Leading articles


The conference opened with a look at the great advances in the diagnosis of infectious diarrhoea; in up to 80% of cases the causative agent can now be established. But, because of the delay in obtaining laboratory results, administration of specific antibiotic therapy still tends to be a clinical decision based upon the severity and possible invasiveness of the illness. The decision to use chemotherapy in campylobacter enteritis seems to be similar to that in salmonella or shigella infections, although there is no evidence that antibiotics prolong excretion of the organism. Strains of Campylobacter spp. are resistant to cotrimoxazole, sometimes resistant to ampicillin (30-40%) but only occasionally resistant to erythromycin. Gentamicin is maintained by some to be first choice therapy for the seriously ill but erythromycin is probably a more reasonable alternative for most patients in view of its lower toxicity.

Sub-inhibitory doses of antibiotics were noted to be of clinical benefit in another symposium, where in one presentation there was no difference in the outcome of Gram-negative septicaemia (36% fatality), whether peak concentrations were more or less than the MIC. The effects of sub-inhibitory levels of antibiotics on bacteria were discussed and it would seem that the effects range from changes in mucosal adherence to the depression of toxin and enzyme production and changes in morphology and the ability to withstand phagocytosis, all factors which could alter pathogenicity and allow the host defences, under certain circumstances, to cope more readily with the infection. Homeopathic doses of ampicillin (10 mg/day) were thus shown to be efficacious in the treatment of urinary tract infection. Further studies on the effects of low concentration of antibiotics on bacteria and of antibiotic interactions with the immune system, both beneficial and deleterious, obviously need to be pursued. It may be that there are other factors to consider, when dosing antibiotics, than the MIC of the infecting organism and obvious toxicity problems.

At the symposium on β-lactamases their multiplicity of types was emphasized although TEM 1 is by far the most prevalent. Often they are coded for on plasmids or transposons which explains their wide distribution among species of clinical relevance. However, their mediation by plasmids ensures that their distribution is neither geographically nor clinically uniform and they are often less able to protect bacteria than would appear likely from in-vitro studies. Despite this an array of β-lactamase inhibitors is being developed including clavulanic acid, penam derivatives such as β-bromopenicillanic acid and penicillanic acid sulphone and recently a naturally occurring agent izumenolide has been discovered. Although interesting, their clinical use remains to be established and clinical trials with these substances are awaited.
In the symposia on sexually transmitted diseases and unsuspected infection in clinical disease, much time was given to the ever increasing spectrum of chlamydial and mycoplasmal disease. Of particular interest was the beneficial effect on prematurity and low birth weight of giving erythromycin in the third trimester to mothers known to be carrying *Mycoplasma hominis* or *Ureaplasma urealyticum* in their genital tracts; if the antibiotic is given to a group of such mothers in a low-income group it lowers prematurity rates to those characteristic of a high income group. No other factor has been shown to play such a major role in altering prematurity rates.

New penicillins were discussed in a symposium on the ureidopenicillins, the *N*-acyl derivatives of ampicillin such as azlocillin and piperacillin. These were noted to be susceptible to β-lactamases but are probably an improvement over the carboxy penicillins, having activity against Klebsiella pneumoniae and Serratia marcescens and increased activity (at least for azlocillin and piperacillin) against *Pseudomonas aeruginosa*. Synergy studies suggest benefit with aminoglycosides against most Gram-negative aerobic bacilli, Staphylococcus aureus and Streptococcus faecalis, but the situation in combinations with cephalosporins and their derivatives is less clear. There is both *in-vitro* and animal model evidence of antagonism between cefoxitin and mezlocillin or piperacillin against a wide range of Gram-negative rods. Similar effects can be seen occasionally when cephalothin, cefamandole or cefotaxime is combined with mezlocillin or piperacillin. The situation with newer agents such as cefoperazone and moxalactam has not yet been evaluated.

