Optimizing Aminoglycoside Use

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KEYWORDS
- Aminoglycosides
- Gram-negative infections
- Combination chemotherapy
- Minimum inhibitory concentration

The aminoglycoside antibiotics have been used for treating gram-negative bacillary infections in critically ill patients for about 50 years. The main aminoglycosides still in use include gentamicin, tobramycin, amikacin, and netilmicin. However, the appearance of new third- and fourth-generation cephalosporins, carbapenems, and fluoroquinolones have decreased their usage as monotherapy for most gram-negative infections. In a large observational study of patients with gram-negative bacillary bacteremia, aminoglycosides were also shown to be less effective than β-lactams in patients with infection sites other than the urinary tract.1 Thus, for many years, aminoglycosides were used in combination with other antibiotics to enhance bacterial killing and improve overall efficacy. However, most studies have not demonstrated improved outcomes in patients treated with antibiotic combinations when compared with those receiving monotherapy.2,3 Only recently has early combination therapy been associated with reduced mortality in septic shock.4 This article reviews the pharmacokinetics, pharmacodynamics, and toxicodynamics of aminoglycosides, and describes dosing strategies and other effects that could improve outcomes in critically ill patients with serious infections.

PHARMACODYNAMICS

Area Under the Curve or Peak Concentrations

As an antimicrobial class the aminoglycosides demonstrate concentration-dependent killing and produce prolonged postantibiotic effects, illustrated in Fig. 1 (left panel) in the thighs of neutropenic mice following subcutaneous injection of increased doses of tobramycin.5 As the dose was increased from 4 to 20 mg/kg, the rate of killing over the first few hours also increased and became steeper. When tobramycin levels fell below the minimum inhibitory concentration (MIC), regrowth was still suppressed for 3 to 7 hours. The duration of this postexposure growth suppression or postantibiotic effect also increased with higher doses. Hyperoxia also appears to prolong the tobramycin-induced postantibiotic effect with Pseudomonas aeruginosa, which may
be clinically important when patients with *P. aeruginosa* infections are treated with high inspired oxygen tensions. The right panel of Fig. 1 illustrates the bactericidal activity and postantibiotic effect with a large dose of amikacin against *P. aeruginosa* in the thighs of neutropenic mice that had renal impairment to delay elimination and simulate serum concentration seen in humans. The duration of the postantibiotic effect was 10.2 hours for *P. aeruginosa* and even longer (more than 12 hours) with a similar study using a strain of *Klebsiella pneumoniae*.

One would expect that administration of less frequent high doses would show more rapid initial killing than more frequent dosing of low doses, even when the same total amount of drug is given. Using an in vitro pharmacokinetic model, once-daily dosing of netilmicin was shown to be superior to 8-hourly dosing in initial killing of strains of Enterobacteriaceae and *Staphylococcus aureus*. However, at 24 hours the bactericidal efficacy of both dosing regimens was very similar. With *P. aeruginosa*, once-daily dosing also resulted in superior initial killing, but this was followed by the regrowth of resistant mutants. Additional studies showed that this emergence of resistance could be prevented if the peak to MIC ratio was greater than 8.

Dose-fractionation studies reduce the independence among the various pharmacokinetic parameters and can demonstrate which pharmacokinetic parameter is most important in determining overall efficacy. In the neutropenic mouse-thigh infection the area under the curve (AUC) was the major pharmacokinetic parameter correlating with efficacy of gentamicin against *Escherichia coli* and tobramycin against *P. aeruginosa* when dosing regimens varied from 1 to 6 hours. At 8- to 24-hour dosing intervals, time above MIC was the major parameter correlating with efficacy. This difference in major pharmacokinetic parameters based on the frequency of drug administration is a result of the rapid elimination of aminoglycosides in small rodents. Drug half-lives in mice are only 15 to 20 minutes. Later studies with amikacin and isepamicin in mice with renal impairment that simulated human elimination of these drugs showed that AUC was also the major parameter for 6- to 24-hour dosing regimens with various strains of Enterobacteriaceae. Drug half-lives in renal impaired mice were 90 to 120 minutes. Fig. 2 shows one of the dose fractionation studies with amikacin against a strain of *K. pneumoniae*. The 24-hour AUC/MIC ratio had the highest correlation with efficacy followed by the peak/MIC ratio. A 24-hour AUC/MIC of around 50 was associated with
stasis and a value around 100 resulted in 1 to 2 logs\textsubscript{10} of killing. However, for \textit{P. aeruginosa} the peak/MIC ratio had the highest correlation with efficacy, resulting from “adaptive resistance” observed in strains of \textit{P. aeruginosa}, which is dependent on the MexXY-OprM efflux pump.\textsuperscript{11} With overexpression of this pump after initial bacterial killing, the bacteria become more resistant to killing by further doses of amikacin and other aminoglycosides. This effect has also been observed in vivo in rabbits during treatment with amikacin for \textit{P. aeruginosa} endocarditis.\textsuperscript{12}

