

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

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

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

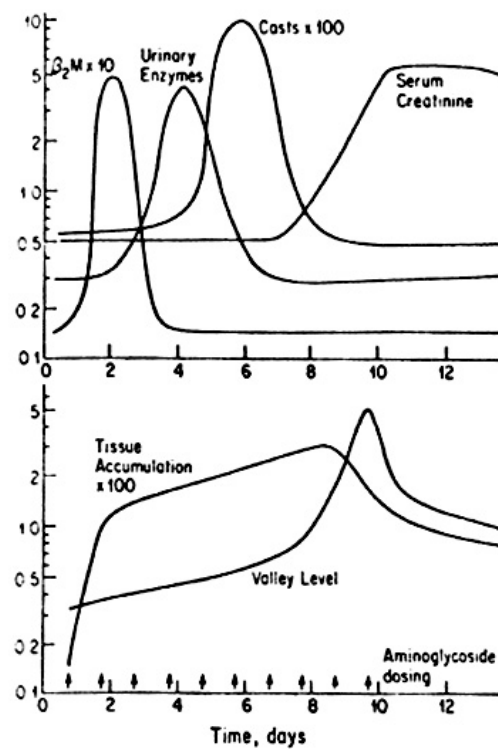
proximal acute tubular necrosis (ATN) $\rightarrow$ $\downarrow$ GFR

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



(from Schentag et al. Aminoglycoside accumulation in critically ill surgical patients. J Surg Res 1979; 26: 270-279).

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

Infection	target peak* ($\mu\text{g/ml}$)	target trough ($\mu\text{g/ml}$)
gram-positive	3	< 1
gram-negative	5-8	< 1
Gram- pneumonia	10-12	< 1

*one hour after infusion begins

1. Select Loading Dose in mg/kg [IDEAL WEIGHT] to provide peak serum levels in range listed below for desired aminoglycoside.

AMINOGLYCOSIDE	USUAL LOADING DOSES	EXPECTED PEAK SERUM LEVELS
Tobramycin Gentamicin	1.5 to 2.0 mg/kg	4 to 10 $\mu\text{g/ml}$
Amikacin Kanamycin	5.0 to 7.5 mg/kg	15 to 30 $\mu\text{g/ml}$

2. Select Maintenance Dose (as percentage of chosen loading dose) to continue peak serum levels indicated above according to desired dosing interval and the patient's corrected creatinine clearance.*

PERCENTAGE OF LOADING DOSE REQUIRED FOR DOSAGE INTERVAL SELECTED				
Cr _{cl} (ml/min)	half life [†] (hrs)	8 hrs	12 hrs	24 hrs
90	3.1	84%	-	-
80	3.4	80	91%	-
70	3.9	76	88	-
60	4.5	71	84	-
50	5.3	65	79	-
40	6.5	57	72	92%
30	8.4	48	63	86
25	9.9	43	57	81
20	11.9	37	50	75
17	13.6	33	46	70
15	15.1	31	42	67
12	17.9	27	37	61
10*	20.4	24	34	56
7	25.9	19	28	47
5	31.5	16	23	41
2	46.8	11	16	30
0	69.3	8	11	21

Hull-Sarubbi nomogram (Ann Intern Med 1978; 89: 612-618)