AMINOGLYCOSIDES

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For the last forty years, aminoglycosides have been used extensively in clinical practice and most clinicians are familiar with their use. The first aminoglycoside, streptomycin was isolated in 1944, and the latest netilmicin, a semi-synthetic derivative of sisomycin was approved for use in the United States in 1983.

The advent of a large number of newer antibiotics have provided alternatives for situations where aminoglycosides have traditionally been used, raising questions about the current role of these drugs(1). This article provides an overview of the current status of aminoglycosides (excluding streptomycin, a traditional anti-tubercular drug).

Indications

The current indications regarding use of aminoglycosides are:

1. Severe infections with Gram negative organisms. Aminoglycosides are used in the initial treatment of serious suspected bacterial infections before precise identification of the organism is made(2). The use is limited due to emerging resistance to aminoglycosides (especially gentamicin), as well as susceptibility to newer drugs, chiefly the newer cephalosporins and quinolones.
2. Infections with *Pseudomonas aeruginosa,* usually in combination with beta-lactam antibiotics.
3. Febrile granulocytopenic agents in combination with beta lactam antibiotics, even though the actions of amino-glycosides decrease in the presence of granulocytopenia(1).
4. Systemic staphylococcal infections in combination with a beta-lactamase stable penicillin.
5. Enterococcal infections in combination with penicillins and vancomycin(3).
6. In bowel infections and surgery along with a drug active against anaerobic organisms.

Structure

Aminoglycosides are aminocyclitol molecules. The different substitutions on various positions on the aminocyclitol ring are responsible for the different properties of the various aminoglycosides(4).

Mode of Action

Aminoglycosides are bactericidal drugs which act by binding irreversibly to the bacterial ribosomes and inhibiting protein synthesis. The drugs are actively transported across the cell membrane; the transport is

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oxygen dependent. The transport of aminoglycosides is inhibited by anaerobic conditions, low pH, hyperosmolarity (as in the presence of exudates), granulocytopenia and in the presence of divalent calcium and magnesium ions(1).

Aminoglycosides have synergistic action with penicillins, cephalosporins and vancomycin(5), the synergism being maximum with amikacin. This is explained by differing modes of action of these drugs. Penicillins and cephalosporins act on the cell wall whereas aminoglycosides act on the ribosomes(6-9).

Pharmacokinetics

Oral absorption is less than 1%; there is rapid absorption when administered parenterally. The injections are relatively painless and non-irritant at the injection site. Inactivation of aminoglycosides may occur when these drugs are mixed with penicillins, cephalosporins, and beta lactam antibiotics, therefore separate syringes should be used(10-12).

Aminoglycosides, excluding streptomycin, are not bound to plasma proteins. Peak concentrations are reached 30-60 minutes after an intramuscular dose and immediately after an intravenous dose. Half-lives of netilmicin and gentamicin are 2 hours and that of amikacin 2-3 hours. Aminoglycosides enter most body fluids at levels which are approximately equal to serum levels, including pleural and ascitic fluids, joint and bronchial secretions(13). They do not cross the blood brain barrier and fail to reach the eye; CSF levels are 10% of plasma levels and may be about 20% in case of meningitis.

The aminoglycosides are excreted by glomerular filtration through the kidney in an active unchanged form; 60% is excreted in the first 3 hours and 85% by 24 hours. The rest of the accumulated dose is slowly excreted 10-20 days after the last dose(1). All aminoglycosides are removed from the body by hemodialysis or peritoneal dialysis.

A loading dose of half the maintenance dose is given to bring the body concentrations to therapeutic levels. If no loading dose is given, 3-4 doses are required before reaching the steady state. The maintenance doses for gentamicin, tobramycin and netilmicin are 6-9 mg/kg/day, and for amikacin and kanamycin 15-25 mg/kg/day(5).

Adjusting Dose for Renal Impairment

The goal of therapy is to keep serum levels within the therapeutic range and avoid toxicity.

This can be achieved by:

(*a*) Increasing the interval between two doses without changing the dose. The adjustment can be made by multiplying the serum creatinine by 8 for gentamicin, tobramycin and netilmicin, and by 9 for amikacin and kanamycin; the value obtained being the desired interval between doses.

(*b*) Decreasing the dose without changing the interval.

$$\text{Adjusted dose} = \frac{\text{Creatinine clearance of patient}}{\text{Normal creatinine clearance}} \times \text{Normal dose}$$

Where facilities for creatinine clearance are not available, the creatinine clearance may be calculated from the serum creatinine in an older child using the Cockcroft Gault equation(14).

The advantage of the second method is that it is associated with less fluctuations of the peak and trough levels. Accepted peak levels (values obtained half hour after dose) are 4-10 μl/ml for gentamicin, tobra-

mycin and netilmicin and 5-25 μg/ml for amikacin and kanamycin. Accepted trough levels (taken half hour before the next dose is due) are 2 μg/ml for gentamicin, tobramycin and netilmicin and 10 μg/ml for amikacin and kanamycin(15).

The dose also needs modification in conditions where the pharmacokinetics are modified such as obesity, newborns (especially preterms), in the presence of major fluid excess (ascitis, cardiac failure), extensive burns, fever, and in patients with cystic fibrosis(5).

