

## Once Daily Dosing of Aminoglycosides – An Update

Evidence has shown that the dosing of aminoglycosides (gentamicin, tobramycin and amikacin) once daily is less toxic and at least as effective, as the “traditional” three-times-daily dosing method. This bulletin summarises the reasons in favour of once daily dosing and discusses the mechanisms of aminoglycoside toxicity.

### Concentration Dependant Killing

Aminoglycoside antibiotics demonstrate “concentration-dependent” killing, where the higher the concentration, the greater the absolute number of bacteria killed. From a clinical perspective, this suggests that higher peak concentrations will improve efficacy. With most other antibiotics eg. penicillins, cephalosporins & vancomycin, the rate of bacterial kill does not increase once a certain plasma concentration is exceeded (usually around 5 x the minimum inhibitory concentration – ‘MIC’). The extent of kill is dependent upon how long the concentration remains above this concentration. Antibiotics exhibiting this kind of bacterial kill are considered to have “time-dependent” or “concentration-independent” killing.

The concentration-dependent killing effect is a major reason behind the move from conventional dosing to “extended interval dosing” of aminoglycosides. Other reasons include the post-antibiotic effect and adaptive resistance.

### Post-Antibiotic Effect

Post-Antibiotic Effect (PAE) describes the time during which antibacterial growth remains suppressed, after the antibiotic concentration has fallen below the MIC. For the aminoglycosides, the PAE ranges from 1-8h depending on the bacteria tested. In addition, a linear correlation exists between the peak plasma aminoglycoside concentration and the length of the PAE - meaning that the higher the concentration, the longer the PAE. The PAE supports the prolongation of the dosing interval with aminoglycosides.

### Adaptive Resistance

Adaptive resistance describes a reversible refractoriness of the bacteria to the action of an antibiotic that develops after initial exposure. It was initially observed in bacterial cultures following an initial incubation with aminoglycosides. Previously susceptible bacteria, that were continuously incubated in media containing gentamicin concentrations greater than 120 times the MIC, developed adaptive resistance and growth continued. These “resistant” bacteria were then resuspended in drug-free media, and reverted to their previous sensitivity over hours to days. This effect has also been shown in humans. Adaptive resistance is not a ‘true’ resistance, in the usual sense of the term, because it easily reverses after a drug free period.

The clinical implications of adaptive resistance with respect to aminoglycoside dosing are that a “drug free” period is required in each dosing interval to allow time for reversal of this effect. During once daily dosing with currently recommended doses, patients with normal renal function have a period when there is little or no drug measurable. This allows reversal of adaptive resistance, and maximises the effect of the next dose.

### Nephrotoxicity

Renal tubular cell uptake of gentamicin displays saturable kinetics, so that small doses of drug given frequently lead to greater overall uptake and toxicity than the same total amount of drug given by a single daily dose. An observed reduction in gentamicin clearance, identified via therapeutic drug monitoring, is an early sign of impaired renal function and precedes an increase in serum creatinine by 2-3 days. Meta-analyses have shown that once daily administration of aminoglycosides has less nephrotoxicity than conventional dosing regimens with the same total daily dose.

### Ototoxicity

Saturable uptake may also occur in the inner ear. Two types of aminoglycoside-induced hearing loss have been described, acute and chronic, with different mechanisms postulated. The acute type has been associated with high doses and appears to be reversible. The more commonly described chronic hearing loss or vestibular dysfunction has been reported to be irreversible in 10 to 55% of patients. Chronic toxicity is unpredictable, often with sudden and severe onset, and may relate to the total area under the concentration-time curve (AUC) over the entire course.

Damage within the cochlea leads to hearing loss, initially affecting higher frequencies. Tinnitus is usually the first symptom noticed, by which time significant high-frequency loss has already occurred. Damage within the vestibular apparatus results in ataxia, positional vertigo and oscillopsia (the sensation that visible objects jump or bob with head movement). Trials using high-tone audiometry have shown reduced ototoxicity with once daily administration, although the evidence is not strong.

### Dosing and Monitoring

CDHB guidelines for initial doses of aminoglycosides range from 3-7 mg/kg (lean body weight), depending on the individual patient’s renal function (measured by creatinine clearance), and the severity of the infection.

Two drug concentrations are measured: 1) at 30minutes after the end of the infusion, and 2) between 6 and 22 hours later (earlier with ‘normal’ renal function, later with more impaired renal function). Laboratory forms must **accurately** record dose, dose time and sample time to allow accurate dose optimisation. Dose individualisation uses the concentration results to calculate an area under the concentration-time curve (AUC). For dose adjustment, contact your pharmacist or the Drug Information Service.

### For further information:

Dosing & monitoring guidelines for gentamicin and tobramycin are shown on page 122 in the 2005 ‘Pink Book’. For further information discussing the initiation and monitoring of aminoglycosides in specific patients, refer to your pharmacist or the Drug Information Service (ext 80900).