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Amikacin and Gentamicin Accumulation Pharmacokinetics and Nephrotoxicity in Critically Ill Patients

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Twenty-five critically ill adults receiving blood level-adjusted doses of amikacin were prospectively studied with serum, urine, and, when possible, tissue amikacin concentrations. These data were fitted to a two-compartment pharmacokinetic model. Prolonged urine collections or postmortem tissues (or both) were used to confirm predicted tissue accumulation. Nephrotoxicity was also investigated. Patients were defined as having renal damage if they showed an increase in serum creatinine of >0.5 mg/100 ml, an increase in urine β_2-microglobulin of >50 mg/day, and presence of urinary casts of >500/ml. Renal damage was attributed to amikacin if there was, in addition to the above, tissue accumulation of amikacin of >600 mg. These patients were matched with 25 patients treated with gentamicin during the same time period. There were no statistical differences between the gentamicin- and amikacin-treated patients in age, sex, weight, base-line creatinine clearance, concurrent cephalosporins or diuretics, treatment duration, site of infection, normalized (amikacin/gentamicin dosing ratio of 3:1) total dose, mortality, or tissue accumulation. More amikacin-treated patients (19 of 25) than gentamicin-treated patients (9 of 25) received prior aminoglycosides ($P < 0.01$). The only pharmacokinetic parameter that differed between amikacin and gentamicin was a greater K_{21} for gentamicin. Nephrotoxicity was observed in 4 gentamicin-treated patients (16%) and 5 amikacin-treated patients (20%). At a 3:1 dosing ratio, there were no significant differences between amikacin and gentamicin two-compartment pharmacokinetics and nephrotoxic potential in matched critically ill patients, but the trend of these data showed greater amikacin tissue accumulation. However, at an amikacin/gentamicin dosing ratio of 4:1, their tissue accumulation potential appeared to be almost identical.

Amikacin and gentamicin are aminoglycoside antibiotics excreted in urine unchanged after glomerular filtration. However, in spite of an average 2-h half-life, total urine recovery is not complete at 24 h because a small portion of each dose undergoes renal tubular reabsorption and accumulates in renal tissue (1, 15). Both of these antibiotics concentrate in human kidneys, even in patients who do not have renal failure and who are given recommended doses (3). Gentamicin has been detected in patient urine, serum, and tissue for prolonged periods after cessation of treatment, and this tissue persistence can be quantitated by using a multicompartment pharmacokinetic model (4, 8, 9), although most investigators continue to evaluate aminoglycoside pharmacokinetics with a one-compartment model (5, 16). Theoretically, amikacin has multicompartment pharmacokinetic characteristics similar to those of gentamicin (4, 9), tobramycin (10), and netilmicin (A. Mangione, T. J. Cumbo, W. J. Jusko, and J. J. Schentag, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta, Ga., abstr. no. 384, 1978), yet the persistence of amikacin in serum, urine, and tissues has not previously been quantitatively evaluated after multiple dosing.

Both aminoglycosides are nephrotoxic, and the incidence of renal damage from gentamicin and amikacin was similar in a double-blind clinical study (14). This study dosed these antibiotics at a 4:1 amikacin/gentamicin dosing ratio and evaluated the change in serum creatinine as a marker of nephrotoxicity. There is no assurance that 4:1 is a correct ratio in acutely ill patients. Furthermore, a rise in serum creatinine may have multiple causes. Utilizing serum creatinine alone as an indicator of aminoglycoside nephrotoxicity ignores the direct influence of other renal tubular insults on serum creatinine rise. Since quantitation of tissue accumulation may be a useful means of determining the best dosing ratio, as well as a cause of renal damage, our purpose was to describe the pharmacokinetics of amikacin and investigate its potential for nephrotoxicity by utilizing both an assessment of tissue uptake and more sensitive and specific tests of renal tubular damage. Because

the correct dosing ratio is not clear, we evaluated tissue accumulation and nephrotoxic potential of both 3:1 and 4:1 ratios.

MATERIALS AND METHODS

Patients. Twenty-five patients receiving multiple doses of amikacin were studied. The majority of these patients were older, critically ill adults in an intensive care unit. Dosing of amikacin was adjusted during therapy to maintain peak serum concentrations 20 to 40 μg/ml, and trough serum concentrations were maintained at less than 5 μg/ml. Frequent serum samples and usually daily 24-h urine samples were collected, both during treatment and for as long as 30 days after amikacin dosing. Urine was analyzed for amikacin and creatinine excretion, β_2-microglobulin (13), and cast count (7). Postmortem tissue samples were also obtained from eight amikacin-treated and two gentamicin-treated patients who died during treatment. Serum, urine, and tissues were assayed for amikacin by radioimmunoassay.

