

## LETTERS TO THE EDITOR

### Spacer devices in asthma

The British guidelines on asthma management and other recent reviews have widely advocated the use of spacer devices for asthmatic patients.<sup>1-3</sup> Spacer devices allow aerosol to be inhaled through a valved mouthpiece during a single inspiratory breath or as is often recommended for children during tidal breathing.<sup>2</sup> During the expiratory phase of a tidal breathing manoeuvre the valve closes. Although this action prevents leakage of aerosol from the spacer and ingress of moisture into the holding chamber, there is an inevitable increase in the expiratory resistance. We have measured the resistance to expiratory airflow in two commonly used spacer devices: the Volumatic (GlaxoWellcome) and the Nebuhaler (Astra-Zeneca) and found it to be high. Expiratory resistance was measured by passing air through the mouthpiece using a sealed connection. Two flow rates were chosen and measured using a Gap Rotameter: 30 l/min designed to mimic airflow during quiet expiration and 100 l/min to mimic more active expiration. Pressures were measured at the mouthpiece using a Hewlett Packard differential pressure transducer and resistances calculated. In an attempt to reduce the resistances the spacers were then modified by drilling four holes of 5 mm diameter proximal to the valve around the mouthpiece. Each hole was covered with a strip of latex rubber attached to the mouthpiece with tape so as to function as a "blow-off valve". Expired air could then flow

out through the "blow-off valves" during expiration but not during inspiration (fig 1). Pressure measurements were repeated and resistances (in cm H<sub>2</sub>O/l/s) were calculated (table 1). The valves of the modified spacers continued to function by closing during expiratory flow despite the lower resistances.

The results indicate high expiratory resistance in both unmodified spacer devices at both low and high flow rates. The values are well in excess of the minimal recommended values of expiratory resistance for diagnostic spirometry (1.5 cm H<sub>2</sub>O/l/s at flow rates of <840 l/min).<sup>4</sup> Introducing blow-off valves significantly lowered the expiratory resistance. The high resistances may explain both our observations and those of others that some patients find it difficult to expire through some types of spacer devices.<sup>3</sup> Over a series of several breaths, tidal volume may reduce while the functional residual capacity increases as the chest becomes progressively hyperinflated. Simple modification of the mouthpiece allows marked reduction in the expiratory resistance. This should facilitate the correct use of spacer devices and enhance drug deposition in the lungs. We therefore urge manufacturers to look at the possibility of modifying their spacer devices. It is likely that such modification would facilitate the correct use of spacer devices leading to enhanced drug deposition in the lungs.

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1 British Thoracic Society, National Asthma Campaign, Royal College of Physicians of London. The British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997;52(Suppl 1):S1-21.

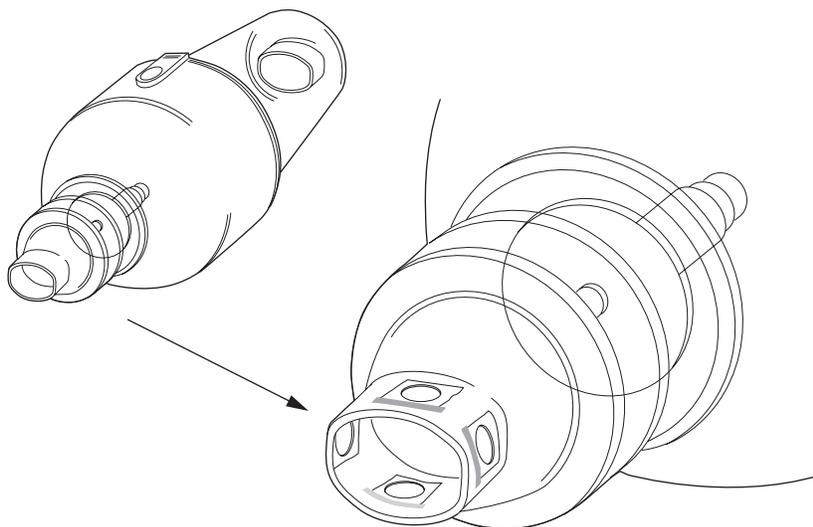


Figure 1 Unmodified and modified (close up) mouthpiece of Nebuhaler device.

Table 1 Expiratory resistances (in cm H<sub>2</sub>O/l/s) of the unmodified and modified Volumatic and Nebuhaler devices measured at 30 and 100 l/min.

