AMINOGLYCOSIDE ANTIBIOTICS

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INTRODUCTION

- These drugs are used primarily to treat infections caused by aerobic gram-negative bacteria; streptomycin is an important agent for the treatment of tuberculosis.
- The aminoglycoside group includes *gentamicin*, *tobramycin*, *amikacin*, *netilmicin*, *kanamycin*, *streptomycin*, and *neomycin*.
- These agents contain amino sugars linked to an aminocyclitol ring by glycosidic bonds.
- They are polycations, and their polarity is responsible in part for pharmacokinetic properties shared by all members of the group.
- For example, none is absorbed adequately after oral administration, inadequate concentrations are found in cerebrospinal fluid (CSF), and all are excreted relatively rapidly by the normal kidney.
- In contrast to most inhibitors of microbial protein synthesis, which are bacteriostatic, the aminoglycosides are bactericidal inhibitors of protein synthesis.
- Because of their use is which associated with serious toxicities, they have been replaced to some extent by safer antibiotics, such as the third and fourth-generation of cephalosporins, the fluoroquinolones, and the carbapenems.

HISTORY AND SOURCE

- Aminoglycosides are natural products or semisynthetic derivatives of compounds produced by a variety of soil ***actinomycetes.***
- Streptomycin was first isolated from a strain of ***Streptomyces griseus.***
- Gentamicin and netilmicin are broad-spectrum antibiotics derived from species of the ***actinomycete Micromonospora.***
- The difference in spelling (-*micin*) compared with the other aminoglycoside antibiotics (-*mycin*) reflects this difference in origin.
- Tobramycin is one of several components of an aminoglycoside complex (*nebramycin*) that is produced by ***S. tenebrarius*** (1967).
- It is most similar in antimicrobial activity and toxicity to gentamicin.
- In contrast to the other aminoglycosides, amikacin, a derivative of kanamycin, and netilmicin, a derivative of *sisomicin*, are semisynthetic products.
- Other aminoglycoside antibiotics have been developed (*e.g.*, *arbekacin*, *isepamicin*, and sisomicin), but they have not been introduced into clinical practice in the United States because numerous potent, less toxic alternatives (*e.g.*, broad-spectrum b-lactam antibiotics and quinolones) are available

MECHANISM OF ACTION

- Susceptible gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes.
- These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. The antibiotic then binds to the 30s ribosomal subunit prior to ribosome formation.
- There, it interferes with assembly of the functional ribosomal apparatus and/or can cause the 30s subunit of the completed ribosome to misread the genetic code.
- Polysomes become depleted, because the aminoglycosides interrupt the process of polysome disaggregation and assembly.
- [Note: the aminoglycosides synergize with î²-lactam antibiotics because of the latter's action on cell wall synthesis, which enhances diffusion of the aminoglycosides into the bacterium.]

