46 Aminoglycoside Antibiotics

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DRUG LIST

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CHEMISTRY

Aminoglycosides are hydrophilic, polycationic, amine-containing carbohydrates that are usually composed of three to five rings. Most aminoglycosides are either natural products or derivatives of soil actinomycetes. They are often secreted by these actinomycetes as mixtures of closely related compounds. The polycationic aminoglycoside chemical structure results in a binding both to the anionic outer bacterial membrane and to anionic phospholipids in the cell membranes of mammalian renal proximal tubular cells. The former contributes to the bactericidal effects of these compounds, while the latter binding accounts for their toxicity. Because of their hydrophilicity, the transport of aminoglycosides across the hydrophobic lipid bilayer of eukaryotic cell membranes is impeded.

The major clinically important aminoglycosides are amikacin (*Amikin*), gentamicin (*Garamycin*), kanamycin (*Kantrex*), netilmicin (*Netromycin*), neomycin (*Mycifradin*), streptomycin, and tobramycin (*Nebcin*). Their pharmacokinetic characteristics are shown in Table 46.1.

MECHANISM OF ANTIBACTERIAL ACTION

The antibacterial actions of the aminoglycosides involve two possibly synergistic effects. First, the positively charged aminoglycoside binds to negatively charged sites on the outer bacterial membrane, thereby disrupting membrane integrity. It is likely that the aminoglycoside-induced bacterial outer membrane degradation accounts for the rapid concentration-dependent bactericidal effect of these compounds. Second, aminoglycosides bind to various sites on bacterial 30S ribosomal subunits, disrupting the initiation of protein synthesis and inducing errors in the translation of messenger RNA to peptides. They also bind to sites on bacterial 50S ribosomal subunits, although the significance of this binding is uncertain. In addition, they have a postantibiotic effect; that is, they continue to suppress bacterial regrowth even after removal of the antibiotic from the bacterial microenvironment. It is likely that ribosome disruption accounts for this postantibiotic activity.

TABLE 46.1 Characteristics of the Aminoglycosides

Drug	Half-life (hr)	Therapeutic Serum Level (μg/ml)	Toxic Serum Level (μg/ml)
Streptomycin	2–3	25	50
Neomycin	3	5–10	10
Kanamycin	2.0–2.5	8–16	35
Gentamicin	1.2–5.0	4–10	12
Tobramycin	2.0–3.0	4–8	12
Amikacin	0.8–2.8	8–16	35
Netilmicin	2.0–2.5	0.5–10	16

Adapted with permission from Drug Facts and Comparisons. St. Louis: Lippincott, 1985:1372.

The postantibiotic effect is characterized by prolonged suppression of bacterial regrowth after the initially high aminoglycoside concentration has fallen to a subinhibitory level. Perhaps resumption of bacterial ribosomal function requires the time-consuming synthesis of new ribosomes after their disruption by aminoglycosides. The postantibiotic effect explains why aminoglycosides can be given in single daily doses despite their short half-life.

Penetration of aminoglycosides through the outer bacterial membrane occurs both by outer membrane disruption and by diffusion through outer membrane porins. Penetration through the inner bacterial membrane occurs in two phases. The first requires that the cytosol have a negative electron potential and therefore be inhibited by the presence of a low pH. The second phase depends on aerobic bacterial metabolism and therefore will be inhibited by low oxygen tension. The latter two observations are of considerable clinical relevance, since both a low pH and a low oxygen tension frequently occur in bacterial abscesses. Administration of β-lactam antibiotics will reverse the negative effects of both low pH and low oxygen tension on the ability of aminoglycosides to penetrate into bacteria; this ability accounts in part for the synergism that occurs between aminoglycoside and β-lactam antibiotic drugs.

MECHANISM OF ANTIBACTERIAL RESISTANCE

The frequency of bacterial aminoglycoside resistance encountered in clinical practice has remained nearly constant over the past 2 decades. Of the three recognized mechanisms of resistance that occur in aerobic gram-negative bacteria, plasmid-mediated expression of enzymes that acetylate, adenylate, or phosphorylate the aminoglycosides is the most important. Ring one is the primary target of these enzymes.

