Leading article

The role of antibiotics given by inhalation in chronic chest disease

Most respiratory tract infections respond satisfactorily to oral or systemic antibiotics in conjunction with other symptomatic treatment. When these measures fail there is usually some underlying problem such as chronic lung disease, resistant organisms, an immunocompromised host, or a combination of these. In long-standing chest disease the anatomy of the airways becomes distorted and in both acute and chronic conditions the blood supply to the affected areas may become inadequate and mucociliary mechanisms and immune systems become deranged. In addition to this drugs vary considerably in their ability to cross the 'blood-bronchial' barrier. The more difficult infections are often caused by problem organisms such as Gram-negative bacteria, especially *Pseudomonas*. These often respond only *in vitro* to drugs that penetrate the lung poorly and are potentially toxic. Such drugs when given systemically may not always reach those parts of the lung where they are most needed. The purpose of this article is to assess the ability of antimicrobials applied directly to the respiratory tract to provide effective treatment, either alone or together with systemic therapy.

Many factors affect the ability of aerosols to penetrate different areas of the respiratory tree. Smaller particles (1–10 μm mass mean diameter) penetrate further but are retained less well. Airways that become distorted in acute or chronic conditions may deprive access to areas needing treatment. Studies with radio-labelled aerosols in adults with chronic bronchitis show, broadly speaking, (a) a predominantly hilar pattern or (b) a patchy distribution (Lourenco, Loddenkemper & Carton, 1972). A similar study in children with cystic fibrosis (Alderson, Seeker Walker & Stominger, 1974) showed that those with more severe disease had a more central distribution and a poor supply to pathological areas. Lastly, some patients with chronic respiratory disease tend to have higher respiratory rates and function at higher lung volumes, factors that limit the more peripheral deposition of an aerosol.

It is now well established that some antibiotics, particularly aminoglycosides, do not penetrate well into the bronchial secretions from the blood (Marks *et al.*, 1971; Mombelli *et al.*, 1981). Sputum levels are generally below the minimum inhibitory concentration for organisms such as *Pseudomonas*, though tobramycin in high doses may achieve this (McCrae, Raeburn & Hanson, 1976; Martin *et al.*, 1980). Even in these studies, levels appreciably above that of the MIC were not achieved. It appears that certain non-aminoglycoside antibiotics such as ampicillin may penetrate inflamed tissue better than non-inflamed (May & Delves, 1965). Though this may occur to some extent with gentamicin (Wieser, Regula & Wundt, 1971) and other aminoglycosides (Klastersky, Thys & Mombelli, 1981), the sputum levels achieved are so low that this effect is probably unimportant. Conversely, aminoglycosides, when administered by aerosol or intratracheal instillation, though reaching a relatively high local concentration, do not give significant serum levels (Baran, Dachy & Klastersky, 1975).

There is, however, no definite evidence that drug levels in sputum bear any relation to clinical response to treatment in chronic or severe tracheo-bronchial infection. For example, McCrae *et al.* (1976) found no significant difference in mean sputum levels of tobramycin given parenterally in the four (out of 17) patients with cystic fibrosis whose sputum was cleared of *Pseudomonas* from those with no clearance.

There may be substances secreted into the bronchi in certain chronic lung conditions that contribute to the failure of antimicrobial therapy. Studies on sputum from patients with cystic fibrosis (Davis & Bruns, 1978) and on pus from pneumococcal empyema (Bryant & Hammond, 1974) show evidence of factors that inhibit the activity of aminoglycosides against most strains of *Pseudo-
monas. This may be related to protein binding within the pus. One way of trying to overcome these problems is to aim for higher levels of antibiotics in the sputum.

Aerosols are themselves not without hazards. Systems that produce them are often ideal sites for colonization of organisms that may be pathogenic to patients with long-standing disease (Editorial, 1975). Scrupulous care of inhalation equipment is therefore needed. The airways themselves are similarly at risk of being colonized with resistant organisms. This may occur with long-term antibiotic treatment under any circumstances, but also more rapidly in the hospital environment. The content of the aerosol itself may be irritant to the lung. Kanamycin and polymyxin have been shown to produce a mild reduction in FEV, (Dickie & De Groot, 1973). Gentamicin has also been shown to produce a 20% reduction in FEV, in some asthmatics, although this may have been due to the carrier fluid rather than the antibiotic (Daly, Kurrle & Breslin, 1978).

