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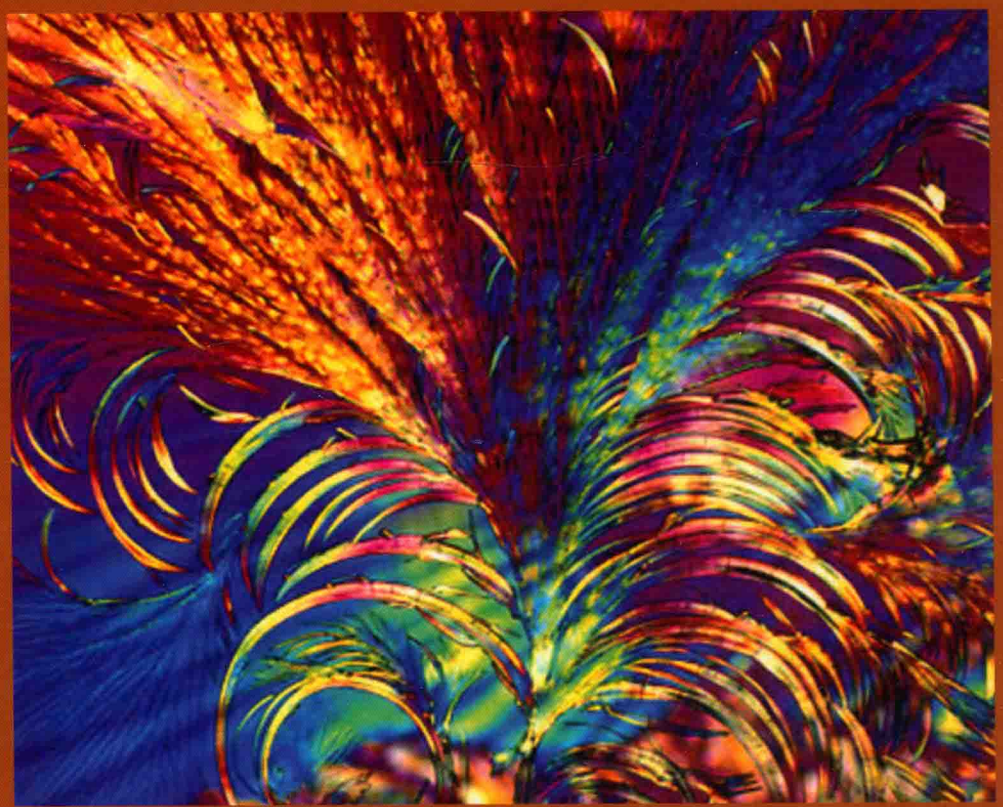
Side Effects of

Antimicrobial Drugs



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Meyler's Side Effects of Antimicrobial Drugs

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Meyler's Side Effects of Antimicrobial Drugs

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ANTIBACTERIAL DRUGS

Alatrofloxacin and trovafloxacin

See also Fluoroquinolones

General Information

Alatrofloxacin is a fluoronaphthyridone that is hydrolysed to the active moiety, trovafloxacin, after intravenous administration. This fourth-generation broad-spectrum fluoroquinolone has activity against Gram-positive, Gram-negative, anerobic, and atypical respiratory pathogens. Because it has significant hepatotoxicity, the list of appropriate indications for trovafloxacin has been restricted.

In a multicenter, double-blind, randomized comparison of trovafloxacin 200 mg and clarithromycin 500 mg bd in 176 subjects with acute exacerbations of chronic bronchitis, the most common adverse effects of trovafloxacin were nausea (5%), dizziness (5%), vomiting (3%), and constipation (3%) (1). Because trovafloxacin is hepatotoxic, the list of appropriate indications has been limited to patients who have at least one of several specified infections, such as nosocomial pneumonia or complicated intra-abdominal infections that are serious and life- or limb-threatening in the physician's judgement.

Trovafloxacin may down-regulate cytokine mRNA transcription in human peripheral blood mononuclear cells stimulated with lipopolysaccharide or lipoteichoic acid (2). Likewise, trovafloxacin inhibited *Salmonella typhimurium*-induced production of TNFα, HIV-1 replication, and reactivation of latent HIV-1 in promonocytic U1 cells at concentrations comparable to the plasma and tissue concentrations achieved by therapeutic dosages (3).

Organs and Systems

Cardiovascular

Phlebitis can occur during parenteral administration of trovafloxacin. High concentrations of trovafloxacin (2 mg/ml) significantly reduced intracellular ATP content in cultured endothelial cells and reduced concentrations of ADP, GTP, and GDP (4). These in vitro data suggest that high doses of trovafloxacin are not compatible with maintenance of endothelial cell function and may explain the occurrence of phlebitis. Commercial formulations should be diluted and given into large veins.

Nervous system

Alatrofloxacin can cause seizures (5).

