Back to the Future: Using Aminoglycosides Again and How to Dose Them Optimally

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Gram-negative organisms have become increasingly resistant to both β-lactam antibiotics and fluoroquinolones. Consequently, aminoglycoside antibiotics have undergone a resurgence in use. Because of the known toxicities of aminoglycoside antibiotics, clinicians have avoided their use, unless no other alternatives were extant. Over the past 2 decades, we have learned much about the relationship between aminoglycoside exposure and the likelihood of a good clinical outcome or the occurrence of nephrotoxicity. For example, minimum inhibitory concentration values ≥2.0 mg/L lead to unacceptably low probabilities of a good clinical outcome, and infrequent administration of doses (i.e., intervals of 24 h and longer intervals for patients with compromised renal function) plays a central role in minimizing the likelihood of toxicity. Using these new insights, we suggest ways of evaluating the dose and schedule of administration of aminoglycosides in empirical therapy to obtain the highest likelihood of an efficacious and nontoxic therapy.

Nosocomial infections caused by gram-negative bacilli have become increasingly difficult to treat over the past 5 years because of the advent of a number of resistance mechanisms that limit the use of some of the best drugs in our armamentarium. Unfortunately, very few new drugs that are active against multidrug-resistant nosocomial gram-negative organisms are expected to be available for 5–10 years. Consequently, many clinicians are starting to again consider the use of aminoglycoside antibiotics. The commentary in this article applies only to gram-negative organisms.

Aminoglycosides were widely used in empirical therapy throughout the 1970s and much of the 1980s. Unfortunately, aminoglycoside use generates a number of toxicities, mostly oto- and nephrotoxicity. It was noted [1] that patients in intensive care units who developed altered renal function had a significantly increased risk of death. Consequently, with the advent of broad-spectrum β-lactams (e.g., third- and fourth-generation cephalosporins; β-lactam and β-lactamase inhibitor combinations, such as piperacillin and tazobactam; and carbapenems, such as imipenem plus cilastatin and meropenem) and fluoroquinolones, use of aminoglycosides decreased, because clinicians felt that they could obtain good resolution of serious infections without using drugs that would generate serious toxicities.

Multidrug-resistant Pseudomonas and Acinetobacter infections, as well as infections caused by extended-spectrum β-lactamase–bearing Enterobacteriaceae species, are often resistant to most or even all of the these newer agents. Frequently, only the aminoglycosides and the polymyxins are available for therapy. Over the course of the past decade, information has become available to guide the use of these aminoglycosides. In this article, we will look at some of these data and apply them, with the objective of achieving maximal therapeutic effect in patients without encumbering them with undue risk of nephrotoxicity.

AMINOGLYCOSIDE TOXICITY

A number of articles based on data from both preclinical and clinical trials have clarified the risk of nephrotoxicity associated with the use of aminoglycosides [2–7]. A preclinical review by Mingeot-Leclercq et al. [2] includes data revealing that aminoglycoside toxicity is driven by the uptake by proximal renal tubular epithelial cells of aminoglycosides from their luminal surface. Similar findings were also demonstrated by Whelton et al. [6, 7]. The key issue here is that the uptake is saturable. Consequently, when concentrations of drug in the tubular lumen at the point of uptake are well above the Km of transport...
therapy for a long period. It is likely that, if a patient received aminoglycoside therapy once daily, any representation of time-to-event analysis is uninformative, with regard to understanding the impact of concurrent vancomycin therapy. Again, because there were no cases of nephrotoxicity in the group of patients who received the drug every 12 h. The effect of concurrent vancomycin use on the time to the occurrence of nephrotoxicity among patients receiving aminoglycoside therapy every 12 h is shown in figure 2.