Two other common mechanisms of resistance are known. Some cases of resistance of aerobic gram-negative bacilli to streptomycin are due to mutations in the proteins of the bacterial ribosomes. Streptococci, staphylococci, and Pseudomonadaceae resist aminoglycosides as a result of decreased transport of the aminoglycosides into the bacterial cytosol.

Anaerobes also are resistant to aminoglycosides because of decreased transport into the bacterial cytosol. Combining an aminoglycoside with an antibiotic that disrupts the bacterial cell wall can overcome this natural resistance.

PHARMACOKINETICS

The blood plasma drug concentrations achieved during multiple daily dose therapy with aminoglycosides usually correlates with clinical outcome in patients with bacteremia and in patients with pneumonia. Raising the aminoglycoside plasma concentration to its in vitro minimum inhibitory concentration against the isolated pathogen is a useful indicator of the adequacy of aminoglycoside dosing.

Both the rate and extent of gastrointestinal absorption of individual aminoglycosides are generally quite low. For example, more than 95% of an oral dose of neomycin is excreted unchanged in the feces. The systemic bioavailability of the aminoglycosides is low across other membranes as well. For example, gentamicin is poorly absorbed from a topical ophthalmic preparation, and there is little systemic absorption of either inhaled tobramycin or aminoglycosides instilled into the urinary bladder. Neomycin bioavailability across intact skin is also low, although absorption across damaged skin can be significant: nephrotoxicity can occur in burn patients treated with topical neomycin.

Because of their aqueous solubility and modest binding to plasma and tissue proteins, the distribution of the aminoglycosides corresponds to that of the extracellular fluid. Four compartments can be distinguished. The central compartment corresponds to the intravascular space; the rapidly equilibrating compartment corresponds to the extracellular visceral space; the slowly equilibrating compartment largely corresponds to that of skeletal muscle; and the extremely slowly equilibrating compartment presumably corresponds to that of bone, proximal renal tubules, otolymph, and other tissue where binding to phospholipids or mineral matrix occurs. Gentamicin fails to reach intraocular fluid or cerebrospinal fluid in significant concentrations after intravenous injection, although it may reach bactericidal levels in cerebrospinal fluid in patients with meningeal inflammation, such as occurs in meningitis. However, direct intrathecal injection of gentamicin may still be required for reliable bactericidal levels.

Most of the enzymes that catalyze the metabolism of foreign compounds are found inside cells. As aminoglycosides do not penetrate most cells, they do not undergo any significant metabolism. Nearly all of an intravenous dose is cleared by the kidneys and can be recovered in the urine. Aminoglycoside clearance is approximately equal to that of the glomerular filtration rate, resulting in fairly high urine concentrations; the latter contributes to the efficacy of the aminoglycosides in urinary tract infections.

CLINICAL USES

Serious Gram-Negative Bacillary Infections

Gentamicin is the aminoglycoside antibiotic most commonly used to treat serious infections due to gram-negative aerobic bacilli, such as *Escherichia coli* and *Klebsiella pneumoniae,* and *Proteus, Serratia, Acinetobacter, Citrobacter,* and *Enterobacter* spp. Gentamicin also has significant activity against *Staphylococcus aureus.* The aminoglycosides are often used in combination with β-lactams in the initial empirical therapy of sepsis and of fever in immunocompromised patients. The combination is used both to ensure adequate antibiotic coverage in these seriously ill patients and to exploit the synergistic antibiotic activity that β-lactams and aminoglycosides have against many species. These drugs should not, however, be injected simultaneously, since the β-lactams can chemically inactivate the aminoglycosides.

Aminoglycosides are often used in patients with gram-negative bacillary pneumonia. Single daily dosing may be of particular importance in patients with pneumonia, since this regimen can increase the peak concentration of the aminoglycosides in bronchial secretions.

Acute salpingitis (pelvic inflammatory disease) due to *Neisseria gonorrhoeae, Chlamydia trachomatis,* or both is often complicated by superinfection with gram-negative bacilli and anaerobes. A combination of gentamicin, clindamycin, and doxycycline has been shown to be an effective treatment for this polymicrobial infection.

The combination of gentamicin and clindamycin is useful in patients with an intraabdominal infection or an abscess secondary to penetrating trauma, diverticulitis, cholangitis, appendicitis, peritonitis, or postsurgical wound infection. These infections are often polymicrobial, including gram-negative bacilli and anaerobes. Definitive treatment of these conditions may also require surgical or other intervention to drain the abscess.

