Optimization of Aminoglycoside Therapy

G. L. Drusano* and Arnold Louie

Ordway Research Institute, 150 New Scotland Avenue, Albany, New York 12208

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Aminoglycosides are experiencing a resurgence in use because of the spread of multiresistant Gram-negative pathogens. Use of these agents is attended by the occurrence of nephrotoxicity. Aminoglycoside optimization of dose can be defined as the dose having the highest likelihood of a good outcome and the lowest likelihood of toxicity. We have defined the metric \( \Delta \) as the difference between the likelihoods of good outcome and toxicity, with higher values being better. We developed a method for explicitly evaluating \( \Delta \) for different daily doses of drug and different schedules of administration. In the empirical therapy setting, when aminoglycosides are administered every 12 h, treatment of infections caused by microbes with MIC values greater than 1 mg/liter cannot attain a high enough likelihood of a good outcome without engendering an unacceptable toxicity likelihood. Daily administration, by decrementing the likelihood of toxicity, allows higher doses to be employed with more acceptable probabilities of toxicity. Obtaining patient-specific information (concentration-time data) allows better identification of the patient’s specific pharmacokinetic parameters and dispersion. As these become better identified, optimal doses become rapidly identified so that optimal outcomes are attained. Optimization of therapy for aminoglycosides requires understanding the relationship between exposure and response as well as that between exposure and toxicity. Furthermore, daily administration is much preferred, and stopping therapy as quickly as possible (a week or less may be optimal) will contribute to the ability to optimize therapy.

Multiresistant Gram-negative organisms are a problem building to a crescendo around the world. KPC enzymes in Klebsiella, the new NDM metalloenzymes, and multiresistance in Pseudomonas aeruginosa and Acinetobacter spp. are all common enough that many intensive care unit (ICU) patients have infections caused by agents to which all \( \beta \)-lactams and all fluorquinolones are resistant. Some have only colistin as the sole active agent.

Against this background, a substantial number of patients are infected with bacterial isolates that are still susceptible to aminoglycoside antibiotics. These agents fell out of favor in the 1980s with the advent of broad-spectrum \( \beta \)-lactams, such as carbapenems and broad-spectrum cephalosporins, as well as \( \beta \)-lactams combined with \( \beta \)-lactamase inhibitors. Part of the move away from the aminoglycosides came from their nephrotoxicity. A considerable amount has been learned about this over the last 2 decades (9, 12). In the clinical arena, intensive care unit clinicians have learned that losing renal function in the ICU is associated with an enhanced probability of death (12). Consequently, these agents became less and less used as the utility of the broad-spectrum \( \beta \)-lactams was proven.

Out of necessity, the aminoglycosides have recently undergone a resurgence in use. Recently, new aminoglycosides have entered evaluation (4, 7). It is the aim of this paper to examine the dosage of aminoglycosides, estimate the likelihood with which they attain an exposure likely to result in a measure of good clinical outcome as a function of dose and MIC, estimate the likelihood of nephrotoxicity, and balance the benefit and risk both in the empirical therapy setting and then after patient-specific information has been obtained.

**MATERIALS AND METHODS**

**Relationships between exposure and response and exposure and nephrotoxicity.** In previous work (3, 6, 11), it has been possible to examine the relationship between the area under the concentration-time curve (AUC)/MIC ratio and a clinical endpoint (time to afebrility) in patients with hospital-acquired pneumonia (only patients treated with gentamicin or tobramycin were included in this analysis). It should be noted that another endpoint, such as clinical outcome or infection-related mortality, would have been preferable, but the endpoint employed was, we believe, the best one available. In the current project, we employed the logistic regression relationship used for estimating the probability of afebrility by day 7 as a function of the AUC/MIC ratio (3, 6). We have also generated a logistic regression function for the relationship between aminoglycoside AUC from time zero to 24 h (AUC\(_{0-24}\)) and the likelihood of nephrotoxicity (nephrotoxicity was defined as an increase in the baseline serum creatinine concentration of 0.5 mg/dl or a 50% increase, whichever was greater, on two consecutive occasions any time during therapy or up to 1 week after the cessation of therapy [10]). The MIC value can be factored out by freezing it at a specific value, and the direct relationship between exposure and response as well as exposure and toxicity can be estimated, as long as the MIC is held at a constant value. In the toxicity relationship, we also evaluated the impact of dosing daily versus every-12-h dosing on the likelihood of aminoglycoside toxicity. These are displayed graphically in Fig. 1. It should be noted that the effect function has the AUC\(_{0-24}/\)MIC ratio as the driver. If the MIC is fixed, the curve shape will change substantially as a function of the MIC value and the dose employed (3).