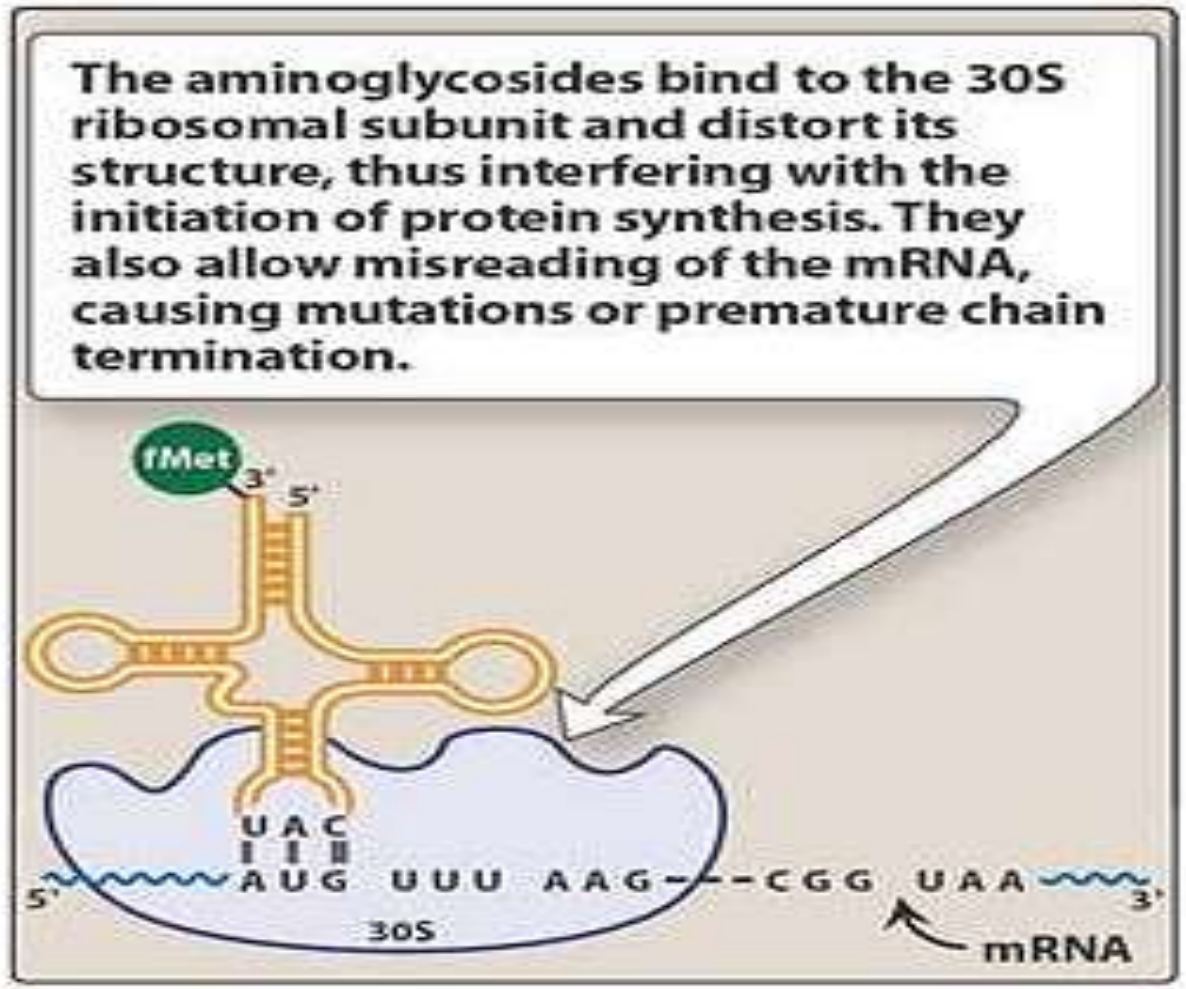


Figure 32.7 Mechanism of action of the aminoglycosides.

ANTIBACTERIAL SPECTRUM

- The aminoglycosides are effective in the empirical treatment of infections suspected of being due to aerobic gram-negative bacilli, including *Pseudomonas aeruginosa*.
- To achieve an additive or synergistic effect, aminoglycosides are often combined with a β-lactam antibiotic, or vancomycin, or a drug active against anaerobic bacteria.
- All aminoglycosides are bactericidal.
- The exact mechanism of their lethality is unknown because other antibiotics that affect protein synthesis are generally bacteriostatic.

TULAREMIA

- Tularemia is commonly acquired during rabbit-hunting season by hunters skinning infected animals.
- Pneumonic tularemia results from infection by the respiratory route or by bacteremic seeding of lung.
- *Gentamicin* is effective in treating this rare lymphoid disease.

Brucella species
(*gentamicin + doxycycline*)

Francisella tularensis
(*gentamicin*)

Klebsiella species
(*gentamicin* + an antipseudomonal penicillin)

Pseudomonas aeruginosa
(*tobramycin* + an antipseudomonal penicillin)

Yersinia pestis
(*streptomycin + doxycycline*)

INFECTIONS DUE TO PSEUDOMONAS AERUGINOSA

- Pseudomonas aeruginosa rarely attacks healthy individuals, but can cause infections under special circumstances, for example, in immunocompromised patients, and in burn victims.
- Treatment includes *tobramycin* alone or in combination with an antipseudomonal penicillin, such as *piperacillin* or *ticarcillin*.

INFECTIONS DUE TO ENTEROCOCCI

- Enterococci are intrinsically resistant to most antibiotic classes and require two synergistic antibiotics for effective therapy.
- Recommended therapy is with *gentamicin* or *streptomycin* plus *vancomycin* or a β-lactam, such as *penicillin G*.

Gram (+) cocci

Enterococcus species
(*gentamicin + penicillin G*)

Streptococcus agalactiae
(*gentamicin + penicillin G*)

RESISTANCE

- Resistance can be caused by

1. Decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides or porin channels are absent.
2. Plasmid-associated synthesis of enzymes (for example, acetyl transferases, nucleotidyltransferases, and phosphotransferases) that modify and inactivate aminoglycoside antibiotics.

- Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance is not an invariable rule.
- Mutations affecting proteins in the bacterial ribosome, the target for these drugs, can confer marked resistance to their action.
- However, most commonly resistance is due to acquisition of plasmids or transposon-encoding genes for aminoglycoside-metabolizing enzymes or from impaired transport of drug into the cell.
- Thus there can be cross-resistance between members of the class.

PHARMACOKINETICS

Administration: The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration. Therefore, all aminoglycosides must be given parenterally to achieve adequate serum levels.

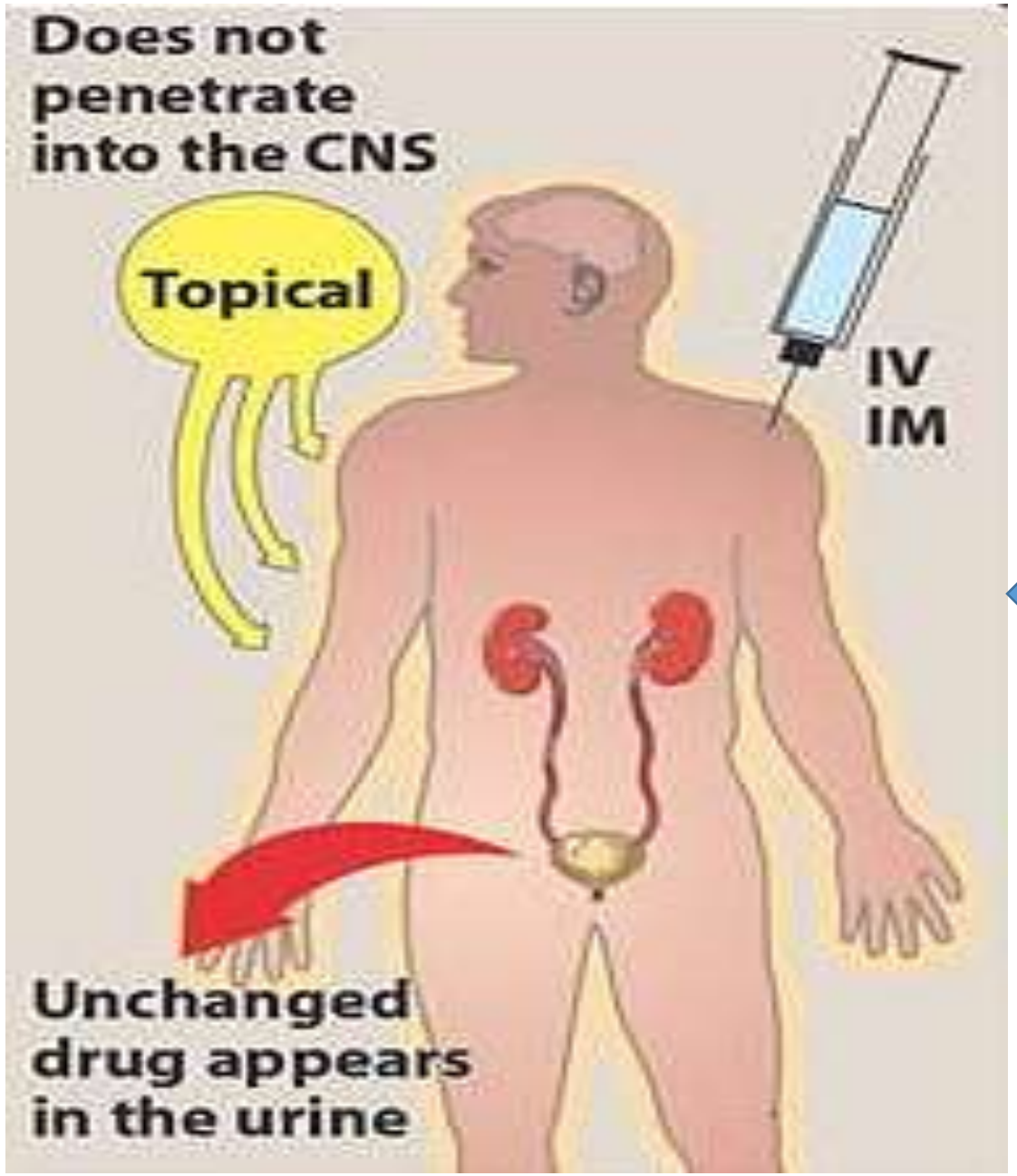
- The bactericidal effect of aminoglycosides is concentration and time dependent; that is, the greater the concentration of drug, the greater the rate at which the organisms die.

