Two-Compartment Comparison of Gentamicin and Tobramycin in Normal Volunteers

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The objective of this study was to determine whether differences in tissue accumulation observed upon multiple dosing of aminoglycosides in hospitalized patients could be identified in appropriate single-dose studies in normal volunteers. Ten volunteers received single intravenous doses of 1.0 mg of gentamicin and tobramycin per kg of body weight in randomized crossover fashion. Multiple serum and urine samples were collected during the next 30 days. Serum aminoglycoside concentrations and urinary excretion rates were fitted to a two-compartment pharmacokinetic model, and parameters were derived. Tobramycin exhibited a higher clearance (P < 0.08) and a lower volume of distribution at steady state (P < 0.1), neither of which was significant. Tobramycin also showed a significantly lower predicted amount of drug in the body at steady state (P < 0.05). These differences are consistent with observations made in patients receiving multiple doses. Single-dose studies appear to be capable of discriminating pharmacokinetic characteristics relevant to the comparative nephrotoxic potential of these two aminoglycosides.

Recent studies have established a significant difference between gentamicin and tobramycin in the incidence of nephrotoxicity (13, 16). In previous studies, we have proposed a relationship between tissue accumulation, as described by an open two-compartment model, and subsequent nephrotoxicity for both gentamicin and tobramycin (8, 11, 12). These studies required hundreds of treated patients owing to the large amount of intersubject variance in a population of critical-care patients. In reviewing the details of these investigations, we noted that the pharmacokinetic parameters of patients who received single doses were predictive of the pharmacokinetic parameters observed in multiple-dose therapy. These pharmacokinetic parameters may identify the risk of toxicity in patients before overt renal damage occurs (14). In particular, a nephrotoxic patient who received both single and multiple doses of gentamicin and a single dose of tobramycin indicated the potential value of single-dose comparisons of aminoglycoside tissue accumulation. Since differences in pharmacokinetic parameters between various aminoglycosides are seen on multiple dosing, studies of tissue accumulation of various aminoglycosides can be conducted with single doses in crossover fashion. Since a crossover design eliminates intersubject variance in tissue accumulation, the differences in tissue accumulation between gentamicin and tobramycin might be demonstrable in small numbers of volunteers. The current report concerns a volunteer study performed to test the predictive value of single-dose design and also presents data on the patient that prompted this study.

MATERIALS AND METHODS

Index case. An 84-year-old diabetic female with recurrent urinary tract infection was treated in April 1977 with gentamicin for 7 days. She exhibited severe but reversible nephrotoxicity associated with a rise in serum creatinine from 1.3 to 6.4 mg/dl. Upon termination of the aminoglycoside therapy, her renal function returned to normal over 3 months and remained so over the next 6 months. In January 1978, the urinary tract infection was treated with a single 60-mg dose of gentamicin. Approximately 6 months later, in June 1978, the patient received a single 60-mg dose of tobramycin for another recurrence.

On all three occasions, informed consent was obtained to draw serum and collect urine samples. Samples were obtained at various intervals during therapy and during aminoglycoside washout.

Serum and urine samples were assayed by radioimmunoassay (RIANEN, New England Nuclear Corp.), and concentrations were fitted to a two-compartment pharmacokinetic model, with model parameters determined by the computer program NONLIN (6).

Single-dose crossover. After informed consent was obtained, 10 normal volunteers had a prestudy history
taken and were given a physical examination including blood chemistry consisting of total protein, albumin, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, serum glutamic pyruvic transaminase, serum glutamic oxalacetic transaminase, total bilirubin, lactate dehydrogenase, glucose, and complete blood count with differential. Two 24-h urine collections were obtained for creatinine clearance and urinalysis before each aminoglycoside dose. Audiometry was also performed immediately before dosing.

Each volunteer then received single intravenous bolus doses of 1.0 mg of gentamicin or tobramycin per kg of body weight in a randomized crossover fashion. After dosing, blood samples were collected at 0, 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h and then at intervals of 48 h for up to 200 h. Urine was collected at 2-h intervals for the first 8 h and then from 8 to 12 h and 12 to 24 h postdose. After that, daily 24-h urine collections were obtained for 28 to 30 days. The laboratory examinations were repeated on days 6 and 14. The second aminoglycoside dose was administered 2 months after the first dose to allow for complete turnover of renal proximal tubular cells between doses. In addition, urine concentrations of aminoglycosides were required to be below 0.02 μg/ml at 60 days, or the crossover dosage was delayed further.

