Once-Daily Aminoglycoside Administration

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Once-daily aminoglycoside dosing is effective in treating gram-negative infections, including those associated with bones and joints.

Aminoglycoside antibiotics have been in wide use for over half a century. They are generally used because of their bactericidal effects on gram-negative bacteria, such as Klebsiella species, Escherichia coli, Enterobacter species, Serratia species, and Pseudomonas aeruginosa, and currently play a pivotal role in the management of serious infections. Commonly used aminoglycosides include gentamicin, tobramycin, and amikacin. The drug class is commonly used to treat a variety of infections, including those affecting bones and joints in orthopedic practice.

Aminoglycosides have been traditionally administered in 1-3 mg/kg doses every 8 to 12 hours. Although this dosing schedule has been shown to be effective in eradicating various strains of bacteria, it has been associated with dose-limiting toxicities, such as ototoxicity and nephrotoxicity. These toxicities have also led to the need for monitoring of peak and trough concentrations to ensure patient safety while administering these drugs. Alternative drug dosage and administration techniques have been developed in response to these concerns.

The emergence of once-daily aminoglycoside administration (also referred to as extended interval dosing) can be attributed to several characteristics of the drug class, including: concentration-dependent killing, the post-antibiotic effect, a diminished propensity for adaptive resistance, and reduced toxicity. A national survey of once-daily aminoglycoside use in 500 acute care hospitals in the United States was conducted in 1999. This survey revealed that 75% of these hospitals were using some form of once-daily aminoglycoside administration.

CONCENTRATION-DEPENDENT KILLING

An aminoglycoside exerts its antibiotic effect by binding to a specific protein on the 30S subunit of the mitochondrial ribosome. This leads to alterations in protein synthesis, which ultimately results in cell death. The rate and extent of bacterial killing are functions of the aminoglycoside concentration. Optimal bactericidal activity is achieved when the peak concentration is approximately 10 times that of the minimum inhibitory concentration. Therefore, higher peak concentrations, which are obtained with once-daily aminoglycoside dosing, can lead to better therapeutic outcomes. In contrast, further increases in concentration above 10 times the minimum inhibitory concentration do not proportionally influence aminoglycoside efficacy.

POST-ANTIBIOTIC EFFECT

Some antibiotics, such as beta lactams, exert time-dependent antimicrobial killing. This means that their efficacy is dependent on consistent drug concentrations above the minimum inhibitory concentration. These agents are administered multiple times per day (dependent on their half-life) or by continuous infusion to ensure that this concentration is achieved. The concentration-dependent killing theory explains how some antimicrobials, including aminoglycosides, can fall below the minimum inhibitory concentration without compromising bacteri-
pharmacology update

Cidal activity. These antimicrobials are said to exert a post-antibiotic effect. The post-antibiotic effect is defined as the amount of time that the drug concentration falls below the minimum inhibitory concentration until the bacteria resume their growth phase. A relatively long post-antibiotic effect is the therapeutic mechanism in once-daily aminoglycoside dosing.1,2,4

Adaptive Resistance

Antimicrobial adaptive resistance has become an issue with many antibiotic regimens. Two major mechanisms are associated with the development of aminoglycoside resistance. The first mechanism involves the plasmid-mediated production of aminoglycoside-altering enzymes, which inactivate the drug. The second mechanism results in decreased cell permeability to the drug via alteration of the aminoglycoside cellular transport system. This adaptive resistance leads to decreased efficacy of the antibiotic regimen and less bactericidal activity. It has been surmised that the resistance is a reversible process if a sufficient drug-free interval is used, which promotes once-daily aminoglycoside use versus the traditional twice- or thrice-daily dosing.5

Toxicity

Two major toxicities have been associated with aminoglycoside therapy—nephrotoxicity and ototoxicity. Ototoxicity is due to damage of the sensory and vestibular epithelial hair cells, while nephrotoxicity is due to drug accumulation in the renal cortex, resulting in a progressive loss of proximal tubular function. There are no definitive studies that yield methods to prevent or predictive etiologies of aminoglycoside-induced ototoxicity. However, a correlation may exist between prolonged duration of therapy and ototoxicity development. Nephrotoxicity has also been related to prolonged therapy duration and elevated trough concentrations.1,2,4

