Increased Aminoglycoside Dosage Requirements in Hematologic Malignancy

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Aminoglycoside pharmacokinetic parameters were studied prospectively in 27 patients with an underlying hematologic malignancy and fever associated with neutropenia and in 18 control patients. Pharmacokinetic parameters and dosages were determined by linear regression analysis of a one-compartment model by the method of Sawchuk et al. (R. J. Sawchuk, D. E. Zaske, R. J. Cippolle, W. A. Wargin, and R. G. Strate, Clin. Pharmacol. Ther. 21:362–369, 1976). Significant differences between the study and control groups were found for aminoglycoside volume of distribution (0.40 ± 0.1 versus 0.27 ± 0.05 liter/kg [mean ± standard deviation], respectively; P < 0.0001), clearance (116.6 ± 48.9 versus 68.6 ± 26.7 ml/min, respectively; P < 0.0001), half-life (2.27 ± 0.66 versus 3.5 ± 1.8 h, respectively; P < 0.0001), and elimination rate constant (0.33 ± 0.11 versus 0.24 ± 0.09 hr⁻¹, respectively; P < 0.001). The percentage of bone marrow blast cells (at the time of diagnosis) in patients with acute leukemia significantly correlated with increased aminoglycoside clearance (R² = 36.98%; P = 0.0001). Patients with stage IV lymphomas (Hodgkins disease and non-Hodgkins lymphoma) had a significantly increased clearance compared with patients with lower stages of lymphomas (105.1 ± 18.5 versus 84.1 ± 14.9 ml/min; P = 0.014). Fever, leukocyte count, or chemotherapy, among other clinical and laboratory parameters that were studied, had no significant correlation or effect on aminoglycoside disposition. The average dose of amikacin required to maintain peak concentrations in serum above 20 μg/ml in patients with a hematologic malignancy was 27.5 ± 8.43 mg/kg per day. Pharmacokinetic parameters and dosages for the control patients were comparable to general literature standards. We conclude that the dosages recommended by the manufacturers or those derived from nomograms underestimate the aminoglycoside volume of distribution and clearance in patients with a hematologic malignancy and result in suboptimal peak aminoglycoside concentrations in serum. We recommend that in febrile neutropenic patients with an underlying hematologic malignancy, amikacin be initiated at 7.5 to 10 mg/kg per dose every 8 h (2 to 2.5 mg/kg per dose every 8 h for gentamicin) and adjusted within 24 h based on individual pharmacokinetic analysis.

Aminoglycosides remain one of the most important groups of antibiotics in the treatment of gram-negative infections (25). To maximize efficacy and minimize toxicity with these agents, determination of the drug concentration in serum is necessary (1, 30). Achieving a peak concentration in serum (Cmax) for gentamicin or tobramycin of 6 to 8 μg/ml and for amikacin of 20 to 28 μg/ml is associated with improved survival in patients with gram-negative bacteremias and pneumonias (1, 17, 25–27). The two major factors that determine the value of the Cmax are the dose and the apparent volume of distribution (Vss) of the drug. The Cmax is directly related to the dose and is inversely related to the Vss.

Aminoglycoside dosage nomograms as well as manufacturer-recommended doses assume a constant Vss of approximately 0.25 liter/kg of body weight (3, 6, 16). It has been observed that in certain patient groups (i.e., those with burns [41], with cystic fibrosis [18], in intensive care units [14], in the postoperative period [29]) the Vss is increased. Dosage schedules based on nomograms and manufacturer-recommended guidelines lead to underestimation of the Vss, and, hence, subtherapeutic aminoglycoside Cmax values in these patient populations (14, 18, 22, 29, 41).

Optimal aminoglycoside dosage is particularly important in febrile neutropenic patients. It has been shown that neutropenic patients with gram-negative bacterial infections require higher peak bactericidal concentrations in serum to improve their outcome when compared with those required in nonneutropenic patients (34).

