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Serial Trough and Peak Amikacin Levels in Plasma as Predictors of Nephrotoxicity

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We studied 113 patients treated with intravenous amikacin to determine the value of determining serial trough and peak amikacin levels in plasma for predicting nephrotoxicity. Thirteen patients (11.5%) developed renal toxicity, with significant increases from 48 to 96 h in both peak and trough amikacin levels (6.7 ± 4.7 [standard deviation] days before the serum creatinine rose). The nontoxicity group had no change or even showed decrements in amikacin levels in plasma. A higher nephrotoxicity risk was seen in patients with increments greater than 1 μg/ml between 48 and 96 h, with odds ratios of 16.4 for trough, 8 for peak, and 7.2 for both levels. We suggest that an increment of at least 1 μg/ml in amikacin levels in plasma from 48 to 96 h may predict the appearance of renal toxicity.

The aminoglycosides are commonly used in the treatment of severe gram-negative-bacillus infections (13). Unfortunately, nephrotoxicity is a common complication that requires discontinuation of therapy (14). Clinical studies have identified several risk factors, such as the underlying conditions of the patient or complications owing to the aminoglycoside itself (8, 11, 15, 18, 19).

The aminoglycosides have a narrow therapeutic margin; patients given similar doses showed a wide disparity in levels in serum (12). The serum immunoassay has been accepted as a useful tool for enhancing drug efficacy, but its value in foretelling renal toxicity is controversial.

This prospective study was designed to estimate the value of serial trough and peak levels in predicting renal toxicity in patients treated with intravenous amikacin.

All hospitalized patients treated with intravenous amikacin for a minimum of 48 h, alone or in combination with other antibiotics, were included in this 3-month prospective study (April to June 1988). Patients with shock (systolic blood pressure less than 90 mm Hg and signs of hypoperfusion for more than 6 h); acute renal failure; hepatorenal syndrome (chronic liver disease plus oliguria, azotemia, and urinary sodium concentration lower than 10 meq/liter); end-stage renal disease under dialysis; and renal, liver, or bone marrow transplantation treated with cyclosporine were excluded from the study.

Amikacin has been the only aminoglycoside used in our hospital since 1981 (17), and it is usually administered intravenously (5 mg/kg [body weight], three times per day) in a 30-min period; the dose was corrected according to the creatinine clearance (CL_{CR}) calculated with the formula described by Cockcroft and Gault (male CL_{CR} = 140 − age × weight/72 × serum creatinine; female CL_{CR} = 0.9 × male CL_{CR}) (5).

The following data were obtained for each patient: age, sex, weight, underlying disease, control serum creatinine, trough and peak amikacin levels in plasma, calculated and given amikacin in milligrams per day, and other antibiotics used. The serum creatinine was determined two times per week until cessation of therapy. The trough and peak amikacin levels in plasma were determined at 48 and 96 h after the treatment was begun, immediately before (trough) and 30 to 45 min after (peak) the morning dose.

Renal toxicity was defined as: (i) an increase in serum creatinine of ≥0.5 mg/dl in patients with control serum creatinine levels of ≤1.9 mg/dl; (ii) an increment in serum creatinine of ≥1 mg/dl in patients with serum creatinine levels from 2.0 to 4.9 mg/dl; and (iii) a rise of ≥1.5 mg/dl for patients with serum creatinine above 5 mg/dl (8). In our laboratory, the coefficients of variation were 10% for serum creatinine below 2 mg/dl and smaller when serum creatinines were above 2 mg/dl.

The serum creatinine was measured in an Autoanalyzer. The serum amikacin was determined in duplicate by radioimmunoassay using a solid-phase kit (22) (Diagnostic Products Co., Los Angeles, Calif.), with inter- and intraassay coefficients of variation of 6.8 and 7.5%, respectively. According to the manufacturer's recommendations, the therapeutic ranges for amikacin were 2 to 9 μg/ml for trough levels and 10 to 20 μg/ml for peak levels.

All data were saved in a PC computer (Hewlett-Packard Vectra-AT). The statistical analysis was performed by using the Software Stat-pak NWA. Chi-square with Yates correction, the Fisher exact test, and two-tailed paired and nonpaired Student *t* tests were used. All data are expressed as the mean ± one standard deviation and difference between means, with confidence intervals of 95% (95% CI) (3, 9). A P value of <0.05 was considered statistically significant.