Below, we show the logistic regression functions for effect, toxicity with daily dosing, and toxicity with every-12-h dosing, and these functions were drawn from references 6 and 11:

\[
\text{Probability of afebrility by day } 7 = \frac{e^{-0.30546 + 0.049 \times \text{(dose/clearance)/(MIC)}}}{1 + e^{-0.30546 + 0.049 \times \text{(dose/clearance)/(MIC)}}} \tag{1}
\]

\[
\text{Probability of nephrotoxicity with daily dosing} = \frac{e^{-37.239 + 0.049 \times \text{dose/clearance}}}{1 + e^{-37.239 + 0.049 \times \text{dose/clearance}}} \tag{2}
\]

\[
\text{Probability of nephrotoxicity with every-12-h dosing} = \frac{e^{-6.402 + 0.049 \times \text{dose/clearance}}}{1 + e^{-6.402 + 0.049 \times \text{dose/clearance}}}. \tag{3}
\]

The optimization function \( \Delta \) is simply the difference between the likelihood of a good clinical effect and the likelihood of toxicity and operates under the assumption that the best regimen has the highest difference between the likelihood of...
effect and the likelihood of toxicity. Unfortunately, we were not able to address the time component of toxicity.

Making the relationships stochastic. We employed the results of a prior population pharmacokinetic analysis (5) to generate 9,999-subject Monte Carlo simulations. Separate simulations were performed for each dose and MIC value examined. Doses of 5, 7, and 10 mg/kg of body weight/day were examined (it should be noted that 10 mg/kg was a larger dose than that administered in the study of Rybak et al. [11]). The variability about the point estimate of clearance would have significant AUC overlap between the highest dose in the study of Rybak et al. (11) and a dose of 10 mg/kg/day. Twofold increments in MIC values between 0.25 mg/liter and 4 mg/liter were examined. The weight distribution was taken from a data set for 39 patients with ventilator-associated pneumonia and was 83.1 ± 22.6 kg (8).

All Monte Carlo simulations were performed with the ADAPT II package of programs of D’Argenio and Schumitzky (2). Normal and log-normal distributions were evaluated for the first dose and MIC, and the fidelity with which the original mean values and their dispersions were recreated by the simulation was the criterion by which the choice was made. This resulted in a log-normal distribution being chosen, which was employed for subsequent simulations.

Optimizing therapy after patient-specific data were obtained. We generated a peak/trough (12-h) concentration-time pair using the simulation option of ADAPT II (2) with the noise-corruption option. These data were then fit with the Bayesian estimation option of ADAPT II. In both instances, the prior parameter values of Incardi and Batra were employed (5). The parameter values identified and their dispersions were then inserted into the Monte Carlo simulation routine, and new 9,999-subject simulations were calculated for 5 and 7 mg/kg with MIC values of 2 and 4 mg/liter.

