Pharmacokinetics of Gentamicin at Traditional versus High Doses: Implications for Once-Daily Aminoglycoside Dosing

DOROTHY J. DEMCZAR,1 ANNE N. NAFLZIGER,2,3 AND JOSEPH S. BERTINO, JR.1,2,3,*

Departments of Pharmacy Services1 and Medicine2 and Clinical Pharmacology Research Center,3 Bassett Healthcare, Cooperstown, New York 13326

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Two doses of gentamicin (2 and 7 mg/kg of body weight) were administered to 11 healthy volunteers in a randomized, crossover single-dose study to compare their pharmacokinetics. Doses were infused over 1 h with a syringe infusion pump, and 14 concentrations in sera were obtained over an 8-h period. Concentration in serum versus time data were fitted to a two-compartment pharmacokinetic model. In addition, to mimic the clinical setting, subjects’ data were fitted by the Sawchuk-Zaske method. Distributional and postdistributional peak concentrations, along with the last obtained concentration in serum, were utilized to compare the following pharmacokinetic variables: volume of distribution at steady state ($V_{ss}$), half-life, clearance (CL), and maximum concentration in serum ($C_{\text{max}}$). With two-compartment pharmacokinetic fitting, significant differences in distribution half-life (average, 21.8 and 41.6 min [P ≤ 0.05]) and gentamicin CL (76.6 ± 6.6 and 67.2 ± 4.2 ml/min/1.73 m² [P ≤ 0.001]) were found between traditional-dose and high-dose groups, respectively. When the data for concentrations in sera were fitted to a one-compartment pharmacokinetic model by using either the distributional or the postdistributional $C_{\text{max}}$, statistically significant differences ($P ≤ 0.001$) were found between $V_{ss}$, half-life, CL, and $C_{\text{max}}$ values for both dosage groups. The results show that the pharmacokinetics of gentamicin at a large dose differ significantly from those at the traditional dose. This information has direct implications for once-daily aminoglycoside (ODA) literature when the $C_{\text{max}}$ values reported are distributional and therefore show falsely high $C_{\text{max}}$/MIC ratio estimates. In addition, ODA nomogram dosing tools developed with distributional $C_{\text{max}}$ values are probably inaccurate.

The concept of once-daily aminoglycoside (ODA) dosing (defined as 5 to 7 mg/kg of body weight/dose given once daily) has become popular because of the perceived potential therapeutic advantages of this dosing method (4, 10–12). Much of the ODA theory revolves around the in vitro pharmacodynamic effects of the antibacterial effect associated with aminoglycosides, in particular, concentration-dependent killing and postantibiotic effect. There are few complete data regarding the pharmacokinetics for once-daily dosing regimens. However, such pharmacokinetic information is important in appropriately adjusting and monitoring the empiric dosing regimens that utilize the above-mentioned high doses of aminoglycosides so that therapeutic benefits may be achieved and toxic effects may be avoided. One nomogram derived from limited pharmacokinetic information has been published as a tool in ODA dosing (10). Applying the known pharmacokinetic principles for traditional dosing to monitoring of these large doses of aminoglycosides may provide inaccurate information about a drug’s pharmacokinetic parameters. For example, it is not known if a large dose undergoes distribution at the same rate as a traditional dose.

The specific aims of our trial were to examine the pharmacokinetics of gentamicin at a traditional (low) dose versus those at a high dose to determine if the drug exhibits similar distribution and elimination patterns at the two doses. Determination of the optimal sampling period for monitoring concentrations in serum is important in the clinical setting, where serum sampling is limited for the comfort of the patient and by considerations of cost. In addition, if the pharmacokinetics of aminoglycosides at high doses differ from those at conventional doses, these data could have significant implications for the commonly used ODA nomogram (10), which was developed by traditional serum sampling methods and application of a one-compartment pharmacokinetic infusion model.

