Today's Treatment

Use of antibiotics

Aminoglycosides

PAUL NOONE

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Aminoglycosides are an important group of antibiotics whose basic compounds contain aminosugars. They are produced either by *Streptomyces* spp (streptomycin, kanamycin, tobramycin, and neomycin) or *Micromonospora* spp (the gentamicins and sissomicin), which accounts for the different spellings. Semi-synthetic derivatives have also been produced (for example, amikacin from kanamycin and netilmicin from sissomicin), and further such compounds are under investigation.

Aminoglycosides are not appreciably absorbed from the gut in normal subjects and must be administered by intravenous, intramuscular (or subcutaneous) injection to treat systemic infections, although in patients with impaired renal function prolonged oral administration (as, for example, neomycin in liver failure) may lead to toxic accumulation of the drug in the body.

Aminoglycosides are well absorbed from injection sites usually, from the peritoneal space, or from large wounds and granulating areas if applied topically. They are distributed throughout the extracellular water compartment of the body—achieving concentrations quarter to half of those attained in the serum, in pleural, ascitic, and joint fluids, in bronchial secretions, and in bile. But they pass poorly into the cerebrospinal fluid even when the meninges are inflamed.

The aminoglycosides are excreted by glomerular filtration in an active form. Their antimicrobial effect is enhanced by an alkaline pH. When renal function is impaired, serum and tissue concentrations may readily increase to toxic levels. This necessitates regulating dosage carefully in such patients either by serum assay or nomogram based on the serum creatinine concentration.

Side effects and toxicity

Hypersensitivity developing from systemic or ingested aminoglycosides is extremely rare, but the same is not true if they are applied topically. Allergy to neomycin in various dermatological preparations is being seen increasingly, and there is often cross-allergenicity among aminoglycosides. Hypersensitivity to streptomycin (and thus to other aminoglycosides) is well known in nurses giving regular injections of the agent, as for example, during the treatment of tuberculosis. Care should be taken to avoid aerosol formation with all aminoglycosides.

Royal Free Hospital, London NW3 2QG
PAUL NOONE, BM, MRCPATH, consultant microbiologist

All aminoglycosides may give rise to ototoxicity and nephrotoxicity, the degree of toxicity varying with the compound. Thus neomycin and framycetin are too toxic for systemic use, invariably causing deafness if used in this way. Gentamicin, tobramycin, and sissomicin are usually described as being primarily vestibulotoxic and kanamycin and amikacin as cochleotoxic, but there is often a mixed deficit with high-tone frequency hearing most at risk (and relatively easily checked).

The nephrotoxicity of systemic aminoglycosides is often difficult to assess as the patients receiving the drugs have often already suffered other nephrotoxic insults such as hypotension and endotoxaemia. In short courses (7-10 days) clinically detected nephrotoxicity is uncommon, particularly if doses are monitored carefully by serum assay. But in longer courses, especially in patients with already impaired renal function, there is a small but definite risk, usually shown as a rise in serum creatinine (or urea) concentration, which reverses on withdrawal of the drug. Evidence has accumulated of a high risk (up to 20-25%) of nephrotoxicity (including tubular necrosis) in patients receiving injectable cephalosporins and aminoglycosides. There appears to be a definite nephrotoxic synergy. Such combinations should be avoided wherever possible.

The aminoglycosides are not hepatotoxic or myelotoxic. Their only other potentially toxic side effect is a propensity for potentiating the neuromuscular blocking action of curare-type drugs. This may have clinical importance in patients on mechanical ventilation or with myasthenia gravis.

Antimicrobial activity

Basically the aminoglycosides are active against the Enterobacteriaceae (*Escherichia coli*, klebsiella, enterobacter, proteus), some other Gram-negative species (pseudomonas, neisseria), staphylococci, and *Mycobacterium tuberculosis*. This is a valuable spectrum in terms of species apt to cause serious sepsis in hospital patients. Some species or strains of species of the listed organisms may show natural or acquired resistance to some or all of the aminoglycosides, and more detail is given below.

The aminoglycosides have no useful clinical activity against strict anaerobes (bacteroides, clostridia, fusobacteria, peptostreptococci) nor are they usefully active *alone* against streptococci, although they may show synergy with β-lactam antibiotics. Thus the combination of penicillin G (or ampicillin) and gentamicin has become the treatment of choice for streptococcal endocarditis (especially streptococci less susceptible to penicillins such as *Str faecalis*).