Distribution: All the aminoglycosides have similar pharmacokinetic properties. Levels achieved in most tissues are low, and penetration into most body fluids is variable. Concentrations in CSF are inadequate, even when the meninges are inflamed.

- Except for neomycin, the aminoglycosides may be administered intrathecally or intraventricularly.
- High concentrations accumulate in the renal cortex and in the endolymph and perilymph of the inner ear, which may account for their nephrotoxic and ototoxic potential.
- All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid (the fluid surrounding a fetus within the amnion).

Elimination: Metabolism of the aminoglycosides does not occur in the host.

- All are rapidly excreted into the urine, predominantly by glomerular filtration.
- Accumulation occurs in patients with renal failure and requires dose modification.



PHARMACOKINETICS OF AMINOGLYCOSIDE

ADVERSE EFFECTS

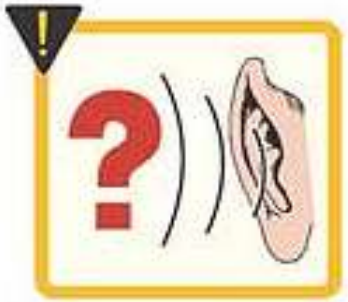
- It is important to monitor plasma levels of gentamicin, tobramycin, and amikacin to avoid concentrations that cause dose-related toxicities.
- Patient factors, such as old age, previous exposure to aminoglycosides, and liver disease, tend to predispose patients to adverse reactions.
- The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. **Ototoxicity:** It (vestibular and cochlear) is directly related to high peak plasma levels and the duration of treatment. The **antibiotic accumulates in the endolymph and perilymph of the inner ear**, and toxicity correlates with the number of destroyed hair cells in the organ of Corti.

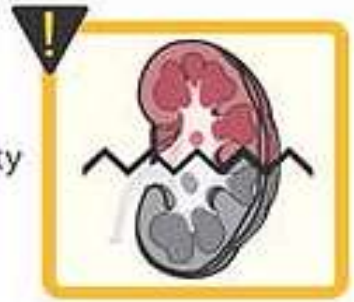
- Deafness may be irreversible and has been known to affect fetuses in utero. Patients simultaneously receiving another ototoxic drug, such as cisplatin or the loop diuretics, furosemide, bumetanide, or ethacrynic acid, are particularly at risk.
- Vertigo and loss of balance (especially in patients receiving streptomycin) may also occur, because these drugs affect the vestibular apparatus.

2. **Nephrotoxicity:** **Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes**, and this results in kidney damage ranging from mild, reversible renal impairment to severe, acute tubular necrosis, which can be irreversible.
3. **Neuromuscular paralysis:** This side effect most often occurs after direct intraperitoneal or intrapleural application of large doses of aminoglycosides. The mechanism responsible is a **decrease in both the release of acetylcholine from prejunctional nerve endings and the sensitivity of the postsynaptic site**. Patients with myasthenia gravis are particularly at risk. Prompt administration of calcium gluconate or neostigmine can reverse the block.
4. **Allergic reactions:** Contact dermatitis is a common reaction to **topically applied neomycin**.

Ototoxicity

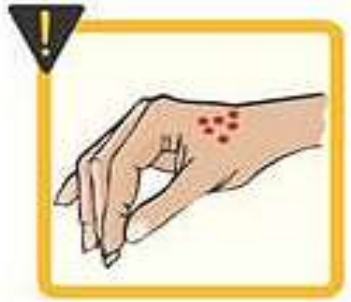


Nephrotoxicity



Paralysis

Skin rash



ADVERSE EFFECTS OF AMINOGLYCOSIDE

THERAPEUTIC USES

- **Bacterial Endocarditis**
- **Tularemia**
- **Plague**
- **Tuberculosis**
- **Urinary Tract Infections**
- **Pneumonia**
- **Meningitis**
- **Peritoneal Dialysis-Associated Peritonitis**
- **Sepsis**
- **Nosocomial gram-negative bacillary infections**

THANKING YOU

Pharmacist is a linker between patient and registered general physician. So, It's Pharmacist's duty to take right decision in perfect pattern.