
Daily Dosage of Aminoglycosides

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When gentamicin and kanamycin were introduced for clinical use in the 1960s, the general rule for dosage of an antimicrobial was to administer the drug at intervals of every two to three half-lives of the drug. Because the half-lives of antimicrobials had been measured at 2.5 to 3 hours in normal volunteers, the primary dosage interval for the aminoglycosides was established at 8 hours. Although subsequent clinical studies demonstrated that high concentrations were needed to enhance efficacy, high concentrations were also associated with an increased risk of toxicity (1,2). Pharmacokinetic dosage was established as a means of producing high peak serum concentrations but low, potentially nontoxic trough concentrations. Although this method of dosage became standard practice at many institutions, there were very few prospective clinical trials comparing the efficacy and toxicity observed with pharmacokinetic monitoring with that seen for standard 8-hour dosing regimens (3). The evolution of an understanding of aminoglycoside pharmacodynamics has provided the basis for the consideration of yet another dosage regimen for these agents—once-daily aminoglycoside dosage. This chapter summarizes the pharmacodynamic rationale for this dosage regimen, reviews the results from therapeutic trials in animals and humans, and provides guidelines for the use of once-daily aminoglycosides in clinical practice.

PHARMACODYNAMIC AND PHARMACOKINETIC RATIONALE

Antibacterial Activity

Concentration-Dependent Killing Pharmacodynamics is concerned with the relationship between drug concentration and antimicrobial effect and has provided the basis for the consideration of once-daily dosage for aminoglycosides. Through *in vitro* and animal model studies, it has been demonstrated that aminoglycosides exhibit concentration-dependent bactericidal activity as the major determinant of their efficacy (4). *In vitro* time-kill curves at various drug concentrations have shown that there

is a continual rise in both the rate and extent of organism killing observed with exposure to increasing concentrations of aminoglycosides.

Animal studies in murine thigh infection and pneumonia models have also been used to correlate pharmacodynamic parameters with therapeutic efficacy. Utilizing a large number of dosage regimens that vary in both amount of drug given and in dosage intervals, it is then possible to separate which parameter correlates best with optimal organism killing. In such models, the magnitude of the area under the concentration-versus-time curve (AUC) and the peak concentration, have proven to be the most important predictors of efficacy for the aminoglycosides (5–7). In contrast, time above the minimal inhibitory concentration (MIC) of an organism has correlated best with bactericidal efficacy for the β -lactams.

Clinical data have supported the correlation between peak concentration and clinical response to aminoglycoside therapy. More et al. (8) found that the ratio of the peak aminoglycoside concentration to the MIC of the organism was associated with therapeutic outcome. By logistic regression analysis, the relative odds of obtaining a clinical response was proportional to an increasing peak level to MIC ratio; achievement of a peak level to MIC ratio of at least 1:8 to 1:10 was needed to produce a clinical response rate of 90%.

Postantibiotic Effects Given the relatively short half-life of 2 to 3 hours when aminoglycosides are administered to patients with normal renal function, it would be expected that for once-daily administration, there would be a substantial amount of the dosage interval when serum concentrations are below the MIC of the organism. However, it has been observed both *in vitro* and *in vivo* that there is suppression of the regrowth of organisms that have been exposed to aminoglycosides, even when the level of drug falls below the MIC of the organism. This phenomenon is termed the postantibiotic effect (PAE). Originally recognized with penicillin and streptococci in the 1940s, PAE has also been demonstrated in animal infection models with various antimicrobial and organism combinations (9).

Factors that influence the presence or duration of PAE include the class of antimicrobial agent, type of organism, and both the drug concentration and duration of exposure of an organism to a given drug. With aminoglycosides, PAEs of 1.5 to 3.0 hours have been demonstrated against gram-negative bacilli *in vitro* (10). However, it is important to realize that *in vivo* PAEs are, in general, much longer than those observed *in vitro*. In fact, the magnitude of *in vitro* PAEs are not at all predictive of the duration of *in vivo* PAEs (11). In a thigh infection model using neutropenic mice, PAEs of 2.0 to 7.5 hours were demonstrated for amikacin, gentamicin, and tobramycin against Enterobacteriaceae and *Pseudomonas aeruginosa* (5,11–13).

