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.1 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%.1 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.2 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 (FEV1 50–70% predicted (mean (SD) 54.9 (9.8)%). All patients were clinically stable and did not receive intravenous antibiotic therapy in the six weeks prior to 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.1 The median DNA content decreased from 0.53 to 0.3 mg/ml sputum, as reported previously.3 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 difference in the change in 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 al4 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 (TLCO) 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. 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.

B G COOPER
Chairman ARTP,
Lung Function Department,
City Hospital,
Nottingham NG5 1PB, UK

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 shamb device for NIPPV over the time periods involved would, in practice, be difficult without the awareness of only one study in which a shamb 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 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 (versely, dependency on technology might have resulted in more attendances due to anxiety or technical failings). However, we do not accept that these 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 is to multiply by 0.335 or divide by 2.886. Transfer coefficient units are mmol/min/kPa/l. The lung volumes in table 1 are quoted in both litres and percentage predicted.

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.

S E JONES
S M PACKHAM
M H HERBDIN
A P SMITH
Chest Department,
Llandough Hospital,
Penarth,
South Glamorgan,
CF64 2XX, UK

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></td>
</tr>
<tr>
<td>Male/female</td>
<td></td>
</tr>
<tr>
<td>33/41</td>
<td></td>
</tr>
<tr>
<td>FVC (% baseline)</td>
<td></td>
</tr>
<tr>
<td>56 (37–82)</td>
<td>59 (41–74)</td>
</tr>
<tr>
<td>FEV1 (% baseline)</td>
<td></td>
</tr>
<tr>
<td>36 (14–70)</td>
<td>41 (21–67)</td>
</tr>
<tr>
<td>Improvement in FVC (%)/6 weeks</td>
<td></td>
</tr>
<tr>
<td>6.5 (–25 to +45)</td>
<td>3 (+22 to +26)</td>
</tr>
<tr>
<td>Improvement in FEV1 (%)/6 weeks</td>
<td></td>
</tr>
<tr>
<td>8.5 (+25 to +59)</td>
<td>6.5 (+14 to +78)</td>
</tr>
</tbody>
</table>

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

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 chronic ventilatory requirements or immunocompromised patients, it is also known to infect patients with chronic ventilatory requirements or immunocompromised patients. 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.

S UREISH
ILOO DOULL
Cystic Fibrosis Respiratory Unit, University Hospital Wales, Heath Park, Cardiff CF4 4XW, UK

Childhood empyema

In October 1997 we reported an increase in the incidence of childhood empyema in Nottingham. 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 1996 and April 1997. 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 by the paediatric department 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.4 Of the children admitted to Nottingham City Hospital in January 1998 was treated with intrapleural fibrinolysis. 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 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 in order to demonstrate any benefit in terms of reducing the incidence of childhood empyema and preventing more invasive procedures.

S D PLAYFOR
R J STEWART
Paediatric Intensive Care Unit, Queen's Medical Centre, Nottingham NG7 2UH, UK

AUTHORS' REPLY We thank Drs 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 that 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 test3) and found it to be normal. We have not assessed her neutrophil chemotaxis since this is not easily done. 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.4 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.

MARTIN LEDSON
MARTIN WALSH
The Cardiothoracic Centre, Thomas Dyers, Liverpool L14 3PE, UK

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. They state that they have used Dickstein's low dose ACTH test4 to do this. However, the dose of ACTH (500 ng/1.73 m2) 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 doses with high dose ACTH cortisol secretory dynamics.5 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 as is currently the case, namely twice the size of the dose used by Crowley et al. The cortisol secretory dynamics in the two low dose tests are likely therefore to differ as timing of the peak cortisol response is partly determined by the timing of ACTH administration. The low dose ACTH test described by Crowley showed that 80% of the time the peak cortisol response after bolus intravenous injection of 500 ng/1.73 m2 ACTH has occurred by 20 minutes, and the test protocol calls for sampling at five minute intervals from 10 to 30 minutes after injection to optimise identification of the peak cortisol response. It is also important to note that the rise in serum cortisol concentration at 20 minutes is identical after both high and low dose ACTH injection in normal volunteers. It is likely that, by taking samples at 30 and 60 minutes only, Fitzgerald has missed the peak cortisol response at 1.73 µg ACTH. Taken in this context, the higher serum ACTH levels observed in the children during treatment with fluticasone may be important. Thus, Fitzgerald's findings regarding adrenal function may not be relevant and should be challenged.

SUZANNE CROWLEY
Department of Paediatric Respiratory Medicine and Intensive Care, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK

AUTHORS' REPLY We thank Dr Crowley for her interest in our recent article regarding the use of a low dose synacthen test (LDST) in monitoring moderately severe paediatric asthmatic subjects with potential for adrenal suppression.1 Dr Crowley challenges the interpretation of our results based upon data in her two papers in “eight healthy young male volunteers aged 20–22 years” and “six healthy young adult males aged 20–22 years.” Firstly, the ACTH dosing regime used in our study was arbitrarily chosen at the time of designing the study following communication with Dickstein’s group in Israel. Dickstein and colleagues published reports in 1991 using ACTH doses of 1 µg in 20 adults4 and in 1995 using 0.5 µg/1.73 m2 in a population of healthy volunteers (n = 33) and asthmatic children and adults (n = 46). In our paper we referenced this work. We are aware of the
work of Crowley et al from 1991' and 1993' using LDST (0.5 µg/1.73 m) 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 entire 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 answered the question about a possible missed cortisol peak. However, Broide et al6 measured serum cortisol levels at 20, 30, and 45 minutes after 0.5 µg/1.73 m³ ACTH and found similar levels at 20 and 30 minutes in both healthy controls and astmatic 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.

DOMINIC FITZGERALD
PETER VAN ASPEREN
CRAIG MELLIS
MAREE A HONNER
LUCIA SMITH
GEOFFREY AMBLER
The Royal Alexandra Hospital for Children
PO Box 3515,
Parramatta, Sydney,
New South Wales,
Australia 2124


Serum angiotensin converting enzyme

Marshall and Shaw in their editorial are correct to hypothesise that the normal range of serum angiotensin converting enzyme (SACE) would be narrower if ACE genotype (insertion/deletion; ID) is also taken into account. This would split its wide normal range into three narrower ranges defined by the genotypes II, ID and DD, with SACE concentrations rising co-dominantly with each copy of the D allele. However, they fail to realise that we have already shown that, not only is this the case, but also if SACE is measured in accordance with ACE genotype its diagnostic sensitivity in acute sarcoidosis is improved by 33.5%. We previously determined a genotype based normal range for SACE with 146 healthy white volunteers. Using this normal range, SACE was measured in 29 patients with histologically proven sarcoidosis. The new SACE genotype based normal range identified 69% of these patients, an improvement of 33.5% on the previous normal range which identified only 51.7% of our patients with sarcoidosis. Importantly, our work has also been independently confirmed.3

We suggest that the genotype based SACE normal range should be determined locally (especially for different racial populations) to improve its sensitivity in the diagnosis of active sarcoidosis.

PANKAJ SHARMA
BHPC Clinician Scientist
Clinical Pharmacology Unit,
University of Cambridge,
Cambridge, UK

IAN SMITH
JOHN SCHNEERSON
Papworth Hospital,
Papworth Everard,
Cambridge CB3 8RE, UK

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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
Domiciliary NIPPV in COPD

B G COOPER

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doi: 10.1136/thx.54.1.91a

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