Pharmacokinetic Studies with Dibekacin, a New Aminoglycoside, After Intravenous and Intramuscular Administration to Human Volunteers

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The pharmacokinetics of dibekacin, a new aminoglycoside antibiotic, was studied in volunteers given the same dose (100 mg) intramuscularly on two separate occasions and intravenously at two different rates of infusion. The kinetic parameters ($t_{1/2}$, 2.24 h, and $V_d$, 0.136 liter/kg, as the overall mean) observed after intramuscular administration appear to be compatible with those of other aminoglycosides and fairly reproducible within the same individuals. Dibekacin was rapidly absorbed ($t_{max}$, 0.84 h), yielding a peak level of 10.4 μg/ml after the 100-mg intramuscular dose. After the 30- or 60-min infusion, the concentrations of dibekacin in serum fell bi-exponentially, giving an elimination half-life ($t_{1/2b}$) of 2.50 to 2.88 h. The highest serum levels after the 30- and 60-min infusions were 15.2 ± 0.9 and 12.1 ± 1.8 μg/ml, respectively. Serum levels at 6 h after completion of infusions were 1.9 ± 0.3 and 1.7 ± 0.4 μg/ml, respectively.

Dibekacin (3’,4’-dideoxykanamycin B), a synthetic derivative of kanamycin B, has significantly greater activity than its parent compound against Escherichia coli and Pseudomonas aeruginosa (20). Thus, the minimum inhibitory concentrations (MICs) of dibekacin range from 1.56 to 3.12 and 3.12 to 6.25 μg/ml for strains of E. coli and P. aeruginosa, respectively, for which the MICs of kanamycin exceed 50 μg/ml (20).

Since dibekacin has some promise for treating infections with gram-negative bacilli and since a knowledge of its pharmacokinetic properties is needed to develop both effective and safe dosage schedules, we have undertaken an investigation of these characteristics. This study was undertaken specifically to (i) elucidate the distribution and elimination kinetics of dibekacin in humans after a single intravenous or intramuscular administration and (ii) develop dosage schedules and methods of administration compatible with observed pharmacokinetic parameters.

MATERIALS AND METHODS

Human volunteers. Five adult male volunteers with no known allergies to antibiotics or other drugs participated in this study after informed written consent had been obtained. None had taken any drug during the month before the investigational period. Their ages ranged from 23 to 54 years (mean ± standard deviation [SD], 36.8 ± 14.1 years), and their body weights ranged from 45 to 62 kg (56.4 ± 6.1 kg). Results of prestudy physical examination and pre- and post-drug laboratory findings were normal. Because of concerns with the nephrotoxicity of aminoglycosides, it is noteworthy that their serum creatinine values ranged from 1.05 to 1.30 mg/100 ml (1.18 ± 0.08 mg/100 ml) during the study period.

Dosage. Dibekacin sulfate (lot RDK-K-14; Meiji Seika Research Laboratories, Tokyo, Japan) was used throughout this study. It was dissolved in 0.9% saline at the concentration of 50 mg/ml for intramuscular administration. For intravenous use, the 100-mg dose was dissolved in 20 ml of 0.9% saline.

Experimental design. Each of the five volunteers received a 100-mg dose (mean ± SD, 1.79 ± 0.22 mg/kg) intramuscularly and intravenously on two separate occasions. One intravenous dose was infused over a 30-min period (3.59 ± 0.44 mg/kg per h), and the second was infused over 60 min (1.79 ± 0.22 mg/kg per h). Treatments were randomized and delivered in a crossover fashion, with monthly intervals separating the respective doses. Subjects were fasted overnight before each study; food was also withheld for 2 h after dosage. An automatic infusion pump (type AIP-2H, no. 2457; Atom Apparatus Co., Tokyo, Japan) was used for intravenous infusion.

Blood specimens (5 ml each) were drawn from an arm vein at 0.25, 0.5, 1, 2, 3, 4, and 6 h after intramuscular administration and at 0 (immediately after intravenous infusion ceased), 0.25, 0.5, 1, 1.5, 2, 4, and 6 h after intravenous infusion. Samples were always withdrawn from the arm contralateral to that used for infusion.