Mode of action

The aminoglycosides act as potent inhibitors of bacterial protein synthesis. The mechanisms concerned have not been

fully elucidated, but they are rapidly bactericidal in most instances. Nevertheless, various bacterial species are killed at different rates. Thus *E coli* may be killed within a few hours, whereas *Ps aeruginosa* takes considerably longer. This has practical importance when dealing with *Ps aeruginosa* infections in patients with neutropenia, when the efficacy of currently available aminoglycosides is appreciably reduced. This is one of the main reasons for using the combination of carbenicillin and aminoglycoside in these patients.

Resistance

When aminoglycoside resistance occurs it is often associated with the production of enzymes that inactivate the antibiotics concerned (table I). The ability to produce these enzymes is usually plasmid-borne and therefore transmissible between bacteria. Aminoglycoside resistance is virtually always linked on such plasmids with resistance to several other (non-aminoglycoside) antibiotics. It is important, therefore, when eradicating or containing hospital infection with, for example, gentamicin-resistant coliforms, *Ps aeruginosa* or *Staph aureus*, not only to restrict gentamicin usage but also the usage of other antibiotics (ampicillin, co-trimoxazole, cephalosporins, tetracycline), resistance to which may also be transferred by the plasmid concerned. The use of any agent represented on the plasmid selects for resistance to all the agents concerned.

TABLE I—*Aminoglycoside-inactivating enzymes in resistant bacteria*

Inactivating process	Enzyme	Antibiotic-substrates
Acetylation	AAC (2′)	Neomycin, kanamycin B, dibekacin, gentamicin, sissomicin, tobramycin
	AAC (3′)	Gentamicin, sissomicin
	AAC (3″)	Neomycin, kanamycin, dibekacin, gentamicin, sissomicin, tobramycin
	AAC (6′)	Kanamycin, neomycin, dibekacin, amikacin, tobramycin, gentamicin C1a (*not* gentamicin C1), sissomicin
Adenylylation	AAD (2″)	Gentamicin, sissomicin, tobramycin, kanamycin, dibekacin
	AAD (4′)	Kanamycin A, amikacin, tobramycin
Phosphorylation	APH (2″)	Gentamicin
	APH (3′)	Kanamycin, neomycin
	APH (3″)	Streptomycin, neomycin, kanamycin

In the clinical microbiology laboratory this varied pattern of substrates means that aminoglycoside resistant coliforms, pseudomonas, etc, should be routinely tested for sensitivity to all other available systemic aminoglycosides. Assumptions cannot be made on the basis of testing only one aminoglycoside.

A more sinister form of resistance is that attributable to permeability factors, where aminoglycosides fail to penetrate the bacterial cell and so fail to act. This kind of resistance tends to operate against all aminoglycosides and poses grave problems for treating life-threatening infections in hospital practice.

Interaction with other antibiotics

The most important chemical interaction seen clinically at present is that between gentamicin and carbenicillin, though similar reactions are seen between aminoglycosides generally and several β-lactam antibiotics.

Although gentamicin and carbenicillin often show antimicrobial synergy against Gram-negative rods, chemical inactivation has been shown both in vitro and in vivo. The molecular binding of the drugs leads to loss of antimicrobial activity. High concentrations of ampicillin show a similar effect.

The in-vitro inactivation in infusion fluids at room temperature is more pronounced than the in-vivo inactivation in plasma at body temperature. The former becomes apparent in as little as half an hour. It is therefore essential to avoid mixing carbenicillin and aminoglycosides in infusion fluids or syringes: the aminoglycosides should be given either as intramuscular or bolus intravenous injections independently of the carbenicillin infusion.

The inactivation that occurs in serum at body temperature in vivo is much less rapid, only 15% loss of gentamicin antimicrobial activity being seen in eight hours, but half the activity is lost after 36 hours. This therefore has little relevance to patients with normal renal function, although it does have clinical significance in those undergoing dialysis or with poor renal function when widely spaced doses of aminoglycoside are given. If carbenicillin treatment is stopped and the aminoglycoside continued the serum concentrations of the latter may suddenly rise with toxic effects. On the other hand, addition of carbenicillin to aminoglycoside treatment can cause a fall in serum concentrations of the latter to subtherapeutic values, necessitating an increase in dosage. In any event, daily monitoring of serum concentrations are advisable in such patients.