### RESULTS

**Outcomes employing every-12-h dosing.** It should be noted that while extended-interval dosing is the norm today, the study of Chuck et al. (1) demonstrated that there are still approximately 25% of all acute care hospitals not employing extended-interval dosing. We examined doses ranging from 5 to 10 mg/kg and MIC values from 0.25 through 4.0 mg/liter. In Table 1, we display the estimates of probability of effect and probability of nephrotoxicity along with their dispersions. Δ is the difference between these two probabilities. The optimal regimen would then have the greatest Δ. It is obvious by inspection that MIC values of 0.25 and 0.5 mg/liter produce robust results with regard to target attainment, with probabilities exceeding 90%. With an MIC of 1.0 mg/liter, response probabilities decline to just under 80%. Values of 2.0 and 4.0 mg/liter, even though they are considered full susceptibility, have response probabilities in the mid-50 to mid-60% range with the 5-mg/kg dose. An important issue is to define the impact that increasing the dose to 7 or 10 mg/kg would have on efficacy and toxicity. Table 1 shows that for these MIC values, response probabilities rise, but they rise only to 71% for an MIC of 2.0 mg/liter and only as high as 58% for 4.0 mg/liter. The Δ demonstrates that 5 mg/kg is not an optimal regimen when MIC values exceed 1.0 mg/liter. This is because the overall point estimate of toxicity engendered by the 5-mg/kg dose is substantial at 24.6%. It should be noted that the standard deviation was greater than the point estimate, indicating that not everyone in the population will have this toxicity probability because of different drug clearances. This mean estimate is higher than that seen previously (3). The difference is that the previous calculations were done with a fixed dose of 400 mg (5 mg/kg for an 80-kg patient), whereas this calculation employed a distribution of weights from a study of patients with nosocomial pneumonia who are receiving mechanical ventilation.

The Δ has an optimal value of 74.8 at an MIC value of 0.25 mg/liter, and the values decline to 69.4 and 55.3 at 0.5 and 1.0 mg/liter, respectively, with 2.0 and 4.0 mg/liter attaining values of 39.5 and 29.0, respectively, because of decrementing values of response probability. Of interest, the Δ gets considerably worse, on average, when the dose is increased to 7 mg/kg (19.9 at 2.0 mg/liter and 6.5 at 4.0 mg/liter) or 10 mg/kg (Δ = 0 at

### Table 1. Optimization of empirical aminoglycoside therapy with administration every 12 h

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>MIC (mg/liter)</th>
<th>Probability of effect (%)</th>
<th>Probability of toxicity (%)</th>
<th>Δ</th>
<th>AUC0–24 (mg·h/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.25</td>
<td>99.4 ± 0.013</td>
<td>24.6 ± 26.2</td>
<td>74.8 ± 25.7</td>
<td>97.1 ± 34.2</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>94.1 ± 0.053</td>
<td>24.6 ± 26.2</td>
<td>69.4 ± 22.8</td>
<td>97.1 ± 34.2</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>79.9 ± 0.086</td>
<td>24.6 ± 26.2</td>
<td>55.3 ± 19.0</td>
<td>97.1 ± 34.2</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>64.1 ± 0.070</td>
<td>24.6 ± 26.2</td>
<td>39.8 ± 19.7</td>
<td>97.1 ± 34.2</td>
</tr>
<tr>
<td>5</td>
<td>4.0</td>
<td>53.6 ± 0.040</td>
<td>24.6 ± 26.2</td>
<td>29.0 ± 22.4</td>
<td>97.1 ± 34.2</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>71.3 ± 0.083</td>
<td>51.4 ± 33.2</td>
<td>19.9 ± 25.3</td>
<td>136 ± 47.9</td>
</tr>
<tr>
<td>7</td>
<td>4.0</td>
<td>58.0 ± 0.054</td>
<td>51.4 ± 33.2</td>
<td>6.5 ± 28.2</td>
<td>136 ± 47.9</td>
</tr>
<tr>
<td>10</td>
<td>2.0</td>
<td>79.9 ± 0.086</td>
<td>80.3 ± 25.9</td>
<td>0.0 ± 18.7b</td>
<td>194 ± 68.5</td>
</tr>
<tr>
<td>10</td>
<td>4.0</td>
<td>64.1 ± 0.070</td>
<td>80.3 ± 25.9</td>
<td>0.0 ± 20.8b</td>
<td>194 ± 68.5</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations.