Despite the widespread use of aminoglycosides in febrile neutropenic patients with an underlying malignancy, only limited data are available on the pharmacokinetic parameters of aminoglycosides in these patients (15; R. P. Manny and P. R. Huston, Letter, Clin. Pharm. 5:629–630, 1986; J. K. Phillips, R. L. Spearing, D. J. Crome, and J. M. Davis, Letter, N. Engl. J. Med. 319:1290, 1988). In a study of infectious complications in patients with acute leukemia (10), we adjusted the aminoglycoside dosage by the method of Sawchuk et al. (32) and observed that doses higher than those recommended by the manufacturer were needed in order to achieve therapeutic aminoglycoside concentrations in serum (unpublished data). Hence, we set out a prospective controlled study to determine the aminoglycoside pharmacokinetic parameters in patients with an underlying hematologic malignancy. In this report we describe the details of our results and propose new aminoglycoside dosage guidelines for adult patients with an underlying hematologic malignancy.
TABLE 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. of patients</th>
<th>No. of observations</th>
<th>Age (yr) [mean ± SD]</th>
<th>Sex (no. M/no. F)</th>
<th>Wt (kg) [mean ± SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>7</td>
<td>40</td>
<td>32.3 ± 15.6</td>
<td>5/2</td>
<td>50.2 ± 7.8</td>
</tr>
<tr>
<td>ALL</td>
<td>3</td>
<td>6</td>
<td>24 ± 19.6</td>
<td>2/1</td>
<td>53.9 ± 11.3</td>
</tr>
<tr>
<td>CLL</td>
<td>2</td>
<td>4</td>
<td>57.5 ± 20.2</td>
<td>1/1</td>
<td>57.5 ± 8.7</td>
</tr>
<tr>
<td>NHL</td>
<td>11</td>
<td>19</td>
<td>35.1 ± 14.8</td>
<td>10/1</td>
<td>53.8 ± 14.8</td>
</tr>
<tr>
<td>HD</td>
<td>4</td>
<td>5</td>
<td>51.4 ± 3.1</td>
<td>2/2</td>
<td>50.8 ± 6.4</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>74</td>
<td>38.2 ± 17.7</td>
<td>20/7</td>
<td>50.8 ± 11.6</td>
</tr>
</tbody>
</table>

Control 18 20 31.6 ± 15.6 11/7 68.3 ± 20.9

| a M. Male; F, female. |
| b Abbreviations: AML, acute myeloblastic leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease. |

MATERIALS AND METHODS

Patient population. Forty-four febrile neutropenic episodes requiring aminoglycoside therapy in 27 consecutive patients with an underlying hematologic malignancy between February 1988 and February 1989 were studied. Patients in the study group were newly diagnosed, in documented relapse, or at various stages of their treatment (induction, reinduction, consolidation, maintenance). Eighteen randomly selected age- and sex-matched adults receiving aminoglycosides for gram-negative bacterial infections (urinary tract infections, diabetic foot ulcers, osteomyelitis, bacteremia, and hospital-acquired pneumonias) admitted to the general medical wards, who did not meet the exclusion criteria, served as controls. Control patients had no underlying malignancy and were otherwise healthy adults, aside from their primary medical problem. All patients were of Arab origin, and their characteristics are described in Table 1. Neutropenia was defined as an absolute neutrophil count of <1,000/mm³. Fever was defined as an oral temperature of >38.5°C on one occasion or >38°C on two occasions in a 24-h period at least 4 h apart that was unrelated to the use of drugs or infusion of blood products.

Patients with ascites, pleural effusions, major surgery, creatinine levels in serum of >196 µmol/liter, or septic shock prior to the initiation of aminoglycoside therapy were excluded from the study and control groups, as these conditions may alter aminoglycoside disposition (24, 39).

Antibiotic treatment. Empiric therapy consisted of intravenous ceftazidime (2 g every 8 h) in combination with intravenous amikacin (7.5 mg/kg every 12 h) or gentamicin (1.3 mg/kg every 8 h) (actual body weight was used in all but one patient, who was obese; lean body weight was used in the obese patient). Vancomycin, metronidazole, amphotericin B, or acyclovir was added as indicated.