There has also been a report that clindamycin, lincomycin, and chloramphenicol interfere with the early killing activity of aminoglycosides against coliforms and *Ps aeruginosa*. This finding by reliable workers[1] has never been followed up on a large scale, but it suggests that it is prudent not to give clindamycin (or the others) with gentamicin unless there is a strong indication for such combined treatment—for instance, strong clinical suspicion of anaerobes being present in a severe infection (see below). Certainly it is not a combination to use casually. It has also been suggested that gentamicin potentiates the production of pseudomembranous colitis by clindamycin (and lincomycin), which adds force to the point.[2]

There seems to be an interaction between flucytosine, the anti-yeast agent, and gentamicin (and perhaps other aminoglycosides). When these two agents are used simultaneously in patients with impaired renal function, the serum concentrations of both may show a pronounced increase, which may have toxic implications. The reason for this is not fully understood but, since the serum creatinine concentrations may be normal, it does not appear to be associated with a nephrotoxic effect.

As mentioned above, injected cephalosporins (cephaloridine, cephalothin, and probably cephazolin) have their nephrotoxicity greatly enhanced by simultaneously administered aminoglycosides. This combination should be avoided wherever possible.

Individual drugs

STREPTOMYCIN

Streptomycin is active against many coliforms, *H influenzae*, and *Staph aureus*, although resistance in the latter organism readily occurs. Resistance to streptomycin among coliforms is more common than resistance to kanamycin or gentamicin. Streptomycin has no useful activity against *Ps aeruginosa*, but it is seldom used nowadays except for antituberculosis treatment in combination with two other drugs such as rifampicin, isoniazid, and ethambutol. Streptomycin should be avoided in the elderly and patients with impaired renal function because of the risk of ototoxicity.

KANAMYCIN, NEOMYCIN, AND FRAMYCETIN

Kanamycin, neomycin, and framycetin have a similar antimicrobial spectrum, but neomycin and framycetin are too toxic for systemic use and are restricted to gastrointestinal and topical application. All three drugs have a wider and more reliable anticoliform and antistaphylococcal spectrum than streptomycin, but the widespread use of oral neomycin has stimulated the development of resistant *Staph aureus* and coliforms in many hospitals. Kanamycin is not clinically useful against *Ps aeruginosa*. In some hospitals kanamycin is still used as a first choice for treating suspected septicaemia, but gentamicin has tended to replace it over the past decade.

Kanamycin is still used to treat gonorrhoea when given as a single intramuscular injection on an outpatient basis. It is

especially useful when penicillin-resistant strains of *N gonorrhoeae* are suspected, although spectinomycin is replacing it.

Kanamycin is occasionally used to treat streptomycin-resistant *M tuberculosis*. Its main drawbacks are ototoxicity and nephrotoxicity, but monitoring of serum concentrations can minimise these problems (table II).

Neomycin and framycetin are useful when taken as "non-absorbable" oral agents designed to "disinfect" the gut—which is invaluable in treating severe liver failure or in the prophylactic treatment of neutropenic patients (< 200 neutrophils/mm^3)—when they are usually combined with colistin and amphotericin (or nystatin) to broaden the antimicrobial spectrum against *Ps aeruginosa* and fungi while the patient is nursed in reverse-barrier isolation and given sterile food and drink.

The topical application of neomycin and framycetin to wounds, bedsores, and other skin lesions is usually of little value and as much if not more could be achieved by proper nursing attention, for example, desloughing and cleaning bed sores, and the use of antiseptics such as eusol, povidone-iodine, or chlorhexidine. The topical use of aminoglycosides does much to promote the proliferation of resistant bacteria.

TABLE II—*Suitable peak and trough concentrations for several drugs*

Antibiotic	Dosage	Desirable peak serum concentrations	Acceptable trough serum concentrations
Gentamicin and tobramycin	Adult: 1·6 mg/kg/dose (8-hourly) Child: 2·0 mg/kg/dose (8-hourly) Neonate: 3·0 mg/kg/dose (12-hourly)	5–12 μg/ml (For pneumonia ⩾8 μg/ml)	<3·0 μg/ml
Amikacin and kanamycin	Adult: 7·5 mg/kg (12-hourly) or 5·0 mg/kg (8-hourly)	20–30 μg/ml	8·0 μg/ml or less
Sissomicin	Adult: 1·0 mg/kg/dose (8-hourly)	4–10 μg/ml	2·0 μg/ml or less
Streptomycin	Adult: 0·5 g-1·0 g daily or 12-hourly	20–40 μg/ml	8·0 μg/ml or less