Furthermore, it has been shown in animal models that both the presence of neutrophils and the simulation of human pharmacokinetics have additional impact on the duration of *in vivo* PAEs. The influence of neutrophils was demonstrated in animal model experiments that measured PAEs simultaneously in both normal and neutropenic mice infected with *Klebsiella pneumoniae*, as demonstrated in Table 11.1 (5,9,13,14). In general, the presence of neutrophils doubled the duration of the *in vivo* PAE. This phenomenon has also been observed *in vitro* and is termed the

Table 11.1 In Vivo Postantibiotic Effects with Aminoglycosides

Organism	Site	Drug	Dose (mg/kg)	In Vivo PAE (hr)		
				Neutropenic	Normal	Renal-Impaired Neutropenic
<i>Klebsiella pneumoniae</i>	Thigh	Gentamicin	3	2.6	5.8	—
			12	5.0, 6.5	9.5, 12.7	—
		Isepamicin	24	7.1	13.4	—
			Netilmicin	3	3.9	10.5
		Amikacin	12	6.8	12.8	—
			15	3.4, 5.5	—	12.2, 14.6
<i>Pseudomonas aeruginosa</i>	Lung	Amikacin	15	9.0	—	15.2
	Thigh	Amikacin	15	4.0	—	10.1

PAE = postantibiotic effect.

SOURCE: Data from References 5, 9, 13.

postantibiotic leukocyte enhancement effect (PALE). In their model, McDonald et al. (15) showed that brief exposure of bacteria to an antimicrobial agent leads to enhanced leukocyte phagocytosis and intracellular killing during the subsequent drug-free interval.

Simulation of human pharmacokinetics in animal models can be accomplished by inducing transient renal impairment with uranyl nitrate. This method produces significant prolongation of the half-life of drugs eliminated by the kidney and results in a longer duration of sub-MIC drug concentrations. As shown in Table 11.1, the in vivo PAEs are substantially prolonged in renally impaired animals. Thus, in vivo PAEs of 10 to 15 hours, even in neutropenic animals, can figure prominently into the effectiveness of once-daily aminoglycoside dosage.

First Exposure Effect Adaptive resistance of gram-negative bacilli to aminoglycosides is an additional phenomenon that makes the concept of once-daily dosage appealing. Also known as the first exposure effect, it is the down-regulation of aminoglycoside uptake into the bacterial cell following the initial exposure of the organism to the drug (16,17) and has been observed with Enterobacteriaceae and *P. aeruginosa* in vitro. This effect can last for several hours, thus making the organism refractory to the bactericidal action of subsequent drug doses (16,18). A murine model with *P. aeruginosa* exposed to netilmicin also demonstrated this phenomenon (17). Following the duration of this effect, organisms revert to being susceptible to the killing activity of the drug. Therefore, a dosage regimen such as once-daily dosing can avoid relative drug resistance by allowing the effect to reverse between subsequent drug doses:

Decreased Emergence of Resistant Subpopulations In vitro studies simulating human pharmacokinetics have evaluated the effect of the peak aminoglycoside con-

centration on the emergence of resistant subpopulations of organisms (19,20). Against Enterobacteriaceae, *P. aeruginosa*, and *Staphylococcus aureus*, bacterial regrowth following the initial dose of netilmicin was prevented only by regimens in which the peak drug concentration was at least eightfold higher than the MIC (20). It is believed that levels of this magnitude prevent the emergence of drug-resistant subpopulations that are present in small numbers at the beginning of therapy. This may be important because animal studies have also shown that aminoglycoside-resistant variants of *P. aeruginosa* can be selected in experimental infections (21).

Enhanced Synergistic Activity Animal model data suggest that there is enhanced synergistic activity between β -lactam antibiotics and aminoglycosides when aminoglycosides dosage is less frequent. In a *P. aeruginosa* murine thigh infection model, the greatest bactericidal activity was observed when ceftazadime was administered frequently and when netilmicin was given infrequently (every 12 hr), which corresponded to the pharmacodynamic predictors of bactericidal efficacy for both β -lactams (time above MIC) and aminoglycosides (peak level/MIC) (22). Similar enhanced synergy for ticarcillin and once-daily administered tobramycin against *P. aeruginosa* has been observed in the same animal model (23).

Drug Distribution

Several studies have evaluated the concentration of aminoglycosides given once-daily in certain body compartments. Studies in animals have shown that higher peak concentrations in respiratory secretions are obtained with once-daily dosage of gentamicin compared with multiple-daily dosage regimens (24). Valcke et al. (25) studied the concentration of netilmicin in bronchial secretions and alveolar lining fluid in patients with pneumonia who required mechanical ventilation. Serial sampling of bronchial secretions and bronchoalveolar lavage fluid was performed after the first dose of netilmicin in these patients. Peak netilmicin concentration in the alveolar fluid was 14.7 mg/liter, corresponding to 41% of the peak plasma concentration. The relatively high levels obtained in the alveolar fluid was believed to be related to the high serum peak levels associated with the single daily dose of netilmicin.

