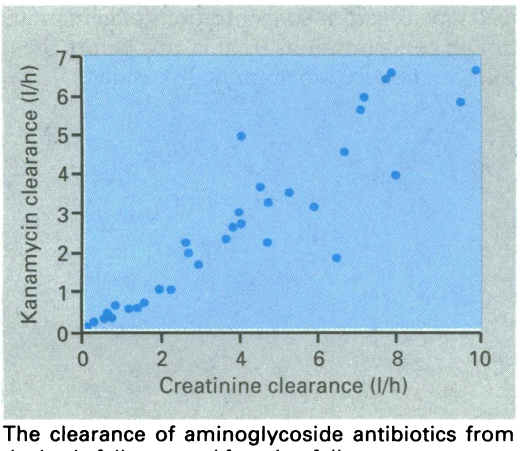
AMINOGLYCOSIDE ANTIBIOTICS

J K Aronson, D J M Reynolds

Aminoglycoside antibiotics (including amikacin, gentamicin, kanamycin, tobramycin, and netilmicin) are used in the treatment of serious systemic infections such as infective endocarditis and Gram negative septicaemia



The clearance of aminoglycoside antibiotics from the body falls as renal function falls.

Monitoring the serum concentrations of aminoglycoside antibiotics is an important part of treatment as their toxic:therapeutic ratio is very low. In addition, the pharmacokinetics of aminoglycosides vary considerably from person to person, making accurate prediction of initial dosage difficult. The sources of this variation are differences in renal function and tissue distribution.

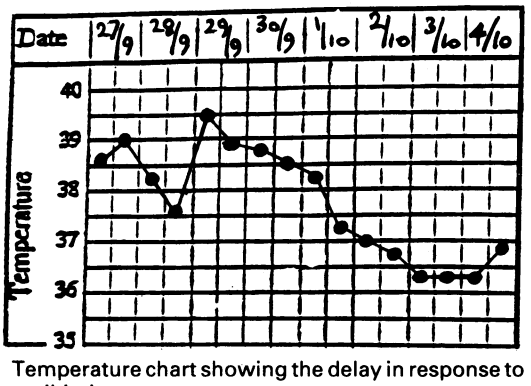
The aminoglycosides are almost completely cleared unchanged from the body by renal excretion; clearance is therefore subject to variation when renal function varies. This is important for two reasons. Firstly, renal function is often impaired in patients with severe sepsis, in whom aminoglycosides are often indicated; furthermore, as the infection resolves improvement in renal function may further alter the pharmacokinetics of the antibiotic. Secondly, the aminoglycosides are themselves nephrotoxic and may therefore impair their own disposition. If this happens a vicious cycle of renal impairment with worsening toxicity may arise. Although the renal toxicity is usually reversible, accumulation of the aminoglycoside may lead to ototoxicity, which may be irreversible.

The distribution of the aminoglycosides to the tissues varies among patients because of a wide range of factors, including age, fever, body weight, anaemia, drug interactions, and overall severity of illness.

The variations in the clearance and apparent volume of distribution of gentamicin result in variation in its initial half life from 0·4 h to 7·6 h in patients with normal renal function.

In this article we apply to aminoglycosides the criteria which must be fulfilled in part or in full before the measurement of their plasma concentrations can be considered worth while.

Criteria for measurement



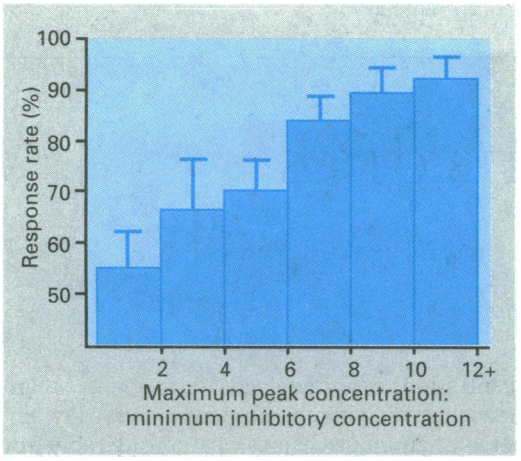
Temperature chart showing the delay in response to antibiotics.

Is there difficulty in interpreting clinical evidence of the therapeutic or toxic effects?

Therapeutic responses to aminoglycosides may take several days to become clinically apparent. It is therefore important during the early phases of treatment to know that you are giving a dose which is likely to have an eventual therapeutic effect. To do this you need to measure the serum concentration, as there is a poor relation between dose and serum concentration but a good relation between serum concentration and the therapeutic effect. Furthermore, even when a therapeutic response starts to occur it can be difficult to know whether it is optimal. Again, measurement of the concentration will help.