Pharmacokinetic analysis. Serum samples were collected after at least five estimated half-lives of the aminoglycoside had elapsed, usually 24 h, to ensure that steady-state concentrations in serum were achieved. A predose sample ($C_{min}$) was taken immediately prior to administration of the next scheduled dose. A second sample ($C_{max}$) was taken 1 h following the start of a timed 30-min infusion. All drugs were administered either in 50 or 100 ml of a 5% glucose solution. Actual times of all serum sample collections and drug administration were recorded and used for pharmacokinetic calculations. Aminoglycoside concentrations in serum were measured by a fluorometric polarization immunoassay (TDx; Abbott Diagnostics Division, Irving, Tex.), and analyses were conducted within 8 h of sample collection. Serum samples were obtained through peripheral venipunctures in all the control patients and in 64 (87%) instances in the study group. The remaining 10 (13%) blood samples were drawn through Hickman catheters, as peripheral venipunctures were technically difficult.

Calculation of individual aminoglycoside pharmacokinetic parameters was performed by the method of Sawchuk et al. (32) by using two serum samples. The following equations were used in the calculation of the pharmacokinetic parameters: $k_{el} = \ln[(C_{max}/C_{min})]/\text{time difference}, V_{ss} = \frac{[k_0 (1 - e^{-k_{el} t})] k_e}{k_0 (t_2/2 - k_{el})}, t_{1/2} = 0.693/k_{el}, K_{e} = [k_0 V_{ss} - \text{peak} D (1 - e^{-k_{el} t})]/[k_0 (1 - e^{-k_{el} t})], C_{min} = C_{max} [e^{-k_{el} t_{1/2}} - t], \text{and } CL = k_{el} V_{ss} 16.67, \text{where } k_{el} \text{ is the elimination rate constant, in hour}^{-1}, K_{e} \text{ is the infusion rate, in milligrams per hour; } t \text{ is the time period of infusion, in hours; } t_{1/2} \text{ is the half-life, in hours; } T \text{ is the dosing interval, in hours; peak } D \text{ is the desired } C_{max}, \text{ in micrograms per milliliter; and } CL \text{ is clearance, in milliliters per minute.}

The results obtained from the initial pharmacokinetic studies for each patient were used to determine the dosage required to achieve a $C_{max}$ of >20 and <30 µg/ml for amikacin or >6 and <10 µg/ml for gentamicin. Desired $C_{min}$ concentrations were <8 µg/ml for amikacin or <2 µg/ml for gentamicin.

After attainment of steady state with the calculated dosage, determination of the aminoglycoside level in serum was repeated by the method described above. If levels in serum were inappropriate, the dosage was recalculated. Aminoglycoside levels in serum were determined weekly to ensure that optimal therapeutic concentrations were maintained. Concentrations of ceftazidime and vancomycin in serum were not measured in any of the patients.

Calculation of pharmacokinetic parameters was conducted by using a proprietary spreadsheet computer program (SuperCalc 4 version 1.0; Computer Associates International) into which the equations were entered. Along with pharmacokinetic data, relevant clinical and laboratory information was recorded within the spreadsheet. Information consisted of weight; height; age; treatment protocol; number of days postchemotherapy; temperature; concomitant administration of parenteral nutrition and amphotericin B; total number of platelet and blood transfusions; creatinine level in serum; leukocyte count; hemoglobin; platelet count; blood urea nitrogen; and serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and bilirubin concentrations. Development of ascites or pleural effusion; positive blood, sputum, or urine cultures; and, where appropriate, the percentage of bone marrow blast cells (defined as the percentage of 1,000 counted nucleated bone marrow cells) present at the time of original diagnosis were also noted. All clinical and laboratory data were recorded concurrently with each determination of the aminoglycoside concentration in serum in order to correlate any changes in pharmacokinetic parameters with the variables mentioned above within each course and between subsequent courses of aminoglycoside administration.

Nephrotoxicity was defined as a rise of the creatinine level in serum of >44 µmol/liter from the base line. Otoxicity was not assessed because of the difficulty in performing audiometric examinations in this patient population.

Creatinine CL was estimated by using the method described by Cockcroft and Gault (5). Estimation of $k_{el}$ was
based on the following equation: 0.0024 (creatinine CL) + 0.01 (9).

Statistical analysis. A two-sample t test (two-tailed) and one-way analysis of variance (ANOVA) were used to determine statistical differences between group means. The Pearson product correlation coefficient (r), simple regression analyses, and coefficient of determination (R²) were used to determine correlations and associations. A probability of <0.05 was considered significant. All statistical analyses were conducted on a proprietary statistical software program (Statgraphics version 2.1, Statistical Graphics Corp.).