GENTAMICIN

Gentamicin has a generally broader antimicrobial spectrum than kanamycin, including most strains of *Ps aeruginosa*, coliforms, and *Staph aureus*. This has made it first choice for treating life-threatening infections such as septicaemia, pyelonephritis, cholangitis, hospital-acquired pneumonia, peritonitis, all serious postoperative sepsis, neonatal sepsis, and sepsis in the debilitated host. Treatment in such cases should be started after specimens for microbiological examination have been taken (including blood cultures) but before the culture and sensitivity results are available. It is the combination of a wide spectrum against most of the major hospital pathogens and a potent, rapid, cidal activity that make the drug so useful.

Other antibiotics may be combined with gentamicin when mixed infection is suspected. Thus if anaerobes may be present (for instance, sepsis from a gastrointestinal tract or female genital tract source) then metronidazole or clindamycin should be added; and if streptococci may be present (pneumonia neonates, patients with severe hepatocellular disease) then benzylpenicillin should be added.

Gentamicin when given in a carefully controlled manner causes few problems with toxicity, the main risks being ototoxicity (often vestibular damage) and nephrotoxicity (enhanced by concurrent cephalosporin administration).

TOBRAMYCIN

Tobramycin has a very similar antibacterial spectrum to gentamicin. In vitro it appears to be more active than gentamicin against *Ps aeruginosa*, but there is no clinical evidence to suggest that it is better in vivo. Most strains of coliform or *Ps aeruginosa* resistant to gentamicin will also be resistant to tobramycin.

Much pressure has been built up suggesting that tobramycin is less nephrotoxic than gentamicin and should be preferred for general use. This is largely based on the results of animal studies but there are pronounced interspecies differences in susceptibility to aminoglycosides, and this work has to be interpreted with reservations. Double-blind trials in man[3] have not shown statistically significant differences between gentamicin and tobramycin (or between gentamicin and amikacin) in terms of nephrotoxicity. At present there seems no convincing reason for replacing gentamicin by tobramycin for general use. It is better to use the drug we have had most experience with.

AMIKACIN

Amikacin is a semisynthetic aminoglycoside derived from kanamycin. A side chain renders it less susceptible to the major enzymes concerned in the inactivation of aminoglycosides, which constitute the basis of much of the resistance found in resistant strains of coliform and *Ps aeruginosa*. Although currently, in overall terms, such resistant strains are a small minority, nevertheless the resistance problem exists and is apt to get worse whenever the twin sins of antibiotic abuse and lack of control of hospital infection occur. Amikacin has at the moment the widest antibacterial spectrum of any aminoglycoside, although curiously it is less active against many strains of *N gonorrhoeae* than kanamycin or gentamicin. Its nephrotoxicity and ototoxicity (primarily deafness) are similar to that of gentamicin when the drugs are given in equivalent clinical dosage (that is, about three times as much amikacin as gentamicin). But amikacin is still much more expensive than gentamicin, and apart from this it is probably wise to reserve it for major sepsis caused by gentamicin-resistant coliforms and *Ps aeruginosa* or where such sepsis is strongly suspected. This is likely to be a local problem in Britain—in particular hospitals or particular units. When the chance of septicaemia being caused by gentamicin-resistant coliforms or Pseudomonas is seriously reckoned as 1 in 10 or less then amikacin should certainly be the first-choice drug. Otherwise gentamicin is still first choice. Such decisions obviously necessitate close collaboration between clinicians and clinical microbiologists.

DIBEKACIN

Dibekacin is another kanamycin derivative apparently widely used in Japan. Its antibacterial spectrum is similar to that of gentamicin (that is, it includes *Ps aeruginosa*). It is not available in the UK. Some reports suggest that it is significantly more nephrotoxic and ototoxic than currently available aminoglycosides.

PAROMOMYCIN

Paromomycin has a similar spectrum to kanamycin and neomycin, that is, it is *not* active against *Ps aeruginosa*. It is not used systemically in Britain but is marketed for this purpose on the Continent (especially Italy) and in the Middle East. It has similar toxicity to kanamycin apparently. At one time it was advocated for the treatment of amoebiasis but has been superseded by metronidazole.