Choice of one aminoglycoside over another for the treatment of serious infections should be guided both by assessment of the antibiotic sensitivities of the specific bacterial strain causing the patient's infection and by familiarity with local patterns of bacterial resistance. *Pseudomonas aeruginosa* is more likely than other gram-negative bacilli to exhibit resistance to gentamicin. However, *Pseudomonas* spp. resistant to gentamicin may be susceptible to amikacin or tobramycin. Streptomycin is the drug of choice for patients with pneumonia due to *Yersinia pestis* (plague) or *Francisella tularensis* (tularemia).

Eradication of Facultative Gut Flora

A combination of neomycin and nonabsorbable erythromycin base given orally prior to colorectal surgery can markedly reduce the incidence of postoperative wound infection. Orally administered neomycin is sometimes used to suppress the facultative flora of the gut in patients with hepatic encephalopathy. It is unclear how this improves coma, but one theory is that it reduces systemic absorption of the bacterial metabolites that allegedly cause hepatic encephalopathy. Although more than 95% of an oral dose of neomycin is excreted unchanged in the stool of normal subjects, the bioavailability of neomycin may be much higher in patients with an abnormal gastrointestinal mucosa.

Neomycin is often combined with other antibiotics, such as polymyxin B and bacitracin, and applied as an ointment to prevent any infection of minor skin abrasions, burns, and cuts.

Cystic Fibrosis

P. aeruginosa is commonly found in the bronchial secretions of patients with cystic fibrosis. In one study, daily inhalation of large doses of tobramycin decreased the colonization by this organism 100-fold and significantly improved pulmonary function.

Endocarditis

A combination of gentamicin and ampicillin is recommended as prophylaxis of endocarditis prior to surgery or instrumentation of the gastrointestinal or genitourinary tracts for patients at high risk for endocarditis. Gentamicin plus vancomycin is recommended as prophylaxis of endocarditis for high-risk patients with a history of β-lactam allergy. Gentamicin or streptomycin will act synergistically with penicillin for the treatment of enterococcal endocarditis.

Meningitis

The degree of penetration of the aminoglycosides into cerebrospinal fluid is proportional to the degree of inflammation of the meninges. However, aminoglycosides are best combined with the β-lactams or other antibiotics in the treatment of meningitis.

Tuberculosis

In response to the increasing prevalence of mycobacterial resistance to standard antibiotic chemotherapy, the use of aminoglycosides is increasing in patients at high risk for having resistant infections. Inhaled aminoglycosides may also have a role in patients with persistently positive sputum despite therapy. Streptomycin is useful in the initial therapy of severe or disseminated tuberculosis, which is most common in immunocompromised patients.

Ophthalmological Infection

Because of the very high concentrations of gentamicin achieved in the conjunctival sac, it is effective against nearly all of the typical bacterial pathogens that cause conjunctivitis. Special high-dose formulations of gentamicin are necessary for treating bacterial ophthalmic keratitis. Gentamicin is not active against viral conjunctivitis, although it may prevent a secondary bacterial infection. Bacterial endophthalmitis, an infection of the vitreous humor, usually requires both vitreous aspiration and intravitreal instillation of gentamicin and cefazolin.

Gonococcal Urethritis

Spectinomycin (*Trobicin*), an aminocyclitol antibiotic chemically related to the aminoglycosides, is occasionally used to treat uncomplicated gonococcal urethritis in patients who are allergic to β-lactam. Treatment failures have occurred, however, when spectinomycin was used in gonococcal pharyngitis or systemic gonococcal infection.

SINGLE DAILY DOSING

Single daily doses of aminoglycosides are at least as effective as and no more toxic than multiple daily doses. Some studies suggest that single daily dosing may actually be less nephrotoxic than more frequent dosing. Since aminoglycoside uptake across the brush border of proximal renal cortical tubular cells is saturable, giving a single large dose should result in less renal accumulation; this has now been shown in patients receiving a single bolus injection of gentamicin compared with those administered a continuous 24-hour intravenous infusion. One clinical trial recently demonstrated that ototoxicity was also reduced when single daily dosing was used.