It is important to note that, in the rather small study (n = 74) by Rybak et al. [9], there were no instances of nephrotoxicity in the group of patients who received the aminoglycoside therapy once daily. Consequently, the logistic regression curve for this group (figure 1B) is quite far to the right, and this would not likely be the case if more patients were involved. For the Kaplan-Meier plot (figure 2), it is clear that concurrent vancomycin therapy had a major influence on the time to the occurrence of nephrotoxicity for the group of patients who received the aminoglycoside therapy twice daily. Again, because there were no cases of nephrotoxicity in the group of patients who received aminoglycoside therapy once daily, any representation of time-to-event analysis is uninformative, with regard to understanding the impact of concurrent vancomycin therapy on such a regimen. The important aspect to note in figure 2 is that occurrence is represented as the time to event. It is likely that, if a patient received aminoglycoside therapy for a long period (>10 days), even if therapy was received only once daily, as the duration of therapy increased, the risk of the patient experiencing nephrotoxicity would increase. This was independently demonstrated in a study by Bertino et al. [10], in which duration of therapy was an independent risk factor for nephrotoxicity in a multivariate logistic regression analysis. Administering aminoglycoside therapy infrequently does not completely obliterate the risk of drug-driven nephrotoxicity but provides a window when patients can be safely treated with these agents. This emphasizes the importance of prescribing a correct dose for the patient to obtain a high probability of a good clinical outcome, administering the dose on a daily basis (or less frequently in the case of patients with compromised renal function), and then stopping the aminoglycoside treatment quickly. Because these agents are concentration-dependent killing drugs, relatively short courses (i.e., ≤7 days) should provide near-maximal effect and near-minimal toxicity. It is important to note that this strategy was tested clinically in a study by Nicolau et al. [11], in which the duration of therapy was a median of 3 days, and the ultimate rate of nephrotoxicity was quite low (1.2% among >2000 patients).

AMINOGLYOSIDE EFFECT

There has been a general feeling among clinicians that aminoglycosides are not overly effective for treating many types of infection. A number of reasons for this seeming lack of efficacy have been suggested (e.g., chelation by WBC DNA in patients with pneumonia and poor tissue penetration). However, one of the major reasons for this perception is the misidentification of the susceptibility break point for these drugs. For both gentamicin and tobramycin, the break point for full susceptibility is 4 mg/L, and for amikacin, the break point is 16 mg/L. As we show below, these values are too high. These break points caused clinicians to use these agents in situations in which the expectation of a good outcome was unacceptably low.

In the 1970s and 1980s, the standard dosage of both gentamicin and tobramycin was also too low, at 80 mg every 8 h (3.0–3.4 mg/kg for a 70–80 kg person). Again, this low dose ameliorated the rate of nephrotoxicity but did not provide a high probability of a good clinical outcome if the MIC was even mildly elevated.

In the 1980s, Moore et al. [12] were able to link aminoglycoside exposure to outcome. Unfortunately, because of sparse serum sampling, they chose the Peak:MIC ratio as the independent variable. Animal data from the study by Craig et al. [13] show that the AUC:MIC ratio is more likely the “correct” dynamically linked variable, although it should be recognized that any study that uses only a single-dose schedule will have maximal colinearity between the Peak:MIC ratio and the AUC:MIC ratio.

Later, Kashuba et al. [14] were able to generate a relationship between aminoglycoside exposure and the probability of a patient becoming afebrile or having normalization of temperature.
in a specific time frame. We use the resolution of fever relationship to demonstrate the ability to optimize aminoglycoside use. In figure 3, we demonstrate the link between the AUC:MIC ratio and the probability of the patient becoming afebrile. There are 3 separate curves for the probability of a patient becoming afebrile by days 5, 7, and 9. For demonstration purposes, we concentrate on the curve showing the probability of a patient becoming afebrile by day 7. To achieve a 90% probability of this response by day 7, an AUC:MIC ratio of 1:156 is required.

**OPTIMIZATION OF THERAPY**

Operationally, optimal antimicrobial therapy can be defined as a choice of drug, drug dose, and schedule of administration that results in an acceptably high likelihood of a good therapeutic outcome, while not burdening the patient with an unacceptably high probability of a concentration-related drug toxicity (in this case, nephrotoxicity).