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MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Bassett Healthcare. Written informed consent was obtained from each subject. Eleven healthy volunteers between the ages of 18 and 55 years participated in this randomized, crossover single-dose study. Subjects were included if they had a normal level of creatinine in serum (0.5 to 1.2 mg/dl), a normal 24-h urine creatinine clearance (CL), a normal urine specimen, and normal levels of electrolytes in serum (sodium, potassium, chloride, bicarbonate, and blood urea nitrogen). Subjects were excluded if they had an allergy to aminoglycosides, had received gentamicin within 1 month prior to the study, or had abnormal renal function as assessed by history, urinalysis, and/or detection of abnormal concentrations of creatinine in serum.

With a random-number table, subjects were randomized to receive either 2 or 7 mg of gentamicin/kg in phase I. Subjects received the alternate dose in phase 2. Subjects were dosed on the basis of total body weight (TBW) unless they were >40% over ideal body weight (IBW). For subjects >40% over IBW, a dosing weight (DW) was calculated as follows: DW = IBW + 40% (TBW – IBW) (2, 15). All gentamicin doses were diluted with 5% dextrose in water to a final volume of 30 ml and placed in a 30-ml syringe. Gentamicin was infused over a 60-min period through a heparin lock catheter with a syringe infusion pump (Auto-Syringe, models AS5D and AS5B; Travenol, Hooksett, N.H.). The heparin lock catheter was flushed with 10 ml of 0.9% sodium chloride after drug administration. Five-milliliter blood samples were collected preinfusion and at the following times postinfusion: 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 120, 240, 360, and 480 min. Blood for gentamicin was obtained via direct venipuncture (in the arm not used for infusion) for the sample obtained immediately after the end of the infusion. The remainder of the samples were obtained through the indwelling catheter, which was flushed with 3 ml of 0.9% sodium chloride before and after the sample was obtained. Samples were immediately stored on ice until they were centrifuged. Two milliliters of serum was transferred from each sample and frozen at −20°C until it was used in the assay.
Following a 1-month washout period, subjects received the crossover gentamicin dose and serum sampling was performed as stated above. The level of creatinine in serum obtained before the drug was administered a second time had to be within 25% of the baseline value. All sample analyses were carried out within 2 months after collection. Gentamicin concentrations were assayed in duplicate by the Opus Magnum automated immunoassay system (Behring Diagnostics, Westwood, Mass.). The intra-assay percent coefficient of variation was 7.3% at 2.2 $\mu g/ml$. The sensitivity range of the assay was 0.2 to 14 $\mu g/ml$. Samples of ≥14 $\mu g/ml$ were diluted at a 1:4 ratio with a calibrated precision pipette and then assayed.

Study data were fitted to both one- and two-compartment intermittent infusion pharmacokinetic models, with the appropriate model being chosen according to the Akaike information criteria (22). A weighting function of 1/y was used, and the goodness of fit was determined by evaluating the standard errors of the parameter estimates and by visual examination of the residuals. A two-compartment model was judged to be appropriate. Pharmacokinetic parameters (distribution and elimination rate constants, volume of distribution at steady state) were estimated by visual examination of the residuals. A two-compartment model was judged to be appropriate. Pharmacokinetic parameters (distribution and elimination rate constants, volume of distribution at steady state) were estimated by visual examination of the residuals.

The elimination rate constants and $V_d$ values were found at both the 2- and 7-mg/kg dose levels when $V_d$ was used, which is what is commonly used in clinical settings. Statistically significant differences ($P \leq 0.001$) in $V_d$, half-life, CL, and maximum concentration of the drug in serum ($C_{\text{max}}$).

**RESULTS**

Pharmacokinetic parameters for nine women and two men were evaluated. Table 1 illustrates subject demographics. Figures 1 and 2 illustrate the data for mean concentrations in sera vs SD versus time for the groups receiving the low dose and high dose of gentamicin, respectively. Both doses clearly show the two distinct phases associated with a two-compartment model.