- A 37-year-old Asian man received several antibiotics (including intravenous ceftazidime, gentamicin, meropenem, metronidazole, and vancomycin) postoperatively. After 3 weeks he was given alatrofloxacin 75 mg in 25 ml of dextrose 5% (1.875 mg/ml) and developed generalized clonus. On rechallenge, infusing at half the initial rate, the seizure recurred. A CT scan of the brain was normal.

Seizures are rare but have occurred during treatment with other fluoroquinolones. This is the first report of a case of seizures associated with slow infusion of alatrofloxacin. However, as of 21 June 2000, the manufacturers had received 53 reports of seizures through worldwide post-marketing surveillance. In rat hippocampus slices, trovafloxacin had significant convulsive potential; the underlying mechanism is hitherto incompletely understood.

Trovafloxacin has been associated with diffuse weakness due to a demyelinating polyneuropathy in a patient without an underlying neurological disorder (6).

Sensory systems

Intravitreal trovafloxacin in doses of 50 mg and higher in the pigmented rabbit eye caused retinal and nerve fiber injury; intravitreal doses of 25 mg and lower appear to be safe, with no evidence of ocular toxicity (7).

Hematologic

Alatrofloxacin has been associated with severe leukopenia (8).

- A 79-year-old white man was treated with intravenous alatrofloxacin mesylate 200 mg bd for 5 days. His leukocyte count fell from 10.9×10^9/l to 2.2×10^9/l; the hemoglobin did not change. Alatrofloxacin was withdrawn, and 3 days later the leukocyte count had increased to 11.5×10^9/l.

The mechanism of trovafloxacin-induced leukopenia is unknown. Nevertheless, since quinolones exert their antibacterial effect by inhibiting bacterial DNA gyrase and since similar topoisomerases are involved in the organization and function of mammalian DNA, it is possible that trovafloxacin acts by modulating bone marrow stem-cell DNA production.

Alatrofloxacin has been associated with severe thrombocytopenia (9).

- A 54-year-old woman was given alatrofloxacin 300 mg intravenously qds and on day 4 developed epistaxis. Her platelet count was 7×10^9/l, with normal hemoglobin and white blood cell counts. Direct antiglobulin testing showed coating of erythrocytes with polyspecific immunoproteins, and platelet-associated antibody testing was positive for IgM and IgG antibodies. Alatrofloxacin was withdrawn and azithromycin was given instead. She was given methylprednisolone 125 mg intravenously bd and the platelet count fell to 2×10^9/l and then rose, reaching 60×10^9/l on day 8.

During clinical trials, thrombocytopenia occurred in under 1% of more than 7000 patients who received alatrofloxacin or trovafloxacin.

Liver

More than 100 cases of hepatotoxicity associated with trovafloxacin have been reported to the FDA.

- A 19-year-old woman developed severe acute hepatitis and peripheral eosinophilia during oral trovafloxacin therapy for recurrent sinusitis (10). Liver biopsy showed extensive centrilobular hepatocyte necrosis, probably causing veno-occlusive disease. Clinical and laboratory abnormalities resolved completely after prolonged treatment with steroids.
- A 66-year-old man had taken trovafloxacin 100 mg/day for 4 weeks for refractory chronic sinusitis (11). For several years he had also taken allopurinol, doxepin, hydrochlorothiazide, losartan, metoprolol, and nabumetone. He developed nausea, vomiting, malaise, and abdominal distension. His white cell count was 8000×10^9/l with 16% eosinophils; his serum aspartate transaminase was 537 IU/l, alanine transaminase 841 IU/l, direct bilirubin 17 μmol/l; total bilirubin 27 μmol/l, alkaline phosphatase 111 IU/l; blood urea nitrogen 5 μmol/l; and creatinine 190 μmol/l. Tests for hepatitis A, B, and C were negative. A biopsy of the liver showed centrilobular and focal periportal necrosis and eosinophilic infiltration; the sinusoids were dilated and contained lymphocytes and eosinophils; many hepatocytes were undergoing mitosis. After withdrawal of trovafloxacin and treatment with prednisone, his hepatic and renal function returned to normal, and the eosinophilia gradually resolved.

Skin

The photosensitizing potential of trovafloxacin 200 mg od has been compared with that of ciprofloxacin 500 mg bd, lomefloxacin 400 mg od, and placebo in 48 healthy men (aged 19–45 years) (12). Trovafloxacin had significantly less photosensitizing potential than either ciprofloxacin or lomefloxacin. Photosensitivity seemed to be induced only by wavelengths in the UVA region, was maximal at 24 hours, and had a short-term effect.

Musculoskeletal

Trovafloxacin inhibited growth and extracellular matrix mineralization in MC3T3-E1 osteoblast-like cell cultures (13). The IC_{50} was 0.5 μg/ml, which is below clinically achievable serum concentrations. The authors suggested that the clinical relevance of this observation to bone healing in orthopedic patients should be evaluated.

In rats experimental fractures systemically exposed to trovafloxacin had impaired healing during the early stages of fracture repair (14).