Microbiological assay. Assays were performed on each study day as serum was collected. The concentrations of dibekacin in serum were determined by an agar (streptomyacin assay agar; BBL Microbiology Systems, Cockeysville, Md.) diffusion test (cup plate method), using Bacillus subtilis ATCC 6633 as the
test organism. Reference standards were diluted (8, 4, 2, 1, and 0.5 μg of dibekacin per ml concentrations) in pooled human serum. Each agar plate contained a homologous standard comprising three points and three test assays, with 1:3, 1:6, and 1:12 dilutions for each assay. After incubation at 37°C for 16 to 18 h, the zones of inhibition were measured, and the antibiotic concentrations were determined by graphical comparison of the mean zone of inhibition of each sample with the mean zones of inhibition of standard dilutions. With this method, concentrations of 0.2 μg of dibekacin per ml or greater in serum could be determined.

Calculation of pharmacokinetic constants. Unweighted serum concentration data (Ci) after single intramuscular doses of dibekacin were fitted to a one-compartment open model by using the following equation (25):

$$C_i = \frac{F \cdot D \cdot K_a}{V_d (K_e - K_d)} (e^{-K_e t} - e^{-K_d t})$$  

(1)

Three constants can be determined in this equation: $K_a$, the apparent first-order absorption rate constant (hour−1); $K_d$, the apparent first-order elimination rate constant (hour−1); $V_d$, the apparent volume of distribution (liter). The value of $V_d$ was calculated by assuming complete absorption ($F = 1.0$). The other factors in the equation are serum drug concentration in micrograms per milliliter ($C_i$), dose in milligrams (D), and time (t) in hours.

The predicted time of the peak serum level after intramuscular administration of dibekacin (tmax) was calculated by using the following equation (7):

$$t_{max} = \frac{1}{K_d - K_e} \cdot \ln \frac{K_a}{K_e}$$  

(2)

The postinfusion $C_i$ data of dibekacin were fitted to the following biexponential equation (6):

$$C_i = R \cdot e^{-\alpha t} + S \cdot e^{-\beta t}$$  

(3)

in which R, S, α (hour−1), and β (hour−1) denote the hybrid constant and t denotes the postinfusion time. The apparent volume of distribution ($V_{d, a}$) was directly calculated by the method of Wagner (23). The distribution rate constants $k_{12}$ and $k_{21}$ (hour−1), $k_{13}$ (hour−1), the elimination rate constant from the central compartment, and area under the curve ([AUC]f) values were calculated by the usual procedure with equation 3 modified by application of the Loo and Riegelman correction (12).

The elimination half-life ($t_{1/2}$) after intramuscular administration was calculated as $t_{1/2} = 0.693/K_e$. The serum elimination half-life ($t_{1/2}$) of dibekacin after intravenous infusion was obtained by a least-squares regression analysis of the log serum concentration versus time during the β phase, followed by the substitution in the relationship of β (hour−1) = 0.693/$t_{1/2}$. The apparent total serum clearance ($C_{tot}$) with both routes of administration was estimated from dose/[AUC]f.

The best values of various pharmacokinetic parameters were calculated by the least-squares method in conjunction with a Toshiba model TOSBAC 40 computer (Tokyo Shibaura Electric Co., Ltd., Tokyo, Japan).

RESULTS

The average concentrations of dibekacin in serum after intramuscular administration of 100 mg were indistinguishable in the two trials (Fig. 1). The observed maximum concentrations ($C_{max}$) ranged from 8.8 to 11.7 (10.1 ± 1.0) μg/ml and from 8.5 to 12.9 (10.7 ± 1.5) μg/ml in trials 1 and 2, respectively. The peak time ($t_{max}$) was observed at 0.5 h (three times) or at 1 h (seven times) after intramuscular administration of dibekacin in all subjects. The mean predicted $t_{max}$ calculated by using equation 2 was 0.81 and 0.85 h in trials 1 and 2 respectively (Table 1).