Table 2 illustrates the pharmacokinetic parameters for gentamicin at the two doses. Distribution constants for the low-dose (1.94 ± 1.43 h$^{-1}$) and high-dose (1.0 ± 0.16 h$^{-1}$) groups differed significantly ($P \leq 0.05$). This resulted in distribution half-lives averaging 21.8 and 41.6 min in the low-dose and high-dose groups, respectively. Based on these data, distribution would be expected to be completed approximately 1.45 and 2.7 h after the beginning of the 60-minute infusion, respectively, for the low- and high-dose groups.

The elimination rate constants and $V_d$ values between the two groups were similar. Although elimination rate constants were similar, the gentamicin CL values for the low- and high-dose groups were significantly different (76.6 ± 6.6 and 67.2 ± 4.2 ml/min/1.73 m$^2$, respectively; $P \leq 0.001$).

Table 3 illustrates the comparative pharmacokinetic data derived when only two concentrations in sera are used and fitted to a one-compartment intermittent infusion model. This is what is commonly used in clinical settings. Statistically significant differences ($P \leq 0.001$) in $V_d$, half-life, CL, and $C_{\text{max}}$ values were found at both the 2- and 7-mg/kg dose levels when the first of the two points used in the calculation was obtained during distribution (i.e., the first point was obtained immedi-

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**TABLE 1. Subject demographics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>38 ± 11</td>
<td>18–55</td>
</tr>
<tr>
<td>TBW (kg)</td>
<td>73 ± 17</td>
<td>49–98</td>
</tr>
<tr>
<td>IBW (kg)</td>
<td>58 ± 8.5</td>
<td>45–71</td>
</tr>
<tr>
<td>Amt of gentamicin (mg)</td>
<td>141 ± 22</td>
<td>100–180</td>
</tr>
<tr>
<td>Amt of gentamicin (mg)</td>
<td>489 ± 81</td>
<td>340–630</td>
</tr>
<tr>
<td>Measured creatinine CL (ml/min/1.73 m$^2$)</td>
<td>115.8 ± 27.5</td>
<td>75–119</td>
</tr>
</tbody>
</table>

*As subjects, two men and nine women were included.*
ately at the end of the infusion) versus when the two points were obtained after the end of distribution (i.e., the first point was obtained at the end of distribution as determined with the two-compartment fitting, specifically, 1.5 h after the beginning of the infusion for the 2-mg/kg dose and 2.7 h after the beginning of the infusion for the 7-mg/kg dose). These data show that the use of concentrations in sera obtained before distri-

bution is completed results in underestimations of that the use of concentrations in sera obtained before distri-

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ning of the infusion for the 7-mg/kg dose). These data show were obtained at the end of distribution as determined with the two-compartment fitting, specifically, 1.5 h after the beginning of the infusion as determined with the two-compartment pharmacokinetic model. This finding, which has previously been discussed in the literature (20), suggests that the use of a one-compartment model with distributional sampling is inappropriate.

DISCUSSION

Early investigations of aminoglycosides, such as gentamicin and tobramycin, suggested that concentration-time data were appropriately fitted to a two-compartment pharmacokinetic model (23). In the clinical setting, where sampling is limited for the comfort of the patient and by considerations of cost, a one-compartment pharmacokinetic model may be applied to drugs, such as gentamicin, if concentrations in sera are ob-

TABLE 2. Pharmacokinetic parameters for gentamicin administered to groups at low and high dosesa

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD at:</th>
<th>P valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low dose</td>
<td>High dose</td>
</tr>
<tr>
<td>Distribution rate constant (h⁻¹)</td>
<td>1.94 ± 1.43</td>
<td>1.0 ± 0.16</td>
</tr>
<tr>
<td>Elimination rate constant (h⁻¹)</td>
<td>0.26 ± 0.11</td>
<td>0.24 ± 0.04</td>
</tr>
<tr>
<td>Vₐ (liters/kg)</td>
<td>0.23 ± 0.11</td>
<td>0.19 ± 0.04</td>
</tr>
<tr>
<td>CL (ml/min/1.73 m²)</td>
<td>76.6 ± 6.6</td>
<td>67.2 ± 4.2</td>
</tr>
<tr>
<td>AUCₙ₋₀ₖₐₗ (µg · h/ml)/100 mg</td>
<td>20.3 ± 2.1</td>
<td>22.8 ± 1.8</td>
</tr>
</tbody>
</table>

a The low dose was 2 mg/kg, and the high dose was 7 mg/kg.

b P values indicate the differences between low- and high-dose groups.