	Flow rate 30 l/min		Flow rate 100 l/min	
	Unmodified	Modified	Unmodified	Modified
Volumatic	8.8	1.8	21	3.2
Nebuhaler	12.0	0.4	32	2.1

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### Intravenous montelukast

Dockhorn *et al* reported a comparison of the effect of intravenous and oral montelukast and placebo on forced expiratory volume in one second (FEV<sub>1</sub>).<sup>1</sup> They found the mean percentage change from baseline was significantly higher from 15 minutes to one hour with intravenous compared with oral montelukast, and suggested that this may be the result of more favourable interaction kinetics with the cysteinyl leukotriene receptor. The doses of montelukast chosen were based on an unpublished study which showed that the area under the plasma concentration time curve (AUC) for the 7 mg intravenous dose was comparable to the 10 mg oral dose. The time over which the AUC was measured was not stated by the authors, and all other aspects of the pharmacokinetics of these two formulations were not described. It is known that the T<sub>max</sub> of intravenous montelukast is within the first hour<sup>2,3</sup> and that the T<sub>max</sub> of oral montelukast is at approximately three hours.<sup>2,4</sup> Distribution of montelukast to the lung cysteinyl leukotriene receptors would therefore be expected to be more rapid with the intravenous formulation, causing a greater increase in FEV<sub>1</sub> at the earlier time points. The authors do not appear to have considered this possibility. The faster onset of action of intravenous montelukast was well demonstrated in this study, but we feel that an important possible explanation for this finding was inadequately discussed.

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- Zhao JJ, Rogers JD, Holland SD, *et al*. Pharmacokinetics and bioavailability of montelukast sodium (MK-0476) in healthy young and elderly volunteers. *Biopharmaceutics and Drug Disposition* 1997;18:769-77.
- Cheng H, Leff JA, Amin R, *et al*. Pharmacokinetics, bioavailability, and safety of montelukast sodium (MK-0476) in healthy males and females. *Pharm Res* 1996;13:445-8.
- Schoors DF, De Smet M, Reiss T, *et al*. Single dose pharmacokinetics, safety and tolerability of MK-0476, a new leukotriene D<sub>4</sub>-receptor antagonist, in healthy volunteers. *Br J Clin Pharmacol* 1995;40:277-80.

### Pseudomonas infection in CF

Elborn *et al*<sup>1</sup> have attempted to address the important question of whether it is better to treat patients with cystic fibrosis (CF) who have chronic *Pseudomonas aeruginosa* infection with intravenous antibiotics on the basis of symptoms or to treat them electively, and

found no significant difference between their groups. They chose a particularly unwell subgroup of the CF population to study, and one might expect a policy of increasing from three symptomatic to four elective courses of intravenous antibiotics to make the least difference in such patients. We believe that patients who require 2–4 courses of intravenous antibiotics per year anyway are not those for whom this question of treatment is most pressing to answer. The benefit of elective treatment needs to be investigated in patients who have only recently acquired *Pseudomonas aeruginosa*, as per the Danish model.<sup>2</sup> It is this group of patients for whom a recommendation of four intravenous treatments per year would be the greatest departure from current practice in most centres, and for whom strong evidence of benefit, including replication of the Danish results, is needed.

Of great concern in the study by Elborn *et al* is the finding of an excess of deaths at five years in the group treated electively. This is not well accounted for by the authors. It is possible that the patients treated electively adopted a "sick role" with concomitant reduction in physical activity contributing to deterioration. In addition, patients admitted to hospital have increased opportunity for exposure to more virulent bacteria. In the study by Elborn *et al* the organisms were identified by their resistance patterns and were similar between the groups. However, research currently underway at our institution indicates that infection with certain genotypes of *P aeruginosa* gives a worse prognosis than others, and sharing of such organisms among those frequently admitted may account for the difference in outcome at five years. We would suggest that it is important to study *P aeruginosa* genotypes to identify more accurately the possibility of cross infection being responsible for the worse outcome of the group treated electively.

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- 1 Elborn JS, Prescott RJ, Stack BHR, *et al*. Elective versus symptomatic antibiotic treatment in cystic fibrosis patients with chronic *Pseudomonas* infection of the lungs. *Thorax* 2000;55:355–8.
- 2 Frederiksen B, Koch C, Høiby N. Changing epidemiology of *Pseudomonas aeruginosa* infection in Danish cystic fibrosis patients (1974–1995). *Pediatr Pulmonol* 1999;28:159–66.

