In The Name of God

Aminoglycosides

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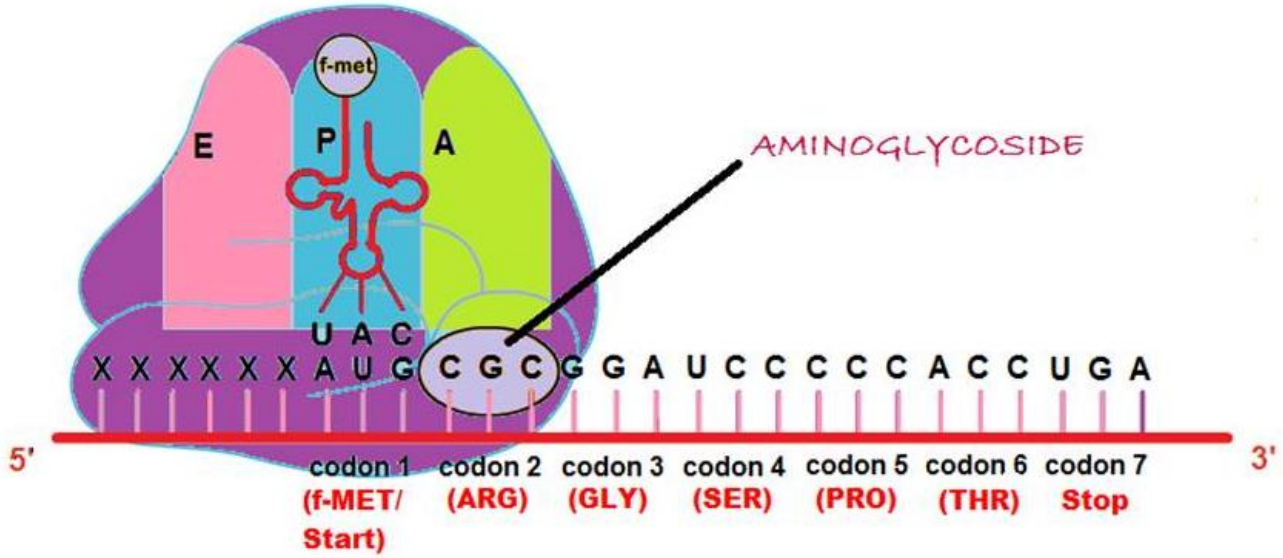
MECHANISM OF ACTION

- The AG primarily act by binding to the aminoacyl site of the 30S ribosomal subunit, leading to misreading of the genetic code and inhibition of translocation
- The ensuing antimicrobial activity is usually bactericidal against susceptible aerobic gram-negative bacilli.
- AG initially penetrate the organism by disrupting the magnesium and calcium bridges between lipopolysaccharide moieties. They are transported across the cytoplasmic membrane in an energy-dependent manner. This step can be inhibited in vitro by divalent cations, increased osmolality, acidic pH, and an anaerobic environment.
- The microbiologic activity of aminoglycosides is pH dependent. As a result, the antimicrobial effect may be reduced at the low pH found in lung and bronchial secretions



Aminoglycosides bind irreversibly to the 30S ribosomal subunit.

SPECTRUM OF ACTIVITY

1. Broad spectrum of aerobic gram-negative (Enterobacteriaceae, *Pseudomonas* spp, *Acinetobacter* spp, and *Haemophilus infuenzae)*
2. Gram-positive organisms (*Staphylococcus aureus.* However, are not adequate as monotherapy). Insufficient activity against pneumococci, streptococci, and enterococci. Although may have additive or synergistic effects with other agents and in the absence of high-level resistance.
3. Mycobacteria

- Anaerobic bacteria are intrinsically resistant to aminoglycosides

SPECTRUM OF ACTIVITY

- **P. aeruginosa**: Tobramycin > Gentamicin
- **Enterobacteriaceae**: Plazomicin > Amikacin > Gentamicin
- **Mycobacteria**: Streptomycin, Tobramycin, and Amikacin

  ➡ Mycobacterium tuberculosis: Streptomycin

  ➡ Mycobacterium fortuitum, Mycobacterium abscessus, and Mycobacterium chelonae: Amikacin

- Enterococci: intrinsically resistant to low to moderate levels of aminoglycosides. Have synergy in combination with a cell wall active agent, such as penicillin or vancomycin.

