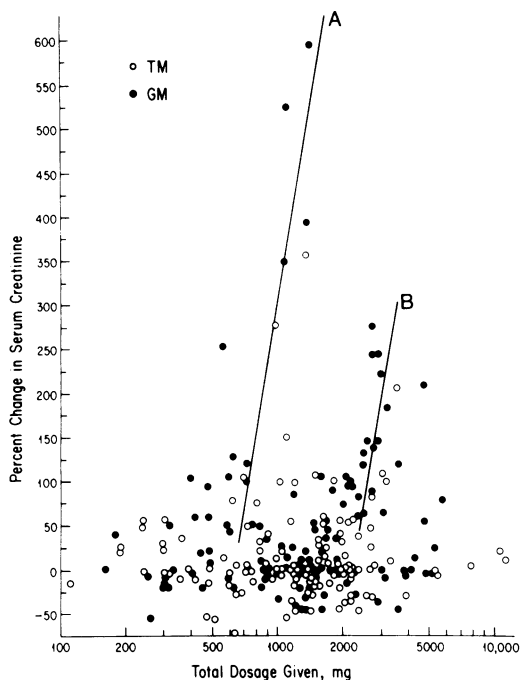


FIG. 2. Relationship between total dosage and creatinine level increase for tobramycin (TM)-treated patients (○) and gentamicin (GM)-treated patients (●). Reference line A illustrates seven patients who appeared abnormally sensitive to these drugs and had severe renal damage. Reference line B illustrates a population of patients who were less sensitive but experienced moderate levels of renal damage after total doses of 2,000 to 5,000 mg.

TABLE 4. Comparative nephrotoxicities in single-course patients

Group	Total no.	No. without toxic reaction	No. with nephrotoxic reaction ^a
Gentamicin	80	61	19 (31) ^b
Tobramycin	56	52	4 (8)

^a Difference between gentamicin-treated group and tobramycin-treated group significant at $P < 0.02$ ($\chi^2 = 5.37$; Yates correction applied to chi-square table).

^b Values in parentheses are percentages.

mycin-treated patients experienced nephrotoxicity, whereas 19 of the 80 gentamicin-treated patients experienced nephrotoxicity ($\chi^2 = 5.4$; $P < 0.02$). Thus, the imbalance resulting from the more frequent previous administration of aminoglycosides to tobramycin-treated patients did not have a major influence on the study findings.

DISCUSSION

Because of reliable dosing nomograms and widespread dosage control-based measurements of serum levels, fewer patients are now overdosed with aminoglycosides. Nevertheless, nephrotoxicity does appear to be a growing problem, even despite dosage control. Perhaps aminoglycoside nephrotoxicity appears more frequently because of close observation, or perhaps it was even more frequent before dosage control was based on blood levels. Regardless of the reasons for the more frequently reported nephrotoxicity, it is clear that the toxicity now observed clinically is different from overdose toxicity and it may be related to factors such as individual sensitivity, abnormal renal uptake, or synergy between aminoglycosides and clinical risk factors. Animal models based on overdoses and previous human comparative trials in which doses were poorly controlled have limited value either in differentiating comparative nephrotoxicities or in identifying patients at risk. The appropriate model is critically ill patients.

Once blood levels are controlled within the therapeutic range, the nephrotoxicities of two compounds can be studied in a double-blind randomized fashion by using a clearly defined endpoint as the criterion for differentiation. For the study of aminoglycosides, serum creatinine level increases have been the criterion used for a long time, yet this definition of nephrotoxicity is potentially too nonspecific to reliably identify tubular damage in situations where concurrent renal insults are so frequent. Furthermore, the double-blind trial design precluded any analysis of data until the final stages and because of this did not allow a constant search for new mechanisms or better criteria for nephrotoxicity. Our investigative plan permitted intensive analysis

of urine in search of new parameters and the development and evaluation of new and potentially more specific criteria for identifying the site of aminoglycoside damage. Simultaneous yet blind clinical analyses allowed us to compare any new criterion with standard clinical assessments. In the clinical analysis, we attributed essentially all serum creatinine level increase to aminoglycoside nephrotoxicity, fully realizing the difficulties inherent in using a nonspecific test to judge toxicity in critically ill patients. The advantage of this approach to our clinical definition was a low dropout rate, whereas the disadvantage was a high rate of nephrotoxicity.

In our pharmacokinetic analysis, the quantitative nature of the criteria used and the fact that they were supported in 89 cases by either tissue analysis or urine recovery lend validity to the use of these criteria in nonblind fashion. Tissue accumulation is a highly specific criterion as only 4 of our patients experienced abnormal aminoglycoside tissue accumulation without a subsequent increase in serum creatinine levels. Finally, the results of a double-blind randomized comparative trial in which nephrotoxicity was defined by serum creatinine level increases also agreed with our pharmacokinetic assessment that gentamicin was more nephrotoxic than tobramycin (17). The two studies were complementary, as our findings support the use of serum creatinine levels in less acutely ill patients, such as those employed in this double-blind trial, whereas the conclusion that gentamicin is more nephrotoxic than tobramycin in a study designed to be free of interpretive bias lends further support to the utility of the pharmacokinetic assessment of nephrotoxicity in severely ill patients.

In a group of critically ill patients, the use of the pharmacokinetic criteria lowers the overall incidence of nephrotoxicity attributable to both gentamicin and tobramycin, perhaps because these criteria more reliably distinguish the nephrotoxic potential of these agents in a manner consistent with the known pathogenesis of aminoglycoside renal damage. However, the absolute specificity of the pharmacokinetic criteria can only be determined when there is a group of infected patients at equal risk not given aminoglycosides, an impossible study design until non-nephrotoxic alternatives to aminoglycosides become available.

In our 240 courses of treatment, there can be no doubt that older age, concurrent disease, critically ill status, and concurrent multiple-drug treatments combined to produce an extremely high overall incidence of renal damage. Our population was one of the most seriously ill popu-

lations studied to date (average mortality, 25%), yet these patients were representative of the patients who most often require these agents and therefore deserved study. We found that gentamicin-treated and tobramycin-treated patients were at equal risk for renal damage. There were no clinical parameters unbalanced against the gentamicin-treated group, and thus we could not explain the greater occurrence of gentamicin nephrotoxicity on clinical grounds. On the contrary, the clinical differences which we did find between the gentamicin-treated and tobramycin-treated groups uniformly favored increased tobramycin nephrotoxicity. For example, the tobramycin-treated group had significantly more males, who are perhaps at greater risk of renal damage (R. A. Parker, W. M. Bennett, C. E. Plamp, D. C. Houghton, D. N. Gilbert, and G. A. Porter, Program Abstr. Int. Cong. Chemother. 11th, Boston, Mass., abstr. no. 938, 1979). The tobramycin-treated group showed a trend toward longer duration of treatment. Finally, almost twice as many gentamicin courses were less than 5 days long, again favoring increased tobramycin nephrotoxicity.

Although there were no differences in dose or blood levels, the predominant pharmacokinetic difference between the gentamicin-treated and tobramycin-treated groups was an increased tissue accumulation in the gentamicin-treated group. Since our prospectively studied gentamicin-treated and tobramycin-treated groups did not differ in base-line risk factors or in risk factors developing during the treatment period, we propose that differences in the rates of renal damage resulted from differences in the tissue accumulation-related nephrotoxic potentials of gentamicin and tobramycin.

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