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Nebulised bronchodilators, corticosteroids, and rhDNase in adult patients with cystic fibrosis

S P Conway, A Watson

Bronchodilator therapy

Bronchodilators are commonly prescribed for adult patients with cystic fibrosis and their judicious use is seen by most physicians as "good clinical practice". There is, however, a dearth of clinically relevant research addressing their efficacy, optimal dosage, method of delivery, or responses to single and combined therapy with β agonists and anticholinergic agents. The importance of allergy and hyperreactivity remains poorly understood. Published studies are bedevilled by small patient numbers, short term results, often heterogeneous patient groups, different outcome criteria, and a concentration on the use of metered dose inhalers.

RATIONALE FOR BRONCHODILATOR USE IN ADULT PATIENTS WITH CYSTIC FIBROSIS

The lungs of patients with cystic fibrosis are progressively compromised by airway obstruction.[1–3] Viscid secretions, increased compressibility of the airways in expiration,[4] and fixed structural damage to the bronchial tree from ongoing airway inflammation may all contribute to symptoms. Lung function is compromised by air trapping, loss of lung recoil, and reduced expiratory flow,[5 6] with resulting wheeze and exercise limitation,[7–9] but airway obstruction is not irreversible in all patients. Bronchoconstriction responsive to bronchodilator therapy makes a variable contribution to the overall airway obstruction.[3]

Bronchodilators are beneficial during hospital admissions for intravenous antibiotic treatment of acute respiratory exacerbations[10] when airway obstruction is often increased.[11] Hordvik *et al* showed responsiveness to nebulised isoetherine increasing during hospitalisation, with the response significantly correlating with improvements in baseline forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and mid forced expiratory flow ($FEF_{25–75}$) measurements.[12] This probably reflects bronchodilator induced mobilisation of secretions with resultant increases in lung function.

The ability of bronchodilator drugs to increase mucociliary clearance may be as important as their primary action and they are particularly useful before chest physiotherapy or bronchial drainage.[5 13 14]

Regional Adult Cystic Fibrosis Unit, Seacroft Hospital, Leeds LS14 6UH, UK
S P Conway
A Watson

Correspondence to:
Dr S P Conway.

BRONCHIAL HYPERREACTIVITY IN PATIENTS WITH CYSTIC FIBROSIS

Bronchial hyperreactivity, shown by short term improvement in spirometric values after bronchodilators and by positive bronchoprovocation tests (see below), has been reported in 25–66% of study populations.[2 7 9 15–20] Although hyperreactivity may be a distinct and separate condition in patients with cystic fibrosis, it is more likely to be a reflection of the underlying disease, the progressive inflammation and epithelial damage altering mucosal permeability and histamine penetration.[21] Both the extent and prevalence of bronchial hyperreactivity and obstruction may increase with age.[18 22] Thus, as airways become more structurally damaged they may also become more responsive to bronchodilator treatment.[20 23]

Probably because of the additional factor of airway instability,[24] the bronchial hyperreactivity seen in cystic fibrosis differs from that seen in uncomplicated asthma.[2] The less responsive cystic fibrosis airway may require optimally delivered, high dose, long term bronchodilators to maximise the therapeutic response.

Patients with bronchial hyperreactivity are perhaps those most likely to respond to nebulised bronchodilator therapy,[20] and those whom clinicians might wish to preselect for such treatment. They may form a special subgroup characterised by a more rapid clinical deterioration, more severe disease, and more respiratory exacerbations, and are thus particularly in need of maximal therapy.[18] There is, however, no reliably easy way of identifying them.

Bronchial provocation testing is the best method for detecting bronchial hyperreactivity in patients with cystic fibrosis but it is not routinely available, is poorly repeatable,[25] and may not predict all patients who will benefit from bronchodilators.[20]

EVIDENCE FOR THE EFFICACY OF BRONCHODILATOR THERAPY IN CYSTIC FIBROSIS

There is a paucity of acute response data to bronchodilators[26] and no studies of long term nebulised bronchodilator therapy in cystic fibrosis. It is therefore necessary also to refer to data from work on delivery by metered dose inhaler.[19] Inhalation of high dose nebulised bronchodilator for 10 minutes might reasonably be expected to have the greater efficacy, given the viscid mucus barrier between drug and receptor. Mixed study populations of adults and children have shown significant increases in expiratory flow in up to one third of patients after β agonist or anticholinergic bronchodilators delivered by metered dose inhaler[27] and nebuliser.[15 28] Adult patients are more likely to show a response.[17 20 22]

