Leading articles

Antimicrobial potentiating agents
The last few years have seen a proliferation of antimicrobials available in clinical practice or under investigation. The main areas of growth that have been discussed in these columns are the penicillins, particularly the substituted ampicillins (Wise, 1977) and the cephalosporins (Williams, 1978). It is possible that the coming years may see a change of emphasis. All would agree it is desirable that the antimicrobials be used to their best advantage. It is also important that we examine the clinical use of combination chemotherapy. There are now a number of compounds under study which, at least in vitro, potentiate the activity of other antimicrobials, yet only have modest or minimal activity themselves; some have other drawbacks which make them less than ideal for the treatment of infections as the sole agent.

The β-lactamase inhibitors, clavulanic acid (Reading & Cole, 1977) or CP 45,899 (Retsema, English, Girard & Presslitz, 1978) are examples of this approach to chemotherapy. These interesting compounds themselves have negligible activity but in combination with, for example, amoxycillin, will extend the range of the latter, not only to include β-lactamase producing strains, which are otherwise sensitive, but also may make amoxycillin-resistant bacteria such as Bacteroides fragilis susceptible to the combination. The preliminary reports of clavulanic acid in combination with amoxycillin in the treatment of urinary tract infections suggest that the in vitro findings will be borne out (Goldstein, Kitzis & Acar, 1978).

The amidino penicillin, mecillinam, is also being discussed as a possible potentiating agent (not so much in the U.K., but elsewhere). Mecillinam is a potent antibiotic active against many common Gram-negative pathogens, but there are important gaps in its spectrum. This, together with its interesting mode of action (Spratt, 1977), spurred the investigation of possible synergistic associations. The combination with ampicillin has been found to be synergistic in its activity against Haemophilus influenzae (Wise et al., 1976) and many Gram-negatives (Neu, 1977). Cephadine has also been suggested as a potential partner (Kerry et al., 1977). Even fusidic acid together with mecillinam has been shown to be synergistic against H. influenzae (Wise et al., 1976). The suggestion has, therefore, been made that rather than using mecillinam for the treatment of urinary tract infections (for which there are a plethora of agents) a better use would be in the treatment of serious sepsis, when it would be combined with another β-lactam.

There is another approach: the possible use of relatively simple compounds which act at an early stage of bacterial cell wall synthesis. The phosphonopeptide family, of which alaphosphin (Ro 03-7008) is the most thoroughly investigated, is a simple dipeptide mimetic which accumulates in bacterial cells and selectively inhibits peptidoglycan synthesis at two points by interfering with the attachment of alanine to N-acetyl muramic acid (Allen, 1978). Although alaphosphin has a modest antibacterial spectrum which includes the Enterobacteriaceae (but not Proteus spp. or Pseudomonas spp.) and Streptococcus faecalis which might suggest its use as an agent for the treatment of urinary tract infections, it is very susceptible to pH and inocula effects and the possibility of resistant variants emerging is higher than with other agents. Our own studies have shown that alaphosphin is a modest potentiator of cephalaxin and cefoxitin, the MIC of the β-lactam being reduced two to fourfold and the rate of killing increased, in the presence of achievable levels of alaphosphin.

Another compound showing certain similarities to alaphosphin is fosfomycin, which again acts at an early stage of cell wall synthesis. It combines irreversibly with phosphoenolpyruvate inhibiting the formation of UDP-N-acetylmuramic acid. The spectrum of activity of fosfomycin is somewhat broader...
than alaphosphin and includes the majority of Enterobacteriaceae, staphylococci, Pseudomonas aeruginosa and Serratia marcescens (Woodruff et al., 1977). Again resistant mutants may be a problem and the activity compound is highly inoculum dependent both in vitro and in vivo (Goto, 1977). This compound has been widely used, mainly in Spain and Italy, usually in the treatment of urinary tract infections (Neuman & Fluteau, 1977). Modest in vitro synergy has also been demonstrated with this compound against a number of \( \beta \)-lactams and other agents (Olay et al., 1978; Woodruff et al., 1977). In a poorly designed, yet interesting study Figueroa, Baquero, Otal & Rodriguez (1977) have described synergy between fosfomycin and ampicillin or chloramphenicol in the treatment of typhoid.

The concept of using more than one antimicrobial agent in certain indications is well established. The use of an aminoglycoside plus \( \beta \)-lactam in the treatment of subacute bacterial endocarditis, and of combinations to increase the breadth of antibacterial spectrum in the treatment of severe infection and to prevent the emergence of resistant organisms in tuberculosis is accepted by most. The more widespread use of one agent to enhance the activity of another is a somewhat different idea. Medical microbiologists should be cautious in their approach. The cynic may argue that combinations used in this way merely permit a relatively weak antimicrobial to be reinforced and supported by a better agent (though this criticism may not apply to the \( \beta \)-lactamase inhibitors). The enthusiast might say that the idea of antimicrobial enhancement is exciting, as this allows the clinician greater flexibility in his treatment. This matter can only be resolved by controlled clinical trials, though the setting up and interpretation of them will be unusually difficult, if not a near impossibility.

RICHARD WISE
Dudley Road Hospital,
Birmingham B18 7QH, England


Penetration of antibiotics into the pleural fluid

In man pleural fluid is formed by capillary filtration due to colloid-osmotic and hydraulic pressure differences across the visceral and parietal surfaces of the pleura. Reabsorption takes place via lymph vessel drainages of both pleural membranes (Agostini & Mead, 1964). The pleural volume of a normal human lung is about 2.0 ml (Miserocchi & Agostini, 1971). The protein content of the pleural fluid ranges

References


Penetration of antibiotics into the pleural fluid

In man pleural fluid is formed by capillary filtration due to colloid-osmotic and hydraulic pressure differences across the visceral and parietal surfaces of the pleura. Reabsorption takes place via lymph vessel drainages of both pleural membranes (Agostini & Mead, 1964). The pleural volume of a normal human lung is about 2.0 ml (Miserocchi & Agostini, 1971). The protein content of the pleural fluid ranges