Comparison of the in vitro and in vivo response to inhaled DNase in patients with cystic fibrosis

Recombinant human DNase has been shown to reduce sputum viscosity and improve pulmonary function in patients with cystic fibrosis. The individual response is, however, highly variable with between one third and two thirds of patients showing an improvement in their forced expiratory volume in one second (FEV₁) of more than 10%. In view of the high cost of this treatment and the lack of long term studies confirming its safety, prediction of the response of individual patients is an important issue. In a larger series of patients both baseline pulmonary function and the clinical status of the patient were unable to predict the outcome.

As part of a multicentre phase IIb trial we have compared the in vitro response assessed by total DNA content and fragment length in sputum with the response in pulmonary function in 92 patients with cystic fibrosis after six weeks of treatment with DNase. The study population consisted of 42 males and 50 females with a mean (SD) age of 20.6 (7.7) years with moderate pulmonary disease (50 females with a mean (SD) age of 20.6 (7.7) years with moderate pulmonary disease). All patients were clinically stable and did not receive intravenous antibiotic therapy in the month preceding the study. Most of the patients were chronically colonised with Pseudomonas aeruginosa. Sputum samples and pulmonary function tests were obtained at baseline and after six weeks of treatment with 2.5 mg DNase inhaled via a sidestream jet nebuliser with a Portaneb 50 compressor once daily. The median improvement in pulmonary function for the total group was +8% of baseline FEV₁ (range –25% to +138%) and +5.6% of baseline FVC (range –22 to +102%), similar to that reported in previous studies. The median DNA content decreased from 0.53 to 0.3 mg/ml sputum, as reported previously. A marked reduction in DNA fragment length was observed in the majority of cases but it remained unchanged in 18 patients. There was a small but significant change in the difference between the mean FVC for patients with reduced DNA content compared with those in whom the DNA content remained unchanged (median FVC 8.1% versus 3.9%, p = 0.04, Wilcoxon test). No difference was found in the improvement in pulmonary function after six weeks of treatment in those patients with biochemical evidence of DNA fragmentation when compared with those with unaltered DNA fragment length (table 1). In addition, baseline DNA content and fragment length had no influence on the individual patient’s pulmonary function after six weeks of treatment.

Assessment of sputum DNA content and fragment length are therefore not helpful in predicting the clinical response of patients receiving DNase treatment. Heterogeneity of the sputum sample or non-uniform distribution of inhaled DNase within the lung may be among the factors responsible for this finding.

Domiciliary NIPPV in COPD

I was surprised to find that the paper by Jones et al did not come up to the normally high standard of the journal. Firstly, the study design itself lacks a control group and yet attempts to make a contribution to the debate about using non-invasive positive pressure ventilation (NIPPV) to improve survival in COPD. Clearly, comparing before and after treatment as a measure of survival can be misleading as it may introduce a “placebo effect” bias that may easily swamp out any physiological improvement. In these days of systematic reviews this evidence is flimsy and may well dilute the effect of good prospective controlled randomised studies. There were a few minor errors in table 1 which, firstly, presents the transfer factor (KCO) in non-SI units and offers no conversion factor as quoted in the instructions for authors. Secondly, the units for the transfer coefficient (Kco) are expressed in ml/min instead of mmol/min/kPa/l. I would also have preferred to see the lung volumes, that were expressed as percentage of predicted, have their measured units as litres instead of just “percentage” of predicted value. Despite these shortcomings, I strongly support the final paragraph that more prospective studies on larger patient groups with clearly defined enrolment criteria are desperately needed to help secure essential funding to what providers of this service all believe is effective medical care.

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Table 1 Median (range) response in pulmonary function with DNase treatment in relation to the biochemical response assessed by DNA fragment length in sputum

<table>
<thead>
<tr>
<th>Fragment length reduced (n = 74)</th>
<th>Fragment length unchanged (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22</td>
</tr>
<tr>
<td>Male/female</td>
<td>33/43</td>
</tr>
<tr>
<td>FVC (% baseline)</td>
<td>56 (37–82)</td>
</tr>
<tr>
<td>FEV₁ (% baseline)</td>
<td>36 (14–70)</td>
</tr>
<tr>
<td>Improvement in FVC (% 6 weeks)</td>
<td>6.5 (21 to +45)</td>
</tr>
<tr>
<td>Improvement in FEV₁ (% 6 weeks)</td>
<td>8.5 (–25 to +59)</td>
</tr>
</tbody>
</table>

Lung function parameters are given as a percentage of reference values.