Second-Generation Effects

Teratogenicity

In an ex vivo study, trovafloxacin crossed the human placenta by simple diffusion and neither accumulated in the media nor bound to tissues or accumulated in the placenta (15). This implies that it should have no effects on the fetus if given during pregnancy.

Susceptibility Factors

Age

The pharmacokinetics of a single intravenous dose of alatrofloxacin have been determined in six infants aged 3–12 months and in 14 children aged 2–12 years (16). The peak trovafloxacin concentration at the end of the infusion was 4.3 μg/ml; the volume of distribution at steady state was 1.6 l/kg, clearance 2.5 ml/min/kg, and the half-life 9.8 hours, with no age-related differences. Less than 5% of the administered dose was excreted in the urine over 24 hours.

Other features of the patient

The pharmacokinetics of trovafloxacin after the administration of alatrofloxacin were not substantially altered in seven critically ill patients (three men, four women) with APACHE II scores of 27 (range 15–32) and normal or mildly impaired hepatic function (17).

Monitoring Therapy

In 17 patients aged over 18 years with severe acute community-acquired pneumonia trovafloxacin concentrations were persistently high in the sputum, bronchial secretions, bronchoalveolar lavage fluid, and epithelial lining fluid, with no significant difference between these compartments (18). The authors proposed that measurement of sputum concentrations could be used to monitor the outcome of treatment.

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Amikacin

See also Aminoglycoside antibiotics

General Information

Amikacin is a semisynthetic derivative of kanamycin with similar pharmacokinetic properties and dosages. It is resistant to many of the bacterial R factor-mediated enzymes that inactivate kanamycin and gentamicin. Noteworthy is its effect against *Pseudomonas aeruginosa* and against most Gram-negative aerobes that are resistant to gentamicin and tobramycin. There are strains of *Staphylococcus aureus* that inactivate amikacin by phosphorylation and adenylation. Ticarcillin or azlocillin plus amikacin is considered one of the most efficacious empiric antibiotic combinations in febrile granulocytopenia in patients with cancer. On a weight basis amikacin is less active than gentamicin, and so the usual dose is 10–20 mg/kg/day. Wherever possible, peak concentrations of 40 μg/ml and troughs of 10 μg/ml should not be exceeded during twice-daily dosing.

Organs and Systems

Cardiovascular

Episodes of hypotension have been attributed to amikacin (1).

- A 68-year-old woman on continuous ambulatory peritoneal dialysis was given amikacin (250 mg/day) and on the third day fainted and had a blood pressure of 90/60 mmHg. On the next 2 days, she had episodes of postural hypotension of between 90/60 and 80/50 mmHg two or three times a day. She was given antibiotics for the next 6 days and felt very bad the entire time, with a blood pressure of 80/50 mmHg. Her condition improved 2 days after withdrawal of amikacin and the episodes of hypotension did not recur.

Respiratory

Amikacin may have been the causative agent in an apneic episode in an infant on peritoneal dialysis (2).

Sensory systems

Ears

- A 43-year-old man, who was receiving hemodialysis through a permanent catheter developed severe irreversible sensorineural hearing loss after using an amikacin–heparin lock for 16 weeks (3). He suddenly developed a high-frequency sensorineural hearing loss of 40 decibels. His condition progressed over 1 week, despite immediate withdrawal of the amikacin–heparin lock, and he developed severe irreversible hearing loss below 80 decibels for both high and low frequencies.

Retinal toxicity can occur when aminoglycosides are given intravitreally for endophthalmitis.

- Preretinal hemorrhages developed in a 58-year old man who was treated with two intravitreal injections of amikacin (0.4 mg) and cefazolin (2.25 mg) 48 hours apart for postoperative endophthalmitis following routine extracapsular cataract extraction (4).
- Macular toxicity followed the use of intravitreal amikacin 0.2 mg for postoperative endophthalmitis in a 69-year-old white woman (5).

Ototoxicity was observed in three of 195 patients who received amikacin (15 mg/kg/day) with either cefepime (2 g bd) or ceftazidime (2 g tds) (6). Two patients had severe loss of hearing, which persisted after drug withdrawal and resulted in permanent disability. The other had mild ototoxicity that required no action and resolved spontaneously.

Olfaction

Olfactory disorders are among the rare adverse effects of antibiotic therapy. Reversible anosmia has been described.

- A 50-year-old man with lymphangitis of the forearm was given intravenous amikacin sulfate 500 mg bd and intravenous co-amoxiclav 1.2 g tds for 5 days (7). Before treatment began, there was no investigation of his nose or sense of smell. However, after a septoplasty

some 5 years earlier he thought that his olfaction was completely normal. At the end of the treatment period, he noticed a disturbance in his ability to smell, which led to complete anosmia within a few days. Psychometric examination was compatible with complete anosmia. Some 18 months later, he reported that his sense of smell had largely returned during the previous 6 months.In a guinea-pig model the non-ototoxic dose of amikacin (20 mg/kg/day) administered before the ototoxic dose (400 mg/kg/day) had a statistically significant protective effect on the basal turns of the cochlea, observed histologically (8).