Assessment of bronchodilator responsiveness in individual patients is complicated further by within patient variability,[12 16] reflecting the fluctuations in the degree of inflammation, secretory load, mucosal oedema, or bronchospasm present at different points in time, and the effect of acute infective changes on the underlying chronic lung disease.[3] Most studies have reported no relationship between the degree of bronchodilator response and atopy.[12 17 20 24 27]

COMBINED β AGONIST AND ANTICHOLINERGIC THERAPY

Nebulised bronchodilator therapy appears to be a useful adjunct in the management of acute respiratory exacerbations.[10 12] Hordvik *et al* showed significant improvements in baseline spirometric tests in patients admitted to hospital treated with either nebulised albuterol or placebo before physiotherapy.[29]

The potential for an additive bronchodilator effect by combining ipratropium bromide and a β agonist has not been widely addressed. Weintraub *et al* studied the acute response to inhaled placebo, ipratropium bromide 40 μg, metaproterenol 1500 μg, and combined bronchodilator therapy delivered by metered dose inhaler in 10 randomly selected adult patients.[22] Eight had a clinically significant improvement with at least one of the regimens, with a tendency for those who responded to one regimen to respond to the others. Only two of the 10 patients showed a marked benefit from combination therapy. Sanchez reported a better response of respiratory function tests (FEV_1 increasing by 17%) and airway resistance to albuterol 5 mg and ipratropium bromide 250 μg delivered by nebuliser and face mask than to either drug when used alone in a mixed patient group of children and adults. Ipratropium bromide was needed to achieve a fall in FRC and residual volume (RV).[30]

Ipratropium bromide appears to be more effective in patients with negative bronchoprovocation test results.[20] We recommend that all patients should have respiratory function tests monitored before and after inhalation of both β agonists and anticholinergic bronchodilators, singly and in combination, to determine the optimal treatment regimen.

POTENTIAL FOR A DETRIMENTAL BRONCHODILATOR EFFECT ON LUNG FUNCTION IN ADULT CYSTIC FIBROSIS

Zach[3 4] has proposed, on theoretical grounds, that bronchodilation may reduce end expiratory flow rates and thus perhaps reduce coughing efficiency. The relevance of this to clinical practice is uncertain.[31] Deterioration after inhaled bronchodilator treatment is rare[12 15 23 26 32–34] and is not a problem in practice.

CONCLUSION

A significant percentage of adult patients with cystic fibrosis may benefit from bronchodilator therapy. There is no reliable method for predicting those patients who will respond and all patients should be given a trial of nebulised bronchodilators when clinically indicated.

Corticosteroid therapy

Inhaled corticosteroids, delivered by metered dose inhaler or nebuliser, are widely used in the management of adult patients with cystic fibrosis. There are few controlled studies documenting the efficacy of inhalers and no studies on the use of nebulised corticosteroids.

INDICATIONS

There are three indications for inhaled corticosteroids:

(1) The treatment of bronchial hyperreactivity associated with a worse prognosis and more severe exacerbations.[18]

(2) To decrease the destructive inflammatory responses. Persistent airway inflammation, rather than infection, produces the most significant lung damage in cystic fibrosis.[35] Even patients with mild disease (mean FEV_1 >80% predicted value) show a marked inflammatory response in the epithelial lining fluid.[36] A double blind randomised study of alternate day oral prednisone (2 mg/kg to a maximum of 60 mg) in 45 children with cystic fibrosis improved lung function and reduced the need for hospital admission.[37] Larger follow up studies, however, showed an unacceptable incidence of adverse side effects.[38] Inhaled corticosteroids may confer clinical benefit without producing these side effects, both during acute respiratory exacerbations[39] and as maintenance therapy.[40–42]

(3) To reduce the progressive decline of FEV_1. Retrospective and prospective studies of inhaled corticosteroids in patients with chronic obstructive pulmonary disease suggest that they may reduce the rate of decline of respiratory function[43–48] but there is no evidence in patients with cystic fibrosis.