A total of 113 patients fulfilled the criteria for inclusion in the study: 50 males (44%) and 63 females (55%) with a mean age of 50.2 ± 18.5 years and a serum creatinine of 1.2 ± 0.45 mg/dl. The duration of treatment was 11.6 ± 7.9 days (range, 3 to 45 days). Underlying diseases were diabetes mellitus in 29 cases (25.6%), malignancies in 24 cases (21.2%), chronic

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TABLE 1. Main characteristics of patients with and without amikacin renal toxicity[a]

Patients	Age (yr)	Serum creatinine (mg/dl)	Wt (kg)	No. of patients			Doses (mg/day)	
				Cephalothin treatment	Chronic liver disease	Diabetes mellitus	Given	Calculated
Without toxicity	49 ± 9.2 (100)	1.1 ± 0.49 (100)	58 ± 12 (100)	23 (100)	12 (100)	23 (100)	571 ± 221 (100)	595 ± 259 (100)
With toxicity	61 ± 14.3[b] (13)	1.3 ± 0.50 (13)	55 ± 9 (13)	4 (13)	2 (13)	6 (13)	466 ± 201 (13)	425 ± 179[b] (13)

[a] Values are means ± standard deviation. The total number of patients is given in parentheses.
[b] $P < 0.05$.
[c] $P < 0.001$.

liver disease in 14 cases (12.3%), connective tissue diseases in 10 cases (8.8%), and others in 36 cases (31.8%).

Eight patients received amikacin alone, 62 received amikacin with another antibiotic, and 43 received it as part of a three-drug regimen; 31 patients were treated with cephalosporins (27 received cephalothin [2 to 4 g/day], and the other 4 received cefotaxime); 56 received penicillins; 43 received clindamycin; 10 received sulbenicillin; and 8 received metronidazole.

The numbers of samples collected in our population for determination of trough and peak amikacin levels in plasma were 103 from 113 patients (91%) for determination of both levels at 48 h and 92 from 105 patients (88%) for trough levels and 90 from 105 patients (86%) for peak levels at 96 h. In all cases, peak levels were higher than trough levels.

Of 113 patients, 13 (11.5%) developed nonoliguric renal failure. The control serum creatinine was 1.33 ± 0.49 mg/dl, and the increment was 1.27 ± 1.10 mg/dl (range, 0.5 to 4.1 mg/dl). Table 1 shows the main characteristics of patients with and without amikacin nephrotoxicity. The mean age of patients with toxicity was significantly higher than the mean age of patients in the nontoxicity group. At 48 h, trough and peak levels were not different; at 96 h, trough levels were significantly higher in the group with toxicity ($P < 0.001$); peak levels were also higher, but the difference was not significant.

Figure 1 shows the changes in amikacin trough and peak levels from 48 to 96 h in 9 of 13 patients with renal toxicity. The reasons for the exclusion of four patients from this analysis were nephrotoxicity at 96 h in two patients and lack of either trough or peak samples at 48 or 96 h from the others. There was no evidence of toxicity at 96 h in these nine patients: serum creatinine obtained at this time was not different from the control (Δ 0.12 ± 0.2 mg/dl; $t = 1.73$; 95% CI, −0.04 to 0.28). Also shown in Fig. 1 are the changes in 83 of 100 patients of trough levels and in 76 of 100 patients of peak levels in the group without renal toxicity. The criterion for exclusion of patients from this analysis was the lack of determination of one of the amikacin levels in plasma at either 48 or 96 h.

The patients with nephrotoxicity had significant increments in both levels: trough, Δ 1.76 ± 2.16 μg/ml ($t = 2.3$; 95% CI, 0.10 to 3.4); and peak, Δ 2.5 ± 2.8 μg/ml ($t = 2.5$; 95% CI, 0.35 to 4.6). In contrast, after 96 h of treatment, the group without toxicity showed falls in amikacin trough levels of −0.94 ± 2.8 μg/ml ($t = 2.8$; 95% CI, −1.6 to −0.29) and in peak levels of −0.65 ± 5.2 μg/ml ($t = 1.07$; 95% CI, −1.9 to 0.5).

In the group with nephrotoxicity, increments of amikacin between 48 and 96 h of >1 μg/ml were observed in seven of nine patients (77%) for trough level and in seven of nine patients (77%) for peak level, and five of the patients (55%) showed increases in both levels. In contrast, in the nontoxicity group, the elevation was observed in 13 of 74 patients (17%) for trough levels (Fisher test, $P < 0.0005$), in 21 of 69 patients (30%) for peak levels (Fisher, $P < 0.008$), and in 10 of 68 patients (14.7%) for both levels (Fisher, $P < 0.02$). Thus, the incidences of nephrotoxicity in all patients with an increment greater than 1 μg/ml were 35% for trough levels, 24% for peak levels, and 33% for both levels, with odds ratios of 16.4, 8, and 7.2, respectively. In patients with toxicity, the increment in serum creatinine occurred 10.8 ± 4.7 days after the start of treatment.

The incidence of renal toxicity has been reported to range from 8 to 28%. Smith et al. (19–21, 23) reported incidences of nephrotoxicity with gentamicin ranging from 11 to 26% and with tobramycin ranging from 12 to 28% at the same hospital. In contrast, the incidence that we observed in this study was 11.5%, similar to our previous report (10%) (8). This finding demonstrated that when equal criteria were used to define nephrotoxicity, the incidences in our institution remained the same. Once more, as in our previous observations, these results confirmed old age as a risk factor and that there was no higher risk for toxicity in patients with chronic liver disease or in those treated with the combination of amikacin plus cephalothin (8).