RESULTS

A total of 74 pairs of determinations of aminoglycoside concentrations in serum (60 for amikacin and 14 for gentamicin) were performed during 44 treatment episodes in 27 consecutive adult patients with a hematologic malignancy. Twenty pairs of determinations of aminoglycoside concentrations in serum were recorded for the 18 control patients. No patients with an underlying hematologic malignancy admitted to the hematology-oncology unit for fever and neutropenia met the exclusion criteria or were denied entry into the study. For analysis of pharmacokinetic parameters, results from patients receiving amikacin and gentamicin were combined, on account of their virtually identical dispositions (24). For Cmax and dosage analyses, the two groups were analyzed separately.

There were a total of 17 positive cultures obtained in 15 of the study group patients. Infections included six pneumonias (three gram negative, two gram positive, two fungal, and one acid-fast bacillus), one urinary tract infection (gram negative), five bacteremias (three gram negative and two gram positive), and five catheter-related infections (four gram positive and one gram negative). In the control group, there were 14 positive cultures in 12 patients. Infections included two pneumonias (gram negative), six urinary tract infections (gram negative), two bacteremias (one gram positive and one gram negative), one osteomyelitis (gram negative), and one diabetic foot ulcer (mixed infection).

Vss. Aminoglycoside Vss values were consistently and significantly elevated in those patients with hematologic malignancies as compared with Vss values in the control group. Within the group of patients with a malignancy, there was no statistically significant difference in the mean Vss between the various diagnoses (ANOVA, P = 0.77; Table 2 and Fig. 1). Patients with acute leukemia had several episodes of fever and neutropenia during their treatment which required multiple courses of aminoglycoside therapy. No significant variation in the Vss was observed from course to course of therapy.

The presence of fever, microbiologically documented infection, chemotherapy administration, leukocyte count (both at nadir and after recovery), or any other clinical or laboratory data recorded (mentioned above) had a significant effect or correlation with the Vss.

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The presence of fever, microbiologically documented infection, chemotherapy administration, leukocyte count (both at nadir and after recovery), or any other clinical or laboratory data recorded (mentioned above) had a significant effect or correlation with the Vss.

t1/2. The t1/2 values were significantly shorter in those patients with a hematologic malignancy compared with the t1/2 values in the control group (Table 2). There was no significant difference in the mean aminoglycoside t1/2 between patients with the various hematologic malignancies (ANOVA, P = 0.28). The t1/2 had a significant direct correlation with age (R² = 0.228%; P = 0.00002) but not with the Vss (R² = 4.25%; P = 0.08) in patients with a malignancy. There was no correlation or association between t1/2 and any of the other clinical or laboratory data recorded.

FIG. 1. Aminoglycoside Vss observed in the group of patients with a malignancy. A total of 89% of the observations were greater than the population average of 0.2 to 0.3 liter/kg.

TABLE 2. Aminoglycoside pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Vss (liter/kg)</th>
<th>k0 (h⁻¹)</th>
<th>t1/2 (h)</th>
<th>CL (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>0.41 ± 0.09</td>
<td>0.36 ± 0.07</td>
<td>2.17 ± 0.75</td>
<td>131.4 ± 58.9</td>
</tr>
<tr>
<td>ALL</td>
<td>0.40 ± 0.06</td>
<td>0.31 ± 0.04</td>
<td>2.23 ± 0.30</td>
<td>113.4 ± 38.9</td>
</tr>
<tr>
<td>CLL</td>
<td>0.35 ± 0.04</td>
<td>0.25 ± 0.06</td>
<td>2.92 ± 0.78</td>
<td>80.7 ± 18.4</td>
</tr>
<tr>
<td>NHL</td>
<td>0.40 ± 0.14</td>
<td>0.31 ± 0.07</td>
<td>2.39 ± 0.57</td>
<td>100.6 ± 19.0</td>
</tr>
<tr>
<td>HD</td>
<td>0.38 ± 0.13</td>
<td>0.30 ± 0.02</td>
<td>2.36 ± 0.18</td>
<td>93.0 ± 23.5</td>
</tr>
<tr>
<td>Total</td>
<td>0.40 ± 0.10⁴</td>
<td>0.33 ± 0.11⁴</td>
<td>2.27 ± 0.66⁴</td>
<td>116.7 ± 48.⁹</td>
</tr>
<tr>
<td>Control</td>
<td>0.27 ± 0.05³</td>
<td>0.24 ± 0.09³</td>
<td>3.50 ± 1.81³</td>
<td>68.6 ± 26.⁷</td>
</tr>
</tbody>
</table>