As far as renal toxicity is concerned, it is impossible to distinguish clinically between renal impairment secondary to the illness and that secondary to a toxic effect of the aminoglycosides. However, diagnosing the cause of renal impairment is a secondary consideration, and measurement of the serum aminoglycoside concentration is used to prevent toxicity rather than to diagnose drug induced renal toxicity.

As we describe below, the problem of ototoxicity is more complicated.



The higher the serum gentamicin concentration in relation to the in vitro minimum inhibitory concentration (MIC), the greater the therapeutic effect.

Minimum peak concentrations for a therapeutic response

Gentamicin, tobramycin, netilmicin	5 μg/ml
Amikacin, kanamycin	20 μg/ml

Maximum peak concentrations to avoid toxicity

Gentamicin, tobramycin, netilmicin	10 μg/ml
Amikacin, kanamycin	30 μg/ml

Maximum trough concentrations to avoid toxixity

Gentamicin, tobramycin, netilmicin	2 μg/ml
Amikacin, kanamycin	10 μg/ml

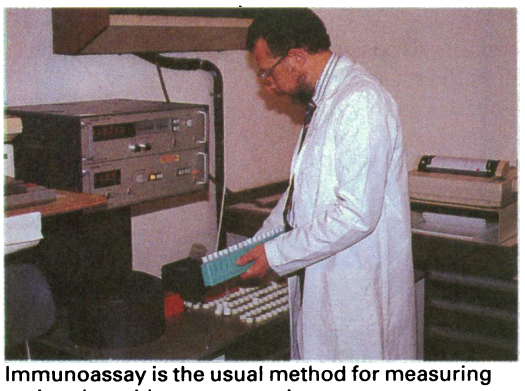
Is there a good relation between the serum concentration and therapeutic or toxic effects?

The therapeutic effect of an antibacterial drug conventionally is assessed by measuring the minimum inhibitory concentration of the drug for the infective organism in vitro. The effective serum concentration is then considered to be achieved when it is higher than the in vitro minimum inhibitory concentration. However, this does not guarantee that an effective tissue concentration will be achieved, since penetration of the drug to the affected tissue will vary among patients and with the infection. This may be affected by factors such as tissue blood flow and host defence mechanisms, including numbers and function of white cells.

Because of these difficulties, recommended target serum concentrations for a therapeutic effect have been based on the results of clinical studies, which have shown that a serum concentration of gentamicin of 5 μg/ml or more 15 minutes after the end of an intravenous infusion or 1 hour after an intramuscular injection should be achieved. The corresponding values for other aminoglycosides are given in the box. Factors that can alter this concentration are discussed below.

There is some debate about the relation between serum concentrations of aminoglycosides and their nephrotoxic and ototoxic effects (see below). For practical purposes, however, it is generally accepted that the risks of adverse effects will be reduced if peak serum concentrations of gentamicin are below 10 μg/ml and if trough concentrations (that is, just before the next dose) are below 2 μg/ml. (See box for other aminoglycosides.)

Measurement techniques



Immunoassay is the usual method for measuring aminoglycosides concentrations.

As heparin may interfere with measurement of aminoglycoside concentration serum samples should be used.

Although the serum concentrations of aminoglycosides can be measured by using their ability to inhibit the growth of bacteria in vitro, bioassays of this kind take too long to be of maximum practical value. For this reason it is now customary to use immunoassay. It is also possible to use high performance liquid chromatography, but this is generally reserved for research purposes.

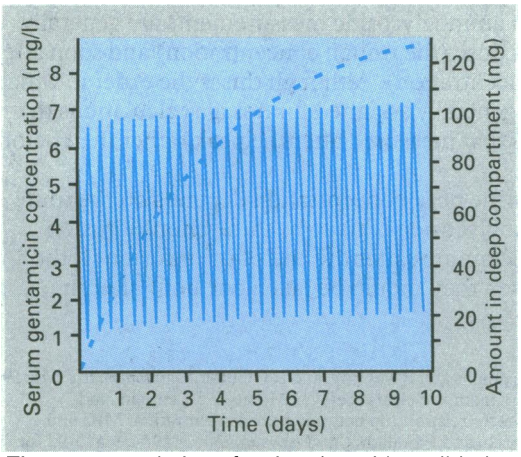
Factors affecting the serum concentration

The main factor that affects serum aminoglycoside concentrations at a given dose is renal impairment. For this reason extra care should be taken in elderly patients.

Since the aminoglycosides are excreted almost exclusively by the kidneys renal function is the main factor affecting serum glycoside concentrations. Dosages of gentamicin should therefore be reduced in patients with renal impairment, using the serum concentration as a guide. Since elderly people may have impaired renal function, age is also an important factor.