TABLE 3. Analysis of data concerning actual serum gentamicin concentrations versus time to determine pharmacokinetic parameters by using a one-compartment model and the Sawchuk-Zaske method

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result at indicated dose of gentamicin (mg/kg) and time of samplingc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 (pre)</td>
</tr>
<tr>
<td>t₁/₂ (h)</td>
<td>1.9 ± 0.22</td>
</tr>
<tr>
<td>CL (ml/min/1.73 m²)</td>
<td>66 ± 5.9</td>
</tr>
<tr>
<td>Vₐ (liters/kg)</td>
<td>0.15 ± 0.03</td>
</tr>
<tr>
<td>Cₘₚₚ (µg/ml)</td>
<td>10.1 ± 1.3</td>
</tr>
<tr>
<td>Cₘₚₚ/MIC ratiod</td>
<td>5.1</td>
</tr>
</tbody>
</table>

a Data are based on distributional (pre) and postdistributional (post) peak concentrations for both dosage levels along with the final concentrations obtained. Distributional peak concentrations are peak (first) concentrations obtained immediately postinfusion. Postdistributional peak concentrations are peak concentrations obtained after distribution was completed (as determined graphically from the two-compartment, concentration-time data obtained 1.5 h after the beginning of the infusion for the 2-mg/kg dose and 2.7 h after the beginning of the infusion for the 7-mg/kg dose). Data are means ± SD, and P values in every instance were ≤ 0.001.

b t₁/₂: half-life.

c Postdistributional Cₘₚₚ.

d Assuming a MIC of 2 µg of gentamicin per ml.
Unfortunately, distribution rate constants from this trial were not reported. Data for another aminoglycoside, isepamicin (given at a dose of 7.5 or 15 mg/kg as a 30-min infusion), showed that distribution half-lives average from 0.23 to 0.6 h (6). Therefore, one expects that distribution would not be completed at the end of a 60-min infusion in some individuals. Our study data show that distribution is not completed until approximately 30 min after the end of a 60-min infusion with gentamicin at the low dose. Thus, these data suggest that sampling 30 min after a 30-min infusion, or immediately after a 60-min infusion, would give concentrations in the distribution phase and invalidate pharmacokinetic calculations determined by a one-compartment model.

One possible explanation for the increase in distribution time with the high dose of gentamicin is saturation of the uptake mechanism responsible for tissue uptake. A study comparing extents of drug accumulation in the renal cortices of patients scheduled for nephrectomy attempted to examine this issue (19). Patients received one dose of either gentamicin (4.5 mg/kg) or netilmicin (5 mg/kg) as a single short-term infusion or as a 24-h continuous infusion 24 h prior to surgery. Renal cortical tissue was sampled at the time of nephrectomy to measure concentrations of the aminoglycosides in tissue. For both aminoglycosides, the single short-term infusion (103 ± 36.3 μg/g for gentamicin and 137.4 ± 34.6 μg/g for netilmicin) resulted in renal drug concentrations significantly lower than those of the continuous infusion (158.1 ± 52.9 μg/g for gentamicin and 178 ± 21.8 μg/g for netilmicin). It should be noted that no human trial has compared accumulation of a single large dose of aminoglycoside in tissue with the accumulation of the same total dose given in increments. Thus, it is unknown if accumulation in tissue is less with single large doses than with multiple daily doses.