Urinary tract

After administration of the recommended doses of amikacin for 10 days, renal damage probably occurs in less than 10% of cases. Limited data support the view that amikacin is less nephrotoxic than other aminoglycosides, possibly because of lower binding affinity to proximal tubular cells or reduced potential to cause phospholipidosis (SEDA-20, 236). In several prospective randomized studies the liability of amikacin to cause nephrotoxicity was no greater than that of gentamicin or tobramycin (9–11). In a prospective study there was significantly lower nephrotoxicity with amikacin 15 mg/kg/day (4% toxicity) compared with netilmicin 7 mg/kg/day (12%) (12). As with other aminoglycosides, renal toxicity is reversible in most cases (13).

Nephrotoxicity occurred in five of 195 patients who received amikacin (15 mg/kg/day) with either cefepime (2 g bd) or ceftazidime (2 g tds) (6). In two patients the deterioration in renal function was mild and resolved without withdrawal of amikacin. In the three other patients, renal insufficiency necessitated drug withdrawal; two of these patients recovered, but one died with sepsis, and renal function was still abnormal at the time of death.

Long-Term Effects

Drug tolerance

In Spain, an epidemic strain of *Acinetobacter baumannii* with resistance to amikacin was isolated in eight different hospitals (14).

Susceptibility Factors

In an open study in eight young healthy Japanese women, the pharmacokinetics of amikacin were affected by the phase of the menstrual cycle (15). In patients with hematological malignancies, bodyweight, renal function, acute myeloblastic leukemia, and hypoalbuminemia were the most important co-variates for the interindividual variability in amikacin pharmacokinetics (16).

Drug Administration

Drug formulations

The pharmacokinetics and toxicity of liposomal amikacin have been investigated in a patient treated for advanced pulmonary multidrug-resistant tuberculosis (17). The serum concentrations of amikacin obtained with the liposomal formulation were considerably greater than those obtained with the conventional formulation. Liposomal amikacin was well tolerated and led to clinical improvement, but the patient's sputum remained smear- and culture-positive during the treatment period and for 9 months.

Drug administration route

Amikacin has been tested for compatibility with a chlorhexidine-bearing central venous catheter, the ARROWg + ard Blue Plus, and did not cause a substantial increase in chlorhexidine delivery (18). The amount of amikacin sulfate that was delivered was slightly less than the amount in the infusion solution (92%), but this was considered acceptable.

Drug–Drug Interactions

Colistin

In a prospective study in 80 patients with cystic fibrosis and normal renal function, the combination of aminoglycosides with the polymyxin antibiotic colistin may have increased the risk of nephrotoxicity; in a multiple linear regression model there was a strong correlation between the use of aminoglycosides and reduced renal function, which was potentiated by colistin (19).

Penicillins

Amikacin may be inactivated by penicillins. This inactivation occurs not only with a mixture of the agents in solution but also in vivo, particularly in patients with renal insufficiency. Amikacin offers, at least in vitro, the advantage of being much less inactivated than tobramycin or gentamicin (20).

Thalidomide

Thalidomide may potentiate the nephrotoxicity of aminoglycosides. Three patients with refractory multiple myeloma taking thalidomide developed severe renal insufficiency shortly after starting to take amikacin for concurrent infections (21).

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Aminoglycoside antibiotics

See also Amikacin, Gentamicin, Isepamycin, Kanamycin, Tobramycin

General Information

Eleven aminoglycosides have been, or are still, important in medical practice: amikacin (rINN), gentamicin (pINN), isepamicin (rINN), kanamycin (rINN), neomycin (rINN), netilmicin (rINN), paromomycin (rINN), sisomicin (rINN), streptomycin (rINN) and dihydrostreptomycin (rINN), and tobramycin (rINN). The following aminoglycosides are also covered in separate monographs: amikacin, gentamicin, isepamycin, kanamycin, and tobramycin.

Being chemically similar, the aminoglycosides have many features in common, in particular their mechanism of antibacterial action, a broad antibacterial spectrum, partial or complete cross-resistance, bactericidal action in a slightly alkaline environment, poor absorption from the gastrointestinal tract, elimination by glomerular filtration, nephrotoxicity, ototoxicity, a potential to cause neuromuscular blockade, and partial or complete cross-allergy (1). Aminoglycosides have a moderate capacity for diffusion into bone tissue (2).

The aminoglycosides have probably more than one mechanism of action on bacterial cells. They cause misreading of the RNA code and/or inhibition of the polymerization of amino acids.

All the aminoglycosides have similar patterns of adverse reactions, although there are important differences with regard to their frequency and severity (Table 1).

Strategies for minimizing aminoglycoside toxicity include early bedside detection of cochlear and vestibular dysfunction, which should lead to prompt withdrawal, use of short periods of treatment, dosing intervals of at least 12 hours, monitoring of serum concentrations, and awareness of relative contraindications, such as renal or hepatic dysfunction, old age, hearing impairment, and previous recent aminoglycoside exposure (3).