One of the most interesting symposia was on the monobactams which are naturally occurring monocyclic β-lactam antibiotics. These are low molecular weight compounds produced by bacteria and have activity mainly against the Gram-negative rods. As with *N*-formimidoyl thienamycin they have not yet reached the stage of clinical trials but *in vitro* results with a new agent SQ 26776 (Squibb) were presented. This is actually a synthetic analogue of a product of *Chromobacterium violaceum*. The compound is said to have low toxicity and is stable against a wide range of β-lactamases. Activity against Gram-negative aerobes is the mainspring of any potential clinical use. Serratia in particular seems more susceptible to SQ 26776 than to any other antibiotic with an MIC90 of about 3 mg/l. The antibiotic also has good activity against *Escherichia coli*, Proteus spp., Enterobacter spp. and *Providencia* spp. with MICs less than 2 mg/l. Klebsiella spp. are also susceptible with promising activity against gentamicin-resistant Klebsiella. *Alkaligenes* spp. and Acinetobacter spp. are relatively resistant having MICs between 4 and 64 mg/l. Antibacterial activity appears very good and comparable to thienamycin. In one study the MIC90 was 8 mg/l but occasional organisms had MICs of between 64 and 128. In general however, activity against *Gram*-positive cocci is very poor, e.g. the MIC90 for *Staph. aureus* was greater than 128 mg/l and the MIC90 for *Bacteroides fragilis* was unimpressive at 32 mg/l. The activity against *Haemophilus influenzae* (MIC90 0·12 mg/l) and the gonoccus (MIC90 0·25 mg/l) is more promising.

Killing curve studies show that SQ 26776 is similar in this respect to other β-lactams and its mode of action appears to be similar to that of mezlocillin or azlocillin. Synergy studies are disappointing but at least no antagonism has been described. The antibiotic is stable to most β-lactamases. However, there does appear to be increased activity against *Bact. fragilis* when combined with clavulanic acid. In one small study of healthy volunteers pharmaco-kinetic studies showed a 2-compartment model with a half life of 15 min and 68% of the drug excreted unchanged in the urine. Serum protein binding was 27% and tolerance appeared very good.

There were two poster sessions on *N*-formimidoyl thienamycin (NFT) a β-lactam derivative that has been available for some time for *in-vitro* study but is still eagerly awaited for clinical trial. The data presented confirmed previous results suggesting it to be a very active agent and more stable than its parent compound thienamycin. Perhaps its greatest strength is that it is one of the most active of the β-lactams against *Ps. aeruginosa* with several presentations confirming an MIC90 of around 2–4 mg/l. It would appear to be remarkably stable to all the β-lactamases but killing does not appear to be as rapid as with gentamicin. Enhanced killing is seen against *Ps. aeruginosa* or *Staph. aureus* when the drug is combined with tobramycin.

Against other Gram-negative non-fermenting organisms activity was also very good...
excepting *Ps. maltophilia* and to a lesser extent *Ps. cepacia*. *Proteus* spp. and *Providencia* spp. have MICs around 2–4 mg/l, *E. coli* about 1 mg/l, *Klebsiella* spp. and *Enterobacter* spp. less than 2 mg/l, *Serratia* spp. less than 4 mg/l and *Acinetobacter* spp. less than 0.5 mg/l. *Enterobacter* spp. resistant to cefotaxime were found to be fully sensitive. Marked antagonism similar to that found with azlocillin was found when NFT was combined with newer cephalosporins such as cefotaxime, cefoperazone and moxalactam. Activity against Enterobacteriaceae is generally comparable with cefotaxime and moxalactam but it is much more active against *Staph. aureus* and *Bact. fragilis* than these compounds; the MIC$_{50}$ for *Bact. fragilis* is around 0.12 mg/l and for *Staph. aureus* 0.06 mg/l. It is also extremely active against coagulase-negative staphylococci, most streptococci and almost all anaerobes except some strains of *Cl. difficile* (MIC$_{50}$ around 16 mg/l).

In a study from Canada of 693 aerobic blood culture isolates NFT compared very favourably with a range of new and commonly used antibacterial drugs and nearly 99% of strains were inhibited by less than 16 mg/l. Perhaps NFT is the most promising of the newer antibiotics presented and if used along with aminoglycosides may offer some hope in the treatment of conditions such as pseudomonal endocarditis.

In summary, I have only been able to comment on a few aspects of the conference that I found of particular interest. Many other topics were discussed in detail but in the antibiotic field nothing startlingly new seemed to emerge. β-lactam derivatives dominated the meeting, each one offering only small benefits over its competitors; perhaps some increased activity or greater stability to the myriad of β-lactamase enzymes. With the advent of aminoglycoside resistance and the dream of less reliance in the future on such toxic antibiotics the new β-lactam derivatives must offer some hope of effective alternatives in treatment but it is difficult to foresee much change in the antibiotic shopping list of the average district general hospital over the next few years.

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