AUTHORS’ REPLY
We thank Dr Cooper for his interest in our paper and agree that a control group might have strengthened our conclusions. However, to establish such a group with a sham device for NIPPV over the time periods involved would, in practice, be difficult. We are aware of only one study1 in which a sham device was used. No improvements in arterial blood gas tensions were found over a three month follow up period but levels of pressure support were low in the treatment group. Inspiratory pressures of 10 cm H₂O, there was not sufficient monitoring to allow correction of CO₂, and the starting Paco₂ was only mildly raised to a mean of 48.5 mm Hg. In our group of patients who had more severe COPD, inspiratory pressures of up to 20 cm H₂O were required and our mean status Paco₂ was 8.0 kPa. A technical intervention such as NIPPV might result in a reduction in hospital or general practitioner visits through the “placebo effect” (conversely, dependency on technology might have resulted in more attendances due to anxiety or technical failings). However, we do not accept that improvement measurements such as improved arterial blood gas tensions or worsening lung function are affected by placebo.

In an attempt to obtain a control group we compared our patients with those from the MRC and NOTT trials; these well recognised studies of LTOT investigated a population similar to our own in terms of baseline characteristics, as stated in our discussion. Without the option of NIPPV, our patients would have remained on LTOT which would have been insufficient to correct hypoxia.

The SI units for transfer factor are mmol/min/kPa; the conversion factor to the customary units as litres instead of just “percentage” of predicted value.

Finally, as Dr Cooper states, most of us working in this area who see the improvement NIPPV makes to patients with severe hypercapnic respiratory failure due to COPD believe that it is an effective medical treatment. Multicentre European trials comparing LTOT with NIPPV are currently underway and the results should help to clarify the role of domiciliary NIPPV in COPD.

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Burkholderia cepacia bronchiectasis

We read with interest the case report by Ledson et al describing a non-cystic fibrosis individual with chronic Burkholderia cepacia bronchiectasis. Although B cepacia most commonly affects patients with cystic fibrosis, it is also known to infect patients with chronic ventilatory requirements or immunocompromised patients. 1 The immunocompromised patient population who appear most vulnerable to B cepacia infection are those with chronic granulomatous disease where the defect in neutrophil burst predisposes them to infection by specific organisms. Although the patient described by Ledson et al had normal immunoglobulins, we wonder whether she has a defect in either neutrophil burst or chemotaxis to explain her unusual complaint.

Childhood empyema

In October 1997 we reported an increase in the incidence of childhood empyema in Nottingham. 1 There had been no cases of childhood empyema in the city between April 1994 and April 1996, yet there had been 11 cases between April 1997 and April 1998. We have now reviewed the data for the following 12 months, from April 1997 to April 1998. During this period we have seen only three children with a diagnosis of empyema at the two paediatric departments in the city—Queen’s Medical Centre and Nottingham City Hospital. During this period there have been no further reports of increased incidence of childhood empyema since the original report by Rees et al. 2 One of the children admitted to Nottingham City Hospital in January 1998 was treated with intrapleural fibrolysin. She received eight doses of urokinase administered into the pleural space via a pigtail catheter at 12 hourly intervals. A dose of 40 000 U urokinase was diluted in 40 ml on normal saline and instilled via the catheter, which was clamped for four hours and then placed on low grade suction for a further eight hours. This patient received 13 days of intravenous antibiotics and remained in hospital for 14 days; both of these values are less than the median values for duration of intravenous antibiotics and length of hospital admission found previously (15.5 days and 17 days, respectively).

It is interesting to read of the increasing use of intrapleural fibrinolysis in children in the form of case reports and small series 3 where the treatment appears to be safe and effective. It is important, however, to emphasise the need for a randomised controlled trial of intrapleural fibrinolysis and in order to demonstrate any benefit in reducing hospital stay and preventing more invasive procedures.

Adrenal function in asthmatic children

In a recent paper published in Thorax Fitzgerald and co-authors purport to have examined the effects of fluticasone propionate and beclomethasone dipropionate on adrenal function in children with asthma. 4 They state that they have used Dickstein’s low dose ACTH test 5 to do this. However, the dose of ACTH (500 ng/1.73 m 2 ) used in Fitzgerald’s paper is a dose taken from a different paper describing a dose-response relationship between ACTH and serum cortisol concentration published by Crowley et al and a later paper by the same author comparing low dose with high dose ACTH cortisol secretory dynamics. 6 Dickstein’s paper described a low dose ACTH test in adults using a test dose of 1 µg. This dose was not standardised for body surface area and antici-

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AUTHORS’ REPLY

Dr Suresh and Doull suggest that the chronic B cepacia colonisation of the respiratory tract in our patient may be due to a peculiar defect in her immune system, specifically an abnormality of neutrophil burst or chemotaxis. We presume they base this speculation on their experience of chronic granulomatous disease in children where acute infections with B cepacia have been described. However, our patient is a mature adult who has had an unremarkable past medical history with no evidence of recurrent childhood infections. She has never required ventilation and, despite exhaustive testing, we have been unable to demonstrate any defect in her immune system.

Furthermore, we have tested her neutrophil burst function (using the nitroblue tetrazolium slide test) 3 and found it to be normal. We have not assessed her neutrophil chemotaxis since this is not easily performed. However, such disorders of neutrophil function predispose to infections with catalase positive organisms and usually present at an early age with staphylococcal or fungal infections, particularly of the skin and lung. 8 Our patient gives no such history and we are therefore confident that she does not have an abnormality of neutrophil chemotaxis.