Observational studies

In an open, randomized, comparative study of the efficacy, safety, and tolerance of two different antibiotic regimens in the treatment of severe community-acquired or nosocomial pneumonia, 84 patients were analysed (4). Half were treated with co-amoxiclav (amoxicillin 2 g and clavulanic acid 200 mg) every 8 hours plus a single-dose of 3–6 mg/kg of an aminoglycoside (netilmicin or gentamicin), and half with piperacillin 4 g and tazobactam

Table 1 Relative adverse effects of aminoglycoside antibiotics on eighth nerve function, the nervous system, and neuromuscular function

		Site of adverse effect[3]			
Aminoglycoside[1]	***Usual parenteral dose (mg/kg/day)***[2]	***Vestibular function***	***Cochlear function***	***Nervous system***	***Neuromuscular function***
Amikacin	10–15	+	++	++	+
Gentamicin	3–6	++	++	++	+
Kanamycin	10–20	+	+++	++	+
Netilmicin	3–6	+	+	++	+
Sisomicin	2–4	++	++	++	+
Streptomycin	10–20	+++	+	+	++
Dihydrostreptomycin	10–20	+	+++	+++	++
Tobramycin	3–6	++	++	++	+

[1]Neomycin and paromomycin: only accidental absorption after topical or gastrointestinal use.
[2]In general, older patients require lower doses. Low doses are required during therapy of infectious endocarditis when an aminoglycoside is given with a penicillin. Monitoring serum concentrations should be considered, particularly when using dosing regimens that involve more than one dose a day and high doses for several days.
[3]The number of signs (+) indicates the relative clinical importance of each reaction.

500 mg every 8 hours. The patients were treated for between 48 hours and 21 days. Clinical cure was achieved in 65% of patients with co-amoxiclav/aminoglycoside and in 81% of patients with piperacillin/tazobactam. Cure or improvement was observed in 84 and 90% respectively. Treatment failures were recorded in 14 versus 7%. One patient in each group relapsed. There was only one fatal outcome in the piperacillin/tazobactam group compared with six in the co-amoxiclav/aminoglycoside group. The adverse event rate was non-significantly lower in the piperacillin/tazobactam group. In one patient given piperacillin/tazobactam, there were raised transaminases. In the co-amoxiclav/aminoglycoside group, acute renal insufficiency developed in two patients and possibly drug-related fever in one. Bacteriological efficacy was comparable (92% versus 96%). The authors concluded that piperacillin/tazobactam is highly efficacious in the treatment of severe pneumonia in hospitalized patients and compares favorably with the combination of co-amoxiclav plus an aminoglycoside.

General adverse effects

The main adverse reactions of aminoglycosides consist of kidney damage (often presenting as non-oliguric renal insufficiency) and ototoxicity, including vestibular and/or cochlear dysfunction. Neuromuscular transmission can be inhibited. Hypersensitivity reactions are most frequent after topical use, which should be avoided. Anaphylactic reactions can occur. Tumor-inducing effects have not been reported.

Pharmacoeconomics

The pharmacoeconomic impact of adverse effects of antimicrobial drugs is enormous. Antibacterial drug reactions account for about 25% of adverse drug reactions. The adverse effects profile of an antimicrobial agent can contribute significantly to its overall direct costs (monitoring costs, prolonged hospitalization due to complications or treatment failures) and indirect costs (quality of life, loss of productivity, time spent by families and patients receiving medical care). In one study an adverse event in a hospitalized patient was associated on average with an excess of 1.9 days in the length of stay, extra costs of $US2262 (1990–93 values), and an almost two-fold increase in the risk of death. In the outpatient setting, adverse drug reactions result in 2–6% of hospitalizations, and most of them were thought to be avoidable if appropriate interventions had been taken. In a review, economic aspects of antibacterial therapy with aminoglycosides have been summarized and critically evaluated (5).

Organs and Systems

Cardiovascular

Anecdotal reports refer to tachycardia, electrocardiographic changes, hypotension, and even cardiac arrest (6). In practice, effects on the cardiovascular system are unlikely to be of any significance.

Respiratory

Severe respiratory depression due to neuromuscular blockade has been observed (7). Bronchospasm can occur as part of a hypersensitivity reaction.

Neuromuscular function

The aminoglycosides have a curare-like action, which can be antagonized by calcium ions and acetylcholinesterase inhibitors (8). The mechanisms include reduced release of acetylcholine prejunctionally and an interaction with the postjunctional acetylcholine receptor-channel complex. While neomycin interacts with the open state of the receptor, streptomycin blocks the receptor (9).

Aminoglycoside-induced neuromuscular blockade can be clinically relevant in patients with respiratory acidosis, in myasthenia gravis, and in other neuromuscular diseases. Severe illness, the simultaneous use of anesthetics, for example in the immediate postoperative phase, and application of the antibiotic to serosal surfaces are predisposing factors (10).

