Clinical Use of Aminoglycoside Antibiotics  
presented by Doug Black, Pharm.D.  
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History

<table>
<thead>
<tr>
<th>Aminoglycoside</th>
<th>Year</th>
<th>Source organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>streptomycin</td>
<td>1944</td>
<td><em>Streptomyces griseus</em></td>
</tr>
<tr>
<td>neomycin</td>
<td>1949</td>
<td><em>Streptomyces fradiae</em></td>
</tr>
<tr>
<td>kanamycin</td>
<td>1957</td>
<td><em>Streptomyces kanamyceticus</em></td>
</tr>
<tr>
<td>paromomycin</td>
<td>1959</td>
<td><em>Streptomyces rimosus</em></td>
</tr>
<tr>
<td>spectinomycin</td>
<td>1962</td>
<td><em>Streptomyces spectabilis</em></td>
</tr>
<tr>
<td>gentamicin</td>
<td>1963</td>
<td><em>Micromonospora purpurea</em></td>
</tr>
<tr>
<td>tobramycin</td>
<td>1968</td>
<td><em>Streptomyces tenebrarius</em></td>
</tr>
<tr>
<td>sisomicin</td>
<td>1972</td>
<td><em>Micromonospora inyoensis</em></td>
</tr>
<tr>
<td>amikacin</td>
<td>1972</td>
<td>semisynthetic derivative of kanamycin</td>
</tr>
<tr>
<td>netilmicin</td>
<td>1975</td>
<td>semisynthetic derivative of sisomicin</td>
</tr>
</tbody>
</table>

Mechanism of action

bactericidal; aminoglycosides bind to the 30S subunit of the bacterial ribosome, interfering with the binding of fMet-tRNA and therefore the formation of the initiation complex. Binding to the 30S subunit may also cause misreading of mRNA codons

β-lactams, vancomycin facilitate uptake by Gram-positive organisms

resistance: via plasmid-mediated aminoglycoside-modifying enzymes

Spectrum of activity

broad gram-negative spectrum including *P. aeruginosa*
gram-positive: synergistic in combination with β-lactams, glycopeptides
anaerobes: negligible activity

amikacin: *Nocardia*, MAI, certain rapid-growing mycobacteria, gentamicin-resistant gram-negative bacilli

streptomycin: multidrug-resistant tuberculosis, tularemia, plague

Pharmacokinetics

poor oral absorption
volume of distribution approximates the extracellular space (about 0.26 L/kg)  
(larger in cystic fibrosis patients, about 0.35 L/kg)
tissue distribution variable (poor CNS penetration)
negligible metabolism
renally eliminated (filtered, with a small amount of proximal reabsorption)
elimination half-life: 2-3 hours (if renal function normal)
Pharmacodynamics

concentration-dependent killing
postantibiotic effect (concentration-dependent)

Adverse reactions

nephrotoxicity

proximal acute tubular necrosis (ATN) → ↓ GFR
likely related to inhibition of intracellular phospholipases in the proximal tubule
tends to be reversible
associated factors: hypotension, dehydration, duration of therapy, concomitant liver
disease, advanced age, other nephrotoxins (vancomycin?)
nephrotoxicity correlates with drug accumulation in the renal cortex

ototoxicity

vestibulotoxic and cochleotoxic
generally irreversible
difficult to assess
high tone frequencies affected first

neuromuscular blockade

rare but potentially serious
enhanced by conditions or drugs affecting the NM junction (e.g., myasthenia gravis, succinylcholine)
can be treated with calcium

Dosage and measurement of serum concentrations

<table>
<thead>
<tr>
<th>Infection</th>
<th>Target peak (µg/ml)</th>
<th>Target trough (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gram-positive</td>
<td>3</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>gram-negative</td>
<td>5-8</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Gram- pneumonia</td>
<td>10-12</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

*one hour after infusion begins