Leading articles

Control of antibiotic use in the United Kingdom

Over the last 30 years many surveys have demonstrated the problem of clinical misuse of antibiotics, but despite attempts at control it is certain that considerable misuse still continues worldwide. Considering the proliferation of antibiotics and other drugs available to the clinician and the many different sources of drug information, rational informed prescribing must be difficult (Cooke, Salter & Phillips, 1980). Some of the problems associated with this situation are financial waste, unnecessary exposure to toxic side effects and increased antibiotic resistance with consequent loss of efficacy. There is thus a societal perspective as well as individual patient implication from this continued misuse.

The problem and potential solutions have been studied most extensively in the United States, although there is accumulating information in the UK. Many hospitals in the UK now attempt some degree of control of prescribing (Collier & Foster, 1985). Probably most base their attempts on the issue of policy guidelines in the form of a local formulary that advises the most appropriate therapy for specific infections. Some attempt more strict control by limiting the availability of certain agents, for example, by having a limited drug list or by requiring consultant approval, or discussion with a microbiologist or infectious diseases physician, for certain prescriptions (Woodward et al., 1987).

Some other methods of control that have been described include educational campaigns (Mashford, 1986) restricted sensitivity reporting (sometimes including costs of agents) (Kunin, 1985), educationally oriented prescription forms (Avorn et al., 1985) and categorised prescriptions (Durbin, Lapidas & Goldmann, 1981). The last two examples involve, respectively, providing the prescriber with relevant information (e.g. about pharmacokinetics) on the drug order form, or require the prescriber to commit himself to one of several reasons for the prescription (e.g. prophylaxis, treatment for a specific pathogen or empirical therapy). Automatic stop dates or limits on the drug category allowed might then apply. Similarly, preprinted prescription forms for antibiotic prophylaxis (Beam, 1986) and automatic stop dates (Avorn et al., 1987) have been successful, again limiting the duration of prophylaxis and/or the drugs that may be prescribed. Antibiotic management systems (Beam, 1986), employing computer stored data on everything to do with drug prescribing, have been developed. Users can obtain information at the press of a button on many aspects of prescribing (e.g. cost comparisons, side effects and efficacy, allowing guidance on day to day use of antibiotics). National formulary guidelines, for example those used in Zimbabwe (PEDLIZ, 1981), attempt to provide an antibiotic policy for a whole country. This is an ambitious task, fraught with difficulties, but might at least stop the proliferation of diverse regional policies. Perhaps a national policy with built in regional variations (possibly rotational) might be worthy of investigation. Finally, the appointment of antibiotic utilization coordinators (Beam, 1986) and antibiotic committees to review prescribing habits (Dzierba, Reilly & Caselnova, 1986), probably reflects for the moment, the most strict monitoring of prescribing.

Do any of these measures work? There are problems in assessing the effects of controls on prescribing. As well as true cost savings, which can be difficult to assess, other factors such as efficacy, toxicity and antibiotic resistance need to be considered (Gladen, 1986). In addition, the position of pharmaceutical companies should be considered e.g. with regard to funding of research and education (Kunin, 1985). Audits probably have no impact on antibiotic usage (Swindell et al., 1983). Education programmes can have some impact, at least on a temporary basis, but probably need to be novel to capture the attention of busy prescribers and on a person to person, physician to physician basis (Beam, 1986; Mashford, 1986; Avorn et al., 1987). Maintaining interest over the years in any policy is crucial to continued success. The physicians most in need of education are the most difficult to target (Moleski & Andriole, 1986). Issue of policy guidelines in the form of a local formulary may be of benefit in certain hospitals, but their effect will depend on many
factors. More strict forms of control such as limited drug lists and consultant approval for restricted antibiotics may have a place in certain situations and indeed may be the most effective means of control (Moleski & Andriole, 1986). However, the consensus probably is that restrictive policies can be burdensome (Emmerson, 1980). Certainly a strong therapeutics committee is essential, but the co-operation of prescribers is needed.

Recently, in the USA, The National Institute of Health and The Infectious Diseases Society of America have commissioned task forces to review the problems worldwide (Moleski & Andriole, 1986; Infectious Diseases Society of America, 1987) and for some years accreditation of hospitals has depended upon peer review of antibiotic prescribing (Cooke et al., 1980). In the UK, we are ignorant about which methods of control are followed, whether they work to any degree, and indeed, how to assess their true benefits. In view of this and the self-evident need for cost control in the National Health Service — when antibiotics account for approximately 25% of hospital drug bills — Council of The British Society for Antimicrobial Chemotherapy (BSAC) has set up an ad-hoc group to discuss the remit of a proposed working party on this subject. Any member of the BSAC with objective evidence of the effect (or lack of effect) of attempted control of antibiotic prescribing will be invited to submit evidence. Some of the many subjects for possible consideration by a working party include the most common methods of attempted control of antibiotic usage and their effectiveness, the role of microbiologists, infectious disease physicians, pharmacists and infection control nurses in the control effort in hospitals, the problem in general practice, an infectious disease physicians, pharmacists and infection control nurses in the control effort in hospitals, the problem in general practice, an outline UK antibiotic policy, a peer review council to monitor the use of antibiotics nationwide, and the possibly undesirable effects of control of antibiotic prescribing on the pharmaceutical trade in the UK.

