Thorax 1987;**42**:702–3

Correspondence

Paradoxical response to nebulised salbutamol in wheezy infants

SIR,—We were interested in the paper by Dr Anne Prendiville and others (January 1987;**42**:86–91) showing a significant decline in maximum flow at functional residual capacity (V̇maxFRC) in wheezy infants after nebulised salbutamol, while the airways resistance (Raw) remained unchanged. The authors claim that this results from the relative effects of bronchodilator drugs on airway calibre and airway compliance.

We, however, have found that Raw and specific conductance (sGaw) worsen after administration of salbutamol. This paradoxical deterioration was greatest at 5 minutes and lasted for up to 15 minutes.[1] We proposed that the deterioration in lung function arose because the solution used was both acidic and hypo-osmolar, properties well known to produce bronchoconstriction in asthmatic subjects.[2 3] We now have additional support for this, as in further studies we have found similar temporary deterioration in lung function after both nebulised beclomethasone and sodium cromoglycate (unpublished data). Both solutions are acidic and hypo-osmolar; neither would be expected to increase airway compliance immediately after administration.

One possible explanation for the discrepancy between our results and those of Dr Prendiville and colleagues is one of timing: we found that Raw had often returned to baseline values by 15 minutes, the time selected for measurement by Prendiville *et al*. It may be that change in V̇maxFRC persists for longer than change in Raw.

We suggest that the changes which they and we have reported will disappear if care is taken to ensure that the solutions used are pH neutral, isotonic, and preservative free.

C O'CALLAGHAN
AD MILNER
Children's Respiratory Unit
University Hospital
Nottingham NG7 2UH

1 O'Callaghan C, Milner AD, Swarbrick A. Paradoxical deterioration in lung function after nebulised salbutamol in wheezy infants. *Lancet* 1986;ii:1424–5.
2 Goodall RJR, Gervis JE, Carper DN, Bernstein A, Temple JG. Relationship between asthma and gastro-oesophageal reflux. *Thorax* 1981;**36**:116–21.
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SIR,—Dr Anne Prendiville and others recently reported that a reduction in forced expiratory flow rate may occur after inhalation of nebulised salbutamol in wheezy infants. Their findings are similar to those reported by O'Callaghan *et al*,[1] who on the basis of measurements made by a quasi-static method of measuring airways resistance proposed that the airflow obstruction was due to the osmolality or acidity of the salbutamol nebuliser solution.

We would like to propose that the bronchoconstriction following nebulised salbutamol may be due to the benzalkonium chloride present as a bacteriostatic "preservative" in the solution. When inhaled by asthmatic subjects in concentrations equivalent to that present in the salbutamol respiratory solution (0·02% v/v), benzalkonium chloride is a potent bronchoconstrictor agonist.[2] Furthermore, sensitisation to benzalkonium chloride has been reported with its repeated use in an adult with three months exposure to this agent.[3]

It is a matter of concern that a number of different nebuliser solutions, contain not only benzalkonium chloride but also other preservative agents, such as EDTA[2] and sodium metabisulphate,[4] which are known to be bronchoconstrictor agonists. Our recent work has indicated that, unless nebuliser solutions are prepared in a sterile unit dose form, antibacterial preservative agents are required to prevent colonisation of the nebuliser units by pathogenic organisms.

We recommend that nebuliser solutions are either packaged in sterile unit dose vials or formulated with preservative agents that do not cause bronchoconstriction or have the potential to increase bronchial reactivity.

RICHARD BEASLEY
PAUL RAFFERTY
STEPHEN HOLGATE
Medicine
Southampton Hospital
Southampton SO9 4XY

1 O'Callaghan C, Milner AD, Swarbrick A. Paradoxical deterioration in lung function after nebulised salbutamol in wheezy infants. *Lancet* 1986;ii:1424–5.
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3 Innocenti A. Asma professionale da benzalconio cloruro. *Medicina del Lavoro* 1978;**69**:713–5.
4 Koepke JW, Selner JC, Dunhill AL. Presence of sulfur dioxide in commonly used bronchodilator solutions. *J Allergy Clin Immunol* 1983;**72**:504–8.

**These letters were sent to the authors, who reply below.

SIR,—In replying to Dr O'Callaghan and Professor Milner we think that it is important to distinguish between observation and hypothesis.

Our airway resistance (Raw) data are entirely compatible with their report that in wheezy infants changes in resistance after nebulised salbutamol persisted for up to five minutes and were marginally increased (with a mean value of 1·4 cm H_2O_2 l^{-1} s) at 10 minutes. We made our measurements 15 minutes after nebulisation and found that Raw had not altered significantly. At that time there was a significant decline in the forced expiratory flow rate (V̇maxFRC). We did not claim that this discrepancy between Raw and V̇maxFRC was due to the relative effects of salbutamol on airway calibre and compliance but suggested, with evidence, that this could be the explanation.

We used salbutamol "nebules," which are isotonic. Small changes in osmolality, which presumably occurred during the nebulisation of control normal saline solution, had no significant effect on V̇maxFRC. O'Callaghan *et al* (their ref 1) presented no control data in their study. Their hypothesis

that changes in osmolality during nebulisation could have led to bronchoconstriction is not borne out by the failure of nebulised saline control to cause any reduction in ṾmaxFRC.