CONCLUSIONS

Inhaled corticosteroids have significant theoretical therapeutic potential in cystic fibrosis where ongoing inflammation is at the heart of the disease process. It would be reasonable to consider treating those patients who have shown reversibility with bronchodilators, a history of asthma or allergy, or a previous response to oral prednisolone, although there is no reason to deny any patient a therapeutic trial. We do not know the optimal dose, nor if delivery by nebuliser is more effective than by metered dose inhaler. Studies in chronic obstructive pulmonary disease, however, suggest that high doses are needed for maximal effect. Well defined, controlled clinical trials are urgently needed. We favour twice daily, high dose (1 mg) nebulised budesonide as additional treatment for a respiratory exacerbation and for maintenance therapy. Patients already receiving nebulised antibiotics, bronchodilators, and/or rhDNase may not comply with this additional

encroachment on their time,[41] especially as they are unlikely to perceive any immediate benefit, and should be offered treatment with metered dose inhalers.

rhDNase (Dornase alpha, Pulmozyme)

The epithelial lining fluid from the lung of patients with cystic fibrosis shows a large predominance of polymorphonuclear leucocytes compared with normal controls.[36] The thick purulent sputum characteristic of cystic fibrosis is enriched with DNA derived from disintegration of these neutrophils[49 50] as the inflammatory process outstrips the ability of deoxyribonuclease 1 (DNase 1), a naturally occurring human enzyme, to digest extracellular DNA. The latter is a viscous polyanion and a major determinant of the viscosity of the respiratory secretions. DNA containing fractions of the sputum may further decrease the efficacy of treatment by binding aminoglycoside antibiotics.[51 52]

Human DNase 1 has been cloned, sequenced, and expressed as recombinant DNase 1, rhDNase (Pulmozyme), and shown to reduce dramatically the viscosity of the sputum in cystic fibrosis.[50] Well defined phase I, II, and III trials of rhDNase in patients with mild to moderate cystic fibrosis (FVC >40% predicted) have shown that it results in a modest improvement in respiratory function and a modest decrease in the frequency of respiratory exacerbations.

SUMMARY OF PHASE I, II, AND III TRIALS

In phase I studies[53 54] rhDNase was well tolerated to a maximum dose of 30 mg/day without development of DNase antibodies and with significant improvement in lung function. FEV_1 increased by 10–20% from baseline but returned to pretreatment levels within one week of the study. As the total sputum volume did not increase with treatment it was hypothesised that rhDNase enhanced the removal of mucus from areas where the normal cough and mucociliary mechanisms were ineffective.

Phase II studies confirmed the safety profile of the drug and showed short term efficacy.[55 56] Almost one third of patients showed a >20% increase in FEV_1 with 2.5 mg rhDNase twice daily.[56] Both studies reported a significant reduction in subjective perception of cystic fibrosis related symptoms. Adverse events were limited to mild upper airway irritation.

A double blind placebo controlled phase III study[57] in 968 patients over 24 weeks showed a sustained improvement in FEV_1 of approximately 6% and a reduced relative risk of a respiratory exacerbation requiring intravenous antibiotics of 31% in patients treated with rhDNase 2.5 mg once or twice daily. Patients experienced less dyspnoea and an increased sense of well being. The major side effect was transient voice alteration. This trial was continued as an open label study of rhDNase, 2.5 mg daily, and the treatment continued to be well tolerated at two years. The risk of infection related respiratory infection remained lower than during placebo treatment and the improvement in respiratory function was maintained.[58]

Subgroup analysis of the phase III study showed that patients with mild lung disease (baseline FVC >85% predicted) also benefited from treatment with a decrease in the relative risk of pulmonary exacerbations and an increase in FVC of about 4%. Chronic inflammation is present even in the mildly affected lung.[36] By mobilising secretions and decreasing the incidence of respiratory exacerbations, rhDNase may effect a delay in the progression of lung disease in these patients.

LATEST RESEARCH

Early studies of rhDNase use in acute respiratory exacerbations and severe disease (FVC <40%) were not sufficiently powerful to assess efficacy but showed good patient tolerance of the drug.[59 60] An open label 12 week study in the latter group has since shown a significant increase in lung function,[61] perhaps not surprising as all severely affected patients are likely to have markedly increased levels of DNA in their sputum. Compared with placebo, FEV_1 increased by 7% and FVC by 5% with treatment. The study power was insufficient to show a significant reduction in infective exacerbations in the treatment group.