For ODA dosing, a 30- to 60-min infusion has commonly been used in clinical trials assessing pharmacokinetic parameters (1, 5, 7, 10, 13, 16–18). Although attempts were made to assess distribution pharmacokinetics in these trials, abbreviated concentration-time data were obtained. That is, insufficient serum samples were obtained during the early sampling time to adequately describe distribution. Researchers in a one-compartment model. The data on these 20 patients were evaluated prior to reaching steady state. From these two concentrations, pharmacokinetic parameters were calculated with a one-compartment model. The data on these 20 patients were then pooled with data on 35 additional patients receiving conventional doses of aminoglycosides to develop an ODA nomogram. It appears that this dosing nomogram was developed with the commonly held principles that aminoglycoside distribution is completed at the end of a 60-min infusion and that serum sampling at the end of the infusion gives postdistributional concentrations. Our data show that distribution is not complete for high doses of gentamicin until 1.7 h after the end of a 60-min infusion and, thus, that the principles used to construct this nomogram are inaccurate.

The implications for sampling during the distribution phase and incorrectly applying the data to a one-compartment pharmacokinetic model are significant. In our study, obtaining concentrations in sera prior to the end of the distribution phase resulted in a significant misestimation of half-life, $V_{ss}$, CL, and $C_{max}$ when the data were fitted to a one-compartment model as depicted in Table 3. Concentrations in sera obtained prior to the completion of distribution resulted in underpredictions of approximately 25% in half-life, 50% in $V_{ss}$ and 35% in CL and in an overprediction of 72% in $C_{max}$. Our data bring into question $C_{max}$ values reported for ODA when these concentrations were obtained during distribution, whether they were obtained immediately at the end of a 60-min infusion or 30 min after a 30-min infusion. Since the published dosing nomogram (10) was developed with peak concentrations obtained before distribution was complete, it likely incorrectly estimates the dosing frequency for high doses of aminoglycosides and greatly overestimates postdistributional $C_{max}$. Dosing frequency and postdistributional $C_{max}$ are the pharmacokinetic and pharmacodynamic bases for the support of ODA.

Finally, obtaining distributional concentrations in sera by administration of high or low doses of aminoglycosides may have pharmacodynamic implications because of the impact on the $C_{max}$/MIC ratio. The analysis by Moore et al. examined the association of aminoglycoside (gentamicin, tobramycin, and amikacin) $C_{max}$ values and the MIC for the infecting organism with therapeutic outcome in the treatment of various infections (9). Peak concentrations of aminoglycosides were measured 1 h after a 30-min infusion (standard dose), suggesting that these peak concentrations were obtained postdistribution. The authors concluded that the highest $C_{max}$/MIC ratio or the mean $C_{max}$/MIC ratio was strongly associated with clinical response. There was a linear relationship between an increasing $C_{max}$/MIC ratio and the rate of response. A $C_{max}$/MIC ratio of ≥10 was associated with a >90% response rate, compared with a $C_{max}$/MIC ratio of 4, which was associated with a 70% response rate. Table 3 illustrates a 40% difference in the $C_{max}$/MIC ratio for the 2-mg/kg dose when distribution and postdistribution peak concentrations are used. The difference in the $C_{max}$/MIC ratio is magnified to 73% for the 7-mg/kg dose when distribution and postdistribution peak concentrations are used. Based on these data, obtaining a peak concentration during distribution overestimates the $C_{max}$/MIC ratio.

It appears that gentamicin at the high dose has a significantly longer distribution time and lower CL than at the low dose. If sampling is performed immediately at the end of a 60-min infusion, distributional concentrations in sera are obtained. Assuming that the distribution rate constant is similar with a shorter infusion time (i.e., 30 min), sampling 30 min later would still be in the distribution phase. Pharmacokinetic calculations with the concentrations obtained before distribution is complete appear to provide incorrect information.

After a 60-min infusion of aminoglycoside at the high dose, prolonging the time to obtain a peak concentration to approximately 1.7 h is appropriate. In addition, our data suggest that for the conventional dose of gentamicin, distribution is not complete until 30 min after a 60-min infusion. Nomograms or other dosing tools developed with concentrations in sera obtained before the completion of distribution are likely inaccurate and their use should be avoided.

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REFERENCES