⁵ Values are means ± standard deviations. Probabilities were determined by the two-sample t test.
  ³ See footnote b of Table 1 for abbreviations.
  ⁴ P = 0.000004.
  ⁵ P = 0.00005.
  ⁶ P = 0.00005.
direct correlation with aminoglycoside CL \( (R^2 = 15.79\% \); \( P = 0.0006 \)). There were no significant correlations or effects upon aminoglycoside CL by any of the remaining clinical or laboratory data recorded.

\( k_{el} \). Patients with an underlying hematologic malignancy had a significantly increased \( k_{el} \) compared with the \( k_{el} \) values in the control group (Table 2). There was no significant difference between the means of the estimated and actual \( k_{el} \) values for the patients with a malignancy \( (P = 0.95) \), and there was a significant correlation between the two \( (R^2 = 13.38\% \); \( P = 0.001 \)). Actual \( k_{el} \) values had a significant but weak correlation with creatinine CL \( (R^2 = 10.54\% \); \( P = 0.005 \)).

**Dosage and \( C_{max} \).** Those patients with an underlying hematologic malignancy who achieved a steady-state \( C_{max} \) equal to or above 20 \( \mu \)g/ml and \( C_{min} \) values less than 8 \( \mu \)g of amikacin per ml required 27.50 \( \pm \) 8.43 mg/kg per day (Fig. 3) versus 19.48 \( \pm \) 4.77 mg/kg per day in those patients with \( C_{max} \) values of less than 20 \( \mu \)g/ml \( (P = 0.00003) \).

Of the 14 observations in patients receiving gentamicin, there were only three with a \( C_{max} \) of greater than 6 \( \mu \)g/ml. In these three observations, the average dosage was 6.8 mg/kg per day.

The mean interval required to maintain \( C_{max} \) values of amikacin above 20 \( \mu \)g/ml and gentamicin above 6 \( \mu \)g/ml was 8.67 h, with a median of 8 h and a range of 6 to 12 h.

![Graph](image1.png)

**FIG. 2.** Linear regression analysis of CL regressed on the percentage of bone marrow blast cells at presentation. Omission of outliers did not significantly influence the value of the correlation coefficient.

**Toxicity.** No patient had a significant rise in creatinine concentration in serum that was directly attributed to aminoglycoside administration. One 60-year-old patient with acute myeloblastic leukemia, who received multiple courses of high-dose aminoglycoside therapy, did have a rising \( C_{min} \) without a rise in the creatinine level in serum. The dosage was recalculated without further sequelae. Another patient with non-Hodgkin lymphoma did have a significant rise in his creatinine level in serum, but he was also receiving amphotericin B. When amphotericin B was withheld for 2 days, the creatinine level in serum returned to base-line levels.

**DISCUSSION**

Infectious complications account for 50 to 70% of deaths in patients with a hematologic malignancy (2, 4). Aminoglycosides are widely used in empiric treatment of febrile episodes in neutropenic patients (33). Because of the narrow range between subtherapeutic, therapeutic, and toxic concentrations, appropriate dosage calculation can only be achieved through determinations of the concentration in serum in these patients, who are often seriously ill (23, 30). Several studies have demonstrated that an improved outcome in patients with gram-negative infections is directly related to the \( C_{max} \) of the aminoglycoside (1, 17, 25-27). Likewise, attainment of an adequate \( C_{max} \) from the first dose contributes to therapeutic efficacy (14).

Klatresky (19) has shown that as the absolute neutrophil count decreases, higher bactericidal activity in serum is required for successful treatment. A peak bactericidal activity in serum of at least 1:8 is required in neutropenic patients (absolute neutrophil count, <1,000), while in severely neutropenic patients (absolute neutrophil count, <100) peak bactericidal activity in serum of 1:16 is required. At lower aminoglycoside concentrations, synergism between the beta-lactam and the aminoglycoside may not occur. This can be overcome by increasing the dose of the aminoglycoside to attain a higher \( C_{max} \) (19). Through aminoglycoside concentrations in serum have not been correlated with an improved outcome in patients with gram-negative infections (25-27).

