

## Nebulisers for bronchiectasis

D C Currie

Almost all patients with bronchiectasis expectorate sputum intermittently or daily. The sputum ranges from mucoid to purulent and from scanty to copious. Patients with bronchiectasis have a number of other symptoms – some are breathless with impaired lung function, usually predominantly an obstructive ventilatory defect, and asthma is frequent with an incidence of 28% (10 of 36) and 39% (nine of 23) having been reported in studies from Ireland<sup>1</sup> and England.<sup>2</sup> Bronchial hyper-reactivity to histamine<sup>3</sup> and methacholine<sup>4</sup> reported in 48% and 69% of patients is of uncertain significance in the presence of bronchi damaged by the primary disease process. In addition to local symptoms, patients with daily purulent sputum expectoration have systemic symptoms such as malaise and tiredness both during and between acute exacerbations.<sup>2</sup>

Patients with bronchiectasis are at risk of disease progression. Forced expiratory volume in one second (FEV<sub>1</sub>) declined by >50 ml/year in 80% of a group of 71 patients<sup>5</sup> and radiographs had deteriorated in 18% of a group of 84 patients by the time of tertiary referral.<sup>6</sup> Daily purulent sputum expectoration, indicative of a significant host inflammatory response,<sup>7</sup> is likely to be an important risk factor for progression, although this is unproven.

### Indications for nebulisers in bronchiectasis

Few studies have been published on the use of nebulisers in bronchiectasis. The possible indications for nebulisers are (1) reversal of airways obstruction with bronchodilators in patients with and without asthma, (2) improvement of mucus clearance, and (3) reduction of the microbial load in the bronchial tree.

#### BRONCHODILATOR REVERSAL OF AIRWAYS OBSTRUCTION

No studies have been identified that were designed to evaluate the use of bronchodilator drugs for reversal of airways obstruction in patients with bronchiectasis. At present it is therefore appropriate to follow guidelines for patients with asthma<sup>8</sup> and chronic obstructive pulmonary disease<sup>9</sup> without bronchiectasis (see also paper by O'Driscoll on pp S49–52). Those patients prescribed nebulised antibiotics may require nebulised bronchodilators beforehand (see paper by Webb and Dodd on pp S69–71).

#### IMPROVEMENT OF MUCUS CLEARANCE

The immediate value of single nebulised doses of terbutaline and 0.9% saline as adjuncts to

modern chest physiotherapy were evaluated in a randomised study<sup>10</sup> of eight patients with stable bronchiectasis. Both nebulised treatments significantly increased the yield of expectorated fluid/mucus by a small amount, similar to the weight of the nebulised solution (only a 25% increase in the expectorated weight compared with physiotherapy alone). Interestingly, nebulised terbutaline also increased the radioaerosol clearance rate in patients with stable bronchiectasis.<sup>8</sup> Nebulised water<sup>11</sup> combined with physiotherapy resulted in an increase in the amount of sputum expectorated and the total lung radiolabel clearance rate that was similar to physiotherapy alone in a group of seven patients with bronchiectasis and no evidence of asthma.

Hypertonic saline (7.1%) significantly increased the weight of sputum produced and the whole lung radioaerosol clearance rate in 11 patients with chronic bronchitis.<sup>12</sup> In the same study the mucolytic agent, 2-mercaptoethane sulphonate, had similar effects to hypertonic saline, although they were not significantly different from the control studies.<sup>12</sup>

There are no published studies on the use of N-acetylcysteine in patients with bronchiectasis without cystic fibrosis. Sixty patients with stable purulent bronchiectasis treated for two weeks with nebulised rhDNase showed no improvement in FEV<sub>1</sub> or sputum production in a double blind placebo controlled study.<sup>13</sup>

The clinical importance of these observations on mucus clearance is unknown.

#### REDUCTION OF COLONISING MICROBIAL LOAD IN THE BRONCHIAL TREE

The objective of nebulised antimicrobial therapy in patients with bronchiectasis is to reduce the colonising microbial load in the lungs, improve symptoms, and prevent progression of the disease. Nebulised antimicrobial agents are usually prescribed for control of background symptoms and for the reduction of severity or prevention of acute exacerbations rather than for treatment of acute exacerbations.

#### Methodology

Evaluation of the effectiveness of nebulised antimicrobial agents in bronchiectasis should include assessment of sputum character and volume.<sup>14</sup> The 24 hour volume of sputum should be estimated from the history or, preferably, measured. A fresh four hour morning sample of sputum should be examined to establish the proportion of purulent sputum and the degree of purulence (colour (green/yellow) and intensity of colour). This allows estimation of the 24 hour volume of purulent sputum. The

Dewsbury and District  
Hospital, Healds  
Road, Dewsbury, West  
Yorkshire WF13 9HS,  
UK

D C Currie

Correspondence to:  
Dr D C Currie.

volume of purulent sputum was a better discriminator than sputum elastase levels for separating the antibiotic treated group from the placebo group in a study of long term higher dose amoxicillin (3 g twice daily for seven months).<sup>2</sup> The erythrocyte sedimentation rate and white blood count are inconsistently raised in patients with purulent bronchiectasis between exacerbations<sup>2</sup> with no obvious correlation to purulent sputum volume. Serial quantitative sputum bacterial culture<sup>14</sup> is a possible way of monitoring the response to nebulised antibiotics. However, no recognised pathogens were isolated in eight of 36 patients with purulent bronchiectasis despite extensive and repeated culture on selective and non-selective media.<sup>2</sup> Lung function seems less likely to be reduced by the presence of purulent sputum or its production in patients with bronchiectasis without cystic fibrosis than in patients with cystic fibrosis. Prolonged higher dose oral amoxicillin (3 g twice daily) reduced the volume of purulent sputum in a double blind placebo controlled study but did not alter lung function.<sup>2</sup> Data on nebulised antibiotics in patients with cystic fibrosis may not be applicable to other patients with bronchiectasis. In addition, quality of life between exacerbations and severity of exacerbations should be evaluated.