Resistance

Resistance to aminoglycosides may occur due to anaerobic conditions, variants with non-permeable cell walls, a mutant defective membrane receptor site, or due to enzyme production which leads to alteration in the aminoglycoside molecule. Of these, the plasmid mediated enzymes are the most important medianism. There are 9 such transferases. Gentamicin is susceptible to 8 of the 9; amikacin is the most stable being resistant to 8 while the others have varying susceptibilities(5).

Spectrum of Activity

Major groups susceptible to aminoglycosides include Gram negative aerobic bacilli and *Staphylococcus*. *Table I* suggests that amikacin is the aminoglycoside most likely to be successful against the suceptible organisms.

Side Effects

Nephrotoxicity: This is defined as the decrease in creatinine clearance by 50% or more or serum creatinine increment of 0.5 mg/100 ml or a 50-100% increase over baseline levels(5,15). It is the commonest side effect and causes the most concern. Gentamicin is the most nephrotoxic (4-53%), followed by tobramycin (2.6-58%), amikacin (0-38%), and netilmicin (0-31%) which is the least(15-22).

Nephrotoxicity depends on 2 main factors. These are the extent to which the antibiotic is absorbed into the proximal tubular cells and the tendency of the drug to damage the intracellular organelle.

In an attempt to limit the nephrotoxicity when aminoglycosides are used, an attempt has been made to identify risk factors. Some of these are liver disease(17), volume depletion(17,23), diuretic therapy(5) and the additive effect of nephrotoxicity when aminoglycoside are given along with cephalothins(5,16,17) and vancomycin(18). Estimates of beta 2 microglobulins have been used as early indicators of renal damage especially in patients with liver disease(19,21).

The renal insufficiency is generally transient, mild and nonoliguric. There is no clear evidence that aminoglycosides cause permanent or subsequent renal damage(23).

Ototoxicity: This occurs in about 2% of all cases treated with aminoglycosides, although transient changes in vestibular function or auditory acuity are probably more common(24-26). *Table II* summarizes the ototoxicities of various aminoglycosides in different clinical trials(15). Netilmicin is the least ototoxic of the aminoglycosides. Streptomycin and gentamicin are more likely to cause vestibular damage. Amikacin and Kanamycin are more likely to cause cochlear toxicity, whereas tobramycin and netilmicin have almost equal effects on the vestibular and cochlear portions of the eighth nerve.

TABLE I—*Comparison of Activity of Aminoglycosides against Susceptible Organisms*

Organism	Gentamicin	Tobramycin	Amikacin	Netilmicin
Acinetobacter	+	++	+++	++
Citrobacter	+++	++	+++	++
Enterobacter	+++	++	++	++
Escherichia coli	+++	++	++	++
Klebsiella	+++	+++	+++	+++
Proteus	+++	+++	+++	+++
Corynebacterium	+	+	+	+
Neisseria meningitidis	++	++	++	++
Neisseria gonorrhea	++	++	++	++
Staphylococcus aureus	±	++	+++	++
Pseudomonas aeruginosa	+	++	+++	++
Hemophilus influenzae	+	+	+	+

+++ 90% sensitive strains
++ 80-90% sensitive strains
+ 70-80% sensitive strains
± 30-70% sensitive strains
Adapted from Pancoast *et al.*(5)

The mechanism by which aminoglycosides damage the inner ear is not known with certainty, but animal studies have shown that hair cells in the organ of Corti are destroyed in a manner similar to the damage in the proximal convoluted tubular cells. It has been suggested that aminoglycosides bind to a lipid receptor (possibly phosphotidylinositol diphosphate or phosphotidylinositol diphosphate)(28,29). The local enzyme function may be inhibited due to disruption of the lipid environment essential to some enzyme function.

From animal studies it seems that the damage to the organ of Corti is permanent, but clinically there is a possibility of considerable recovery especially from vestibular toxicity due to the compensation by external cuing(27).

TABLE II—*Relative Ototoxicities*

Drug	Vestibular toxicity (%)	Cochlear toxicity (%)
Gentamicin	2.7	9.7
Tobramycin	2.2	11.9
Amikacin	2.8	14.9
Netilmicin	0.9	3.3

Allergic reactions in the form of fever, rash and eosinophilia occur in 1-3% of all patients receiving aminoglycosides.

Neuromuscular blockade is believed to be caused by inhibition of acetyl creatine release at the presynaptic cholinergic junction. The onset is usually characterized by respiratory failure or muscle weakness which cannot be explained by the attendant pathology(31). At risk are patients with myasthenia gravis, those receiving other neuromuscular blocking agents or anesthetic agents like either, and those with hypocalcemia and hypomagnesemia(30,31).

Other complications include hypomagnesemia(32), delirium and peripheral neuropathy.

Relative Cost: The cost of one day's requirement for a 10 kg child is Rs. 6/-

to tubular reabsorption in rabbits. Antimicrob Agents Chemother 1984, 25: 168-172.

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NOTES AND NEWS

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The book provides clear guidelines for the diagnosis and management of various problems that constitute emergencies. Prompt recognition of emergencies along with their appropriate and adequate initial management is essential to save lives and prevent complications. In a number of situations the doctors cannot do very much and must send the patient to the casualty services of a hospital. One needs to be aware of such conditions. What not to do is also important. Emergencies in the newborn present very different and often unique problems that require special skills and proficiency for their recognition and management. A group of outstanding contributors have presented the various topics in an informative and lucid manner. The book has 58 chapters spread over 500 pages.

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