Comparison of Aminoglycoside Pharmacokinetics in Asian, Hispanic, and Caucasian Patients by Using Population Pharmacokinetic Methods

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Received 1 November 1993/Returned for modification 31 March 1994/Accepted 21 June 1994

A population pharmacokinetic model for aminoglycosides was developed from 24 Hispanic, 16 Asian, and 22 Caucasian patients. A nonparametric expectation maximization algorithm for population modeling was used. With this one-compartment model, the parameters were the slope of the apparent volume of distribution versus weight (VS) and the slope of the elimination rate constant versus the creatinine clearance rate (KS). The mean VS (± standard deviation) was not different at 0.264 (± 0.055), 0.248 (± 0.055), and 0.260 (± 0.080) liter/kg of body weight for Asian, Hispanic, and Caucasian populations, respectively (P > 0.10). The KS means (± standard deviations) were 0.00424 ± 0.00129, 0.00404 ± 0.00160, and 0.00394 ± 0.00103 [h(ml/min/1.73 m²)]⁻¹ ± for Hispanic, Asian, and Caucasian populations, respectively. Again, there was no statistical difference among the groups (P > 0.10). In conclusion, there are no differences in aminoglycoside pharmacokinetics among Asian, Hispanic, and Caucasian patients.

In the past decade, interest in therapeutic drug monitoring and individualization of dosage regimens have been evident not only in the United States but also all over the world. This is especially true in the Asian countries of Japan, Korea, and China (10, 14). With easy access to Bayesian pharmacokinetic programs, clinicians in these Asian countries are actively utilizing such software (14). Although a population modeling program is available for hospital-specific use in the United States (8), the limited access and utilization of such a program in Asian countries have led to the use of population models derived from non-Asian populations. This has led to some concern for clinicians since inter racial differences in the pharmacokinetics of drugs have been reported (2, 9, 15).

Several investigators have reported the use of a nonparametric expectation maximization (NPEM) algorithm for population modeling (3–5, 8). NPEM does not rely on a parametric assumption in its statistical model. However, it does describe a pharmacokinetic structural model parametrically. This is in contrast to a program such as NONMEM which relies on parametric methods for both statistical and structural models. We used NPEM to determine the population parameters of aminoglycosides for Asian, Hispanic, and Caucasian patients. We studied the relationship of these pharmacokinetic parameters in Asian, Hispanic, and Caucasian appendicitis patients.

The purpose of this research was to develop a population pharmacokinetic model of aminoglycosides for Asian, Hispanic, and Caucasian populations and to compare them on the basis of ethnic differences.

MATERIALS AND METHODS

Patient population. Timed serum aminoglycoside concentrations were obtained from 16 Asian patients (12 males and 4 females), 24 Hispanic patients (16 males and 8 females), and 22 Caucasian patients (18 males and 4 females). All patients were part of comparative antibiotic trial groups receiving aminoglycosides for the treatment of complicated appendicitis. With the exception of two Asian patients who received tobramycin, all patients received gentamicin. Patients with a serum creatinine level of <2.5 mg/dl were included. All patients were not grossly underweight (40 kg or less) and were free of other infections including sepsis. As patients were a part of comparative antibiotic trial, each patient gave informed consent for the procedures of the study, and the study protocol was approved by the institutional review board. The dosage regimen for gentamicin and tobramycin were individualized for a target peak of 5 to 9 mg/liter and a trough of <2 mg/ml. The Jelliffe method was used for creatinine clearance estimations (6).

Two to eight blood specimens were collected from each patient (i) just before a regularly scheduled infusion and (ii) 0.5 h after the end of a 0.5-h infusion. Samples were obtained 48 h after therapy initiation.