It is possible that the low pH of salbutamol solution could have induced bronchoconstriction. The pH of our normal saline ampoles is 6·0 and of salbutamol nebules is 4·0 (not 7·6 and 6·25, as found by Dr O'Callaghan). However, neither histamine solution in low concentrations (below that which induced bronchoconstriction—pH around 5) nor ipratropium bromide nebuliser solution (pH 4·0) have caused a significant decline in ṾmaxFRC in our studies.[1 2] The hypothesis that the pH of the nebuliser solution is a critical factor therefore remains speculative. More research in infants is clearly required.

In answer to the comments of Dr Beasley and colleagues, the salbutamol respirator solution used in the study performed by O'Callaghan *et al* and the salbutamol "nebules" in our study contain benzalkonium chloride. Thus the reduction in ṾmaxFRC seen 15 minutes after salbutamol nebulisation could be preservative induced.

We have performed a further study[2] of change in airway function in 17 wheezy infants after nebulised ipratropium bromide, which also contains benzalkonium chloride. At 15–20 minutes after nebulisation of 1 ml of ipratropium bromide in 1·5 ml 0·9% sodium chloride there was a significant reduction in specific airway resistance with no significant change in ṾmaxFRC. Thus benzalkonium chloride, at least when present in nebulised ipratropium bromide, does not appear to induce bronchoconstriction in these infants.

ANNE PRENDIVILLE
MICHAEL SILVERMAN
Department of Paediatrics and Neonatal Medicine
Royal Postgraduate Medical School
London W12 0HS

1 Prendiville A, Green S, Silverman M. Ipratropium bromide and airways function in wheezy infants. *Thorax* 1987;**42**:92–9.
2 Prendiville A, Green S, Silverman M. Ipratropium bromide and airways function in wheezy infants. *Arch Dis Child* 1987;**62**:397–400.

Book notices

Recent Advances in Respiratory Medicine. No. 4. Eds DC Flenley, T Petty. (Pp 285; £37.50, hardback) Edinburgh: Churchill Livingstone, 1986. ISBN 0-443-034117.

The difficulty about reviewing an anthology is that, almost always, the contributions are of varying standard, varying interest, and varying degrees of suitability for inclusion. There is no such problem here; all of the 16 chapters are well prepared, stimulating, and relevant to the practising clinician. This is the fourth volume of *Recent Advances in Respiratory Medicine* to appear after a regular interval of three years and many of the "plum" subjects for review have already been covered in earlier numbers. It is all the more remarkable that Professor Flenley and Dr Petty have managed to obtain such an interesting collection of informative reviews. Topics and authors are spread widely. The epidemiology of asthma is reviewed from New Zealand, airways responsiveness from Canada, and cell receptors and airway function in asthma from the United Kingdom. Pulmonary manifestations of AIDS are reviewed from the United States (San Francisco), the use of cephalosporins in lung disease from Italy, and the control and surveillance of tuberculosis from The Netherlands. It will be apparent already that this is a much more international collection than any of the previous volumes. Some of the contributions are condensed overall reviews of the subject rather than commentaries limited to recent advances and this is the case with the chapters on sarcoidosis, cryptogenic fibrosing alveolitis, pulmonary thromboembolism, and pleural effusion. The editors' particular interests are reflected in the next few chapters on the early pathogenesis and identification of chronic obstructive airways disease, various topics in chronic bronchitis and emphysema (diagnosis of emphysema, protease-antiprotease theory, pulmonary vasodilators, improving airflow limitation, inspiratory muscle training), domiciliary and ambulatory oxygen treatment in chronic respiratory insufficiency, and breathing during sleep in adults. There are two contributions on lung cancer—one on early identification and one on staging. Overall this is an excellent collection of reviews, which is well up to the standard of the previous volumes and which will be much thumbed over the next few years by clinicians with an interest in respiratory medicine.—RALB

Acute Lung Injury. Pathogenesis of adult respiratory distress syndrome. H Kazemi, AL Hyman, PJ Kadowitz. (Pp 270; £27.50, hardback.) Massachusetts: PSG Publishing Company, 1986. ISBN 0-88416-536-6.

This book summarises a symposium on the pathogenesis of the adult respiratory distress syndrome (ARDS) held in 1984 under the auspices of the Cardiopulmonary Council of the American Heart Association. In 19 chapters it reviews areas of lung injury research which shed light on the pathogenesis of ARDS. The authors, 43 in total, are a cross section of active researchers in ARDS in the United States. They give detailed and relatively up to date reviews of their own research and that of allied workers. There are good reviews of the pathology and pulmonary haemodynamics of human ARDS from the Boston group, but most of the chapters concentrate on experimental work in animal models or in vitro systems and have as yet little direct clinical application. The organisers of the symposium are to be congratulated for not allowing the role of the neutrophil to dominate, so that in this volume the neutrophil is viewed in the context of other mechanisms. There are two extremely good chapters on alveolar epithelial function, including active transport mechanisms and permeability and its assessment, which are balanced by chapters discussing the role of the pulmonary endothelium in vasodilatation and the generation of cyclic GMP by vascular smooth muscle, and others on the regulation of fluid balance in the lungs. Animal models of injury,