These 25 amikacin-treated patients were retrospectively matched with 25 patients who had received gentamicin and were studied in an identical manner during the same time period. The retrospective matching was performed without knowledge of renal function changes or pharmacokinetic parameters. Criteria for matching were: age, base-line creatinine clearance, concurrent nephrotoxic drugs (oral neomycin, amphotericin B, and/or furosemide), mortality, and prior aminoglycoside therapy (any exposure within 1 month). Gentamicin dosing was also adjusted based on blood levels, but the desired peak serum concentrations for gentamicin were 4 to 10 μg/ml, and trough serum concentrations were maintained at less than 2.0 μg/ml (12).

Pharmacokinetic analysis. Figure 1 provides an overview of blood sampling, computer analysis, and the pharmacokinetic model we employed to describe the data. The biphasic decline in serum aminoglycoside concentrations during the washout period post-therapy was fitted to a two-compartment open model by using the NONLIN least squares regression computer program (6). The two-compartment pharmacokinetic parameters, plus the patient's actual dosing, were then used to predict actual serum concentrations during and after therapy. The accuracy of data fit to our two-compartment model was determined by agreement of measured and predicted serum concentrations within 20% at all time points during and after therapy. Then the two-compartment parameters for distribution and elimination were used to calculate the amount of drug in the tissue compartment both during treatment and at the end of dosing. The reported tissue accumulation was the highest value measured after the final dose. This pharmacokinetic prediction was verified in 8 amikacin-treated patients with postmortem tissue analysis and in 17 patients with total urine collections and analysis during the washout period.

Nephrotoxicity attributable to aminoglycoside was defined as an increase in serum creatinine of >0.5 mg/100 ml, which was preceded by renal tubular damage (as evidenced by a rise in cast count of >500 casts per ml and/or a rise in β_2-microglobulin excretion in excess of 50 mg/24 h) and excessive aminoglycoside tissue accumulation.

In these studies, accumulation and dosing of amikacin was initially divided by 3 as an adjustment for dosing and potency in relation to gentamicin, since this is the ratio of their recommended doses. Nephrotoxic accumulation was defined as 200 mg for gentamicin and 600 mg for amikacin (12). We later assessed the value of a 4:1 amikacin/gentamicin dosing ratio for tissue accumulation, as this has been employed in a recent double-blind randomized clinical trial (11).

Simulated dosing. Because of differences in renal function and therapeutic priorities, not all patients received the same dosage or duration of treatment. To analyze the variability in data which might be due to differences in duration of treatment or dose, each patient was also "dosed" by computer simulation for 10 days with a calculated regimen based on body weight and renal function and their individual two-compartment pharmacokinetic parameters. We have previously done this to compare gentamicin and tobramycin (11). Serum concentrations and tissue accumulation results from these simulations were then used to compare gentamicin and amikacin.

Statistical evaluation was performed by using Student's t test or chi-square with Yates correction. Statistical significance was defined as $P < 0.05$.

RESULTS

Clinical comparison. The clinical characteristics of the two groups are presented in Table 1. Patients in the gentamicin- and amikacin-treated groups were similar in age, sex, and body surface area. The average base-line creatinine clearance was 45 ml/min in both groups and indicates that patients in each group had renal impairment. Mean duration of therapy was about 10 days, and the average total dose did not differ statistically when a potency factor of 3 was used to correct amikacin. At 4:1, the dosages were almost identical.

About equal numbers of each group were managed in the intensive care unit. Patients were also well matched for type of infection and incidence of bacteremia. Fourteen of the amikacin-treated patients and 13 of the gentamicin-treated patients died during hospitalization, with most patients in either group dying from their underlying disease.

The patients in each group were not statistically different in concurrent carbenicillin, cephalosporins, and/or other potentially nephrotoxic drugs. A similar number in each group received greater than standard dosing (3 to 5 mg/kg per day for gentamicin and 9 to 15 mg/kg per day for amikacin). The amikacin-treated group had a significantly higher incidence of prior aminoglycoside exposure.