A combination of 4 clinical trials comparing different aminoglycosides in patients with gram-negative bacillary infections showed that the peak/MIC ratio in serum was an important determinant of clinical efficacy.\textsuperscript{13} As shown in Fig. 3, an increasing response was observed between the maximal peak level/MIC and clinical response. For a peak aminoglycoside level/MIC ratio of 0 to 2, clinical efficacy was just 55\%, whereas with a peak level/MIC ratio of 8 to 10, clinical efficacy rose to 90\%. The AUC was not specifically measured in these studies, but it would also be expected to correlate with clinical response because all 4 aminoglycosides were administered by identical 8-hour dosing regimens. In another study in patients with severe gram-negative infections treated with tobramycin monotherapy, the 24-hour AUC/MIC value was predictive of outcome.\textsuperscript{14} If the ratio was less than 110, the efficacy
was only 47%. However, when values were greater than 110 the efficacy was 80%.

Two recent studies have correlated peak level/MIC and AUC/MIC to improvement in forced expiratory volume over 1 second (FEV₁) in cystic fibrosis patients with *P. aeruginosa* infections. In one study the peak/MIC ratio produced the more significant correlation, whereas in the other the 24-hour AUC/MIC was the only index correlating with efficacy.¹⁵,¹⁶

Kashuba and colleagues¹⁷ examined the role of both peak/MIC and 24-hour AUC/MIC ratios in determining rapidity of fever and leukocytosis resolution in 78 patients with pneumonia produced by various gram-negative bacilli. Both parameters were significant predictors of resolution but the peak/MIC ratio was slightly better. A peak/MIC ratio of 10 or higher was associated with a 90% resolution of fever and the leukocyte count in 7 days. The 24-hour AUC/MIC ratio to produce a 90% resolution in temperature and leukocyte count in 7 days was 150 and 175, respectively. Based on the serum levels Kashuba and colleagues obtained in these patients, these goals were reached only with organisms that had a MIC of 0.3 µg/mL or lower. However, organisms in the United States are considered susceptible up to an MIC of 4 µg/mL. With a dose of 7 mg/kg one can achieve a peak/MIC ratio of 10 or higher 90% of the time for organisms with MICs of 1 µg/mL or less. To achieve this for organisms with MICs of 2 and 4 µg/mL would require loading doses slightly more than 10 and 20 mg/kg, respectively. Synergistic activity with a β-lactam antibiotic might also allow coverage of organisms with MICs of 2 and 4 µg/mL at aminoglycoside doses of 7 mg/kg.

In summary, these studies suggest than total bacterial killing by the aminoglycosides with strains of Enterobacteriaceae correlates best with the 24-hour AUC/MIC. Peak/MIC ratios may be slightly better than the 24-hour AUC/MIC values for killing of *P. aeruginosa* because of the phenomenon of “adaptive resistance” related to over-expression of the Mex XY-OprM efflux pump. Still the initial rate of killing, even for Enterobacteriaceae and staphylococci, is dependent on the magnitude of the dose and is enhanced when large doses are administered at widely-spaced intervals.

**Dosing Regimens**

Studies evaluating the efficacy of once-daily dosing of aminoglycosides in animal models have produced conflicting results. Equal efficacy of once-daily and multiple-daily dosing has been primarily observed in medium-sized, nonneutropenic animals that are usually infected with *P. aeruginosa*.¹⁸,¹⁹ On the other hand, studies in small neutropenic rodents infected with various strains of Enterobacteriaceae have usually shown less efficacy with once-daily dosing than with multiple-daily dosing.²⁰,²¹ This difference is due primarily to the rapid renal elimination of the aminoglycosides in small rodents compared with larger animals and humans. Furthermore, *P. aeruginosa* is an organism that grows slower in vivo than most strains of Enterobacteriaceae, and full recovery from the postantibiotic effects takes longer with this organism. Studies of amikacin and isepamicin in neutropenic mice with normal renal function demonstrated less efficacy with once-daily dosing than with 6- and 12-hour dosing of the same total amount of drug.⁷,²² However, in mice with uranyl nitrate–induced renal impairment that produced drug half-lives similar to humans, once-daily dosing was equally efficacious with 6- and 12-hour dosing of the same total amount of drug.

