Choice of an aminoglycoside

The dispute about preference of one aminoglycoside over another in clinical therapy, has mainly been focused on differences in toxicity. On the basis of well designed animal experiments (Brummett et al., 1972; DeRosa et al., 1974; Igarashi, Levy & Jerger, 1978) the conclusion might be drawn that tobramycin should be preferred over gentamicin and possibly netilmicin over tobramycin, because of less ototoxicity and/or nephrotoxicity. In man on the other hand, there is only slight indication that tobramycin is less ototoxic (Fee, Vierra & Lathrop, 1978) and less nephrotoxic (Kahlmeter, Hallberg & Kamme, 1978) than gentamicin; in clinical trials like the one of Klastersky, Hensgens, Henri & Daneau (1974) these differences were not evident. The discussion on the subject in this journal (Marsh, 1978; Noone, 1978) is ample proof of differences in viewpoints regarding the relevance of these data for clinical therapy.

Without underrating the importance of potential toxicity in the choice of an aminoglycoside, one wonders whether other criteria are not under-valued. It is often stated that only clinical data can indicate which antibiotic is the more potent and less hazardous. Fundamentally correct as this may be, the present avalanche of new antibacterial agents with only small differences within their group (e.g. aminoglycosides, cephalosporins) makes it almost impossible to obtain reliable clinical data which indicate the superiority of one antibiotic over its fellow drug. It is not suggested that we should not search any more for this kind of evidence, but that for clinical practice the other factors, such as pharmacokinetic behaviour, intrinsic activity, spectrum and especially risks of development of resistance and inactivation should have more attention.

The pharmacokinetics of these drugs do not show essential differences (Jackson, 1977) taking into account the higher dosage and blood levels of kanamycin (K) and amikacin (A) as compared to gentamicin (G), tobramycin (T), netilmicin (N) and sissomicin (S). In vitro activity against separate species of Gram-negative bacilli has been well documented by many investigators and can be narrowed down to essentially the following order: E. coli, G, N, S > A, T > K; Klebiella sp., N > S > A, G, T > K; Enterobacter sp., G > N, S > A, T > K; Serratia sp., G > A, N, S > T > K; Providencia sp., A, K > G > N, T; Proteus sp. indole+, S > G, N > T > A, K; Proteus mirabilis, S > G, N, T > A > K; Pseudomonas aeruginosa, S, T > G > A, N.

For the individual patient the choice must depend on the organism causing the infection and its sensitivity pattern, or if this is not known, on the local situation regarding the occurrence of resistant strains. One approach could be to aim at prescribing the most active drug by following the general trend of sensitivities of species as given above, allowing for higher dosage and blood levels of kanamycin and amikacin.

As is true for some other antibiotics the preference for an aminoglycoside should also be guided by a policy aiming at the preservation of favourable antibiotic sensitivity patterns in the hospital population. Although we do not know all the factors which are related to the emergence of resistance, particularly by R-factors and their in vivo transfer (see Jackson, 1979), we do know that the resistance rate of an antibiotic in a hospital is usually related to the consumption of that antibiotic. This has also been confirmed for kanamycin (Starkey & Gregory, 1971; Mouton, Glerum & Van Loenen, 1976) and gentamicin (Christol et al., 1971; Holder, 1976). However, cross resistance between two or more aminoglycosides is frequent and seemingly thwarts a policy aiming at low resistance rates by restricted use of the newer drugs. Although this complicates matters, data on cross-resistance are now available which make it possible to apply our knowledge of the above relationship to formulating an outline of aminoglycoside policy. These data are simplified in the following. Cross-resistance between kanamycin and gentamicin is caused by R-factors with genes for one of the acetylating or adenylating enzymes (Le Goffic, Martel & Witchitz, 1974; Shannon, Phillips & King, 1978). However, since kanamycin resistance is mostly present without gentamicin resistance (though varying between hospitals) it seems probable that phosphorylating enzymes which do not inactivate gentamicin are more often the cause of kanamycin resistance. Low resistance rates of gentamicin in the presence of high rates of resistance to kanamycin, due to frequent use, are common in the Netherlands and form an argument for this assumption. Although cross resistance between gentamicin and tobramycin is not complete (Crowe & Sanders, 1972; Shannon et al., 1978), most strains of Enterobacteriaceae and Pseudo-
monas do show a combined resistance (Burger, Sanford & Zweighaft, 1973). Cross resistance between gentamicin and sissomicin seems to be almost complete if we allow for small differences in activity (Grimm, 1976; Shannon et al., 1978). Netilmicin resistance has been found where this drug had not yet been used (Mouton & De Kok-Broeren, 1977). An explanation for this resistance can be found in the presence of one of the acetylating enzymes (AAC(2'), AAC(6')-I and AAC(3)-II) which inactivate sissomicin, gentamicin and tobramycin and may inactivate netilmicin, or in chromosomal cross-resistance. Seligman (1978) found 28 (44%) of 66 gentamicin resistant strains of Gram-negative bacilli (including 9 of 10 Pseudomonas strains) to be also resistant to netilmicin. Thus, cross resistance as well as dissociated resistance between gentamicin and netilmicin occur. Low rates of amikacin resistance correlate with low occurrence rates of AAC(6') and APH(3')-III which inactivate amikacin (Price, Defuria & Pursiano, 1976; Shannon et al., 1978).