Gentamicin assay. Serum gentamicin levels were determined in batch mode on the day the serum samples were obtained and analyzed by an enzyme-multiplied immunoassay technique. The means of 17 samples, ranging from 0.9 to 17.8 µg/ml, and their standard deviations obtained from 2,512 reporting laboratories provided the data. The relationship between the measured concentration and the standard deviation was fitted to a polynomial equation as seen below. The variability of the assay can be determined by calculation of the

<table>
<thead>
<tr>
<th>Race (no.) of patients tested</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Estimated creatinine clearance rate (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic (24)</td>
<td>29.2 ± 9.8</td>
<td>66.7 ± 11.2</td>
<td>101.1 ± 18.0</td>
</tr>
<tr>
<td>Asian (16)</td>
<td>35.5 ± 11.3</td>
<td>63.3 ± 10.3</td>
<td>85.8 ± 10.3</td>
</tr>
<tr>
<td>Caucasian (22)</td>
<td>25.0 ± 5.0</td>
<td>75.3 ± 14.9</td>
<td>105.9 ± 19.4</td>
</tr>
</tbody>
</table>

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* All data are the means ± standard deviations. All patients received gentamicin, except two Asian patients who received tobramycin.
standard deviation by the following equation: SD (μg/ml) = 0.14078 - (0.002263 × C) + (0.018406 × C²), \( r^2 = 0.991 \), where SD is the standard deviation and C is the observed gentamicin concentration expressed in (micrograms per milliliter).

NPEM pharmacokinetic analyses. Pharmacokinetic models were developed by using NPEM for each ethnic population. The slope of the apparent volume of distribution versus weight (VS) and the slope of the elimination rate constant versus the creatinine clearance rate (KS) were the parameters of interest.

![Diagram](http://aac.asm.org/)  
**FIG. 1.** Three-dimensional plots of PDFs for KS and VS parameterization for Asian (A), Hispanic (B), Caucasian (C), and combined (D) populations. The boundaries were set at 0.0 to 1.0 liter/kg for VS and 0.0 to 0.017 hr⁻¹/(ml/min/1.73 m²) for KS.

### TABLE 2. NPEM statistical summary for aminoglycoside models

<table>
<thead>
<tr>
<th>Race (no.) of patients tested</th>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>Mode</th>
<th>CV (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic (24)</td>
<td>VS</td>
<td>0.248</td>
<td>0.211</td>
<td>0.190</td>
<td>22.3</td>
</tr>
<tr>
<td></td>
<td>KS</td>
<td>0.00404</td>
<td>0.00358</td>
<td>0.00322</td>
<td>39.6</td>
</tr>
<tr>
<td>Asian (16)</td>
<td>VS</td>
<td>0.264</td>
<td>0.254</td>
<td>0.276</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>KS</td>
<td>0.00424</td>
<td>0.00432</td>
<td>0.00550</td>
<td>30.5</td>
</tr>
<tr>
<td>Caucasian (22)</td>
<td>VS</td>
<td>0.260</td>
<td>0.211</td>
<td>0.190</td>
<td>30.6</td>
</tr>
<tr>
<td></td>
<td>KS</td>
<td>0.00394</td>
<td>0.00358</td>
<td>0.00470</td>
<td>26.0</td>
</tr>
<tr>
<td>Combined (62)</td>
<td>VS</td>
<td>0.255</td>
<td>0.211</td>
<td>0.232</td>
<td>23.7</td>
</tr>
<tr>
<td></td>
<td>KS</td>
<td>0.00406</td>
<td>0.00358</td>
<td>0.00470</td>
<td>34.4</td>
</tr>
</tbody>
</table>

a VS is expressed in liters per kilogram; KS is expressed in \([\text{h(ml/min/1.73 m^2)}]^{-1}\).

b CV, coefficient of variation.
ASIAN, HISPANIC, AND CAUCASIAN PHARMACOKINETICS

These parameters were used in the context of a one-compartment model. The assumption was that there was no intercept to the relationship for volume of distribution versus weight. However, an intercept of 0.01 was used for the slope of elimination rate constant versus the creatinine clearance rate (8). The boundaries were set at 0.0 to 1.0 kg of body weight and 0.0 to 0.017 [h(mL/min/1.73m^2)]^-1 for V/S and KS, respectively. The output includes a three-dimensional plot of the joint probability density function (PDF), two marginal PDF plots, means, variances, modes, quartiles, skewness, kurtosis, and covariance and correlation coefficient between parameters.