Penetration into the cerebrospinal fluid (CSF) with different gentamicin-dosage regimens has been studied in a rabbit model of meningitis (26). The highest peak CSF levels were obtained with once-daily dosing compared to administration three times a day of the same daily amount of drug. The ratio of peak CSF to peak serum concentrations, however, was similar for both dosage regimens.

Toxicity

Kinetics of Uptake into Renal Tubular Cells The mechanism of aminoglycoside nephrotoxicity relates to the binding of drug to the renal proximal tubule brush border, uptake into the tubular cell, and storage of the intracellular drug within lysosomes. Aminoglycosides can inhibit lysosomal enzymatic activity and thus lead to accumulation of phospholipids inside lysosomes. Eventually these structures can rup-

ture, release their contents inside the renal tubular cell, and lead to cell necrosis and death. Experimental models in rats and other animals have demonstrated that the kinetics of renal cortical uptake of aminoglycosides is a saturable process (27). Therefore, one would expect more efficient uptake into tubular cells with sustained low serum concentrations versus intermittent high peak concentrations of drug. This effect has been demonstrated in patients undergoing a nephrectomy for renal cell carcinoma (28,29). Preoperatively, patients received gentamicin or netilmicin as either a single dose during a period of 30 minutes or the equivalent dose given by continuous infusion during a period of 24 hours. Renal cortical tissue was sampled after 1 day for drug concentration, and, as shown in Figure 11.1, tissue levels after the single dose were significantly lower than levels after a continuous infusion of the same total amount of drug. In the study by De Broe et al. (29), a group of patients received divided doses of the same total amount of amikacin before nephrectomy. This regimen also resulted in higher renal cortical concentrations of amikacin than concentrations observed when the drug was given in a single dose (see Figure 11.1). With tobramycin, there was a trend toward higher renal cortical concentrations with continuous or more frequent daily dosage, but the differences were not statistically significant, which may reflect the more linear relationship between serum concentrations and renal cortical accumulation of tobramycin that has been observed in animal models (29). Also, the higher lipid

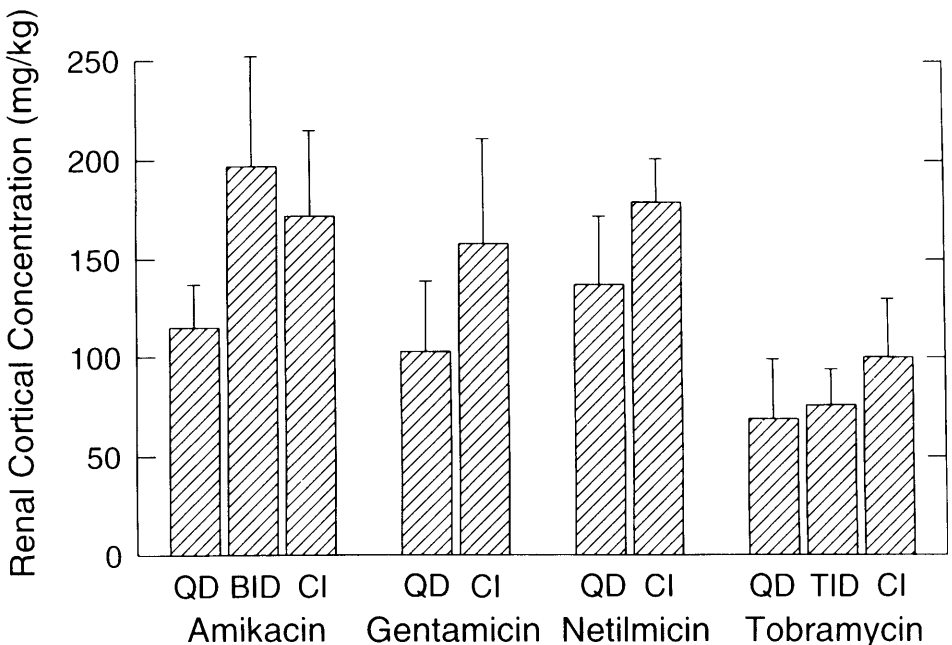


Figure 11.1. Renal cortical concentrations (mg/gm) of amikacin, gentamicin, netilmicin, and tobramycin following 24 hours of drug administration by continuous infusion, once daily, twice daily, or three times daily.