For the older drugs these data seem to allow the conclusion that the selection of strains with transferable resistance against the specific aminoglycosides (and possible of chromosomal mutants) tends to be related to the use of the drugs, with the annotation that sissomicin and usually also tobramycin belong to the category of gentamicin. For netilmicin this conclusion is not valid. For amikacin we probably may expect the same tendency to a correlation between consumption and resistance rates.

Which conclusions with regard to the choice of an aminoglycoside may be drawn from these data? Evidently we want to combine optimum therapy for the individual patient with a policy aiming at low resistance rates. Past experience has taught us that resistance to gentamicin may be avoided by using kanamycin where possible, firstly in cases of proven sensitivity, secondly in cases of blind therapy in areas or hospitals where kanamycin resistance is not common and Pseudomonas infection improbable. The second situation is rare though nowadays, but if these conditions do not exist why not use gentamicin and tobramycin on the basis of greater activity for individual species i.e. gentamicin for most of the Enterobacteriaceae and tobramycin for Pseudomonas aeruginosa? If sissomicin is available this might be fitted in in the same way, while netilmicin, if available, could be reserved for strains with the KTG resistance pattern.

Reserving amikacin for special cases with the KTG(N) resistance pattern may avoid high rates of resistance to this drug.

Whichever choice is finally made regular monitoring of the blood level, creatinine tests and if possible, audiograms should be done and so help keep the risk of toxic side effects to a minimum (Nooene et al., 1978). Naturally the above reasoning should not distract us from consideration regarding the appropriateness of aminoglycoside therapy.

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References


Hospital infection by multi-resistant Gram-negative bacilli

Outbreaks of hospital infection by Gram-negative bacilli, resistant to gentamicin and many other antimicrobials, have become familiar occurrences. Foci of infection by resistant Klebsiella species are widespread in the British Isles (Casewell et al., 1977; Curie et al., 1978), and there are reports of Serratia sp (Meers, Foster & Churcher, 1978) and Enterobacter sp (E. G. Dowsett, personal communication, 1979). These outbreaks share a number of features, such as the dominance of urinary infection (especially in catheterized males) and of intensive therapy units, the importance of staff hands and, to a lesser extent, contaminated bedpans and urinals, as means of spread, and the occurrence of clinically serious infection in relatively few of those colonized. Some differences have become clear, too; for example, our experience bears out the observation that the gut is an important reservoir of infection in klebsiella outbreaks, whereas this is not generally true for Serratia marcescens.

That the introduction of an antimicrobial agent will be followed by the appearance and spread of bacterial strains resistant to it has been the experience throughout the antibiotic era (Finland, 1970). As in the case of gentamicin, some years may elapse before clinically significant resistance is seen, and then there may be many contemporaneous appearances of resistant strains, which seem unlikely to be due to national or international spread of a single resistant clone. Increased use of a given antimicrobial in a hospital may be clearly seen to be followed by the arrival of particular resistant strains, as, in Bristol, by the appearance of multi-resistant K. aerogenes after increased use of co-trimoxazole, which has been shown to be highly selective for such bacteria, and later by the appearance of S. marcescens in response to general and immediate use of cephalosporins—use of newer cephalosporins for the klebsiella problem, but also increased use of first generation cephalosporins in surgical treatment and prophylaxis. The very broad spectra of activity of these drugs may make them unlikely at first to encourage superinfection but paradoxically make them powerful selectors when resistant strains appear in the hospital population. In Bristol, an increase in trimethoprim resistance among urinary coliforms from 2–5% in 1971 to 13–2% in 1977 was almost entirely due to the occurrence of a single epidemic strain of K. aerogenes, and the percentage fell to 4–2% when the outbreak was controlled (Marks, Bruten & Speller, 1977). For a resistant strain to be manifested other conditions are neces-