Aminoglycosides have also been studied in animal models in combination with various β-lactams. The combinations of tobramycin/ticarcillin and netilmicin/ceftazidime have been studied in the mouse thigh model using various dosing regimens.²³ The largest synergistic activity of the 2 combinations was observed when the aminoglycoside was administered at 12- or 24-hour dosing frequencies.
There have been at least 45 mostly prospective clinical trials comparing once-daily aminoglycoside administration with conventional 8-hourly or 12-hourly administration. These trials include more than 6500 patients receiving gentamicin, tobramycin, amikacin, and netilmicin for 7 to 14 days of therapy, and were performed primarily in nonneutropenic adults.\textsuperscript{24–28} The studies have examined comparative efficacy and safety in a wide range of infections such as gram-negative infections, intra-abdominal infections, pneumonia, febrile neutropenia, pelvic inflammatory disease, and urinary tract infections. There are 9 formal meta-analyses of different combinations of these clinical trials.\textsuperscript{24–32} Five of the meta-analyses have shown a small but statistically improved clinical outcome with once-daily dosing. Three meta-analyses have also shown a significantly lower incidence of nephrotoxicity with once-daily dosing. The meta-analyses have also shown equivalent ototoxicity or a trend to lower ototoxicity with once-daily dosing. Several clinical trials identified the day when toxicity developed, which demonstrated that nephrotoxicity with once-daily dosing of gentamicin develops later than with traditional 8-hourly dosing. However, with prolonged dosing out to 10 to 14 days, the incidence of nephrotoxicity was much the same with both dosing regimens.

In a model designed to correlate the serum AUC of amikacin with the probability of nephrotoxicity, Rougier and colleagues\textsuperscript{33} showed that nephrotoxicity is delayed more by once-daily dosing than with twice-daily dosing of the same total amount of drug. The difference in nephrotoxicity between once- and twice-daily dosing of amikacin was greatest at a cumulative AUC of 2500 mg-h/L, which corresponds to 1000 mg/d for 6 days. For cumulative AUCs of amikacin above 2500 mg-h/L, the difference between the 2 regimens slowly decreases to zero. A randomized, double-blind trial of amikacin, gentamicin, and tobramycin administered once- or twice-daily also used shorter courses of therapy and demonstrated a significantly lower incidence of nephrotoxicity with once-daily dosing.\textsuperscript{34}

Another study compared the onset of nephrotoxicity with once- and twice-daily dosing of primarily gentamicin and tobramycin. The modeling showed that nephrotoxicity started to be observed with twice-daily dosing when the daily AUC was more than 100 mg-h/L. Nephrotoxicity was not observed with once-daily dosing but it was predicted to occur if the AUC exceeded 700 mg-h/L. This study also confirmed the role of concomitant vancomycin, but not amphotericin B, in decreasing the time to onset of nephrotoxicity for both once- and twice-daily dosing regimens.

In conclusion, once-daily dosing regimens have similar efficacy or are slightly more efficacious than multiple-daily dosing regimens. Once-daily dosing can also delay the onset of nephrotoxicity compared with multiple-daily dosing if shorter courses of therapy are used. Current recommendations for once-daily dosing of all aminoglycosides are for only up to 5 to 6 days.\textsuperscript{33,35,36} Concomitant vancomycin can also shorten the time to nephrotoxicity, but the effect is still less with once-daily administration.

\section*{A COMPARISON OF DIFFERENT AMINOGLYCOSIDES}

\textit{Pharmacokinetics}

The pharmacokinetics of the various aminoglycosides is very similar. Less than 1\% of aminoglycosides are absorbed from the gastrointestinal (GI) tract, and they must be administered either intravascularly or intramuscularly. Serum concentrations of gentamicin, tobramycin, and netilmicin after a dose of 7 mg/kg infused over 30 minutes range from 15 to 20 $\mu$g/mL.\textsuperscript{37,38} This corresponds to an AUC of 70 to 100 mg-h/L. A similar 30-minute infusion of amikacin at 15 mg/kg produces peak concentrations from 41 to 49 $\mu$g/mL and an AUC from 110 to 145 mg-h/L.\textsuperscript{39,40} Binding of the
aminoglycosides to serum proteins is very low and is usually less than 10%. The penetration of the aminoglycosides into epithelial lining fluid ranges from 32% to 54% of serum concentrations. The drugs distribute primarily in extracellular fluid and do not readily penetrate into cells. The volume of distribution is often higher, and therefore peak serum levels are lower, in patients with sepsis, severe burns, fever, congestive heart failure, and peritonitis. The drugs are rapidly eliminated unchanged through the kidney with half-lives of 1.8 to 2.6 hours in individuals with normal renal function; elimination is very slow, with a mean half-life of 30 to 56 hours in patients with creatinine clearance less than 10 mL/min.