PRACTICAL ASPECTS OF RHDNASE ADMINISTRATION IN CYSTIC FIBROSIS

Patients should commence treatment with rhDNase under the guidance of a cystic fibrosis centre to ensure that they receive the proper training for drug administration, and the maintenance and cleaning of the equipment.[62 63] Daily treatment is necessary to maintain the therapeutic benefit. Patients must use a recommended nebuliser system only and inspire at a normal rate and depth through a mouthpiece while sitting upright. Currently recommended delivery systems include the Hudson T Up-draft II, Marquest Acorn 11, or the Respirgard II with the DeVilbiss Pulmo-Aide compressor, the Pari LC nebuliser/Pari Proneb compressor, the Airlife Misty with Tee Adaptor, the Pari LL with the Inhalierboy or Master compressor, the Aiolos with an Aiolos compressor, or a Sidestream nebuliser with a CR50 compressor.[64] The latter is used by most UK centres and can be obtained through Genentech-Roche. The more powerful CR60 compressor coupled with the Sidestream nebuliser may be more effective in severe lung disease[65] but should not be used until evaluated by further clinical trials. Only jet nebulisers have been shown to deliver rhDNase effectively. Ultrasonic devices may cause thermal coagulation of rhDNase. Battery operated compressors have insufficient power.

The following points need to be emphasised when rhDNase is prescribed:

(1) To prevent degradation of the protein, rhDNase must be protected from excessive heat and strong light. It should be stored in its foil pouch in a refrigerator at 2–8°C. Special

cool boxes can be obtained for use when travelling. rhDNase should not be used if it has been exposed to room temperature for 24 hours or longer, or if it becomes cloudy or discoloured.
(2) rhDNase must not be combined with any other medications in the nebuliser as changing the characteristics of the solution might alter the rhDNase protein.
(3) We recommend that rhDNase should be inhaled after morning physiotherapy or in the late afternoon or early evening. This will maximise the effect of the before bed physiotherapy session. It is advisable to leave about two hours – and an absolute minimum of half an hour – between rhDNase inhalation and physiotherapy. Similarly, at least half an hour should be allowed between nebulised rhDNase and any nebulised antibiotic inhalation.

Because of the cost of rhDNase and the importance of continued evaluation of this new therapy, the response of all treated patients must be repeatedly assessed by monitoring spirometric values, the frequency of respiratory exacerbations, and subjective changes in dyspnoea, cough, sputum production, fatigue, appetite, sleep, exercise tolerance, and ease of sputum clearance. Patients with moderate impairment of respiratory function are likely to respond within two weeks of starting treatment. More severely affected patients may benefit most from a reduction in the frequency of respiratory exacerbations and should be assessed over a period of months.

RECOMMENDATIONS FOR RHDNASE USE IN ADULT CYSTIC FIBROSIS

Studies to date document objective and subjective benefits from rhDNase 2.5 mg daily in patients with a wide range of disease severity. The recommendations of the North American Consensus Committee for initiating treatment with rhDNase are noticeably unrestrictive. The only criterion is the physician's judgement that there is sufficient lower airway inflammation for rhDNase to be of benefit. Any patient should be considered eligible for consideration to receive DNase "if such therapy is deemed appropriate by the cystic fibrosis specialist treating the patient."[62] We would endorse these recommendations, remembering that, in a disease characterised by an annual fall in lung function that is eventually fatal at a mean age of about 30 years, any stabilisation is an important gain and any treatment that offers the possibility of improvement must be fully explored. The increase of about 6% in FEV_1 values documented in phase III studies will accrue substantial benefit to the patient over time, especially when compared with the usual decline in respiratory function. Our own practice has been to offer rhDNase therapy to the following patients:
(1) All severe patients because of the potential for preservation of lung function. These patients may need more than 2.5 mg rhDNase daily. Any increase should be in increments of 2.5 mg with sufficient time allowed between them to assess any improved response.[62] There is almost no protocol experience of doses greater than 20 mg/day.
(2) All patients showing rapid deterioration in FEV_1 despite maximal use of routine therapy.
(3) All patients with more than usual difficulties in expectorating tenacious secretions.
(4) Patients with mild to moderate disease severity (those shown to respond in phase I–III trials).
(5) Patients experiencing difficulty with moving secretions in an acute respiratory deterioration.
We do not yet recommend prophylactic rhDNase in those with normal FEV_1 or FVC values and no significant sputum production.

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