Pharmacokinetic comparison. Table 2 summarizes the results of the pharmacokinetic comparison. The volume of the central compartment (V_c) was 25 to 30% of total body weight, with the volume of distribution at steady state

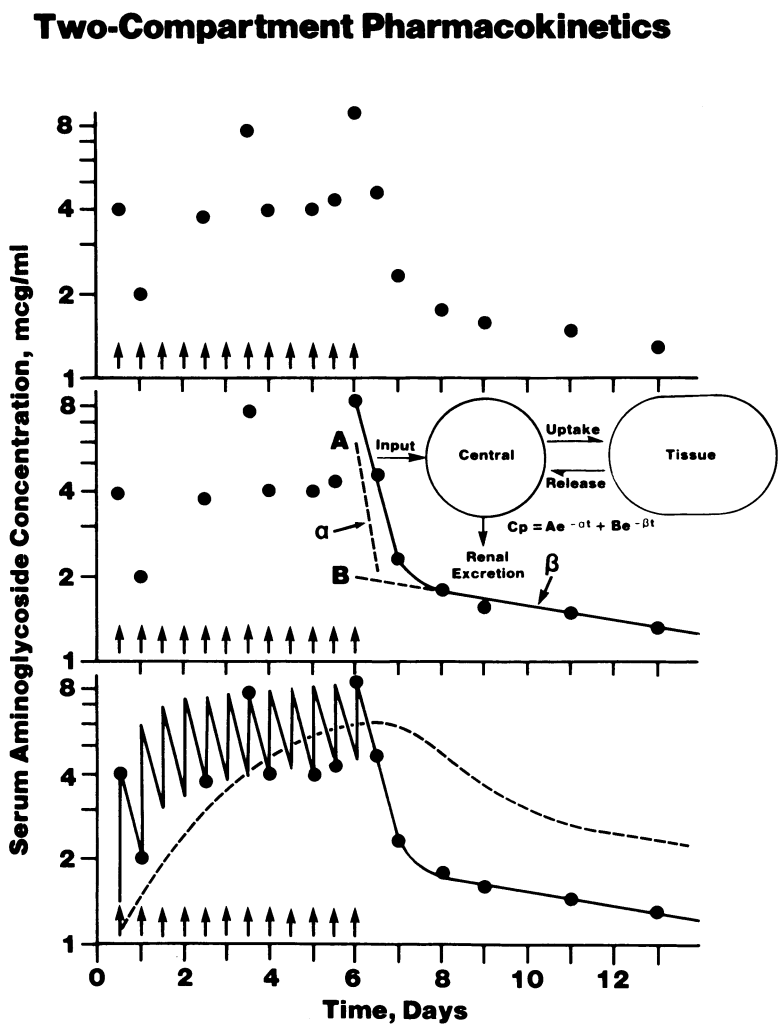

FIG. 1. *Protocol for patient studies and data analysis, including peak and trough serum concentrations during multiple-dose therapy, the two-compartment open model used to fit the washout data in the center frame, and the fitted serum concentrations as a solid line in the bottom frame. Also shown is the simulated peripheral compartment uptake amount as a dashed line (scale, ×10).*

(V_{dss}) about four times larger. The terminal half-life exceeded 7 days in both groups. The ratio of rate of influx of drug into tissue (K_{12}) to rate of efflux (K_{21}) for both drugs was similar and greater than one. Total body clearance of the drugs (calculated from dose divided by area under the curve) averaged 30 ml/min, representing an average of 80% of creatinine clearance. After making the correction for the 3:1 dosing ratio, the amount of amikacin in the tissue compartment at the last dose was not statistically different from the amount of gentamicin, but the trend was toward a higher amikacin accumulation (Table 2). At 4:1, the values were essentially identical for these two compounds. When simulated dosing was done for 10 days, and the predicted amount of drug in the tissue compartment was compared, no significant differences between these antibiotics were found. According to the two-compartment model used, about 10% of the total dose was left in the tissue compartment after 10 days of simulated dosing.

Correlation between base-line creatinine clearance and amikacin terminal half-life ($t_{1/2\beta}$) was poor ($r = 0.09$). Poor correlation was also found between the milligrams-per-kilogram body load of amikacin and base-line creatinine clearance ($r = 0.08$).

Nephrotoxicity. Four of the gentamicin-

TABLE 1. *Comparison of clinical characteristics of amikacin- and gentamicin-treated patients*[a]

Parameter	Gentamicin	Amikacin
No. of patients	25	25
Age (yr)	62 ± 15	58 ± 14
Sex (F/M)	15/10	10/15
Surface area (m^2)	1.71 ± 0.22	1.73 ± 0.21
Base-line creatinine clearance (ml/min)	46.6 ± 30.3	43.4 ± 40.1
Prior aminoglycoside therapy[b]	9	19[c]
Concurrent drug therapy		
Cephalosporins	9	7
Carbenicillin	1	1
Other nephrotoxic drugs	19	18
Both cephalosporins and another nephrotoxin	8	6
Infection[d]		
Bacteremia	14	18
Soft tissue	9	6
Urinary tract	7	12
Pneumonia	8	11
No. of patients in intensive care unit	15	17
Mortality	15	10
Dosing		
No. of patients given >standard dose[e]	6	7
No. of patients given ≤standard dose[e]	19	18
Days of therapy	9.7 ± 5.5	11.0 ± 6.0
Total dose (mg/kg)	31.73 ± 27.26	40.60 ± 42.67[f]