With regard to this effect, neomycin is the most potent member of the group. Several deaths and cases of severe respiratory depression due to neomycin have been reported (11). Severe clinical manifestations are rare in patients treated with aminoglycosides that are administered in low doses, such as gentamicin, netilmicin, and tobramycin. In some cases the paralysis was reversed by prostigmine.

Sensory systems

Eyes

Collagen corneal shields pre-soaked with antibiotics are used as a means of delivering drug to the cornea and anterior chamber of the eye. Gentamicin damages the primate retina, particularly by macular infarction, and amikacin can have a similar effect; a subconjunctival injection of tobramycin causes macular infarction (SEDA-19, 245). This potentially devastating consequence suggests that care must be exercised when contemplating instillation of aminoglycosides directly into the eye. Allergic contact dermatitis causing conjunctivitis and blepharitis has been reported with topical ophthalmic tobramycin (12).

Ears

Ototoxicity is a major adverse effect of aminoglycoside antibiotics (13). They all affect both vestibular and cochlear function, but different members of the family have different relative effects (Table 1).

Differences between different aminoglycosides

Ototoxicity due to amikacin is primarily cochlear; however, in comparisons with equipotent dosages, ototoxicity was of the same order as that caused by gentamicin (14–16).

In 40 patients tobramycin had little effect on audiometric thresholds, but produced a change in the amplitude of the distortion products, currently considered an objective method for rapidly evaluating the functional status of the cochlea (17). In one case, tobramycin caused bilateral high-frequency vestibular toxicity, which subsequently showed clinical and objective evidence of functional recovery (18).

In a quantitative assessment of vestibular hair cells and Scarpa's ganglion cells in 17 temporal bones from 10 individuals with aminoglycoside ototoxicity, streptomycin caused a significant loss of both type I and type II hair cells in all five vestibular sense organs (19). The vestibular ototoxic effects of kanamycin appeared to be similar to those of streptomycin, whereas neomycin did not cause loss of vestibular hair cells. There was no significant loss of Scarpa's ganglion cells.

Incidence

The incidence of ototoxicity due to aminoglycosides varies in different studies, depending on the type of patients treated, the methods used to monitor cochlear and vestibular function, and the aminoglycoside used (20). Clinically recognizable hearing loss and vestibular damage occur in about 2–4% of patients, but pure-tone audiometry, particularly at high frequencies, and electronystagmography show hearing loss and/or vestibular damage in up to 26 and 10% respectively, despite careful dosage adjustment (21). In patients with *Pseudomonas* endocarditis receiving prolonged high-dose gentamicin, auditory toxicity was found in 44% (22,23).

A review of nearly 10 000 adults suggested rates of 14% for amikacin, 8.6% for gentamicin, and 2.4% for netilmicin. Aminoglycoside toxicity is markedly lower in infants and children, with an incidence of 0–2%. A long duration of treatment and repeated courses or high cumulative doses appear to be critical for ototoxicity, which occurs in high frequency hearing beyond the range of normal speech.

There is a discrepancy between clinical observations, in which very few patients receiving aminoglycosides actually complain of hearing loss, and the reported incidences of ototoxicity in studies of audiometric thresholds. A major reason for this discrepancy relates to the fact that aminoglycosides cause high-frequency hearing loss well before they affect the speech frequency range in which they can be detected by the patient (21).

Gentamicin also damages the vestibular apparatus at a rate of 1.4–3.7%, resulting in vertigo and impaired balance. This effect is reversible in only about 50% from 1 week to 6 months after administration.

In a retrospective study in 81 men and 29 women, hearing loss of 15 decibels at two or more frequencies, or at least 20 decibels at at least one frequency, was found in 18% of patients treated with aminoglycosides (amikacin, kanamycin, and/or streptomycin) (24). In those treated with kanamycin the rate was 16%. Age, sex, treatment duration, total aminoglycoside dose, and first serum creatinine concentration were not associated with hearing loss.

Dose-relatedness

Hearing loss was attributed to repeated exposure to aminoglycosides in 12 of 70 patients with cystic fibrosis (one child) (25). There was a non-linear relation between the number of courses of therapy and the incidence of hearing loss. The severity of loss was not related to the number of courses. Assuming that the risk of hearing loss was independent of each course, the preliminary estimate of the risk was less than 2 per 100 courses.

Presentation

Clinically, cochlear ototoxicity is more frequent and easier to detect than vestibular toxicity; combined defects are relatively rare. Symptoms of cochlear damage include tinnitus, hearing loss, pressure, and sometimes pain in the ear. The manifestations of vestibular toxicity are

dizziness, vertigo, ataxia, and nystagmus. These are often overlooked in severely ill, bed-ridden patients.

Symptoms of ototoxicity can occur within 3–5 days of starting treatment, but most patients with severe damage have received prolonged courses of aminoglycosides. In some cases, hearing loss progresses after the administration of the causative drug has been interrupted. The ototoxicity is reversible in only about 50% of patients. Permanent deafness is often seen in patients with delayed onset of symptoms, progressive deterioration after withdrawal of treatment, and hearing loss of over 25 db (21).