** When Δ is <0.0, it is scored 0.0.
both MIC values), even though there is a marginal increase in the response probability. This is because of the increase in mean nephrotoxicity probability at higher doses.

**Outcomes employing daily dosing.** When daily dosing is employed, there is very little nephrotoxicity observed (10, 11). The trial from which the logistic regressions were generated had no observed cases of nephrotoxicity in the daily dosing group (11). The occurrence of one case of toxicity would have caused a significant shift in the likelihood of toxicity with once-daily dosing but would still have remained significantly different from that with every-12-h dosing. Because of this, the quantification of toxicity risk should be somewhat discounted, we believe.

In Table 2, we show the likelihood of response, likelihood of toxicity, and \( \Delta \) for a dose of 10 mg/kg once daily against an isolate with an MIC value of 4.0 mg/liter. At 10 mg/kg, this MIC value is reasonably treatable, with an outcome probability of nearly 80%. The daily dosing provides a low probability of nephrotoxicity (although not as low as the calculations would indicate [see above]). As long as the probability of nephrotoxicity can be ameliorated, high doses may bring higher MIC values into the probability range where aminoglycoside therapy makes clinical sense.

**Optimizing outcomes after patient-specific data are available.** We used the simulation with the noise-corruption option of ADAPT II to simulate two data points. Data were generated at time 1/2 hour after a 1-h infusion and at the trough. Prior parameter values were drawn from a previous one-compartment aminoglycoside population pharmacokinetic analysis, and the mean values were clearance equal to 4.4 liters/h and volume equal to 24.16 liters (5). The dose was 5 mg/kg/day, administered on a 12-hourly schedule. The exact outputs (without random noise corruption) were 7.177 mg/liter at 1.5 h and 1.06 mg/liter at 12 h. The noise-corrupted values were 5.79 mg/liter at 1.5 h and 0.962 mg/liter at 12 h.

We then employed Bayesian estimation to obtain patient-specific estimates of clearance and volume, using ADAPT II. The same parameter estimates mentioned above were used as Bayesian prior values. The Bayesian posterior estimates were clearance equal to 5.03 \( \pm \) 0.368 liters/h and volume equal to 29.05 \( \pm \) 2.723 liters. These values were then employed to evaluate new doses with a Monte Carlo simulation. These are displayed in Table 3. The \( \Delta \) increases here because the new estimate of the standard deviation associated with clearance after the patient-specific data became available was much smaller than the original pre-Bayesian estimate and the mean value was slightly higher, resulting in lower estimates of nephrotoxicity probability.

**DISCUSSION**

Aminoglycosides are seeing a resurgence in use, forced by multiresistant Gram-negative pathogens. Because of the toxicity of aminoglycosides, it is important to get the dosing correct for these agents. In this examination, we displayed a method for examining dose empirically to choose the best dose (highest likelihood of response, smallest likelihood of toxicity) for the therapy of a patient.

An important consideration is to identify methods to ameliorate the onset of nephrotoxicity, as this is the dose-limiting issue for these agents. Aminoglycoside uptake into the nephrotoxicity site, the proximal renal tubular epithelial (PRTE) cell, is governed by Michaelis-Menten kinetics (9). Consequently, administering the drug once daily instead of in divided doses leads to slower uptake in the PRTE cell. This means that for any specific duration of therapy, there will be less aminoglycoside toxicity, on average, when daily administration is employed. It also shows that therapy duration is critical. If drug is given long enough, the amount sequestered in the PRTE cell will ultimately attain the threshold necessary for a nephrotoxic event. Consequently, for minimization for the probability of nephrotoxicity, doses should be given daily and should be stopped as early as possible. The time dependency of nephrotoxicity can be seen in Fig. 2, which is drawn from a randomized, double-blind study of once- versus twice-daily aminoglycoside therapy (11). Even with administration on a 12-hourly basis, the rate of nephrotoxicity stays below 10% up to day 9. The important message is to use daily administration and to foreshorten therapy as much as possible.