The magnitude of the rapid-killing effect and the duration of the postantibiotic effect of the aminoglycosides are proportional to their peak concentration at the site of the infection; that is, the higher the peak concentration, the more pronounced these effects. Giving aminoglycosides as a single daily dose results in a higher peak tissue concentration than if the total daily dose were divided and given more frequently. Single daily dosing with amikacin results in higher drug concentrations in the bronchial secretions of patients with pneumonia.

Clinical trials of single daily dosing of aminoglycosides have been done in adults, pregnant women, and children for a variety of indications, including serious infections, pelvic inflammatory disease, abdominal sepsis, cystic fibrosis, and the empirical treatment of neutropenic patients with fever. While single daily dosing of aminoglycosides is justified in most patients, it may be inadequate when given to provide synergism with β-lactam antibiotics in enterococcal endocarditis.

TOXICITY

Aminoglycosides cause nephrotoxicity, and the relative toxicity of the various aminoglycosides can be correlated with the number of constituent amine groups that each contains; neomycin is the most nephrotoxic and streptomycin is the least. Although their polycationic structure prevents their entry into most cells, aminoglycosides can diffuse from the tubular lumen across the apical membrane of proximal renal tubular cells following drug filtration through the glomerulus. Passage of the aminoglycosides across the apical membrane occurs via a saturable process of adsorption of polycationic aminoglycoside molecules to the proximal renal tubular lumen's anionic brush border and subsequent endocytosis and accumulation in lysosomes.

Once the drug is within the lysosomes, it will bind to anionic phospholipids, inhibiting lysosomal phospholipase A_2. This leads to lysosomal distension, rupture, and release of acid hydrolases and the aminoglycoside into the cytosol. Free aminoglycoside then binds to other cellular organelles. Gentamicin accumulation in mitochondria displaces Ca^{++}, leading to mitochondrial degeneration and cell necrosis. The necrotic cellular debris then sloughs off and is passed in the urine, leaving a denuded basement membrane. The development of toxicity depends upon the duration of aminoglycoside therapy and the mean trough blood plasma drug concentration. Nephrotoxicity is more likely in aminoglycoside-treated patients with gram-negative bacillary bacteremia than in those with staphylococcal bacteremia. Nephrotoxicity is most common and most severe in patients with extrahepatic biliary obstruction, hepatitis, or cirrhosis.

The severity of aminoglycoside nephrotoxicity is additive with that of vancomycin, polymixin, gallium, furosemide, enflurane, cisplatin, and cephalosporins. Aminoglycoside nephrotoxicity is synergistic with that of amphotericin B and cyclosporine.

Even quite severe aminoglycoside-induced nephrotoxicity is nearly always reversible upon prompt discon-

tinuation of the drug. Verapamil and Ca^{++} can lessen the nephrotoxicity, but the latter may also inhibit the antibacterial effect of the aminoglycosides. Polyaspartic acid is a promising new agent that lessens aminoglycoside nephrotoxicity, although it also may partially inhibit the drug's antibacterial activity.

Aminoglycosides accumulate in otolymph and can cause both vestibular and auditory ototoxicity, both of which can be irreversible. Uptake is driven by the concentration gradient between blood and the otolymph; this process is saturable. Sustained high concentrations in otolymph first destroy hair cells that are sensitive to high-frequency sounds. Streptomycin is more likely to cause vestibular toxicity than ototoxicity. The severity of aminoglycoside-induced ototoxicity is worsened by the coadministration of vancomycin, furosemide, bumetanide, and ethacrynic acid. Ca^{++} may lessen the ototoxic effect.

Aminoglycosides can cause neuromuscular junction blockade by displacing Ca^{++} from the neuromuscular junction, inhibiting the Ca^{++}-dependent prejunctional release of acetylcholine and blocking postsynaptic acetylcholine receptor binding. This is usually clinically significant only in patients with myasthenia gravis, hypocalcemia, or hypermagnesemia or when the aminoglycoside is given shortly after the use of a neuromuscular blocking agent. The neuromuscular blockade can be reversed by administration of intravenous calcium.