There are interesting differences in the toxicity patterns of aminoglycosides in animals. Gentamicin and tobramycin affect the cochlear and vestibular systems to a similar extent, while amikacin, kanamycin, and neomycin preferentially damage the cochlear and streptomycin the vestibular system. Netilmicin appears to be the least toxic (26,27).

In man, differences in the ototoxic risks of the currently used aminoglycosides are difficult to evaluate (20). There have been no prospective comparisons of more than two drugs using the same criteria in similar patient populations. However, several controlled comparisons of two aminoglycosides are available and provide some information. A survey of 24 such trials showed the following mean frequencies of ototoxicity: gentamicin 7.7%, tobramycin 9.7%, amikacin 13.8%, netilmicin 2.3% (28). There was also a lower incidence of netilmicin-induced inner ear damage compared with tobramycin in two studies (29,30).

Of 20 patients with Dandy's syndrome, 15 had previously been treated with aminoglycosides (13 with gentamicin and 2 with streptomycin), of whom 10 had symptoms of pre-existing chronic nephrosis or transitory renal insufficiency. In all 13 patients who had gentamicin, peripheral vestibular function was destroyed or severely damaged, whereas there was no hearing loss (31).

Mechanism

The mechanism of ototoxicity by aminoglycosides is still not fully clarified. Most of the experimental data have been gained in the guinea-pig model, which seems to resemble man.

Animal studies

Traditionally, toxic damage is considered to be the consequence of drug accumulation in the inner ear fluids (32,33). After a period of reversible functional impairment, destruction of outer hair cells occurs in the basilar turn of the cochlear duct and proceeds to the apex. Similar changes are found in the hair cells of the vestibular system. Gentamicin was detected in the outer hair cells in the cochlea of animals receiving non-ototoxic doses of the drug and continued to increase for several days after withdrawal (34). This was followed by a third and very much slower phase of elimination (estimated half-life 6 months), and in the absence of ototoxicity gentamicin could still be detected in the outer hair cells 11 months after treatment. This may explain why patients who receive several courses of aminoglycosides in a year may be more susceptible to ototoxicity, and suggests that the cumulative dose (and by implication the duration of therapy) is the more important determinant of cochlear damage. However, it has been questioned whether ototoxicity correlates with plasma perilymph or whole-tissue concentrations of aminoglycosides (33).

The effects of aminoglycosides on the medial efferent system have been assessed in awake guinea-pigs (35,36). The ensemble background activity and its suppression by contralateral acoustic stimulation was used as a tool to study the medial efferent system. A single intramuscular dose of gentamicin 150 mg/kg reduced or abolished the suppressive effect produced by activation of the olivocochlear system by contralateral low-level broadband noise stimulation. This effect was dose-dependent and could be demonstrated ipsilaterally on the compound action potential, otoacoustic emissions, and ensemble background activity of the eighth nerve. Long-term gentamicin treatment (60 mg/kg for 10 days) had no effect, at least before the development of ototoxicity. Single-dose intramuscular netilmicin 150 mg/kg displayed blocking properties similar to gentamicin, although less pronounced, while amikacin 750 mg/kg and neomycin 150 mg/kg had no effect. With tobramycin 150 mg/kg and streptomycin 400 mg/kg a decrease in suppression was usually associated with a reduction of the ensemble background activity measured without acoustic stimulation, which may be a fist sign of alteration to cochlear function. There was no correlation between specificity and degree of aminoglycoside ototoxicity and their action on the medial efferent system.

Possible mechanisms and preventive strategies have also been investigated in pigmented guinea-pigs (37–39). Animals that received alpha-lipoic acid (100 mg/kg/day), a powerful free radical scavenger, in combination with amikacin (450 mg/kg/day intramuscularly) had a less severe rise in compound action potential threshold than animals that received amikacin alone. In a similar study in pigmented guinea-pigs, the iron chelator deferoxamine (150 mg/kg bd for 14 days) produced a significant protective effect against ototoxicity induced by neomycin (100 mg/kg/day for 14 days). The spin trap alpha-phenyl-tert-butyl-nitrone also protected against acute ototopical aminoglycoside ototoxicity in guinea-pigs. These studies have provided further evidence for the hypothesis that aminoglycoside ototoxicity is mediated by the formation of an aminoglycoside-iron complex and reactive oxygen species.