It is important to note that the relationship for toxicity (figure 1A) has $AUC_{0-24}$ as the independent variable, and the relationship for effect (figure 3) has the $AUC_{0-24}$:MIC ratio as the independent variable. To explicitly determine how these relationships interact, the independent variables must be the same, which can be achieved, in this instance, by factoring out the MIC and fixing it at a specific value. In figure 4, the curves for efficacy and toxicity are shown on the same scales, with the MIC fixed at 0.25 mg/L, 0.5 mg/L, and 1.0 mg/L. Empirically, the horizontal lines represent the values at which the efficacy
WHAT IS THE NECESSARY DOSE TO ATTAIN THE OPTIMAL EXPOSURE?

There are 2 distinct circumstances for which we can determine the necessary dose to attain optimal exposure. The first is the empirical therapy situation, in which no information is available about the concentration-time profile for the patient. The second is the circumstance in which the clinician has obtained gentamicin and tobramycin concentration determinations for the patient. In the latter circumstance, the determination of the necessary dose for optimal exposure requires the use of stochastic control techniques and represents a topic requiring its own review. Here, we will partially address the first circumstance, in which therapy is empirical.

We used the population pharmacokinetic analysis performed by Inciardi and Batra [15] and performed two 9999-subject Monte Carlo simulations, using a dosage of 5 mg/kg per day of an aminoglycoside administered as a 2.5-mg/kg dose every 12 h or a 5-mg/kg dose once daily. For the analysis, we assumed an 80-kg patient; therefore, the treatment regimens were 200 mg of an aminoglycoside every 12 h and 400 mg once daily. We then used the logistic regression functions for toxicity and effect shown in figures 1 and 3, generating toxicity probability distributions and effect probability distributions for MIC values of 0.25 mg/L, 0.5 mg/L, and 1.0 mg/L. These are shown for the treatment regimen in which a 200-mg dose of drug was administered every 12 h (figure 6).

If the problem is approached classically (i.e., if the clinician would like the patient to have no more than a 10% probability of toxicity and at least a 90% probability of a good clinical outcome), then this dosage (200 mg every 12 h) produces only a 60.9% likelihood of having a probability of nephrotoxicity of ≤10%. At an MIC of 0.25 mg/L, 100% of subjects have a >90% probability of having a probability of nephrotoxicity of ≤10%. At an MIC of 0.25 mg/L, 100% of subjects have a >90% probability of having a probability of nephrotoxicity of ≤10%. At an MIC of 0.25 mg/L, 100% of subjects have a >90% probability of having a probability of nephrotoxicity of ≤10%.

WHAT IS THE OPTIMAL EXPOSURE?

Again, operationally, the optimal exposure can be defined as the drug dose and schedule of administration that provide the largest difference between the effect probability and the toxicity probability. Alternatively, a clinician may state the problem somewhat differently. Often, a clinician would like to have at least a 90% probability of a good outcome for the patient and no more than a 10% probability of engendering a concentration-related toxicity. The latter part of this dilemma is shown in figure 4, which illustrates the idea of a toxic-therapeutic window. The former formulation is somewhat deterministic and identifies a specific exposure (figure 5). The maximal differences between effect and toxicity occur at an AUC value of 65 when the MIC is 0.25 mg/L (AUC$_{0-24}$:MIC, 1:260) and at an AUC value of 75 when the MIC is either 0.5 or 1.0 mg/L (AUC$_{0-24}$:MIC, 1:150 and 1:75, respectively).

Figure 2. Effect of concurrent vancomycin use on the time to the occurrence of nephrotoxicity in patients receiving a twice-daily aminoglycoside regimen.

Figure 3. Probability of resolution of fever by days 5, 7, and 9 of aminoglycoside therapy, as determined by logistic regression analysis. The squares are break point values, as determined by classification and regression tree analysis. AUC, area under the curve.
Figure 4. The probability of effect (temperature defervescence) versus the probability of nephrotoxicity, as a function of daily area under the curve (AUC). The effect probability differs as a function of MIC. A, MIC of 0.25 mg/L. B, MIC of 0.5 mg/L. C, MIC of 1.0 mg/L.
Figure 5. The logistic regression curves for probability of effect (temperature defervescence) and the probability of nephrotoxicity, presented as a function of area under the curve (AUC). The blue curve is the difference between these probabilities, and the maximum value of this curve represents one measure of an optimal aminoglycoside exposure. The effect probability differs as a function of MIC. A, MIC of 0.25 mg/L. B, MIC of 0.5 mg/L. C, MIC of 1.0 mg/L.
probability of a good clinical outcome; at an MIC of 0.5 mg/L, this value is 90.2%, and at an MIC of 1.0 mg/L, this value is 4.5%.

