New and future antibiotics in the treatment of acute respiratory tract infections

At first sight it might be thought that there are too many antibiotics available and that the last thing one would want is yet more agents. Such a nihilistic approach, however, is both inaccurate and shortsighted. We live in a changing world and, as far as bacteria are concerned, very much a global village. The conservative prescribing habits of one group of clinicians may be influenced by clinical activities further afield— for example, the increased numbers of penicillin insensitive pneumococci in Iceland may well have come from abroad,1 possibly from Spain, where resistance rates are as high as 42.5%.2 The rate in Birmingham, UK, is 5–7% and rising. Similarly, the increasing importance of the enterococcus in nosocomial pneumonia in North America,3 possibly related to high cephalosporin use, will pose a great therapeutic problem, especially if the strain is resistant to vancomycin. In addition, advances are being made which will aid the diagnosis of infections caused by Chlamydia pneumoniae and Mycoplasma pneumoniae.4 Those interested in the treatment of respiratory tract infections must therefore keep abreast of the advances in antimicrobial chemotherapy.

Quinolones

The major change to have occurred in the last few years is the part played by fluoroquinolones in the treatment of acute lower respiratory tract infections. Ofloxacin and ciprofloxacin have been useful additions to the antibiotic armory for the treatment of nosocomial respiratory tract infections, especially those that are commonly encountered on the intensive care unit. The dosage regimen of ciprofloxacin has recently been reappraised and earlier suggestions that 200 mg intravenously or 500 mg by mouth twice daily were sufficient have been revised. A comparison of twice daily doses of 400 mg and 200 mg given intravenously showed that seven of 13 patients were “cured” or “improved” on the lower dose compared with 30 of 31 patients who received the higher dose.5 The results are impressive but the study contained no statistical evaluation. The cost implications of such doses of intravenous ciprofloxacin are considerable, but we have shown that, from a pharmacokinetic viewpoint, 750 mg by mouth is equivalent to 400 mg intravenously,6 so intravenous treatment should be switched to oral administration as soon as possible. Most would agree that, although these compounds are active against the organisms causing lower respiratory tract infections in the community, their main use should not be for such infections at present. If pneumococcal resistance to β-lactams (especially high level resistance) increases there may be a case for re-evaluation. The reality of the situation is, however, that in both Europe and North America quinolones are being used primarily in the treatment of relatively trivial lower respiratory tract infections in the community.

The other quinolones under clinical development are fleroxacin, lonfloxacin and, especially, sparfloxacin. The latter has enhanced activity against the pneumococci, being 4–8 times more potent than ciprofloxacin,7 and other respiratory pathogens— for example, Chlamydia sp—are similarly more susceptible to the new agent than to ciprofloxacin. Studies of the respiratory tract penetration of sparfloxacin have shown that, whereas most quinolones have a twofold concentration in the bronchial mucosa (compared with serum), a 2–3-fold concentration in the alveolar epithelial lining fluid, and a 9–15-fold concentration in alveolar macrophages,8 sparfloxacin is concentrated threefold in the bronchial mucosa, 11-fold in the epithelial lining fluid, and over 40-fold in the alveolar macrophages. Early clinical trials are promising and a comparison of sparfloxacin with amoxycillin in 177 patients with pneumococcal pneumonia has shown equivalence.9 If the side effect profile is comparable with other agents it is possible that sparfloxacin may become the quinolone of choice in the treatment of respiratory tract infections.

Other potent quinolones under development include levofloxacin which is the most active of the two isomers of the racemic mixture that makes up ofloxacin and is generally twice as active as ofloxacin, DU 6859a from Daiichi,10 CP 99219 from Pfizer,11 clinafloxacin from Warner Lambert,12 and OPC 17116 from Otsuka,13 which all have the advantage of being 4–8 times more active against the pneumococci and are usually more active against intracellular respiratory pathogens. Some quinolones have recently failed to be marketed because of toxicological problems and scrutiny of these new agents will be intense.

Macrolides

Macrolide antimicrobials such as azithromycin, clarithromycin, and dirithromycin are now available in certain countries. These compounds have been developed to overcome the internal rearrangement of the erythromycin molecule which occurs at low pH (as in the stomach) causing alteration to gut motility with consequent side effects. The main differences between erythromycin and these newcomers are the longer elimination half lives (and hence longer dosing intervals) and the somewhat lower incidence of side effects. There are no major differences in antimicrobial activities and cross resistance amongst the group is the rule. An interesting facet of these agents is the superior intracellular penetration of azithromycin and clarithromycin.1415 This implies that, not only are they effective against intracellular pathogens, but clarithromycin, at least, is effective in Mycobacterium avium-intracellulare infections where the therapeutic options are very limited. These new agents may well supplant erythromycin for the treatment of "atypical pneumonia" but the pressure to use them in more trivial infections of the upper airway should be resisted.

Beta-lactams

There have been lesser advances amongst the β-lactam antimicrobials. The injectable cephalosporins, cefpirome and ceftipeime, have modest pharmacokinetic advantages over some earlier agents and are generally more stable to the bacterial hydrolysing enzymes, the β-lactamas. They will find a role in the treatment of nosocomial pneumonia.
Meropenem is a carbapenem like imipenem but, unlike its predecessor, the new compound does not require to be administered with an enzyme blocking agent. Undoubtedly meropenem will also be used to treat the seriously ill patient with a nosocomial pneumonia.

Oral cephalosporins are proliferating. They have more in common with each other than they have differences, tending to be more active, more stable to the β-lactamases, and more expensive than the earlier compounds, cephalxin and cefaclor, to which they have not, to my knowledge, been shown to be clinically superior other than in frequency of administration. Generally, those that are more active against Gram negative pathogens – for example, cefixime and cefditene – are less active against streptococci. Cefpodoxime appears to be a reasonable compromise but no paediatric formulation is yet available. Loracarbef is not strictly a cephalosporin (rather a carbacephem), is available in a number of countries (but not the UK), and is a modest advance on earlier agents. The problem in assessing the usefulness of any of these oral agents in chest infections in the community (their main market) is the quality of the clinical trials themselves. Many are performed in patients with acute bronchitis or in the less severely ill patient with acute exacerbations of chronic bronchitis when antibiotic use is only marginally, if at all, influences outcome.\textsuperscript{16,17} There is marketing pressure for the increased use of oral cephalosporins in upper respiratory tract infections, particularly in children. Clinical trials do not show any consistent advantage except that the longer dosing intervals may enhance compliance. The use of oral cephalosporins in pharyngitis remains controversial.

Tetracyclines
A novel development has been a reassessment of the tetracyclines. These agents were initially used in the treatment of respiratory tract infections after their introduction some 50 years ago. A large number of “me too” compounds were then introduced and their widespread use led to the development of plasmid-mediated resistance in many bacterial species and the consequent decline in their clinical efficacy. Just as the quinolones were revisited 10 years ago when nalidixic acid was modified to give the currently available compounds, the same may be about to occur with the tetracyclines. Lederle Laboratories have synthesised two new glycyclines, one a substituted minocycline (CL329,998) and the other a modification of 6 methyl-6-deoxotetracycline (CL331,002).\textsuperscript{18,19} Not only are they more active than tetracycline against the respiratory pathogens \textit{Haemophilus influenzae} and \textit{Streptococcus pneumoniae}, but they are also active against those strains which have become resistant to tetracycline. Perhaps there will be a renaissance in this group of agents if their toxicological and pharmacokinetic assessment is trouble-free.

In the rapidly changing world of bacterial pathogens another group of antimicrobial drugs to join the armamentarium would be welcome.

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