[a] Results expressed as mean ± standard deviation.
[b] Less than one month before.
[c] Statistically significant difference.
[d] Each patient can have more than one infection site, in addition to bacteremias.
[e] Standard doses were 3 to 5 mg/kg per day for gentamicin or 9 to 15 mg/kg per day for amikacin with adjustment for renal function.
[f] Amikacin divided by three as a normalization factor for potency differences.

TABLE 2. *Comparison of pharmacokinetic values and incidence of nephrotoxicity for amikacin and gentamicin*[a]

Parameter	Gentamicin	Amikacin
No. of patients	25	25
V_c, central (liters/kg)	0.257 ± 1.100	0.305 ± 0.088
K_{12}, rate in (h^{-1})	0.025 ± 0.030	0.016 ± 0.015
K_{21}, rate out (h^{-1})	0.010 ± 0.009	0.005 ± 0.003[b]
K_{12}/K_{21}	2.74 ± 1.80	3.25 ± 2.89
K_{10}, overall elimination rate (h^{-1})	0.18 ± 0.21	0.10 ± 0.08
Total body clearance (ml/min)	29.53 ± 18.10	33.45 ± 24.60
Total body clearance/creatinine clearance	0.80 ± 0.65	0.78 ± 0.46
V_{dss}, steady state (liters/kg)	0.93 ± 0.49	1.34 ± 0.98
Half-life, terminal (h)	146.5 ± 115.4	187.7 ± 62.5
Predicted amount of drug in tissue at last dose (mg)	117.4 ± 83.1	173.5 ± 186.3[c]
Predicted amount of drug in tissue at last dose with simulated dosing (mg)[d]	149.3 ± 141.7	203.0 ± 166.0[c]
Predicted accumulation/total dose with simulated dosing (%)[d]	8 .23 ± 7.14	9.43 ± 7.17
No. of aminoglycoside-nephrotoxic patients	4	5

[a] Results expressed as mean ± standard deviation.
[b] Statistically significant difference, $P < 0.05$.
[c] Amikacin divided by three (at 4:1, this value becomes 152).
[d] Computer simulated dosing for 10 days based on weight, renal function, and individually derived pharmacokinetic parameters in each patient.

treated patients and five of the amikacin-treated patients met the tissue accumulation criteria for aminoglycoside nephrotoxicity at a 3:1 ratio. At a 4:1 ratio, there were four amikacin-nephrotoxic patients, identical to gentamicin. The nephrotoxic patients were not the overdosed individuals, as only two of the five amikacin-nephrotoxic patients had received over the standard dose, compared with none of the four gentamicin-nephrotoxic patients. Also quite remarkably, these nephrotoxic patients had initial peak and trough concentrations similar to those of the nontoxic patients. However, by the end of therapy, the nephrotoxic patients had trough serum concentrations as high as twice the values of nontoxic patients.

In examining the effects of prior aminoglycoside exposure, three of five (60%) of the amikacin-nephrotoxic patients had received prior aminoglycoside therapy, as had 16 of 20 (80%) of the nontoxic patients. None of the four gentamicin-nephrotoxic patients had prior aminoglycoside exposure, whereas 9 of 21 (43%) of the nontoxic patients had.

Tissue recovery. Permission for autopsy was obtained in only one of the amikacin-nephrotoxic patients who expired. Tissue concentrations of amikacin are shown in Table 3. As in nontoxic individuals, much of the body amount was concentrated in the kidneys, which also had the highest tissue/serum amikacin concentration ratio. Consistent with accumulation theory, the 361:1 concentration ratio we noted here was higher than the 21:1 to 60:1 ratios previously seen with amikacin in nontoxic patients (3). The total body amount of 798 mg was 88% of the 915 mg predicted from the two-compartment model. Essentially all tissues had higher concentrations than did serum, including even such poorly perfused sites as fat, bone, and the mitral valve. The patient died 120 h after the last dose, yet the measured tissue concentrations were all above the minimal inhibitory concentrations for sensitive gram-negative rods.