The same study also developed logistic regression relationships for daily versus twice-daily therapy. The daily therapy group had no cases of nephrotoxicity. Consequently, the actual daily logistic regression function should be viewed with caution.

### Table 2. Optimization of empirical aminoglycoside therapy with administration daily

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>MIC (mg/liter)</th>
<th>Probability of effect</th>
<th>Probability of toxicity</th>
<th>( \Delta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>4.0</td>
<td>0.912 ( \times 10^{-4} )</td>
<td>0.908 ( \times 10^{-2} )</td>
<td>79.7 ( \pm ) 8.61</td>
</tr>
</tbody>
</table>

\( \Delta \) values are means \( \pm \) standard deviations.

### Table 3. Optimization of aminoglycoside therapy after patient-specific data become available with administration every 12 h

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>MIC (mg/liter)</th>
<th>Probability of effect</th>
<th>Probability of toxicity</th>
<th>AUC_{0-24}^a (mg \cdot h/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2.0</td>
<td>60.74 ( \pm ) 0.049</td>
<td>12.29 ( \pm ) 14.24</td>
<td>48.45 ( \pm ) 10.06</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>67.36 ( \pm ) 0.061</td>
<td>34.97 ( \pm ) 26.87</td>
<td>32.38 ( \pm ) 20.98</td>
</tr>
</tbody>
</table>

\( a \) Values are mean \( \pm \) standard deviations.
We defined the difference between the probability of response (6) and the probability of nephrotoxicity (11) as the factor that identified optimal regimens. In Table 1, it is clear that \( \Delta \) drops rapidly as a function of MIC, until at MIC values of 2 and 4 mg/liter \( \Delta \) values are under 40 and 30, respectively, for therapy with a 5-mg/kg daily dose (here, administered 12 hourly). Normally, the reflex is to increase the dose. The likelihoods of response do increase to 71% and 58% for MIC hourly). Normally, the reflex is to increase the dose. The likelihoods of response do increase to 71% and 58% for MIC values of 2 and 4 mg/liter, respectively, for 7 mg/kg/day and to 80% and 64% for these respective MIC values for 10 mg/kg/day. Unfortunately, the \( \Delta \) values decline to below 20 for an MIC of 2 mg/liter and to 6.5 at an MIC value of 4 mg/liter at the 7-mg/kg/day dose because of the increase in toxicity. At 10 mg/kg/day, both \( \Delta \) values are 0.

In contrast, daily dosing, with the logistic function that we currently have, demonstrates that the 10-mg/kg dose provides an 80% probability of response, even for an MIC of 4.0 mg/liter, with a negligible likelihood of toxicity. Consequently, ways of mitigating the nephrotoxicity risk are a key issue in using larger doses to be able to successfully treat patients with infections caused by organisms with MIC values in excess of 1 mg/liter with currently available aminoglycosides.

All the above data are drawn from the empirical therapy setting. Once we have patient-specific information through obtaining measured aminoglycoside concentrations, our knowledge of the patient’s pharmacokinetic parameters is markedly improved in terms of both the point estimate of the mean and, more importantly, the standard deviation about the mean value. When using these better, patient-specific values, we see substantially improved likelihoods of response and \( \Delta \) values, because we are not dealing with values of volume and clearance that are in the far tails of the original distribution, as the specific patient information markedly foreshortens the distribution.

In summary, aminoglycosides will be used more. We must embrace optimal modes of administration, such as daily therapy and employing the shortest courses of therapy possible to get optimal results consisting of the highest probability of response and the lowest probability of toxicity. Patient-specific data can ameliorate the risk of using larger doses. It should be noted that all the data in this evaluation were drawn from adult patient data sets and are not applicable to children. Newer agents with better resistance to aminoglycoside-modifying enzymes would be welcome.

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References