Aminoglycoside-induced ototoxicity may be in part a process that involves the excitatory activation of cochlear NMDA receptors (40). In addition, the uncompetitive NMDA receptor antagonist dizocilpine attenuated the vestibular toxicity of streptomycin in a rat model, further stressing that excitotoxic mechanisms mediated by NMDA receptors also contribute to aminoglycoside-induced vestibular toxicity (41). In two studies in guinea-pigs, nitric oxide and free radicals, demonstrated by the beneficial effect of the antioxidant/free radical scavenger

alpha-lipoic acid, have been suggested to be involved in aminoglycoside-induced ototoxicity (38,42). In contrast, insulin, transforming growth factor alpha, or retinoic acid may offer a protective potential against ototoxicity caused by aminoglycosides. However, they do not seem to promote cochlear hair cell repair (43). In guinea-pigs, brain-derived neurotrophic factor, neurotrophin-3, and the iron chelator and antioxidant 2-hydroxybenzoate (salicylate), at concentrations corresponding to anti-inflammatory concentrations in humans, attenuated aminoglycoside-induced ototoxicity (44,45). In rats, concanavalin A attenuated aminoglycoside-induced ototoxicity, and kanamycin increased the expression of the glutamate-aspartate transporter gene in the cochlea, which might play a role in the prevention of secondary deaths of spiral ganglion neurons (46,47). Finally, 4-methylcatechol, an inducer of nerve growth factor synthesis, enhanced spiral ganglion neuron survival after aminoglycoside treatment in mice (48).

In hatched chicks repeatedly injected with kanamycin, afferent innervation of the regenerated hair cells was related more to the recovery of hearing than efferent innervation (49).

In an animal model of ototoxicity, the most severe degeneration in the cristae ampullaris, utricle, and saccule was observed after administration of streptomycin. The severity of the vestibular damage in terms of magnitude was in the order streptomycin > gentamicin > amikacin > netilmicin (50).

Human studies

There is evidence that the site of ototoxic action is the mitochondrial ribosome (51,52). In some countries, such as China, aminoglycoside toxicity is a major cause of deafness. Susceptibility to ototoxicity in these populations appears to be transmitted by women, suggesting mitochondrial inheritance. In Chinese, Japanese, and Arab-Israeli pedigrees a common mutation was found. A point mutation in a highly conserved region of the mitochondrial 12S ribosomal RNA gene was common in all pedigrees with maternally inherited ototoxic deafness (51). A mutation at nucleotide 1555 has been reported to confer susceptibility to aminoglycoside antibiotics, and to cause non-syndromic sensorineural hearing loss. Outside these susceptible families, sporadic cases also have this mutation in increased frequency. In patients bearing this mitochondrial mutation hearing loss was observed after short-term exposure to isepamicin sulfate (53). These findings might create a molecular baseline for preventive screening of patients when aminoglycosides are to be used (SEDA-18, 1) (51).

Differences between sera from patients with resistance or susceptibility to aminoglycoside ototoxicity have been described in vitro (54). Sera from sensitive but not from resistant individuals metabolized aminoglycosides to cytotoxins, whereas no sera were cytotoxic when tested without the addition of aminoglycosides. This effect persisted for up to 1 year after aminoglycoside treatment.

Table 2 Factors that increase susceptibility to the adverse effects of aminoglycosides

Patient factors	*Drug-related factors*
Prior renal insufficiency	High temperature
Prior abnormal audiogram	Dose (blood concentration exceeding the usual target range)
Age (mainly older patients)	Total cumulative dose
Septicemia	Prolonged duration of therapy (2–3 weeks)
Dehydration	Prior aminoglycoside exposure

Susceptibility factors

Several factors predispose to ototoxic effects (Table 2). Drug-related toxicity is influenced by the quality of prescribing. Overdosage in patients with impaired renal function, unnecessary prolongation of treatment, and the concomitant administration of other potentially ototoxic agents should be avoided. The exact mechanism of increased toxicity in patients with septicemia and a high temperature is not clear; the possible relevance of additive damage by bacterial endotoxins has been discussed (55). Dehydration with hypovolemia is probably the main reason for the increased toxicity experienced when aminoglycosides are given with loop diuretics, but furosemide itself does not seem to be an independent risk factor (56,57). Attempts have been made in animals to protect against ototoxicity by antioxidant therapy (for example glutathione and vitamin C), as well as iron chelators and neurotrophins (58).

Hereditary deafness is a heterogeneous group of disorders, with different patterns of inheritance and due to a multitude of different genes (59,60). The first molecular defect described was the A1555G sequence change in the mitochondrial 12S ribosomal RNA gene. A description of two families from Italy and 19 families from Spain has now suggested that this mutation is not as rare as was initially thought (61,62). The A1555G mutation is important to diagnose, since hearing maternal relatives who are exposed to aminoglycosides may lose their hearing. This predisposition is stressed by the fact that 40 relatives in 12 Spanish families and one relative in an Italian family lost their hearing after aminoglycoside exposure. Since the mutation can easily be screened, any patient with idiopathic sensorineural hearing loss may be screened for this and possible other mutations.

In an Italian family of whom five family members became deaf after aminoglycoside exposure, the nucleotide 961 thymidine deletion associated with a varying number of inserted cytosines in the mitochondrial 12S ribosomal RNA gene was identified as a second pathogenic mutation that could predispose to aminoglycoside ototoxicity (63). Molecular analysis excluded the A1555G mutation in this family.

The A1555G mutation in the human mitochondrial 12S RNA, which has been associated with hearing loss after aminoglycoside administration (64) and has been implicated in maternally inherited hearing loss in the