DISCUSSION

This analysis shows that the pharmacokinetic characteristics of amikacin are predictable from the two-compartment model and are similar to

TABLE 3. *Postmortem tissue concentrations and tissue recovery in a patient with amikacin nephrotoxicity (the patient expired 120 h after the final dosage)*

Recovery site	Weight[a] (g)	Amikacin content			
		Concn (μg/g)	Amt (mg)	% of total drug in organ	Tissue/serum ratio
Kidney	260	793.8	206.4	25.8	361:1
Liver	2,000	30.1	60.2	7.5	14:1
Heart	350	20.0	7.0	0.9	9:1
Lung	1,000	47.6	47.6	5.9	22:1
Bone	4,571	22.1	101.0	12.6	10:1
Fat	8,571	2.8	23.9	3.0	1.3:1
Skeletal muscle	27,857	11.3	314.9	39.6	5:1
Pancreas	130	9.8	1.3	0.2	4.4:1
Gastrointestinal tract	2,700	8.5	22.9	2.9	3.9:1
Spleen	250	20.2	5.0	0.6	9:1
Mitral valve		8.6			4:1
Serum	3,571	2.2	7.9	1.0	
Total	51,300		798.1	100.0	
Measured	50,000				

[a] The kidney, liver, heart, lung, spleen, and pancreas weights were measured at autopsy; the others were estimated from physiological data in age-matched persons.

those of other aminoglycosides. The central volume is about 30% of total body weight; total clearance is about three-quarters of the creatinine clearance; steady state distribution volume is four times larger than central volume, and the terminal half-life of the drug in tissue and blood is about 7 to 10 days. Like other aminoglycosides, much of each amikacin dose resides in the central compartment initially, but a small portion of each dose distributes extensively and is not cleared completely by glomerular filtration. This portion of drug remains in the body to be eliminated very slowly. The slow washout of this portion, about 10% of the total dose, accounts for the prolonged serum half-life.

The use of the two-compartment pharmacokinetic model was verified in this study by recovery of the drug from tissue and from serum and urine over a prolonged time. Like other aminoglycosides, amikacin is probably reabsorbed by the renal tubules, as evidenced by the fact that amikacin total body clearance was less than creatinine clearance, whereas complete recovery of the dose in urine indicated that no metabolism of the drug occurred.

Considering that the mean terminal half-life of amikacin in this study was 7.8 days, and that the drug is ordinarily dosed every 12 h, it is understandable that every patient treated accumulates amikacin. In our patients who received the recommended dosage for their individual renal function, neither the predicted amount of drug in the tissue (milligrams per kilogram of total weight) nor the terminal half-life correlated well with the base-line creatinine clearance. This demonstrated that the process of uptake of drug into tissue, and later release from tissue, is essentially not dependent upon glomerular filtration. Although the K_{21} was significantly greater for gentamicin, it is also important to consider the ratio of K_{12}/K_{21} since K_{21} or K_{12} alone is a derived parameter. There was no difference between these drugs in the K_{12}/K_{21} ratio. Since the ratio is greater than one for both drugs, the drug is taken into the peripheral compartment faster than it is released, and a net accumulation occurs with each succeeding dose. This net accumulation is also influenced by the rate of renal excretion, but net accumulation due to tissue uptake occurs so slowly that changes in renal excretion have little actual effect on terminal half-life. Therefore, in patients who have appropriate serum concentrations and are given recommended doses, decreased renal function alone does not necessarily lead to excessive tissue accumulation or itself predispose to nephrotoxicity. However, overdosed individuals would still be expected to also accumulate high tissue amounts and be at high risk of nephrotoxicity.

Our study purpose was to compare pharmacokinetic parameters in similar patients. In these similar patient groups, we found no significant difference between amikacin and gentamicin nephrotoxicity. Perhaps the amikacin-treated patients had been predisposed to nephrotoxicity, since they had more frequently received prior aminoglycoside therapy. If this were the case, however, the greater number of patients receiving prior aminoglycosides would have developed nephrotoxicity. A greater number of nontoxic patients were given prior aminoglycosides in both the gentamicin- and amikacin-treated groups. Sixty percent of the amikacin-nephro-

toxic patients had this prior exposure, but 80% of the nontoxic patients also did. With gentamicin as well, a greater incidence of exposure to prior aminoglycosides was noted in the nontoxic group. Thus, the prior use of aminoglycosides in some of our patients had little apparent effect on subsequent nephrotoxicity.

In this small sample of critically ill aminoglycoside-treated patients, gentamicin and amikacin displayed similar two-compartment pharmacokinetics and produced a similar incidence of nephrotoxicity. Our results suggest that a 4:1 potency factor is consistent with the clinical literature regarding relative nephrotoxicity. At this ratio, the tissue accumulation pharmacokinetics of these two compounds appear almost identical.

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