There have been reports that frusemide may increase plasma gentamicin concentrations by impairing its renal excretion. However, the interaction of the drugs is complicated by the fact that both frusemide and the aminoglycosides have direct ototoxic effects. This combination is therefore better avoided, and if a loop diuretic is required in a patient also receiving an aminoglycoside then bumetanide, which is less ototoxic than frusemide, is to be preferred.

Factors affecting interpretation



Tissue accumulation of aminoglycoside antibiotics increases during repeated administration over several weeks, even though the serum concentrations do not increase during that time.

The relation between the serum aminoglycoside concentration and its toxic effects changes with duration of treatment. This is because as treatment proceeds aminoglycosides tend to accumulate in the tissues without there being at the same time a comparable increase in the peak and trough serum concentrations. This means that a serum concentration that was not associated with toxic effects during the first few days of treatment can be associated with toxic effects during longer term treatment. The risk of toxicity begins to increase after about a week of continuous treatment.

The most important consequence of this change in the relation between serum and tissue concentrations is that with increasing duration of treatment there is an increased risk of ototoxicity and nephrotoxicity. Special care should therefore be taken in any patient in whom treatment may need to be continued for more than one to two weeks. Important indications for this category include infections due to Gram negative organisms such as *Streptococcus faecalis*, causing infective endocarditis; osteomyelitis; and infections of vascular grafts. In these patients it is wise, if possible, to determine baseline auditory and vestibular function before treatment and to reassess after one week and then at weekly intervals. It may also be advisable to use netilmicin, which is thought to be less ototoxic than other aminoglycosides.

Use of serum measurements

Case history: high peak/acceptable trough

A 55 year old man with a serum creatinine concentration of 110 μmol/l was given gentamicin and benzylpenicillin for infective endocarditis due to *Streptococcus viridans*. After a loading dose of 120 mg and two maintenance doses of 80 mg at eight hourly intervals his peak gentamicin concentration was 18 μg/ml and his trough concentration 1·2 μg/ml. The dosing interval in this case was thus equal to about four half lives (18-9, 9-4·5, 4·5-2·25, and 2·25-1·125 μg/ml). The maintenance dose was halved to 40 mg, and the peak concentration fell to 9 μg/ml. The dosage interval was reduced by 25% to six hours (three half lives), and this achieved approximately the same trough concentration as before.

Conclusion

Appropriate treatment was achieved by reducing the total daily dose from 240 mg to 160 mg and by using a different dosage interval.

Patients with normal renal function usually start treatment with a loading dose (say 120 mg intravenously or intramuscularly) and then continue with a maintenance dosage of about 80 mg three times a day in the first instance. After 24 hours take two blood samples, one just before giving the next dose to measure the trough concentration, and the other soon after the next dose to measure the peak concentration. Blood samples should not be taken through lines through which the drug has been given.

Subsequent dosages should be based on both the peak and trough concentrations. Note that a dosage adjustment aimed at altering the peak concentration will also alter the trough concentration and it is therefore often necessary to alter both the total dose given and the frequency of administration.

Case history: ototoxicity during long term treatment

A 60 year old man with mild mitral regurgitation developed an influenza-like illness, and *Streptococcus faecalis* was grown from his blood. He was given ampicillin and gentamicin intravenously. The loading dose of gentamicin was 120 mg and the maintenance dose 80 mg eight hourly. His peak and trough serum concentrations during steady state treatment were always satisfactory. After two weeks his mitral regurgitation was worse so gentamicin was given for a further three weeks. His peak and trough concentrations continued to be acceptable. At the end of this time his mitral regurgitation had improved and gentamicin was stopped. However, he was unsteady on his feet, and formal testing showed impaired auditory and vestibular function. Although some of this impairment reversed, he was left with a slight residual disability.

Conclusion

This case illustrates that adverse effects of the aminoglycosides can occur during long term treatment despite satisfactory serum concentrations throughout the period of treatment.

Case history: high peak/high trough

A 78 year old woman with a serum creatinine concentration of 160 μmol/l was admitted with septicaemia caused by *Escherichia coli* secondary to a urinary tract infection. She was given ampicillin and gentamicin intravenously. Because of her increased creatinine concentration the initial loading dose of gentamicin was 80 mg, and this was followed by maintenance doses of 60 mg at intervals of eight hours. Despite this reduction in dosage her peak serum gentamicin concentration two days later was 16 μg/ml and the trough concentration was 8 μg/ml. The dosing interval in this case was thus equal to one half-life (16-8 μg/ml). The next dose was therefore delayed until the serum concentration had fallen to 2 μg/ml (that is, two half lives or 16 hours). At this stage 2/16 of the original body load was still present.