The mean data on kinetic disposition of dibekacin after the intramuscular administration, analyzed by using equation 1, have been summarized in Table 1. The pharmacokinetic parameters obtained for the same individuals at the two study periods were very similar. The largest individual difference of $K_{el}$ was only 0.03 h−1, $K_{el}$ being highly reproducible within the same subject ($r = 0.950$; $P < 0.02$). $K_{el}$ in different individuals varied from 0.246 to 0.420 h−1.

The mean $C_{tot}$ value was 0.764 ± 0.122 ml/min per kg (42.6 ± 5.1 ml/min). The $V_d$ value varied between 0.124 and 0.200 liter/kg and was an average 13.6% of body weight (Table 1).

The mean $C_i$ values of dibekacin after 30- or 60-min intravenous infusions of the 100-mg dose

![Fig. 1. Serum concentration-time curves of dibekacin after 100-mg intramuscular dose administration on two separate occasions in five volunteers. There was no significant difference of serum concentrations at any time point between two trials. The data of mean ± SD are plotted.](http://aac.asm.org/)

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Table 1. Pharmacokinetic parameters of dibekacin after administration of a 100-mg intramuscular dose on two separate occasions in five volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Trial</th>
<th>Overall a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>$K_{el}$</td>
<td>h⁻¹</td>
<td>0.31 ± 0.06</td>
<td>0.33 ± 0.06</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>h</td>
<td>2.28 ± 0.40</td>
<td>2.20 ± 0.41</td>
</tr>
<tr>
<td>$V_d$</td>
<td>Liters/kg</td>
<td>0.137 ± 0.004</td>
<td>0.134 ± 0.007</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>µg/ml</td>
<td>10.1 ± 1.0</td>
<td>10.7 ± 1.5</td>
</tr>
<tr>
<td>$C_{min}$</td>
<td>µg/ml</td>
<td>2.3 ± 0.4</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td>$T_{max}$</td>
<td>h</td>
<td>0.81 ± 0.08</td>
<td>0.85 ± 0.21</td>
</tr>
<tr>
<td>Predicted d</td>
<td></td>
<td>0.80 ± 0.24</td>
<td>0.90 ± 0.20</td>
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<tr>
<td>Observed</td>
<td></td>
<td>39.1 ± 3.9</td>
<td>40.1 ± 4.5</td>
</tr>
<tr>
<td>[AUC]b</td>
<td>(µg/ml)·h</td>
<td>0.775 ± 0.132</td>
<td>0.754 ± 0.112</td>
</tr>
<tr>
<td>$Cl_{tot}$</td>
<td>ml/min per kg</td>
<td>3.17 ± 0.28</td>
<td>3.22 ± 1.19</td>
</tr>
</tbody>
</table>

a Data are given as mean ± SD.

b Mean ± SD obtained from 10 observations of all subjects.

c Serum dibekacin concentration at 6 h (the last recorded level) after intramuscular administration.

d Calculated by using equation 2.

are shown in Fig. 2. Pharmacokinetic parameters calculated from application of the two-compartment open-model methodology (6) are given in Table 2. The postinfusion $C_{max}$ (15.2 ± 0.9 µg/ml) after the 30-min infusion was significantly higher ($P < 0.02$) than that after the 60-min infusion (12.1 ± 1.8 µg/ml). This trend continued for 1 h after the end of infusion (Fig. 2), but had disappeared by 6 h, when mean $C_t$ values approximated 2 µg/ml. The $V_d$ for dibekacin administered intravenously ranged from 14 to 16% of body weight (Table 2). Other pharmacokinetic parameters were not affected by the rate of infusion (Table 2). The mean values for $t_{1/2}$, $[AUC]_b$, and $Cl_{tot}$ obtained with intravenous infusion were not different from the values obtained after intramuscular administrations.

**DISCUSSION**

The above observations suggest that the pharmacokinetic properties of dibekacin are similar to those of other aminoglycoside antibiotics (1, 9, 14). Thus, the $t_{1/2}$ of dibekacin when administered intramuscularly is close to the values reported for gentamicin (13, 16), tobramycin (13, 16), amikacin (3, 4), kanamycin (3, 4), and sisomicin (17) delivered by the same route.