We thank the authors for their comments and welcome any further suggestions that may throw light on the management of this difficult clinical problem.

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We thank the authors for their comments and welcome any further suggestions that may throw light on the management of this difficult clinical problem.
work of Crowley et al from 19911 and 19931 using LDST (0.5 µg/1.73 m2) and are happy to acknowledge their contribution of patients to the literature. However, the relevance of the papers by Crowley et al1 to our paediatric asthmatic population is unclear. Indeed, the data presented by Crowley et al are not in asthmatics, nor in subjects chronically exposed to high dose inhaled and intermittent systemic corticosteroids. Whether their data are directly applicable to an entirely different cohort of paediatric patients with chronic disease should be further investigated.

In our study an additional cortisol sample 14 minutes after ACTH administration would have allowed the question about a possible missed cortisol peak. However, Broide et al2 measured serum cortisol levels at 20, 30, and 45 minutes after 0.5 µg/1.73 m2 ACTH and found similar levels at 20 and 30 minutes in both healthy controls and asthmatic subjects on inhaled corticosteroids. Thus, we believe it unlikely that we have missed the peak cortisol response. Furthermore, we could not demonstrate a difference between treatment sequences in other measures of adrenal suppression including the baseline and 60 minute cortisol levels and the 24 hour urinary free cortisol levels. The marginally higher ACTH levels (p<0.04) in the subjects who did not receive systemic corticosteroids during the study whilst on fluticasone propionate therefore remain of uncertain significance.

We believe that to suggest our data are “largely irrelevant” seems harsh based upon the evidence currently available.

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2 Crowley S, Hindmarsh PC, Holownia JW, et al. The use of low doses of ACTH in the investigation of adrenal function in normal subjects who did not receive systemic corticosteroids during the study whilst on fluticasone propionate therefore remain of uncertain significance. Furthermore, we could not demonstrate a difference between treatment sequences in other measures of adrenal suppression including the baseline and 60 minute cortisol levels and the 24 hour urinary free cortisol levels. The marginally higher ACTH levels (p<0.04) in the subjects who did not receive systemic corticosteroids during the study whilst on fluticasone propionate therefore remain of uncertain significance.

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AUTHORS’ REPLY We thank Drs Smith and colleagues for their welcome comments regarding our excellent paper published in the Lancet last year. We are delighted that their findings concord with the hypothesis we raised in our editorial on serum angiotensin converting enzyme polymorphisms. We apologise for not referring to it in the text.

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BOOK REVIEW


The editors of this second edition have created a series of detailed reviews of recent advances in lung cancer research. Each chapter presents a succinct review of a relevant topic with a detailed and very useful reference list. There are chapters dealing with susceptibility and predisposition to lung cancer and clinical evaluation. Several chapters are devoted to recent advances in therapy, including surgery, radiotherapy, chemotherapy and combination therapy. Newer methods of detection are discussed in two chapters and finally novel experimental approaches to the treatment of lung cancer are discussed in three chapters. Most of the chapters are predominantly text with limited use of tables, graphics and images. However, each of the chapters is written in a succinct way that makes for easy reading.

This would be a useful text to bring one up to date with recent advances. In the preface the editors state that they “hope that this book will provide a succinct and timely summary of recent advances and new research in the field of lung cancer”. They have fulfilled this aim admirably. —DB

NOTICES

Scadding-Morrison Davies Joint Fellowship in Respiratory Medicine 1999

This fellowship is available to support visits to medical centres in the UK or abroad for the purpose of undertaking studies related to respiratory medicine. Applications are invited from medical graduates practising in the UK, including consultants and irrespective of the number of years in that grade. There is no application form but a curriculum vitae should be submitted together with a detailed account of the duration and nature of the work and the centres to be visited, confirming that these have agreed to provide the facilities required. Please state the sum of money needed for travel and subsistence. A sum of up to £15 000 can be awarded to the successful candidate, or the sum may be divided to support two or more applications. Applications should be sent to Dr I A Campbell, Secretary to the Scadding-Morrison Davies Fellowship, Llandough Hospital, Penarth, Vale of Glamorgan CF64 2XX, UK by 31 January 1999.

Basic Clinical Allergy

The 13th course on Basic Clinical Allergy will be held at the National Heart & Lung Institute, Imperial College School of Medicine, London on 15–19 March 1999. CME approval has been sought (1998 course maximum 30 credits). The main topics will include: basic mechanisms in allergic disease; cells in allergic disease; immunotherapy; allergic rhinitis; asthma (aetiology and pathogenesis); recent trends in asthma research; treatment of asthma; major allergic problems. Further details can be obtained from the Education Centre, National Heart & Lung Institute, Imperial College School of Medicine, Dovehouse Street, London SW3 6LY, UK (telephone +44 171 351 8172; fax +44 171 351 8246; e-mail a.c.allen@ic.ac.uk; www.med.ic.ac.uk/dh/div/mgts.htm).

Letters to the editor

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