Statistics. One-way analysis of variance was used to compare the means of the V/S and KS for the three populations. Statistical significance was set at 0.05, and estimates of P values were reported.

RESULTS

Patients' characteristics are summarized in Table 1. Asian patients tended to be slightly older. Caucasian patient tended to be heavier, and creatinine clearance rates were somewhat lower for the Asian patients.

A summary of the NPEM pharmacokinetic analysis is given in Table 2 for all populations. The mean V/S was not different at 0.264, 0.248, and 0.260 liters/kg for Asian, Hispanic, and Caucasian populations, respectively (P > 0.10). The mean KSs were 0.00424, 0.00404, and 0.00394 [h(mL/min/1.73m^2)]^-1 for Asian, Hispanic, and Caucasian populations, respectively. Again, there was no statistical difference among groups (P > 0.10). Table 2 provides the mean, median, and mode for each parameter. The mean value can be used a priori in a Bayesian dose prediction program. Figure 1 is a three-dimensional plot of the PDFs for the three populations and a combination of all three. Figure 2 shows plots of the marginal density function for V/S, designated f(V/S). Figure 3 plots the marginal density function for KS, designated f(KS). The distributions of parameters for the three populations in Fig. 1, 2, and 3 can essentially be superimposed and are comparable to that of the combined population, suggesting that Asian, Hispanic, and Caucasian subjects are subpopulations of a single population. The corre-
DISCUSSION

Pharmacokinetic differences of many agents based on ethnicity have been previously shown. However, most research has been done with agents that are metabolized by the hepatic route (2, 9, 15). For example, Potkin et al. (12) and Lin et al. (11) performed pharmacokinetic studies and reported higher concentrations of haloperidol in serum in Asian patients than in Caucasians even after controlling for weight and body surface area. There are, however, fewer reports on ethnic differences with regard to agents that are renally eliminated. It is theorized that no major differences may occur across the races with respect to renally eliminated agents. Honda and Suzuki's (6) observation that Caucasians have higher lithium clearance rates and a larger volume of distribution is based on a short-term study of a small number of patients. Other pharmacokinetic data (1, 13) show almost no differences for these values. Our findings are consistent with these latter reports.

Because NPEM does not assume a normal distribution of its data and because our sample size is limited, it is difficult to visualize (Fig. 2 and 3) a true Gaussian distribution. Although, at a glance, some of the distributions may appear to be bimodal, it is difficult to make that judgment with our limited sample size. It may be more appropriate to apply a nonparametric test to compare the differences in the population parameters. However, the output of NPEM is such that results of individual parameters are not readily available. Moreover, inspection of the means, medians, and modes (Table 2) supports the view of a normal distribution; therefore, a parametric statistical analysis was performed.
In our assay variability equation, we used the variability of the gentamicin assay for the two tobramycin patients in the Asian population, as there was no technique available to incorporate the tobramycin assay variability. This may have contributed to an error in our NPEM analysis.

There have been few reports of aminoglycoside pharmacokinetics for appendicitis patients. Hurst et al. (7) reported \( V/S \) to be 0.215 ± 0.039 liter/kg and \( K/S \) to be 0.0056 ± 0.0018 [h(ml/min/1.73 m²)] for gentamicin in appendicitis patients. These parameters are slightly different from our findings.

Despite ample availability of alternative antibiotics, aminoglycosides are still widely used for treatment of gram-negative infections in the United States as well as in countries abroad. Furthermore, because of their associations with nephrotoxicity and auditory nerve damage, they are frequent candidates for therapeutic drug monitoring. As mentioned, NPEM and other population model programs are available in the United States. However, because of many factors, these programs will not be available to or will not be utilized by clinicians abroad for many years, especially in Asian countries. Meanwhile, clinicians will continue to rely on population models developed in the United States on the basis of Caucasian or non-Asian patients. Through our study, we conclude that there are no differences in aminoglycoside pharmacokinetics among Asian, Hispanic, and Caucasian appendicitis patients.

REFERENCES

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