The mean values of $V_d$ and $V_{dm}$ for dibekacin (Tables 1 and 2) are slightly less than those...
Table 2. Pharmacokinetic parameters of dibekacin after the intravenous administration of the 100-mg dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>h⁻¹</td>
<td>1.99 ± 0.69</td>
<td>2.24 ± 0.92</td>
</tr>
<tr>
<td>β</td>
<td>h⁻¹</td>
<td>0.28 ± 0.04</td>
<td>0.25 ± 0.05</td>
</tr>
<tr>
<td>k₁₂</td>
<td>h⁻¹</td>
<td>0.58 ± 0.34</td>
<td>0.79 ± 0.40</td>
</tr>
<tr>
<td>k₃₁</td>
<td>h⁻¹</td>
<td>1.27 ± 0.35</td>
<td>1.25 ± 0.51</td>
</tr>
<tr>
<td>k₃₂</td>
<td>h⁻¹</td>
<td>0.43 ± 0.03</td>
<td>0.45 ± 0.09</td>
</tr>
<tr>
<td>t₁/₂</td>
<td>h</td>
<td>2.50 ± 0.32</td>
<td>2.88 ± 0.63</td>
</tr>
<tr>
<td>Vₕₐ</td>
<td>Liters/kg</td>
<td>0.135 ± 0.010</td>
<td>0.155 ± 0.015</td>
</tr>
<tr>
<td>Postinference Cₘₐₓᵇ</td>
<td>µg/ml</td>
<td>15.2 ± 0.9</td>
<td>12.1 ± 1.8</td>
</tr>
<tr>
<td>Postinference Cₘᵢₙᶜ</td>
<td>µg/ml</td>
<td>1.9 ± 0.3</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>[AUC]ᵣᵈ</td>
<td>(µg/ml)-h</td>
<td>42.8 ± 5.5</td>
<td>42.4 ± 6.1</td>
</tr>
<tr>
<td>Clₜₒₜ</td>
<td>ml/min per kg</td>
<td>0.706 ± 0.151</td>
<td>0.738 ± 0.145</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD.

The Cₘₐₓ values for dibekacin were essentially identical after intramuscular and intravenous administrations, characterizations common to gentamicin (16, 10, 16), amikacin (4), kanamycin (4), tobramycin (16), sisomicin (15), and netilmicin (10).

The elimination rate constant of dibekacin (k₃₂) from the central compartment, 0.45 ± 0.15 h⁻¹ after the 60-min infusion, was close to the constants of gentamicin, tobramycin, and sisomicin after such an infusion (11).

The mean Cₘₐₓ levels of dibekacin in serum after the 30- and 60-min infusions of a 100-mg dose were 15.2 and 12.1 µg/ml, respectively (Table 2), but levels at 6 h approximated 2 µg/ml, irrespective of infusion rate. These observations, which suggest that the MICs of 1.56 to 3.12 and 3.12 to 6.25 µg/ml required for E. coli and P. aeruginosa (20), respectively, would be exceeded for the same time when 100 mg of dibekacin is infused with either schedule, might favor the use of the 60-min schedule with its lower peak serum levels and possibly lower toxicity.

Aminoglycosides are usually administered at 6- to 8-h intervals, a procedure which yields high peak serum concentrations (18, 26) and troughs below the MICs of such derivatives as gentamicin sulfate, sisomicin, and tobramycin for many gram-negative bacilli (8, 16, 17, 18, 26). These dips to subinhibitory concentrations may be a liability for the neutropenic patient with inadequate host defense mechanisms (2). Recent studies have indicated that aminoglycosides may be more effective when administered by continuous infusions than by intermittent injections (2, 5, 21). Their efficacy might be further improved by using a schedule which would maintain at all times the serum concentration above the MIC of the antibiotic against infecting organisms (2). To sustain a serum level of 7 µg/ml, which is greater than the MIC of dibekacin (20) for P. aeruginosa, in a 70-kg patient with normal renal function would require an infusion of 0.374 mg/min. To obtain a concentration of 7 µg of dibekacin per ml of serum rapidly would require a loading dose of 66 mg to be administered intramuscularly.

LITERATURE CITED

23. Wagner, J. G. 1976. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. J. Pharmacokinet. Biopharm. 4:443-467.