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 nephrotoxicity 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.

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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.

Table 1. Main characteristics of patients with and without amikacin renal toxicity

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (yr)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Wt (kg)</th>
<th>No. of patients</th>
<th>Doses (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without toxicity</td>
<td>49 ± 9.2 (100)</td>
<td>1.1 ± 0.49 (100)</td>
<td>58 ± 12 (100)</td>
<td>23 (100)</td>
<td>Cephalothin treatment</td>
</tr>
<tr>
<td>With toxicity</td>
<td>61 ± 14.3 (13)</td>
<td>1.3 ± 0.50 (13)</td>
<td>55 ± 9 (13)</td>
<td>4 (13)</td>
<td>Chronic liver disease</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes mellitus</td>
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<td>Calculated</td>
</tr>
</tbody>
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*Values are means ± standard deviation. The total number of patients is given in parentheses.

P < 0.05.

P < 0.001.

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
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.

LITERATURE CITED

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