Serum and urine samples were assayed for aminoglycoside concentration by radioimmunoassay (RIANEN, New England Nuclear Corp.). The coefficient of variation for this assay ranged from 5 to 10% over the concentration range studied. Urinary β₂-Microglobulin was analyzed by radioimmunoassay (Pharmacia Fine Chemicals), and alanine aminopeptidase was assayed by an enzymatic method (15). Cast counts (9) were performed within 24 h of urine sample collection.

By means of the computer program NONLIN, serum aminoglycoside concentrations and urinary excretion rates were fitted independently to a two-compartment open model (2). Independent fitting was necessary for two reasons. First, renal clearance was nonlinear early in the terminal elimination phase (10). Second, serum concentrations were undetectable (<0.02) after 72 h, and there was not enough present after the single dose to reliably estimate the terminal half-life. Accordingly, the terminal half-life was obtained from data on the urinary excretion rate versus time. Volume, clearance, and amount at steady state (X₀ss) were calculated from the two-compartment parameters, and differences between the two aminoglycosides were evaluated by a paired Student’s t test, with P < 0.05 defined as a significant difference.

RESULTS

Index case. Values obtained from the index patient for the relevant parameters are shown in Table 1. Single-dose gentamicin data were in excellent agreement with the data for gentamicin determined after multiple dosing, even though the patient exhibited nephrotoxicity during multiple dosing. Most important, the predicted X₀ss for the single dose was almost identical to the X₀ss measured from urine excretion after multiple dosing. Treatment of the patient with both aminoglycosides allows a comparison between single doses of gentamicin and tobramycin. This comparison revealed less extensive tissue accumulation potential for tobramycin (Table 1).

Crossover study. In the 10 volunteers, no significant changes from base-line values were observed in audiometry, cast excretion, alanine aminopeptidase excretion, or creatinine clearance. All hematology and serum chemistry tests also remained within the normal ranges throughout the studies. No discomfort or side effects were reported. Urine mass balance was complete within 30 days, at which time 99 ± 6% of the administered dose had been recovered in the urine. Only 70 to 90% of the administered dose was recovered in the first 24 h. These 24-h recovery values agree with those obtained in previous 24-h single-dose studies (5) and illustrate why extended urine collections are needed to achieve total recovery of the administered dose.

<table>
<thead>
<tr>
<th>TABLE 1. Two-compartment pharmacokinetic data for a patient who was given single doses of gentamicin and tobramycin and multiple doses of gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Tobramycin, single dose (June 1978)</td>
</tr>
<tr>
<td>Gentamicin</td>
</tr>
<tr>
<td>Single dose (January 1978)</td>
</tr>
<tr>
<td>Multiple doses (April 1977)</td>
</tr>
</tbody>
</table>

*Abbreviations: Vₑ and Vₑₚ, Volumes of distribution of central compartment and at steady state, respectively; k₁₂, k₂₁, and k₁₀, microconstants for central to peripheral, peripheral to central, and central outputs, respectively; Cₑ, total clearance; t½β, terminal half-life; X₀ss, steady-state amount in body assuming 60 mg given every 8 h to steady state.*
TABLE 2. Two-compartment pharmacokinetic data for gentamicin and tobramycin in 10 normal volunteer subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gentamicin</th>
<th>Tobramycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vc</td>
<td>Vdss</td>
</tr>
<tr>
<td>1</td>
<td>0.101</td>
<td>0.73</td>
</tr>
<tr>
<td>2</td>
<td>0.152</td>
<td>0.71</td>
</tr>
<tr>
<td>3</td>
<td>0.193</td>
<td>1.39</td>
</tr>
<tr>
<td>4</td>
<td>0.196</td>
<td>0.89</td>
</tr>
<tr>
<td>5</td>
<td>0.224</td>
<td>1.41</td>
</tr>
<tr>
<td>6</td>
<td>0.173</td>
<td>0.71</td>
</tr>
<tr>
<td>7</td>
<td>0.144</td>
<td>0.71</td>
</tr>
<tr>
<td>8</td>
<td>0.159</td>
<td>0.77</td>
</tr>
<tr>
<td>9</td>
<td>0.167</td>
<td>0.65</td>
</tr>
<tr>
<td>10</td>
<td>0.265</td>
<td>2.93</td>
</tr>
<tr>
<td>Mean</td>
<td>0.177</td>
<td>1.09b</td>
</tr>
<tr>
<td>SD</td>
<td>0.05</td>
<td>0.71</td>
</tr>
</tbody>
</table>

For abbreviations, see Table 1, footnote a.

b Not significant; P < 0.1.
c Not significant; P < 0.08.
d Tobramycin significantly different; P < 0.03.