The clinical value of aerosol antimicrobial therapy is not easy to assess. The role of systemic antibiotics in the management of most respiratory infections is already established so that there are ethical problems in using aerosol therapy alone in comparison with systemic treatment or placebo. Most trials have used aerosols in conjunction with other treatment. The origin of organisms cultured in sputum, the role they play in causing infection or exacerbation of disease, and the value of eradicating such organisms from the sputum as a way of assessing success or failure of treatment are complex problems. Consideration needs to be given to whether antibiotics are to be used to prevent colonization, to suppress infection or colonization, or to try to eradicate completely the pathogens concerned. Evidence is also needed to show that the treatment of an exacerbation of a chronic illness alters the long-term history of the condition significantly.

Since about 1960 aerosols have been used mainly in the management of chronic lung disorders such as cystic fibrosis and also in the treatment or prophylaxis of Pseudomonas infections in severely ill patients. Pines, Rafaat & Plucinski (1967) reported a little success in treating chronic purulent bronchial infections with gentamicin as an aerosol, or intramuscularly, but no particular route seemed preferable, nor was there any obvious advantage from the administration by both routes simultaneously. He later (Pines et al., 1970) studied the use of colistin, carbenicillin and gentamicin via these routes in similar patients with severe Pseudomonas infections. These authors found that the most effective therapy was intramuscular carbenicillin and gentamicin in combination and that there was little evidence of any increased benefit from the improved sputum levels obtained when aerosol therapy was added. His patients did not tolerate these aerosols too well. Klustersky, Geuring & Mouawad (1972), however, using endotracheal installation of gentamicin in tracheomotized patients with severe underlying illness and serious tracheobronchial infections due to Gram-negative bacilli, achieved results they considered superior to those with systemic gentamicin.

Cystic fibrosis is a chronic illness where Gram-negative organisms, particularly Pseudomonas, are implicated (Geddes, 1982). The relevance of culturing these organisms is not always clear, however. The treatment of choice of exacerbations of cystic fibrosis, particularly when Pseudomonas may be involved, has yet to be agreed. Ideally such therapy should be shown by a well controlled trial not only to improve the acute exacerbation but also to slow down the inexorable deterioration of pulmonary disease. Aerosols have been used in patients with cystic fibrosis, but there have been few good studies to assess their efficacy. The only double-blind randomized cross-over trial of the effects of aerosol antibiotics was carried out by Hodson, Penketh & Batten (1981). This study looked for ways of improving the outlook for cystic fibrotics given six month courses of inhaled gentamicin and carbenicillin. They specifically chose those with more severe disease because of the association of resistant organisms with any long-term treatment. Both subjective and objective improvements were noted in the group receiving active therapy, there were fewer hospital admissions, and resistant organisms were not a problem. Aerosols have also been used in attempts to reduce infections in seriously ill patients in intensive care units who are at risk of infection with Gram-negative organisms particularly Pseudomonas. Gram-negative bacilli colonize the trachea of most patients within three days of endotracheal intubation (Schwartz et al., 1978). Infection (as opposed to colonization) with these organisms has a strong association with mortality, but the dividing line between these two is not always clear. It is tempting to believe that pneu-
monic infection is preceded by tracheobronchial colonization; but this may not always be the case (Cooper, 1981). Nevertheless, polymyxin used either as a spray or applied via an endotracheal tube has been shown to hinder colonization of the upper airway and to reduce the number of Pseudomonas pneumonias (Klick et al., 1975). The emergence of resistant organisms was also avoided by using two monthly cycles with and without the spray. More recently a prospective controlled trial (Vogel et al., 1981) of intratracheal gentamicin in patients on ventilators lessened the incidence of colonization and infection of the respiratory tract. Emergence of resistant organisms was not significantly greater in the treated group.

In summary, most bacterial respiratory tract infections respond well to oral or parenteral antibiotics. Problems arise, however, in lungs already compromised by long-standing disease such as cystic fibrosis. Infections, especially those caused by Gram-negative bacteria responding only to drugs that may be toxic when given systemically, commonly occur. Aerosols have been shown to provide a way of achieving good sputum levels of antibiotics without necessarily creating high levels in the blood. Results of some interest have been obtained in the prophylaxis and treatment of respiratory tract infections with Pseudomonas in severely ill patients in intensive care units. With the potentially serious risk of the emergence of resistant organisms, more work is needed to identify groups of patients at risk of developing these infections and to develop more effective prophylactic techniques. The case for the use of antimicrobial inhalation therapy in the management of serious tracheo-bronchial infections is by no means proven, but the most recent trial (Hodson et al., 1981) suggests that, at least in cystic fibrosis, it may have a real part to play.

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References


