Canterbury District Health Board
Te Poari Hauora ō Waitaha

Clinical Pharmacology Bulletin

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Once Daily Dosing of Gentamicin in Adults

Gentamicin was discovered in the early 1960s when it was isolated from a culture of the Micromonospora species, a common bacterium found in water and soil. When it was first introduced, the standard gentamicin dosing interval in patients with normal renal function was 8 hourly. However, studies have since shown that once daily dosing of gentamicin increases efficacy and decreases toxicity. This once-daily or "extended interval" dosing was adopted in Christchurch in the early 1990s. The following is an update on the therapeutics of gentamicin.

Indications

Gentamicin is an aminoglycoside antibiotic. It is indicated for the treatment of many infections, but particularly those caused by Gram-negative bacteria (e.g. Gram-negative sepsis).

Dosing regimen at CDHB hospitals

Unlike most other drugs, the initial dose of gentamicin is based on renal function rather than volume of distribution. This is to avoid continued high concentrations in renal impairment after the higher first dose during once daily dosing. Gentamicin is almost completely renally cleared, thus dose modifications are required according to the patient's calculated creatinine clearance. (See table below)

CrCl (mL/min)	Dose in mg/kg (lean body weight)	Time of second blood sample (hours)
> 66	5 - 7 } depending on the	6 - 14
55 - 66	5 - 6 } severity of infection	8 - 16
41 - 54	5	10 - 18
31 - 40	4	12 - 20
20 - 30	3	14 - 22
< 20	aminoglycoside not recommended	

A blood sample is taken 30 minutes post infusion (a "peak" concentration) and in the middle of the dosing interval in order to calculate further doses (facilitated by ward pharmacists). The timing of the second sample is determined by the patient's renal function (see table above) and is used to extrapolate a "trough" concentration.

This dosing regimen aims for high peaks of >10mg/L, low troughs of <1mg/L, and an area under the concentration-time curve (AUC) of between 70 to 100mg/L.hr.

Concentration-Dependent Killing

Gentamicin exhibits *concentration-dependent* killing. The higher the gentamicin concentration, the greater the number of bacteria killed. Therefore, high peak concentrations should theoretically improve efficacy. Most other antibiotics (such as penicillins, cephalosporins & vancomycin) exhibit *time-dependent* or *concentration-independent* killing where the extent of kill is dependent upon how long the concentration remains above a certain concentration (usually 5 x minimum inhibitory concentration (MIC)).

The concentration-dependent killing effect of gentamicin is the major reason behind the use of the once-daily dosing regimen, because it allows high peak concentrations. Other reasons that favour a long dose interval include the **post-antibiotic effect** and **adaptive resistance**

Post-Antibiotic Effect (PAE) describes the time in which bacterial growth remains suppressed after the antibiotic concentration has fallen below the MIC. For gentamicin, the PAE ranges from 1 to 8 hours depending on the bacteria tested. In addition, a strong correlation exists between the peak plasma gentamicin concentration and the length of the PAE - meaning that the higher the concentration, the longer the PAE.

Adaptive Resistance describes a reversible resistance of the bacteria to the action of an antibiotic that develops after initial exposure. Susceptible bacteria that are continuously exposed to high gentamicin concentrations develop adaptive resistance. These "resistant" bacteria revert to their non-resistant status over a period of hours to days. Adaptive resistance is not a 'true' resistance, as it reverses after a drug-free period.

The clinical implications of adaptive resistance with gentamicin are that a drug-free period is required in each dosing interval to allow time for reversal of this effect. Once daily dosing results in a period of time with little or no measurable drug. This allows reversal of adaptive resistance, and maximises clinical effect.

Nephrotoxicity

Gentamicin undergoes reuptake by active transport in the renal tubules. This process is saturable, so that if small doses of drug are given frequently, there is a greater overall reuptake and thus greater toxicity than if the same amount is given as a single daily dose. Impairment in renal function follows, and is identified through monitoring of gentamicin concentrations as a reduction in gentamicin clearance. This generally precedes an increase in serum creatinine by 2-3 days. Meta-analyses have shown that once daily administration of gentamicin causes less nephrotoxicity than conventional dosing regimens with the same total daily dose.

Ototoxicity

Saturable uptake of gentamicin may also occur in the inner ear. Gentamicin-induced hearing loss has been described as both acute and chronic, with different mechanisms postulated for each. Acute hearing loss has been associated with high doses of gentamicin and appears to be reversible. The more common 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 AUC over the entire gentamicin 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.

For further information:

Dosing and monitoring guidelines for gentamicin are shown on p142 in the 2008 'Pink Book'. For further information about starting and monitoring gentamicin in specific patients, refer to your pharmacist or the Drug Information Service (ext 80900).