Previous retrospective studies emphasized the difficulty of obtaining adequate samples for determination of trough and peak aminoglycoside levels in the same patient (1, 2, 7). In the present study, sampling was done at precise times. Trough and peak determinations were very reliable because they were done in pairs for more than 85% of our population, and the peak level was always higher than the trough level.

Moore et al. (16) found in a multivariate analysis that the initial peak but not trough levels of gentamicin in samples taken within 48 h after the start of treatment were significantly higher in patients with nephrotoxicity. Goodman et al. (10) and Dahlgren et al. (6) reported that trough but not peak levels were higher in the toxicity group. Our results clearly showed no difference in trough and peak levels at 48 h among the toxicity and nontoxicity groups (Table 1), but at 96 h we observed a significant difference in trough levels between groups. However, the difference in peak levels, even when the values were higher in patients who developed nephrotoxicity, was not significant.

Our results suggest that one isolated determination of trough or peak amikacin level at either 48 or 96 h was not enough to predict nephrotoxicity, because either trough or peak levels at 48 and 96 h were within the therapeutic range in both groups. Interestingly, it is the increment in trough and peak levels from 48 to 96 h that actually predicted the appearance of nephrotoxicity. The rise in trough and peak amikacin levels in patients who developed nephrotoxicity was evident 6.7 ± 4.7 days before the elevation of serum creatinine. This change in levels of amikacin in plasma was not the result of overdose; furthermore, the patients of the

TABLE 1—*Continued*

Total amikacin dose (mg)	Treatment duration (days)	Concn (μg/ml)			
		48 h		96 h	
		Trough	Peak	Trough	Peak
6,483 ± 4,514 (100)	11.6 ± 6.4 (100)	4.9 ± 2.8 (93)	9.7 ± 4.6 (91)	3.0 ± 2.4 (83)	8.8 ± 4.1 (76)
6,365 ± 3,145 (13)	14.8 ± 6.0 (13)	4.1 ± 1.6 (11)	7.5 ± 3.5 (10)	6.0 ± 2.1[c] (12)	11.2 ± 3.5 (10)

group with toxicity received lower doses of amikacin than the patients without renal toxicity. This finding is supported by the study of Cabrera et al. (4) of patients with chronic liver disease; these investigators found an elevation in trough levels of gentamicin several days before the increase in serum creatinine.

Reports made by others (16, 18) and our previous (8) and current data showed that either trough or peak aminoglycoside levels in patients who developed nephrotoxicity were within the therapeutic range. Therefore, the therapeutic range should not be used by itself to adjust the aminoglycoside dose to prevent nephrotoxicity. The patients with rises in amikacin levels in plasma greater than 1 μg/ml between 48 and 96 h had a higher incidence of nephrotoxicity and a significant increase in relative risk. For this reason, we believe that it is mandatory to determine the levels of amikacin in plasma two or three times per week and that any increment above 1 μg/ml in trough or peak levels (even within the therapeutic range) must be taken as an early sign of the development of nephrotoxicity. Although only 25 to 35% of patients with such increases in amikacin levels may develop nephrotoxicity, it is possible that dosage or dose correction may help to prevent nephrotoxicity without reducing efficacy.

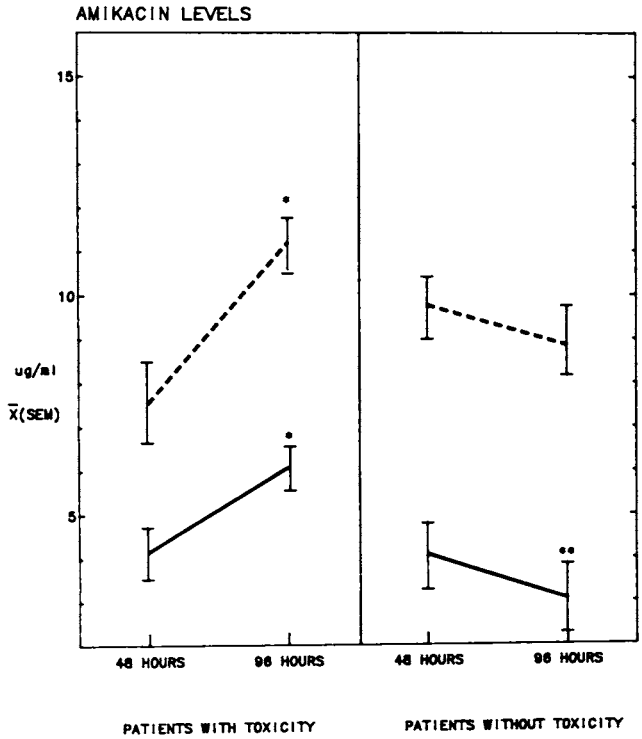

FIG. 1. Change in trough (solid line) and peak (dashed line) amikacin levels in plasma between 48 and 96 h of the start of treatment in patients with and without renal toxicity. SEM, Standard error of the mean; *, $P < 0.05$; **, $P < 0.02$.

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