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Clinical considerations for gentamicin dosing

As an antibiotic, gentamicin possesses a number of defining characteristics that influence its clinical use - these are discussed here.

Concentration dependent bactericidal effect:
Bactericidal efficacy is solely dependent on the peak concentration of gentamicin achieved, or more specifically the ratio of the gentamicin peak to the minimum inhibitory concentration (MIC) of the bacteria (its relative susceptibility). Nearly all other antibiotics are time-dependent, and rely on the total time spent above the MIC. In terms of maximizing bactericidal efficacy, a reasonable peak (10mg/L or more) should be aspired to. The importance of this has been demonstrated clinically in patients critically ill with gram negative pneumonia, where an initial gentamicin peak above or below 7mg/L was responsible for a significant 3-fold difference in mortality. For those patients with renal impairment this can often mean increasing the dosing interval to more than one day, rather than decreasing the dose, hence maintaining a suitable peak, but allowing the patient time to clear the dose. Assuming a volume of distribution of 0.4L/kg, the minimum dose required to generate a gentamicin peak of 10mg/L is 4mg/kg.

Administration approach:
The gentamicin peak concentration is significantly greater when the drug is administered as a bolus over 5 minutes compared to that achieved with an infusion. This significantly increases the bactericidal activity. There is no indication that bolus administration is associated with any adverse effects.

Adaptive resistance:
Within hours of an initial exposure to gentamicin, bacterial cell walls shut down the channels that allow gentamicin the internal access required for its efficacy. This adaptive resistance is present for 36 hours or more after exposure to gentamicin. Thus the adaptive resistance is still present when the next dose is due. Clinically, this means the most effective dose the patient receives is the first dose.

Post-antibiotic effect:
This is the well demonstrated lag time of 4-6 hours after the disappearance of any gentamicin when there is no further discernible bacterial growth, when the bacteria has yet to start multiplying again.

Nephrotoxicity:
High concentrations are not necessarily associated with greater toxicity, as the uptake rate into the renal tubule cells is saturable. The prolonged presence of gentamicin over a number of doses, even at lower concentrations, leads more readily to nephrotoxicity, and can be caused by not allowing sufficient time between doses.

These characteristics lend themselves to once-daily dosing of gentamicin, with the exception of those with renal impairment, who should be considered for dosing every two days in order to maintain effective gentamicin peaks.

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FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au
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