Peak concentrations are higher and the AUCs are larger in patients with renal impairment. The suggested initial dose for the different aminoglycosides and the dosing frequency for patients with different creatinine clearances are listed in Table 1. Dosing every 48 hours occurs when the creatinine clearance is 30 mL/min or less. About 40% to 50% of the aminoglycosides are cleared by a 6-hour hemodialysis. Many of the new techniques such as continuous venovenous hemofiltration (CVVH), continuous venovenous hemodiafiltration (CVVHDF), and continuous renal replacement therapy are extensively used in critical care units and they also remove aminoglycosides. Dosing of aminoglycosides in morbidly obese patients is based on excess body weight (the difference between total body weight and ideal body weight) multiplied by 0.45 plus the ideal body weight. Monitoring of aminoglycoside concentrations is very important in optimizing their use. A peak concentration obtained within the first 48 hours is important for correlating peak/MIC relationships with response. Obtaining a second value 6 to 10 hours later can be used with the peak concentration to estimate the AUC. With single-dose therapy, this can also be related to the MIC to be correlated with prior AUC/MIC related responses.

Nephrotoxicity

The aminoglycosides do accumulate in the kidney, and can account for 40% of the total drug in the body. About 85% of the drug in the kidney is located in the renal cortex. The drug enters the kidney from the lumen of the renal tubules by binding to the basement membrane. The aminoglycosides actually bind to megalin, a large glycoprotein on the

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brush border of renal tubular cells, which is required for internalization of the drug by pinocytosis. Animals made deficient in megalin do not accumulate aminoglycosides in the kidney cells and do not develop nephrotoxicity. After pinocytosis the aminoglycoside endosomes fuse with lysosomes and continue to accumulate drug in the cell. Later permeabilization of the lysosomes occurs, and some aminoglycoside can reach the cytosol. When it reaches a critical concentration in the cytosol, the drug activates apoptosis, which causes death to the cell. Glomerular dysfunction appears to arise subsequent to proximal tubular damage, and is caused by activation of the renin-angiotensin system and resulting vasoconstriction.

There are differences among the aminoglycosides in terms of renal accumulation and activation of the apoptosis pathway. Gentamicin and netilmicin have higher renal accumulation than tobramycin and amikacin. Activation of apoptosis is less with netilmicin and amikacin than with tobramycin and gentamicin. Still, a survey of aminoglycoside nephrotoxicity in approximately 10,000 patients described in clinical trials over a 7-year period published between 1975 and 1982 found relatively similar average frequencies: 14.0% for gentamicin, 12.9% for tobramycin, 9.4% for amikacin, and 8.7% for netilmicin. Comparative nephrotoxicity appears to be relatively unimportant for choosing which aminoglycoside to use in a clinical situation.

In a large study of almost 1500 patients, risk factors for aminoglycoside nephrotoxicity included concomitant vancomycin, longer duration of therapy, pneumonia, rapidly fatal prognosis, leukemia, preexisting renal or liver disease, shock, larger volume of distribution, male sex, older age, and location in intensive care. Many of these risk factors are present in patients with severe gram-negative bacillary infections, but their role in producing nephrotoxicity can be largely reduced by once-daily administration for only several days.

**Ototoxicity**

Gentamicin and other aminoglycosides penetrate into the endolymph and vestibular and cochlear tissue; it enters the endolymph slowly and leaves the endolymph even slower. Prolonged therapy for 10 days or more, preexisting renal impairment, and prior treatment with aminoglycosides are risk factors for ototoxicity. Damage is manifest as auditory (cochlear) and vestibular toxicity, but these do not always occur together. The mechanism of toxicity is damage to the sensory hair cells in the cochlea and the labyrinth. The relationship between aminoglycoside pharmacokinetic parameters and auditory toxicity is unclear. Animal models suggest that ototoxicity is related to the AUC of concentrations in cochlear endolymph, which in turn are proportional to the AUC in serum. This result suggests that administration of the same total daily dose will have the same incidence of ototoxicity, which accounts for the lack of significant differences in ototoxicity between once-daily and multiple-daily dosing of different aminoglycosides.