#### STUDIES

Sputum volume and purulence decreased and peak expiratory flow rate (PEFR) improved during prolonged treatment with nebulised amoxicillin 500 mg (intravenous preparation diluted in 5 ml sterile water, unlicensed indication) twice daily in an open study<sup>15</sup> of six patients whose daily purulent sputum expectoration had failed to improve with oral higher dose amoxicillin (3 g twice daily). These improvements occurred despite culture of apparently resistant organisms.

Prolonged nebulised antifungal therapy with natamycin was unhelpful in a double blind placebo controlled study<sup>16</sup> of patients with allergic bronchopulmonary aspergillosis, many of whom had evidence of bronchiectasis (D C Currie, personal communication).

#### TECHNIQUE AND DRUGS

The main potential problems with nebulised antimicrobial therapy are bronchospasm and/or chest tightness. These are especially relevant in a disease characterised by increased bronchial hyperreactivity and asthma. The characteristics of the final drug solution, in particular isotonicity, and the nebuliser system are important. The clinical relevance and frequency of the selection of antibiotic resistant organisms are unknown. The frequent use of antibiotics orally and intravenously in patients with purulent sputum complicates the assessment of the balance between risk and benefit of the nebulised route for antibiotics.

Nebulised colistin,<sup>17</sup> aminoglycosides, antipseudomonal penicillins, and third generation

cephalosporins have been prescribed for individual patients in recent years. Controlled studies of efficacy are long overdue.

#### Recommendations for the use of nebulised antibiotics in bronchiectasis

Long term nebulised antibiotics should be considered when background symptoms, severity of acute exacerbations, or risk of progression warrant them, provided that antibiotics by other routes combined with regular postural drainage have been found unsuccessful, unsatisfactory, or not tolerated. Nebulised antibiotics should usually be used *as an adjunct* to regular home postural drainage and courses of oral or intravenous antibiotics for acute exacerbations.

#### CHOICE OF ANTIBIOTIC

Sputum culture may not reveal the particular bacteria responsible for triggering the host inflammatory response. The presence of *Pseudomonas aeruginosa* makes response to non-antipseudomonal antibiotics less likely<sup>2</sup> and should encourage use of nebulised antipseudomonal antibiotics analogous to their usage in patients with cystic fibrosis with similar drugs and dosages (see paper on pp S69–71). Nebulised gentamicin (80 mg twice daily, each dose diluted with 0.9% saline to a total volume of 4 ml, unlicensed indication) is presently the author's preferred choice. In addition, nebulised amoxicillin (500 mg twice daily diluted in 3–5 ml sterile water; unlicensed indication) is worth considering in patients intolerant of oral amoxicillin as a result of gastrointestinal side effects or vaginal candidiasis.

#### ANTIBIOTIC DELIVERY

Antibiotics require either a breath controlled open vent nebuliser such as the Ventstream (Medic-Aid Ltd) with a standard compressor or a high powered compressor with a standard nebuliser (see paper by Webb and Dodd on pp S69–71). A single dose trial of nebulised antibiotic is advisable with measurement of PEFR and spirometric parameters before, immediately after, and 15 minutes after nebulisation.<sup>18</sup>

It is logical for nebulised antibiotics to be preceded by self-physiotherapy and, if necessary, bronchodilators. Precise recommendations with respect to use of outflow filters or venting out of the window are not possible. Further research is required in this area. The approach outlined in the paper on cystic fibrosis is one possible strategy. However, it may be possible to use filters for longer and it may be helpful to use them at home as well as in hospital.

#### EVALUATION

Treatment must be carefully evaluated in each patient. Specific questions should be answered. Is the purulent sputum volume between exacerbations reduced after starting nebulised

antibiotics? Does the patient feel better? Are the sputum-related acute exacerbations reduced in frequency and/or severity? Is lung function improved?

If the drug is ineffective or not taken regularly, it should be stopped. A guide time for the evaluation of benefit from nebulised antibiotics is three months.

### Conclusion

A therapeutic trial of long term nebulised antibiotics with careful evaluation is justified in individual patients when background symptoms, severity of acute exacerbations, or risk of progression warrant antibiotic therapy, provided that antibiotics by other routes combined with regular postural drainage have been unsuccessful. Nebulised antibiotics should usually be used as an adjunct to home postural drainage and courses of oral or intravenous antibiotics for acute exacerbations.

Nebulised bronchodilator therapy is indicated in a small number of patients with bronchiectasis and the need should be evaluated as for patients with asthma and chronic obstructive airways disease.

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