**AUTHOR'S REPLY** We thank Drs Roseby and Massie for their comments on the British Thoracic Society study comparing elective and symptomatic antibiotic treatment in patients with cystic fibrosis (CF). They raise a number of issues which are important. The patients studied were not a particularly unwell group of CF patients and they represent a very average group of patients in their second and third decade. The main difference from the patients studied in Copenhagen is that treatment in their group was initiated early in the course of *P aeruginosa* infection while patients in the BTS study had been infected for some time. We agree that

the patients who respond best to the intervention of elective intravenous antibiotics are likely to be those who have recently been infected with *P aeruginosa*. It would be useful for a further study to examine but, as most centres would have insufficient patients, this would need to be a study involving a considerable number of CF clinics.

The issue of excess deaths is concerning. This study was designed to be as simple as possible for the participating physicians so unfortunately we do not have the organisms available to look for genotypes or virulence markers. However, there was no suggestion that the patients who died had any different *in vitro* antimicrobial resistance patterns from those of survivors.

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## BOOK REVIEW

**Asthma in the Workplace. 2nd Edition**  
Leonard Bernstein, Moira Chan-Yeung, Jean-Luc Malo, David I Bernstein, Editors. (Pp 742, hardback; \$225.00). New York: Marcel Dekker, 1999. ISBN 0 8247 1963 8

Asthma caused by occupational exposures accounts for a small but important proportion of cases seen by most practising physicians. In clinical practice occupational asthma can be difficult to recognise, and once diagnosed can present substantial difficulties for both patient and physician, particularly when the diagnosis means that to a greater or lesser degree someone is going to have to change their occupation completely, or at least adopt very different working practices. The individual social and economic implications of these changes can be substantial. Given the immense scale of the spectrum of the causes of occupational asthma, it is also inevitable that many clinicians are relatively inexperienced in identifying and dealing with specific exposures. Most clinicians therefore will at some stage need a definitive and authoritative text on occupational asthma, and this book goes a great deal of the way to meeting that need.

The strength of the book is not so much in the breadth of the topics that it covers, which is essentially the same as that found in the relevant sections of any major respiratory textbook. The advantage of this text is its detail. For example, many textbook chapters include a list of exposures that have been implicated in occupational asthma, but often do not provide the specific sources of information for many exposures listed. The referencing in this book is extremely extensive, and the reader who wishes to look up detailed background material will find most of the important references listed here. This book thus provides the necessary resource for the clinician faced with an individual patient

with an individual occupational exposure to investigate what is known about that exposure, and to give the patient some context for his/her own disease. This is also likely to be very helpful for those physicians who become involved in the compensation and medico-legal arguments that may then ensue. Beyond the breadth of the literature covered by the book, there are strong chapters on the generic methodology of occupational asthma and extensive reviews of individual causes. Overall this book is a powerful resource and, on the strength of that, probably justifies its cost.—JB

## NOTICES

### Basic and Clinical Allergy 2001

Basic and Clinical Allergy will be held at the National Heart & Lung Institute, Imperial College School of Medicine, London on 2–6 April 2001. CPD/CME approval pending (2000 course maximum 28 credits). Further details are available from the Short Courses Office, Education Centre, National Heart & Lung Institute, Imperial College School of Medicine, Dovehouse Street, London SW3 6LY, UK. Telephone +44 207 351 8172; fax +44 207 351 8246; email: shortcourses.nhli@ic.ac.uk; www.med.ic.ac.uk/dh/div/mtdgs.htm.

### Pediatric Pulmonology

The 2nd World Congress of Pediatric Thoracic Disciplines will take place in Izmir, Turkey on 26–28 April 2001. For further information contact Professor Dr Oktay Mutaf, Ege University Faculty of Medicine, Pediatric Surgery Department, Izmir, Turkey. Fax +90 232 3751288; email: omutaf@med.rgr.rdu.tr

### 3rd European Meeting on Pulsewave Analysis and Large Artery Function

The 3rd European Meeting on Pulsewave Analysis and Large Artery Function will be held at the Royal Society of Medicine, London, UK on 26 February 2001. Registration fees £195.00 (full rate), £145.00 (student rate). For further information contact the Secretariat, Hampton Medical Conferences Ltd, 127 High Street, Teddington, Middlesex TW11 8HH, UK. Telephone +44 020 8977 0011; fax +44 020 8977 0055; email: hmc@hamptonmedical.com

### 4th International Symposium on Angiotensin II Antagonism

The 4th International Symposium on Angiotensin II Antagonism will be held at the Queen Elizabeth II Conference Centre, London, UK on 3–5 April 2001. For further information contact the Secretariat, Hampton Medical Conferences Ltd, 127 High Street, Teddington, Middlesex TW11 8HH, UK. Telephone +44 020 8977 0011; fax +44 020 8977 0055; email: AIIA@hamptonmedical.com