Dosage nomograms and manufacturer-recommended doses are derived from either a specific patient population or, more commonly, healthy adults, rather than the populations for which the drug is intended (8). The aminoglycosides exhibit wide inter- and intrapatient variabilities in their pharmacokinetic parameters (38) and are known to be affected by various disease states (30). Our data show that dosages recommended by the manufacturer and those based on nomograms are not appropriate for patients with an underlying hematologic malignancy. The \( V_{ss} \) and CL values of aminoglycosides in our patients with a hematologic malignancy were significantly elevated compared those in the control population, who did not have a malignancy. The use of manufacturer-recommended dosages or those of dosage nomograms underestimated the \( V_{ss} \) in patients with a hematologic malignancy and, hence, led to a reduced \( C_{max} \). The 500-mg twice-daily dose of amikacin, which is intended for use in adult patients with a normal \( V_{ss} \) (0.25 liter/kg), would result in a 41% reduction in \( C_{max} \) if the \( V_{ss} \) is increased to 0.4 liter/kg (study group mean). If the \( V_{ss} \) is 0.67 liter/kg (study group maximum), a 63% reduction in \( C_{max} \) occurs. Peak concentrations in serum in our patients with a malignancy were raised to optimum levels when the dosage was increased nearly 100% over manufacturer recommendations to compensate for the increased \( V_{ss} \) and CL.

![Graph](image2.png)

**FIG. 3.** Total daily dose of amikacin required by the patients with a malignancy to achieve amikacin \( C_{max} \) values of >20 \( \mu \)g/ml. Only one observation was recorded in which the patient achieved therapeutic amikacin \( C_{max} \) with the recommended dosage of 15 mg/kg per day.
Usually, as the $V_{ss}$ increases, the $t_{1/2}$ increases; this assumes that CL remains constant (39). Our patients with an underlying malignancy did not have an increase in the aminoglycoside $t_{1/2}$ with increasing $V_{ss}$. The $t_{1/2}$ was, in fact, significantly shorter in the patients with a malignancy than in the control group, despite their increased $V_{ss}$ values. Total aminoglycoside CL from the body exceeded creatinine CL significantly. These observations raise the possibility of enhanced renal or extrarenal elimination of aminoglycosides in patients with an underlying hematologic malignancy.

As mentioned above, no single factor that we recorded was associated with the observed increase in aminoglycoside $V_{ss}$. Altered metabolic states (21) produced by the disease process may explain the increase in $V_{ss}$. An increased CL associated with a high percentage of blast cells in the bone marrow at the time of presentation in patients with acute leukemia and in patients with advanced lymphoma (stage IV) represents a previously unreported finding. It is also of interest that none of the pharmacokinetic parameters, including CL, showed significant changes after chemotherapy administration. Therefore, it is unlikely that the disease burden alone is directly responsible for the observed alterations in aminoglycoside disposition. Increased CL may be associated with the severity or advanced state of the disease, but in order to establish a significant correlation, a large prospective trial analyzing CL and complete remission or overall survival would be required. We are, however, reluctant to draw any firm conclusions at this time from the small sample of patients that we studied.

The TDX assay (Abbott) has been shown to result in aminoglycoside pharmacokinetic parameters which differ slightly from those obtained by radioimmunoassay (31). This was not a factor in this study since the TDX was also used in the control group. We used two blood samples to determine the pharmacokinetic parameters. The two-sample method is comparable to the three- and four-sample methods described by Sawchuk et al. (32), and no difference has been shown to exist between the two methods if appropriate steps are taken (35). We realize that the two-sample method, despite the economic and time-saving benefits, is more apt to result in erroneous pharmacokinetic parameters than are the three- or four-sample methods if timing of administration and sampling are inaccurate. Nevertheless, we must point out that in all our patients, we waited until steady state was achieved and strict timing, both for administration and sampling, were adhered to.