Two-compartment pharmacokinetic parameters for tobramycin and gentamicin are given in Table 2. No significant differences between tobramycin and gentamicin were detected in the volume of the central compartment and the terminal half-life. Tobramycin was cleared from the body more rapidly than gentamicin and had a lower volume of distribution at steady state in 8 of the 10 volunteers (Table 2), but these differences were not significant. Total clearance values were plotted against creatinine clearances for the individual subjects (Fig. 1). Both aminoglycosides exhibited clearances consistently lower than the corresponding creatinine clearances, as shown by the identity line drawn for reference.

Values for Xbss differed significantly between the two agents (Table 2). Of the 10 volunteers, 9 showed greater Xbss for gentamicin than for tobramycin (P < 0.03). An X-Y plot of crossover Xbss values demonstrated significantly greater gentamicin tissue uptake within each subject (Fig. 2).

Simulations were performed based on the mean single-dose data for each of the aminoglycosides. The mean data (Fig. 3) indicate that a primary difference between the serum profiles of these two aminoglycosides is in the B intercept.

Tobramycin exhibited a more rapid decline to lower serum concentrations before entering the terminal phase. Figure 3 illustrates the lower intercept and smaller steady-state distribution volume of tobramycin and also explains the slightly higher tobramycin clearance noted in Table 2.

FIG. 1. Aminoglycoside clearance versus creatinine clearance for both tobramycin (■) and gentamicin (□) in each of the 10 volunteers. Line of identity is drawn for reference.

DISCUSSION

Although the one-compartment model has been used to describe aminoglycoside pharmacokinetics since the introduction of these drugs, there are compelling reasons why this simplistic modeling approach should be qualified. The aminoglycosides exhibit at least triexponential pharmacokinetics, and we have primarily studied the second and third phases of decline as the
physiologically relevant components. We have found that in patients the later two phases can be employed to estimate tissue accumulation of these compounds. Tissue accumulation is characteristic of all persons who receive these agents (12), and the initial tissue accumulation rate is at least two to three times more rapid in patients who develop nephrotoxicity than in patients who do not (8). Finally, aminoglycosides such as gentamicin and tobramycin have different accumulation rates, and these differences are associated with a lower nephrotoxic potential for tobramycin than for gentamicin in large studies of patients (13). Other clinical studies of comparative nephrotoxicity verify the difference between gentamicin and tobramycin (16) but have not as yet assessed tissue accumulation as an integral part of study design.

Intersubject variance in tissue accumulation has been the principal reason why large numbers of patients have been required to establish pharmacokinetic differences between gentamicin and tobramycin. However, our case report and this small study in 10 volunteers indicate that the effects of wide intersubject variance can be overcome by using a randomized crossover design.

The basic premise underlying this study is that tissue accumulation and other two-compartment pharmacokinetic parameters are intrinsic characteristics of each individual and that they show little change from year to year. This hypothesis does not preclude aging effects on tissue, which may cause small changes over considerably longer time periods.

There have been few attempts to verify any pharmacokinetic parameter as constant within each individual over time. Nevertheless, in the particular case of the aminoglycosides, limited data have thus far fully supported the constancy of these pharmacokinetic blueprints. Our patient exhibited reproducible pharmacokinetic parameters over the course of 1.5 years for both single and multiple doses (Table 1). In our clinical trials, we have observed that several patients who once experienced nephrotoxicity experienced it repeatedly, even when given lower dosages (13, 14). Finally, of the 10 volunteers in this study uniformly accumulated gentamicin at greater rates than tobramycin, even though the order of exposure was randomized.

We believe that 2 months between exposures is adequate time to remove all possible effects of the previous aminoglycoside dosage. Certainly the turnover rate of renal proximal tubular lining cells is fast enough for 2 months between exposures to ensure that these cells are free of aminoglycosides for each dose. Furthermore, these single doses were well tolerated by the volunteers since no evidence of even minor tubular effects was noted with sensitive tests such as β2-Microglobulin and alanine aminopeptidase.

Independent fitting of the serum concentrations and urinary excretion rate allowed the use of a two-compartment model, even after a single
dose. This approach appears to be sensitive enough to detect differences in the distribution and elimination of tobramycin and gentamicin.

The pharmacokinetics of aminoglycosides determined after single doses appear to be predictive of the parameters and tissue accumulations seen on multiple dosing. Screening potential new aminoglycosides in such a system could substantially shorten the development time of safer molecules. In view of recent challenges to the relevance of animal models (1, 4, 7), the pharmacokinetic methodology proposed here has the ultimate advantage of testing the relative nephrotoxic potential of new aminoglycosides in a model system more closely aligned to their ultimate use. Furthermore, this approach may be applied without exposing volunteers to the risk of nephrotoxic side effects, which develop only upon multiple dosing (3).

ACKNOWLEDGMENT

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LITERATURE CITED