One would expect an exceedingly low incidence ototoxicity with therapy restricted to 5 or 6 days. However, a rare form of auditory toxicity, often occurring after a few doses, has been described, associated with about 5 different mutations in the mitochondrial 12S ribosomal RNA gene. A family history of this type of toxicity should be a contraindication to the use of aminoglycosides. If aminoglycosides had to be used for a longer period of time, the use of aspirin instead of placebo reduced the incidence of ototoxicity from 13% to 3% in about 100 patients in each group.

**Neuromuscular Paralysis**

Neuromuscular blockade is rarely a reported adverse effect of aminoglycoside use, being more likely to occur when given intravenously in patients with renal impairment.
and/or administered concomitantly with neuromuscular blocking drugs or anesthetic agents. Once-daily dosing of gentamicin at 6 mg/kg did not have any adverse effect on maximal inspiratory pressure in patients on mechanical ventilation.67 Use of aminoglycosides was not a significant risk factor for abnormal muscle membrane excitability in patients under intensive care.68 Amikacin is probably the safest drug, as the acute lethal dose in rats and mice is 10 times higher for amikacin than for gentamicin and tobramycin.

**Antimicrobial Activity**

While the aminoglycosides are active primarily against gram-negative bacilli and staphylococci, there are some important differences in potency among the agents. Tobramycin is the most active agent against *P. aeruginosa* with MICs that are 2- to 4-fold more potent than for gentamicin.69,70 This potency increases the peak/MIC and 24-hour AUC/MIC ratios and makes tobramycin the best agent for use in *Pseudomonas* infections. *Acinetobacter* species are also usually more susceptible to tobramycin than to gentamicin, but resistant strains do occur. Gentamicin is the most potent agent against most of the Enterobacteriaceae and is the preferred drug for therapy with these organisms; this is especially true for *Serratia* species.69,70 Although MICs for amikacin against Enterobacteriaceae are 2- to 4-fold higher than for gentamicin, an important feature of amikacin is that it is active against many strains of Enterobacteriaceae (usually >80%) and also a considerable proportion of *P. aeruginosa* (25%–85%), which have acquired gentamicin and tobramycin resistance.71–73 For strains of *S. aureus*, gentamicin and netilmicin have the best potency.

**DIFFERENT CLINICAL INFECTIONS**

As stated earlier, there are several systematic reviews that have demonstrated that monotherapy with the aminoglycosides in severe gram-negative infections is less effective than therapy with β-lactams and fluoroquinolones.1,2 This fact is not surprising, as the peak/MIC and 24-hour AUC/MIC ratios with standard doses are effective for organisms with MICs of 0.5 µg/mL or less for gentamicin, tobramycin, and netilmicin, and MICs of 1 to 2 µg/mL and less for amikacin. However, the susceptibility breakpoints for all these drugs is about 8-fold higher. Thus, there are many organisms with higher but still susceptible MICs that are not adequately treated with these drugs. Even once-daily doses of 7 mg/kg for gentamicin, tobramycin, and netilmicin cover organisms with MICs of 1 µg/mL, whereas once-daily doses of 20 mg/kg for amikacin will treat organisms with MICs of 2 to 4 µg/mL. For these reasons, aminoglycosides should be used in combination primarily with β-lactams but also with fluoroquinolones. The recent study showing a lower incidence of early mortality with combination therapy versus monotherapy in patients with gram-negative bacillary infections with shock strongly supports their combined use in these patients.4

**Bacteremia**

There are several recent studies showing an improved outcome in patients with shock and gram-negative bacillary bacteremia treated with a combination of aminoglycoside and β-lactam.74,75 One of the studies also shows an improved outcome in gram-negative bacillary bacteremia with combination therapy in neutropenic patients.74 The addition of an aminoglycoside also resulted in greater initial appropriate therapy than with monotherapy.75 This study also observed that aminoglycosides provided broader coverage of the infecting pathogen than fluoroquinolones.
Endotoxin release from large inocula of gram-negative bacteria is much lower with aminoglycosides than with β-lactam antibiotics.\textsuperscript{76} Other studies with multiple strains of gram-negative bacilli have shown that the addition of tobramycin to cefuroxime results in a lower release of endotoxin than observed with the aminoglycoside alone.\textsuperscript{77,78} The higher the initial tobramycin concentration, the lower the release of endotoxin with the combination. In a fibrin clot model of sepsis with \textit{K pneumoniae}, amikacin resulted in a much smaller release of endotoxin than observed with ceftazidime and ofloxacin.\textsuperscript{79} Reduction of endotoxin release by aminoglycosides could contribute to the decreased early mortality with combination therapy in patients with shock.

