Nebulised bronchodilators, antibiotics and rhDNase for children with cystic fibrosis

D A Spencer

Bronchodilators
Nebulised bronchodilators are used extensively in children with cystic fibrosis, but in many instances this use is not yet based on objective evidence of clinical benefit.

MODES OF ACTION
The main effect of bronchodilators is probably to reduce smooth muscle spasm in the airways of patients with cystic fibrosis. In addition, improved mucociliary clearance has been shown in vivo following subcutaneous administration of terbutaline to adults with cystic fibrosis and also, theoretically, β agonists might reduce inflammatory damage. The relative importance of these mechanisms and their clinical relevance are unknown.

The occurrence of reversible airways obstruction in children with cystic fibrosis is largely a reflection of the frequency of asthma in the whole paediatric population (perhaps 15%), as well as an increase in bronchial responsiveness secondary to the complex chronic inflammation present in their airways. Over a third of patients with cystic fibrosis will show evidence of reversible airways obstruction at some time, but the response in individuals is extremely variable. The interpretation of these results is hampered by poor reproducibility of pulmonary function measurements. In view of this variability a therapeutic trial of regular β agonists is appropriate in children with cystic fibrosis who wheeze, or in cases where there is a marked improvement in symptoms or pulmonary function following a test dose. The routine use of methacholine challenge is not recommended. It is not known whether the responses to β agonists or anticholinergic agents vary with age.

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long to continue nebulised colistin in patients without new symptoms, or whether it may be advantageous to remain on this medication indefinitely in view of the poorer prognosis associated with chronic infection.17

Similarly, it is not yet known whether initiating treatment with long term nebulised anti-pseudomonal antibiotics at the time of diagnosis may delay or prevent the onset of colonisation.

**PRACTICAL ASPECTS**

A face mask should be used instead of a mouthpiece in infants and younger children who will not tolerate one. Nasal deposition of drugs may be less important in this age group than in adults. A lower flow compressor with an active Venturi system is preferred for children.

**rhDNase**

Treatment of cystic fibrosis with nebulised rhDNase is considered in detail in the paper by Conway and Watson on pp S64-68. The following discussion concerns particular aspects relevant to children.

rhDNase administered by nebuliser in a dose of 2.5 mg once daily to patients with cystic fibrosis with moderately severe suppurative lung disease results in a small but significant improvement in pulmonary function with a mean increase of about 6% in forced expiratory volume in one second.18,19 The onset of benefit is rapid and appears to be maintained for the duration of treatment, at least up to 24 weeks.20 Pulmonary function returns to the previous baseline within 48 hours of discontinuance. Treatment appears to be safe, with the only consistent adverse effect being mild pharyngitis. Longer term treatment is associated with a very small reduction in the likelihood of patients requiring intravenous antibiotics.21 As pulmonary function predicts mortality in patients with cystic fibrosis,22 it can be expected that this treatment might lead to an increased life expectancy but there have, as yet, been no long term studies to examine this.

**PATIENT ELIGIBILITY**

The only published data available are for patients with moderately severe suppurative disease with a forced vital capacity of >40% predicted. One report suggests that a similar degree of benefit is obtained in patients with more severe disease23 but that the time taken to achieve a plateau is longer.

There are no available data on the use of rhDNase in children under five years or in older children with clinically mild disease, and as yet there is no evidence to support the use of rhDNase as a prophylactic agent in preventing the onset of suppurative lung disease.

**PRACTICAL ASPECTS**

The cost of rhDNase treatment has prompted early publication of guidelines both in the USA24 and the UK,25 even though data with which to formulate them are scanty. These guidelines, however, are not intended to be prescriptive and it is emphasised that patients with a broad spectrum of pulmonary disease may benefit. The UK guidelines suggest that patients likely to benefit would fulfil the following criteria: (1) aged over five years; (2) have purulent sputum or, in young children, a productive cough; (3) have had more than one exacerbation of respiratory infection requiring intravenous antibiotics in the last 12 months; (4) a forced vital capacity of <80% predicted for height when in a stable state; and (5) be compliant with previous treatments.

It is recommended that treatment should be initiated under the direct supervision of a cystic fibrosis specialist. Most children with moderate suppurative disease can be managed as outpatients but those with severe or unstable disease may be better beginning treatment as an inpatient under the close supervision of a cystic fibrosis physiotherapist.

The recommended starting dose is 2.5 mg once daily. Occasional patients may benefit from an increase to 2.5 mg twice daily, but there is no evidence of any further benefit from a larger daily dose. Only 30% of patients treated will have a statistically significant improvement in pulmonary function26 and a therapeutic trial is necessary in each case. The optimal duration of such a trial is uncertain. Although most patients with moderately severe disease show a response within 14 days, children with more severe disease may require a trial of up to perhaps, three months.

The current guidelines27-28 assess outcome mainly in terms of improvement in pulmonary function. They take no account of subjective benefits and improved well being resulting from easier expectoration of sputum and there is, as yet, no published information on quality of life. As cystic fibrosis can be a severely debilitating condition in children, such data are urgently required to enable the use of rhDNase to be justified if subjective benefit can be demonstrated even in the absence of changes in lung function.

rhDNase is not licensed for use in children under the age of five years because of limited data on its use in this age group. Nevertheless, it is likely that some young children with suppurative lung disease will benefit, although this may be difficult to quantify because of the problem of obtaining reliable pulmonary function measurements.

References

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