Another aspect the working party might consider is the teaching of antimicrobial chemotherapy to medical students. At the moment, lectures on this subject are tied on to the microbiology or the therapeutics courses — or the infection course if there is one. Shortage of time means that lectures on antibiotics suffer as it is not considered a speciality in its own right. In addition, as a part of therapeutics, it suffers from the traditional emphasis in teaching on aetiology and diagnosis. If antibiotic prescribing is to be improved, this must surely be changed, and also more emphasis must be put on directing research into this subject at a training level among registrars in microbiology and general medicine.

No other group of drugs has such an effect on society by its misuse, not only by the costs involved, but by the effects on bacterial resistance. The time has come for the medical profession to moderate its insistence on clinical freedom to prescribe what it likes when it likes. If the profession does not do this now, then Westminster will sooner or later insist on regulation (Collier & Foster, 1985).

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References


**Teicoplanin revisited**

Four years ago a leading article was published in the Journal about a promising new antibiotic, teicoplanin, which was at that time entering clinical trial (Williams & Gruneberg, 1984). A review of the progress of this antibiotic is now appropriate.

Teicoplanin is a glycopeptide antibiotic obtained as a fermentation product of *Actinoplanes teichomyceticus*, and as such is similar to vancomycin. It is a complex of closely related molecules, each consisting of a linear heptapeptide with two interconnected chlorinated hydroxytyrosine units, five substituted phenyl-glycine systems and an acyl-glucosamine unit. Each of the six major components of the complex (TA2:1–5, TA3) have differing acyl units. These acyl units are postulated to result in the increased lipophilicity of teicoplanin compared with vancomycin (Barna et al., 1984) and to its increased half-life (Pitkin et al., 1986). Teicoplanin works by binding to the D-alanyl-D-alanine residues of the growing peptidoglycan chain, terminating polymerisation and causing, in most susceptible organisms, cell death (Barna, Williams & Williamson, 1985).

It is active against Gram-positive organisms such as *Staphylococcus aureus*, streptococci, clostridia, etc and its activity is little affected by methicillin resistance or the production of β-lactamase (Williams & Gruneberg, 1984).

Little has changed in the perceived microbiology of teicoplanin. There have been discrepancies in MICs, MBCs and killing rates reported in the last four years, and appreciation of the importance of exact speciation of coagulase-negative staphylococci has developed because of the variable in-vitro activity of teicoplanin against these organisms (Wilson et al., 1986a; Arioli & Pallanza, 1987; Brumfitt, Hamilton-Miller & Neville, 1987). Recent evidence suggests that the technique of performing in-vitro susceptibility testing can markedly influence the results (Felmingham et al., 1987). Its activity against *Clostridium difficile* is excellent (Newsom, Matthews & Rampling, 1985), but inactivated by cholesteryamine (Pantosti et al., 1985), and it has useful activity against other Gram-positive bacteria such as *Propionibacterium* spp. (Bonanni et al., 1986).

Teicoplanin, being a complex of six closely related components, has proved difficult to measure. Bioassay is labour-intensive and slow, HPLC although rapid (with well validated methods from several centres published) (Joos & Lüthy, 1986; Levy et al., 1987) is capital-intensive. The Merrell Dow Research Institute has developed a solid phase receptor assay (SPERA), (Cavenaghi et al., 1987), which works on similar lines to an ELISA, except that the antibody layer adsorbed on to the microtiter tray is replaced by D-ala-D-ala residues. Unfortunately, this assay system, although elegant, appears to be temperamental. As yet, no antibody mediated system exists to measure teicoplanin concentrations in serum rapidly and accurately.

The pharmacokinetic perception of teicoplanin has changed considerably since 1984; protein binding, once estimated at 40%, is now thought to be closer to 90% (Wise et al., 1986), and the terminal phase half-life, calculated at approximately 40 h in 1984, now looks to be closer to 70 h (Buniva et al., 1987).

The significance of the persistence of low concentrations of teicoplanin in serum and urine is debatable; once daily dosing does not seem to lead to accumulation of drug, but does mean that pharmacokinetic studies must have a long wash out period to recover all the administered teicoplanin. Studies utilizing 14C-teicoplanin demonstrate that teicoplanin does not appear to be metabolized (Bernareggi, Cavenaghi & Assandri, 1986) and is almost totally excreted by the kidney, with the consequence that varying degrees of renal failure will prolong the half-life yet further, (e.g. T1/2 in one study ranged from 41 h in patients with normal renal function to 157 h in an anuric group). Teicoplanin does not seem to be removed by haemodialysis or CAPD very effectively (Traina et al., 1986). Guidelines for dosage recommendations for varying degrees of renal failure have been published (Bonati et al., 1987).