Aminoglycosides are often administered with β-lactams to treat staphylococcal bacteremia and endocarditis. A recent review was very critical of such use of aminoglycosides because of the development of nephrotoxicity without any clinical benefit.\textsuperscript{80} Another study evaluating the use of aminoglycosides in staphylococcal endocarditis showed a significant earlier defervescence (2 days vs 4 days).\textsuperscript{81}

### Pneumonia

Hospital-acquired pneumonia is commonly caused by gram-negative bacilli such as \textit{P aeruginosa}, \textit{E coli}, and \textit{Klebsiella} or \textit{Serratia} species. Although satisfactory results have been obtained with aminoglycosides alone, combination therapy with a β-lactam gives superior results.\textsuperscript{82} Combination therapy has not improved outcome over monotherapy with β-lactams for gram-negative bacillary pneumonia due to the Enterobacteriaceae. Nevertheless, combination therapy for a few days could be beneficial in patients with shock or hypotension. The role of combination therapy for pneumonia due to \textit{P aeruginosa} is less clear. Some investigators have observed better results with combination therapy than with monotherapy.\textsuperscript{83}

Aerosolized aminoglycosides have also been used in mechanically ventilated patients with pneumonia. In a retrospective case-matched study, inhaled aminoglycoside was compared mostly with combination therapy with an aminoglycoside and β-lactam antibiotic.\textsuperscript{84} Most of the infections were caused by \textit{P aeruginosa}. Patients treated with inhaled aminoglycosides were more likely to have complete resolution of clinical symptoms than those in the intravenous antibiotics group (81% vs 31%) and microbiologic cure group (77% vs 5%). Furthermore, none of the patients receiving inhaled aminoglycosides developed renal dysfunction, whereas the incidence in the intravenous antibiotics group was 31%. Other studies have also shown a good response in patients in intensive care with ventilator-associated pneumonia (VAP) caused by \textit{P aeruginosa} and \textit{Acinetobacter baumannii}.\textsuperscript{85} Inhaled aminoglycosides seem to be a way to enhance antimicrobial activity without producing renal dysfunction. However, more controlled trials of larger numbers of patients are needed.

### Intra-Abdominal Infections

There are 2 meta-analyses in patients with intra-abdominal infections that found lower clinical efficacy response for regimens with an aminoglycoside than those with a β-lactam as the anti-gram-negative bacillary drug.\textsuperscript{86,87} Furthermore, treatment with an aminoglycoside (plus clindamycin) was associated with a higher risk of developing renal dysfunction than seen with monotherapy with β-lactams. Various clinicians have recommended that aminoglycosides not be considered as first-line therapy for intra-abdominal infection. However, in patients with sepsis and shock the addition of an aminoglycoside for a few days would still appear to be indicated.
Pyelonephritis and Complicated Urinary Tract Infections

A recent systematic review of aminoglycoside monotherapy versus other antibiotics did find aminoglycoside monotherapy to produce equal efficacy with β-lactam drugs and fluoroquinolones in urinary tract infection and pyelonephritis. Nevertheless, there was a trend to more nephrotoxicity in the patients receiving the aminoglycosides. There are insufficient data to know whether 5 to 7 days of an aminoglycoside would provide equal efficacy to longer durations for pyelonephritis and complicated urinary tract infections. Aminoglycoside concentrations above the MIC of most gram-negative bacilli are still found in the urine for at least 4 days after the last dose.

SUMMARY

Despite the increasing knowledge on the pharmacodynamics of aminoglycosides and methods to use them for short periods of time, there are still publications downplaying these drugs because of their lower efficacy and nephrotoxicity. The studies that have demonstrated an early survival benefit in patients with septic shock have revitalized their use. Aminoglycosides should be used along with β-lactams or fluoroquinolones primarily in patients with shock or hypotension, as large single-daily doses, and very rarely for more than 5 to 6 days. The use of inhaled aminoglycosides also appears to be a rational use of these drugs in VAP patients with hard-to-treat and resistant organisms without the development of nephrotoxicity and ototoxicity. Further study will identify the overall efficacy and safety of this approach.

REFERENCES

9. Blaser J, Stone BB, Groner MC, et al. Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of