These values seem to correspond with the impression that aminoglycosides are toxic agents and are not very effective, particularly at MIC values $\geq 0.5$ mg/L. However, if, for example, the probability of toxicity is $\geq 20\%$, the patient will not necessarily experience toxicity. Indeed, there is an 80% likelihood that the patient will not experience toxicity. The same thought process applies to the probability of a good clinical outcome. To understand the likelihood of toxicity and good outcome across the patient distribution of the Monte Carlo simulation, it is important to take an expectation. For example, if the toxicity probability among 2000 patients is 0%–10%, the midpoint (5%) is used to calculate the expectation that 100 of these patients would experience toxicity (mean probability of toxicity, $0.05 \times 2000$ patients). This process is repeated throughout the distribution, and the expected number of patients experiencing toxicity is summed and then divided by 9999 to obtain an estimate of the fraction of patients who would experience toxicity overall.

When considering these expectations for the regimen including 200 mg of drug administered once every 12 h, the estimated percentage of patients experiencing toxicity is 18.9%. For MIC values of 0.25 mg/L, 0.5 mg/L, and 1.0 mg/L, the estimated percentages of patients having a good clinical outcome is 100%, 94%, and 79.9%, respectively. These results convey a clear significance. First, at a dosage of 5 mg/kg per day administered once every 12 h, there is an almost 20% likelihood of toxicity overall, which verges on the unacceptable. It should be recognized that use of a schedule in which the drug is administered once daily would ameliorate this problem considerably, particularly if the duration of therapy were limited to $\leq 1$ week. Given that aminoglycosides, like fluoroquinolones, are concentration-dependent killing drugs and that "good clinical outcome" was defined as the patient being afebrile by 1 week, this limitation in duration is reasonable. Second, it is clear that empirical expected response rates are quite robust to an MIC of 0.5 mg/L and reasonable to an MIC of 1.0 mg/L. Higher MIC values will produce unacceptably low expected response rates. Third, there is no doubt that the Clinical and Laboratory Standards Institute break points for aminoglycosides are far too high and result in inadequate therapy for patients infected with strains with these higher MIC values. The counterargument that is most frequently asserted is that aminoglycosides are rarely used as single agents and are used mostly
for synergy. There are 2 errors with respect to this argument. The first is that, at this time, a large number of gram-negative pathogens are already primarily resistant to many of the combination agents (e.g., β-lactams and fluoroquinolones). The second is that, although synergy may be real and clinically helpful, there are few clinical data to support this view, except, perhaps, in the context of *Pseudomonas aeruginosa* infection [16]. Consequently, it is important to optimize dosing of aminoglycosides as if they were the only active agents being used.

In summary, aminoglycosides are undergoing a resurgence in use because of widespread resistance to other therapeutic classes. We have attained a considerable amount of knowledge about the use of aminoglycosides over the past 2 decades. An empirical dosage of 5 mg/kg administered once daily (or less frequently in patients with compromised renal function), with a delimited course of therapy, will allow robust therapy if the pathogen has an MIC of ≤1.0 mg/L. Larger doses (e.g., 7 mg/kg) will provide somewhat better coverage (perhaps an MIC as high as 2.0 mg/L), but an even shorter duration of therapy may be required when a higher dose is administered (perhaps 5 days). Using such a strategy, we can resurrect these agents to provide good therapy for seriously infected patients for whom they are the therapy of last resort. Finally, it should be recognized that, when the therapeutic situation is no longer empirical (i.e., microbiological data and aminoglycoside concentration-time data become available), individualization of patient therapy will remain critical to obtaining an optimal outcome.

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References