Study Questions

1. Many antibiotics appear to have as their mechanism of action the capacity to inhibit bacterial cell wall synthesis. This does NOT appear to be a mechanism of
(A) Aminoglycosides
(B) Penicillins
(C) Bacitracin
(D) Cephalosporins

2. Many antibiotics are not useful in treating infections in the central nervous system because they do not readily penetrate the blood-brain barrier. Which one of the following agents does get into the brain in reasonable concentrations?
(A) Penicillin G
(B) Ampicillin
(C) Cefotaxime
(D) Kanamycin
(E) Neomycin

3. Aminoglycoside antibiotics are frequently used in combination with the β-lactam antibiotics. Which of the following choices best explains the rationale for this use?
(A) The combination provides for a much greater spectrum of activity.
(B) A synergistic effect is often seen when the combination is employed.
(C) The β-lactam antibiotics prevent toxic effects of the aminoglycoside antibiotics.
(D) The combination decreases incidence of superinfections.

4. Patients with myasthenia gravis may exhibit greater toxicity to aminoglycosides than do patients without this condition. The most likely explanation is
(A) Aminoglycosides have muscarinic blocking properties.
(B) Aminoglycosides cause an increased metabolism of acetylcholine.
(C) Aminoglycosides cause a neuromuscular block by displacing Ca^{++} from the neuromuscular junction.
(D) Aminoglycosides inhibit second messenger activity at the neuromuscular junction.

5. As a class, the aminoglycoside antibiotics do not exhibit significant metabolism in the patient. The most likely reason is that
(A) Their chemical structure is unique and not prone to chemical reactions commonly seen in drug metabolism.
(B) The liver does not contain appropriate enzymes to break down the compounds.
(C) The body apparently lacks a necessary cofactor for the metabolism of aminoglycosides.
(D) Aminoglycosides do not readily get to the site of degradative enzymes.

ANSWERS

1. A. The aminoglycosides appear to act by binding to various sites on bacterial 30S ribosomal subunits and disrupting the initiation of protein synthesis. The other agents appear to have the capacity to directly inhibit bacterial cell-wall synthesis.

2. C. The selection of agents to treat brain infections is quite limited because most agents do not penetrate into cerebrospinal fluid or the brain itself.

3. B. A synergistic effect when the combination of an aminoglycoside and β-lactam antibiotic are administered concurrently is well documented. The reasons for the synergistic response are not well documented but may be related to the actions of the β-lactam antibiotic to raise pH and oxygen tension

in areas of abscess and thereby increase the penetrability of the aminoglycoside.

4. **C.** Aminoglycosides can cause neuromuscular junction blockade by the mechanism of displacing Ca^{++} from the neuromuscular junction and thus leading to the Ca^{++}-dependent prejunctional release of acetylcholine. This is of clinical significance only in patients with myasthenia gravis, hypocalcemia, and hypermagnesemia.
5. **D.** Aminoglycosides do not penetrate most cells, and most drug-metabolizing enzymes are found on the inside of the cells. Therefore, aminoglycosides are poorly metabolized, and nearly all of an intravenous dose can be recovered in the urine.

SUPPLEMENTAL READING

Clancy JP et al. Evidence that systemic gentamicin suppresses premature stop mutations in patients with cystic fibrosis. Am J Respir Crit Care Med 2001;163:1683–1692.

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Moore R, Lietman P, and Smith C. Clinical response to aminoglycosides: Importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 1987;155:93–99.

Santre C et al. Amikacin levels in bronchia secretions of 10 pneumonia patients with respiratory support treated once daily versus twice daily. Antimicrob Agents Chemother 1995;39:264–267.

CASE Study Neomycin in Hepatic Encephalopathy

A 50-year-old man diagnosed with hepatic coma was successfully treated with a daily oral dose of neomycin 2 weeks prior to coming to your clinic. The patient complains that he can't hear as well now as he could prior to his recent hospitalization. You suspect that this may be due to the patient's treatment during his episode with hepatic coma. What is your next response?

ANSWER: Ototoxicity and nephrotoxicity are common adverse effects of aminoglycoside therapy, particularly when administered orally. You immediately arrange to check renal function and fortunately discover that renal function is not significantly impaired in this patient. You inform the patient that the hearing loss is probably permanent and that he should carefully check with pharmacists and physicians in the future to be certain that any prescriptions drugs that he might receive do not further aggravate this condition.