PHARMACODYNAMICS AND KINETICS

1. Post-antibiotic effect

2. Concentration-dependent killing: higher concentrations of aminoglycosides (relative to the organism's MIC) induce more rapid, and complete, killing of the pathogen.

✓ Relative to traditional dosing methods, the **consolidated dosing approach** is more likely to achieve optimal peak concentrations that result in concentration-dependent killing.

3. Synergistic effect: Most often with cell wall-active agents (eg, beta-lactam antibiotics)

4. Absorption and time to peak concentrations (IV: 30 to 60 minutes after termination of infusion, IM: 30 to 90 minutes)

- The aminoglycosides are not absorbed after oral administration.

5. Distribution

- The volume of distribution increased in patients with ascites, burns, pregnancy, critical illness, and other conditions (such as cystic fibrosis).
- Reach concentrations in the urine 25- to 100-fold that of serum.
- Poor penetration into the CSF, biliary tree, and bronchial secretions.

6. Elimination

- Approximately 99 percent is eliminated unchanged in the urine, primarily by glomerular filtration.
- The terminal half-life ranges from 1.5 to 3.5 hours in adults with normal renal function.
- The half-life is prolonged in neonates, infants, and patients with decreased renal function.
- Effectively removed by both hemodialysis and peritoneal dialysis ----> supplemental doses required.

TOXICITY

Nephrotoxicity

1. Nonoliguric acute kidney injury
2. Distal tubular dysfunction
3. Electrolyte abnormalities (Hypomagnesemia, hypokalemia, hypocalcemia, and hypophosphatemia)

✓ Renal cortical accumulation is **less** when aminoglycosides are given as **one large, once-daily dosing programs**, because of the saturable nature of the renal cortical uptake

✓ Increased risk with nephrotoxic medications include furosemide, NSAIDs, ACEIs, cisplatin, cyclosporine, clindamycin, and vancomycin.

Neomycin > Gentamicin > Tobramycin > Amikacin > Netilmicin > Streptomycin

Ototoxicity

Aminoglycosides are associated with cochlear and vestibular toxicity

Gentamicin > Tobramycin > Amikacin > Neomycin

✓ N-acetylcysteine (NAC) can be considered in patients with ESRD receiving an aminoglycoside.

Neuromuscular blockade

A rare but serious adverse effect. Most patients experiencing such reactions have disease states and/or concomitant drug therapy that interfere with neuromuscular transmission.

✓ For patients with myasthenia gravis, we recommend avoiding aminoglycosides altogether, regardless of dosing method.

Optimal dosing of aminoglycosides

The first steps in aminoglycoside administration include determination of the dosing weight and estimation of renal function

1. Traditional intermittent dosing strategy: uses smaller doses given several times each day
2. Extended-interval dosing strategy: uses high doses administered at an extended interval.

These two strategies have comparable efficacy and safety.

- ✓ High dose extended-interval administration takes advantage of the pharmacodynamic properties and offers greater ease of preparation, administration, and monitoring.
- ✓ Renal cortical accumulation is **less** with high dose extended-interval administration.
- ✓ For most patients who are expected to exhibit more predictable aminoglycoside pharmacokinetics, we suggest extended-interval rather than traditional intermittent dosing.