Conclusion

The target concentration of 8 μg/ml was achieved by giving about 6/16 of the original maintenance dose (that is, 25 mg). The subsequent dosage interval was 16 hours (two half lives), and this achieved approximately the same trough concentration of 2 μg/ml.

Timing of measurements

Timing of measurements

Intravenous administration

- Peak—15 mins after the end of the infusion
- Trough—just before the next dose

Intramuscular administration

- Peak—1 hour after the dose
- Trough—just before the next dose

Blood samples for serum aminoglycoside measurements are generally taken immediately before a dose (the trough concentration) and soon after the next dose (the peak concentration). Although this is the order in which the samples are taken, it is generally assumed for dosage calculations that the trough concentration is that measured after the peak rather than before it.

The time of sampling for the peak concentration depends on the route of administration. If the aminoglycoside is given by intravenous infusion samples should be taken 15 minutes after the end of the infusion. If the intramuscular route is chosen they should be taken one hour after the injection.

The sources of data presented in the graphs are: B M Orme and R E Cutler, *Clin Pharmacol Ther* 1969; 10:543-50 for creatinine clearance *v* kanamycin clearance; R D Moore, P S Lietman, and C R Smith, *J Infect Dis* 1987;155:93-9 for relationship between peak concentration: MIC and rate of response; and M Wenk, S Vozeh, and F Follath, *Clin Pharmacokinetics* 1984; 9:475-92 for tissue accumulation of aminoglycosides. The data are reproduced with permission of the journals.

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Monoclonal Antibodies in Medicine

Principles of antibody therapy

Stephen J Russell, Meirion B Llewelyn, Robert E Hawkins

This is the third of three articles examining the development and clinical application of monoclonal antibodies

The success of monoclonal antibodies in clinical practice is dependent on good design. Finding a suitable target is the most important part as other properties of the antibody can be altered by genetic engineering. Antibodies that target lymphocyte antigens offer less toxic immunosuppressive treatment than currently available drugs and the first monoclonal antibody approved for human use is an immunosuppressive agent for treating rejection of renal transplants. Human trials of monoclonal antibodies to treat septic shock have been done and antibodies are also being developed to target common pathogens such as herpes simplex virus. Although monoclonal antibodies against cancer have been much heralded, their success has been limited by the poor access to the inside of tumours. Treatment of blood cancers has been more successful and a human antibody against B cell malignancies is being clinically tested. As knowledge about natural immune responses and antibody engineering increases many more monoclonals are likely to feature in clinical practice.

The 1990s will be a testing time for monoclonal antibodies. Potential clinical applications include the treatment of cancer, autoimmune disease, transplant rejection, viral infection, and toxic shock. The Centre for Exploitation of Science and Technology has estimated that the total world market for monoclonal antibodies will reach $1000 million by 1994, rising to $6000 million by the year 2000.[1] It remains to be seen whether the clinical promise of monoclonal antibodies will be realised on such a grand scale, but antibody therapy is likely to be much in evidence in many clinical settings over the next few years. Clinicians will therefore need to familiarise themselves with some of the issues relating to use of clinical antibodies.

As described in the previous article in this series, monoclonal antibodies can be generated against most target antigens, purified, split into fragments, and conjugated to radionuclides, toxins, enzymes, or drugs.[2] The genes can be cloned and reconstructed to give new versions of the antibody with decreased immunogenicity, improved affinity, reduced size, or novel effector domains. For a given clinical application the first task is to choose an appropriate target antigen and then to optimise the therapeutic antibody generated against the chosen target.

Rather than catalogue every antibody with clinical potential or every disease that has responded to monoclonal antibodies, the aim of this review is to underline the principles governing antibody therapy and to illustrate these with specific examples.

Target antigens

Antibodies can neutralise toxins; block the interaction of growth factors, hormones, intercellular adhesion molecules, or viruses with their cognate cellular receptors; and coat bacteria, viruses, or cells, marking them for phagocytosis, antibody dependent cellular cytotoxicity, or complement mediated lysis.

Target antigens can therefore be circulating or on the cell surface. Selecting a suitable target for a given disease depends not only on the aims of treatment but on the precise tissue distribution of the target antigen, its function, and its fate after it has complexed with the therapeutic monoclonal antibody. Finding a suitable target antigen is probably the most important factor determining the ultimate success or failure of antibody therapy. Provided the target has been well chosen it may be possible to modify the corresponding monoclonal antibody in various ways to enhance its therapeutic potential.

Pharmacokinetics

Infused antibodies are diluted almost immediately in the total plasma volume and then diffuse more slowly

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BMJ 1992;305:1424-9