SISSOMICIN

Sissomicin is structurally related to gentamicin and has a similar antibacterial spectrum with some greater activity against *Ps aeruginosa*. Strains resistant to gentamicin tend to be resistant to sissomicin too. Its toxicity is similar. Mouse protection tests

suggest that it is somewhat more active in vivo than either gentamicin or tobramycin. My limited experience suggests that it may be useful in treating refractory infections such as *Ps aeruginosa* pneumonia. It may soon become commercially available in Britain.

NETILMICIN

Netilmicin (N-ethyl sissomicin) is a semisynthetic derivative of sissomicin, which is apparently much less ototoxic than gentamicin or the other aminoglycosides. There is conflicting evidence as yet about nephrotoxicity. It has a similar spectrum to sissomicin (although weight for weight less active against *Ps aeruginosa*) with the important exception that it is resistant to some of the resistance enzymes. Its spectrum against resistant strains is not as wide as that of amikacin but is wider than gentamicin, sissomicin, or tobramycin. It will be undergoing clinical trials in Britain soon.

(*To be concluded next week*)

References

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Medical History

History of medicine in Gibraltar*

C MONTEGRIFFO

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Centuries before the birth of Christ Gibraltar was designated by Phoenician and Greek mariners as Calpe, the northern tier of the Pillars of Hercules. This was the end of the civilised world and beyond it lay the dread unknown. There is no evidence of any Phoenician or Roman settlements on the Rock itself, but archaeological discoveries along the coast on both sides of the straits show that the region was extensively colonised and settled before the Christian era. The Romans, with their strategic military sense, almost certainly established a presence in Gibraltar, and St Michael's Cave is known to have been discovered by Roman legionnaires. The history of medicine in Gibraltar therefore probably began with a military flavour, the first to practise the arts of Apollo and Asculapus being the medical ancillaries of the legions.

With the fall of Rome and the rise of Visigothic kingdoms in Spain the history of Gibraltar (as indeed that of most of Europe) is clouded over and confused, but shortly after AD 700 Tariq, a Moorish chieftain, began the conquest of the Iberian Peninsula and brought the region back into the mainstream of European history and enlightenment. Tariq himself crossed over into Spain through Gibraltar and since then the Rock has borne the name of its conqueror—Gebel Tariq or the Rock of Tariq, now anglicised to Gibraltar.

Little is known of the Moorish settlement of Gibraltar but in the 13th Century the Moorish Castle was built—indeed, the Tower of Homage still dominates the town. Some sort of court was established here and a fairly advanced medical presence may be assumed to have existed. Further down in the town public baths were built at a time when washing was not a practice honoured in Europe generally.

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KGV Psychiatric Unit, Gibraltar
C MONTEGRIFFO, MB, BS, medical superintendent

Spanish period

The history of the city of Gibraltar proper begins, however, with the final Spanish reconquest of the Rock in 1462. Only since this date is there continuous documentation of any historical validity. An urban community soon established itself, and in 1502 Queen Isabella the Catholic formally incorporated Gibraltar into the territories of the Spanish Crown and granted the town its coat of arms—much the same one that it boasts today, with the key and castle as the predominant symbols. With the growth of the city the usual trappings of a civilian community began to appear: churches, markets, and the first rudimentary hospital. The hospital was the creation of probably the most colourful medical personality ever to inhabit these shores—Juan Mateos. In his youth Mateos was active in defending Gibraltar against Algerian pirates and became famous in resisting one of their landings, killing the pirate leader. Possibly capitalising on his fame he became a merchant and amassed a considerable amount of money. Later he became the official "Dispenser of Royal Licences"—a position that must have afforded him many opportunities to make more. Yet in 1567 Mateos seems to have undergone a sudden change of heart, having been particularly affected by the sorry sight of the many sick seamen left stranded in Gibraltar after voyages to the New World as well as by the plight of the poor sick of the town. He turned his large town house into an infirmary, keeping only a small cell for himself. He lived frugally, ate badly, and wore only sackcloth: his considerable fortune he put to charitable work in running the hospital, and when all his money was gone he spent the mornings begging and collecting alms with which to keep the hospital going. Records show that a disproportionate number of the patients treated, particularly sailors, suffered from a virulent form of syphilis brought over from the New World.