Optimal dosing of aminoglycosides

Specifically, we do not routinely use extended-interval dosing for the following patients:

1. Patients with burns (>20 percent • total body surface area)
2. Patients with ascites
3. Pregnant women
4. Patients with creatinine clearance <40 mL/min (including patients requiring dialysis, although some institutions use a lower threshold) OR >120 mL/min

Recommended loading dose for traditional, intermittent dosing of gentamicin or tobramycin in adults

Site of infection or indication	Desired peak concentration		Loading dose, mg/kg* ¶Δ
	Conventional unit	SI unit	
Gentamicin synergy with beta-lactams for treatment of serious gram-positive infections outside of the central nervous system ◊	3 to 4 mcg/mL	6 to 8.5 micromol/L	1 (initial dose, not a loading dose)
Uncomplicated lower urinary tract infection (ie, acute simple cystitis)	2 to 4 mcg/mL	4 to 8.5 micromol/L	1 (initial dose, not a loading dose)
Gram-negative sepsis or other serious gram-negative infections, including pseudomonal infection, gram-negative pneumonia, and acute life-threatening gram-negative infection in a critically ill patient §	7 to 10 mcg/mL	14 to 21 micromol/L	2.5 to 3

Maintenance dose nomogram for traditional, intermittent dosing of gentamicin and tobramycin in adults*

Creatinine clearance ¶ conventional unit (mL/minute)	Creatinine clearance ¶ SI unit (mL/second)	Maintenance dose (percent of loading dose Δ)	Dose interval (hours)
>90	>1.5	84	8
80 to 90	1.3 to 1.5	80	8
70 to 79	1.2 to <1.3	76	8
60 to 69	1 to <1.2	84	12
50 to 59	0.8 to <1	79	12
40 to 49	0.7 to <0.8	72	12
30 to 39	0.5 to <0.7	86	24
20 to 29	0.33 to <0.5	75	24 to 36
<20 ◊	<0.33 ◊		

SI: International System of Units.

* For many patients, the preferred dosing strategy is extended-interval. Refer to the aminoglycosides topic discussion of selection of dosing strategy. Although the dosing adjustments listed in this table should be applicable for amikacin dosing, they have not been validated for use with that agent.

¶ Creatinine clearance may be estimated using the Cockcroft-Gault equation. Calculators for estimation of creatinine clearance are available in UpToDate.

Δ Loading dose recommendations are provided in a separate table.

◊ When the creatinine clearance is below 20 mL/min, a loading dose is recommended, with subsequent doses guided by monitoring of the serum aminoglycoside concentration.

Extended interval aminoglycoside dose and dosing interval in adults by renal function

Creatinine clearance* (mL/min/70 kg)	Initial and maintenance dose ¶	Initial dosing interval (hours)
≥ 120	Use traditional intermittent dosing	
60 to 119	Infuse over 1 hour: 7 mg/kg for gentamicin or tobramycin 15 mg/kg for amikacin	24
40 to 59	Infuse over 1 hour: 7 mg/kg for gentamicin or tobramycin 15 mg/kg for amikacin	36 (or use traditional intermittent dosing)
< 40 Δ	Use traditional intermittent dosing	

The maintenance dose and dosing intervals may need to be adjusted based on results of serum drug concentration monitoring. This is discussed in the topic review of aminoglycoside dosing, section on drug concentration monitoring. Extended interval aminoglycoside dosing is not recommended for particular indications and populations. As an example, the doses listed in this table do NOT apply to aminoglycosides being used as synergistic therapy for gram positive infections or aminoglycoside use in cystic fibrosis or pregnant patients. Such exclusions are discussed in more detail in the topic on aminoglycoside dosing.

* Creatinine clearance may be estimated by use of Cockroft-Gault equation. Calculators for estimation of creatinine clearance are available in UpToDate.

¶ The appropriate dosing weight to use for dose calculation is discussed in the topic on aminoglycoside dosing.

Δ Some institutions use a lower threshold of 20 to 30 mL/min for using traditional intermittent instead of extended interval dosing. In such cases, for patients who have a creatinine clearance between this lower limit and 40 mL/min, the calculated aminoglycoside dose is administered at a 48-hour interval.

Thanks

Any Question?