Pharmacologic, toxicologic and dosing considerations of aminoglycosides.

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Cmax / MIC ≥ 8-10

- Moore et al. J Infect Dis. 1987
- Cmax is inversely proportional to the Vd
- Vd is limited to the extracellular space

Edema
Sepsis
Aggressive intravenous fluid therapy
Total parenteral nutrition
Pleural effusions

Ascites
Hypoalbuminaemia

ICU
Neonates
Oncology patients

Vd ↑

Adaptive resistance

- *Reversible form of resistance.*
- *Positively related to the time and concentration of aminoglycoside exposure.*
- *MIC reversion time (MRT).*
- *Complete clearance of the drug before the subsequent dose.*
- *Down regulation of drug uptake.*
- *In Pseudomonas mainly due to aminoglycoside efflux.*
- *Coadministration with efflux pump inhibitors.*

DOSING INTERVALS SHOULD DEPEND ON GFR

- **Low trough levels are associated with lower risk of toxicity and with greater efficacy.**
- **Aminoglycosides are mainly eliminated by means of glomerular filtration.**
- **Preterm neonates are characterised by long half lives (10 instead of 2 hours) → dosing intervals should be equal to 36-48 hours.**
- **Conditions that enhance renal function augment aminoglycoside's clerance :**

  hemodynamically active drugs

  hematological malignancies

  hyperdynamic conditions occuring in the early phase of sepsis

  protein rich diet (circadian variation of GFR)

Concentration-independent killing on biofilms.

aminoglycosides are positively charged molecules

interaction with negatively charged cyclic glucans on the matrix of extracellular polymeric substances

retarded antimicrobial penetration

Biofilm formation.

- ***Sub-inhibitory concentrations of aminoglycosides can provoke the emergence of S. aureus small-colony variants or even induce P. aeruginosa and E. coli biofilm formation.***

Nephrotoxicity

- the rapidity and extent of observed cellular alterations, such as aberrant vesicle fusion, decreased mitochondrial potential and decreased protein synthesis could not be attributed to the long standing model of nephrotoxicity.
- It has recently been demonstrated that cytoplasmic and intra-nuclear binding of gentamicin do not require endocytosis.
- Ion channels, transporters or pores in the plasma membrane have been implicated as bioregulatory routes for aminoglycoside uptake in renal tubular epithelial cells.
- the vesicular uptake of aminoglycosides is greatly associated with non-specific, fluid-phase endocytosis.

cochleotoxicity

- The pharmacokinetics and mechanism of aminoglycoside entry into strial tissues are distinct and more complex than renal proximal tubule cells.
- There is no saturable, cell-regulated cytoplasmic trafficking of gentamicin in the stria vascularis.
- Two processes have been proposed to result in hair cell death: an early occuring rapid process (<1.5 h) and one or more slower processes, which occur later, (between 1.5 and 24 h)

Enhancing activity of aminoglycosides

- By mutations leading to the inactivation of a 2-component regulator, AmgRS.

- By administration of liposomal formulations of aminoglycosides in order to achieve high concentrations at the nidus of infection with a lower total patient antibiotic exposure.

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