Once-daily aminoglycoside administration has a similar adverse effect profile when compared to multiple daily dosing; however, some studies have revealed a possible decreased incidence of nephrotoxicity. This may be attributed to a possible lack of drug accumulation in the proximal tubules due to drug-free intervals seen with once-daily dosing and lower trough levels due to the extended dosing interval.5,6-9 Some investigators have also reported a delay in the development of toxicity when once-daily dosing is used.2

Dosing and Monitoring

Serum concentrations of aminoglycosides are monitored closely to prevent the development of toxic reac-

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td><strong>Weight Calculations</strong></td>
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<tr>
<td>Weight Category*</td>
</tr>
<tr>
<td>Actual body weight</td>
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<tr>
<td>Ideal body weight</td>
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<td>Dosing body weight</td>
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* All weight measured in kilograms

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<tr>
<td><strong>Initial Dosing Interval of Hartford Nomogram Based on Creatinine Clearance</strong></td>
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<tr>
<td>Estimated Creatinine Clearance (mL/min)</td>
</tr>
<tr>
<td>≥60</td>
</tr>
<tr>
<td>40-59</td>
</tr>
<tr>
<td>20-39</td>
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<td>&lt;20</td>
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*Monitor serial concentrations and administer next dose when <1 µg/mL

tions. This monitoring should still be performed with once-daily aminoglycoside dosing, despite the decreased incidence of toxicity. Several monitoring methods have been proposed; however, the 2 most widely used approaches involve using the Hartford nomogram or obtaining 2 random concentrations.

The Hartford nomogram for once-daily aminoglycoside dosing was published by Nicolau et al in 1995. This nomogram was developed after the investigators surveyed almost 2200 once-daily aminoglycoside administrations. The recommended 7 mg/kg dosing regimen was determined via computer simulation denoting that this dose would be required to achieve the desired concentration of 10 times the minimum inhibitory concentration.

The next phase of the study involved evaluating the dosing model by using the pharmacokinetic parameters of patients who had previously received traditional dosing. The once-daily dosing schedule was given to 20 study patients using the previously defined dosing intervals based on each patient’s creatinine clearance, and the data was extrapolated into a concentration versus time graph. The regression line for each of the groups was used to develop the nomogram that has become so widely used today.

When using the Hartford nomogram, prescribers should ensure that patients receive a 7 mg/kg dose of gentamicin or tobramycin based on dosing body weight. Dosing body weight is more indicative of the actual drug distribution into the tissues in obese patients than ideal body weight and is typically used when the actual body weight is >125% of the ideal body weight (Table 1). The dosage administration interval is determined by the patient’s creatinine clearance (Table 2). A single random aminoglycoside serum level should then be obtained between 6 and 14 hours after the start of the drug infusion. Then, the nomogram is used to determine the subsequent dosing interval based on the newly derived patient-specific response indicators (Figure).

The second monitoring method is similar to that used for traditional dosing. The main difference is that the serum concentrations are drawn on day 1 of therapy rather than in conjunction with the third dose; the latter approach is timed to achieve a steady state concentration of the drug. Instead, patients receive a 5-7 mg/kg tobramycin or gentamicin dose per dosing body weight, then 2 random serum levels are obtained following the aminoglycoside infusion.

The most effective time to obtain these levels has not been established; however, the first level should be drawn at least 1 hour post-infusion. These concentrations are used to determine if the patient is adequately clearing the medication and is achieving a drug-free interval to prevent resistance. Adequate clearance is assessed by the patient having a trough concentration <1 mg/L. If the level is >1 mg/L, patient-specific characteristics should be used to determine the most appropriate dosing interval.

**Special Populations**

Once-daily dosing has not been studied in patient populations that may have altered volumes of distribution or clearance of the drug. These populations include burn, pregnant, and pediatric patients. In addition, patients with ascites and renal failure have not been adequately investigated. Therefore, once-daily aminoglycoside use is not recommended in these patients.

**The Bottom Line**

- Once-daily aminoglycoside dosing is effective in treating gram-negative infec- tions, including those associated with bones or joints.
- Once-daily aminoglycoside dosing has emerged due to knowledge of the post- antibiotic effect, concentra- tion-dependent killing, and possible decreased inci- dence of nephrotoxic effects.
- Once daily aminoglycoside dosing can be monitored using the Hartford nomo- gram or by obtaining two random aminoglycoside concentrations.
- In many hospitals, clinical pharmacists can provide consultation when once-daily aminoglycoside therapy is desired.

**REFERENCES**