The calculated parameters for the aminoglycoside $V_{ss}$, CL, and $t_{1/2}$ in patients without a malignancy corresponded to the results obtained in Western centers for similar patient groups (28). The primary purpose for the inclusion of a control group in the study design was to eliminate ethnic differences as a cause of alteration in aminoglycoside disposition. Since the pharmacokinetic parameters obtained in the control group were similar to those obtained in Western patients, there is no reason to believe that patients of Middle Eastern origin have distinct aminoglycoside dispositions.

Most reported studies on empiric treatment of neutropenic febrile episodes, using an aminoglycoside, make no mention of pharmacokinetic analysis to optimize aminoglycoside therapy (11, 12, 20, 36). Some investigators have used amikacin at a dose of 15 mg/kg per day administered every 6 or 12 h, with the average adult receiving 250 mg four times daily or 500 mg twice daily (11, 12, 20, 36). It was pointed out by the authors of the European Organization for Research on Treatment of Cancer (EORTC) trial III (20) that there were no specific study-wide criteria for evaluating aminoglycoside levels in blood to ensure adequate concentrations of amikacin in serum. Some of the treatment failures in the aminoglycoside, beta-lactam-containing arm of the studies mentioned above may have been due to subtherapeutic aminoglycoside $C_{\text{max}}$. If peak concentrations in serum are low, then the goal of combination therapy to achieve maximal synergistic and bactericidal activities is not fulfilled (19, 33). Our findings raise a question as to the results of studies with aminoglycosides in patients with a hematologic malignancy in which the aminoglycoside dosage is not individualized.

One center, participating in the EORTC trial III, established a protocol to maintain the amikacin $C_{\text{max}}$ above 25 μg/ml. In this center, the average patient required 28.7 mg of amikacin per kg per day to maintain the predetermined concentrations in serum (20). A previous study, which was conducted at the same center and which used a pharmacokinetically derived amikacin dosage, revealed that their patients with granulocytopenic cancer required an average dose of 29 mg/kg per day (7, 13). Another study (15) observed increased $V_{ss}$ as well as CL values in their adult and pediatric patients with cancer. However, as mentioned by the investigators, there were several limitations within the study design. Two recent letters (Manny and Huston, Letter, 1986; Phillips et al., Letter, 1988) noted increased $V_{ss}$ values in their patients with a variety of hematologic and oncologic disorders. Our findings and these observations (7, 13, 15, 20; Manny and Huston, Letter, 1986; Phillips et al., Letter, 1988) establish that aminoglycoside $V_{ss}$, CL, and dosage requirements in patients with an underlying hematologic malignancy are increased.

During the later part of our study, when empiric treatment with an aminoglycoside was required for a febrile neutropenic patient with an underlying hematologic malignancy, amikacin was initiated at a dosage of 7.5 to 10 mg/kg per dose every 8 h (if the patient was obese, the dosage was initiated by using lean body weight). This dosage compensates for the increased $V_{ss}$ and CL and establishes maximal aminoglycoside concentrations in serum at the initiation of therapy. The dosage was subsequently individualized within 24 h.

We observed no signs of nephrotoxicity from these large doses. None of the patients had a significant rise in creatinine in serum, despite multiple courses of high-dose aminoglycoside therapy. It has been shown that the use of individual patient pharmacokinetic parameters to optimize the aminoglycoside dosage is not only associated with improved outcome but decreased toxicity as well (30, 37, 38, 40).

In summary, we reported aminoglycoside pharmacokinetic analysis to show increased $V_{ss}$, CL, and dosage requirements in patients with an underlying hematologic malignancy. Our findings indicate that doses recommended by the manufacturer and those of nomograms underestimate aminoglycoside $V_{ss}$ and CL. Based on our results, we recommend that higher doses (7.5 to 10 mg of amikacin per kg per dose every 8 h) be used initially and adjusted within 24 h, according to individualized pharmacokinetic analysis, in febrile neutropenic patients with a hematologic malignancy. We suggest similar guidelines for gentamicin, with initial doses of 2 to 2.5 mg/kg per dose every 8 h. Studies with aminoglycosides for the treatment of febrile neutropenic patients with a hematologic malignancy which do not explicitly describe in detail individualized aminoglycoside dosage should be interpreted cautiously.
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LITERATURE CITED


