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

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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 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,18 with resulting wheeze and exercise limitation,19 but airway obstruction is not irreversible in all patients. Bronchoconstriction responsive to bronchodilator therapy makes a variable contribution to the overall airway obstruction.1

Bronchodilators are beneficial during hospital admissions for intravenous antibiotic treatment of acute respiratory exacerbations2 when airway obstruction is often increased.11 Hordvik et al showed responsiveness to nebulised isethionate increasing during hospitalisation, with the response significantly correlating with improvements in baseline forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and mid forced expiratory flow (PFEF)25 measurements.17 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.1214

Bronchial hyperreactivity in patients with cystic fibrosis

Bronchial hyperreactivity, shown by short term improvement in spirometric values after bronchodilators and by positive broncho-provocation tests (see below), has been reported in 25-66% of study populations.172022 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.12 Both the extent and prevalence of bronchial hyperreactivity and obstruction may increase with age.2021 Thus, as airways become more structurally damaged they may also become more responsive to bronchodilator treatment.1122

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

COMBINED β agonist and anticholinergic therapy
Nebulised bronchodilator therapy appears to be a useful adjunct in the management of acute respiratory exacerbations.13 14 Hordvik et al showed significant improvements in baseline spirometric tests in patients admitted to hospital treated with either nebulised albuterol or placebo before physiotherapy.15

The potential for an additive bronchodilator effect by combining ipratropium bromide and a β agonist has not been widely addressed. Weintrob ̈t 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.16 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 (FEV1, 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).17

Ipratropium bromide appears to be more effective in patients with negative bronchoconstriction test results.18 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 DEFERMENTAL BRONCHODILATOR EFFECT ON LUNG FUNCTION IN ADULT CYSTIC FIBROSIS
Zach19 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.19 Deterioration after inhaled bronchodilator treatment is rare19 20 21 22 23 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 inhaled and 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.16
(2) To decrease the destructive inflammatory responses. Persistent airway inflammation, rather than infection, produces the most significant lung damage in cystic fibrosis.20 Even patients with mild disease (mean FEV1 >80% of predicted value) show a marked inflammatory response in the epithelial lining fluid.21 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.22 Larger follow up studies, however, showed an unacceptable incidence of adverse side effects.23 Inhaled corticosteroids may confer clinical benefit without producing these side effects, both during acute respiratory exacerbations and as maintenance therapy.24 25
(3) To reduce the progressive decline of FEV1. 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 function26 27 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.28 29 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 therapy.
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. The thick purulent sputum characteristic of cystic fibrosis is enriched with DNA derived from the proteolytic breakdown of the epithelial lining fluid. The sputum of patients with cystic fibrosis may be more viscous than normal due to the presence of DNA and surfactant. The viscosity of the sputum is 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 to other mucus glycoproteins and inhibiting the clearance of mucus by the mucociliary escalator.

Human DNase I has been cloned, sequenced, and expressed as recombinant DNase I (rhDNase, Pulmozyme), and shown to reduce dramatically the viscosity of the spu-
tum in cystic fibrosis. Well defined phase I, II, and III trials of rhDNase in patients with mild to moderate cystic fibrosis (FVC >40%) 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, rhDNase was well tolerated at a maximum dose of 30 mg/day without development of DNase antibodies and with significant improvement in lung function. FEV1 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. Almost one third of patients showed a >20% increase in FEV1, with 2.5 mg rhDNase twice daily. 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 in 968 patients over 24 weeks showed a sustained improvement in FEV1, 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.

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. 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. An open label 12 week study in the latter group has since shown a significant increase in lung function, perhaps not surprising as all severely affected patients are likely to have markedly increased levels of DNA in their sputum. Compared with placebo, FEV1 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. Daily treatment is necessary to maintain the therapeutic benefit. Patients must use a recommended nebuliser system only and ensure that the equipment is 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.

The following points need to be emphasised when rhDNase is prescribed:
1. To prevent degradation of the protein, rhDNase must be protected from exposure to heat and strong light. It should be stored in its foil pouch in a refrigerator at 2-8°C. Special
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between rhDNase inhalation and physio-
theraphy. 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
evacuations, and subjective changes in dys-
phonia, cough, sputum production, fatigue, ap-
petite, sleep, exercise tolerance, and ease of
sputum clearance. Patients with moderate im-
pairment of respiratory function are likely to
respond within two weeks of starting treat-
ment. More severely affected patients may benefit
most from a reduction in the frequency of
respiratory evacuations and should be as-
seeded over a period of months.

RECOMMENDATIONS FOR RHDNASE USE IN ADULT CYSTIC FIBROSIS

Studied to date document objective and sub-
jective 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 appro-
priate by the cystic fibrosis specialist treat-
ing the patient.36 We would endorse these
recommendations, remembering that, in a dis-
ase 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 FEV1 values docu-
mented in phase III studies will accrue sub-
stantial benefit to the patient over time, es-
specially when compared with the usual de-
cine in respiratory function. Our own practice
has been to offer rhDNase therapy to the fol-
lowing 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.36

is almost no protocol experience of doses
greater than 20 mg/day.

2. All patients showing rapid deterioration in
FEV1 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 FEV1, or FVC
values and no significant sputum production.

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