

## LETTERS TO THE EDITOR

### Regular inhaled $\beta$ agonist in asthma: effects on exacerbations and lung function

We read with interest the paper by Dr D R Taylor *et al* (February 1993;48:134-8). In the discussion the authors refer to an abstract with results of our long term intervention study in children with asthma, and focus on the decrease in FEV<sub>1</sub> that was seen after four months' treatment with regularly inhaled salbutamol. Complete results of this study have recently been published.<sup>1</sup> We think that the initial decrease can be explained by the fact that 55% of these patients were treated with inhaled corticosteroid and 48% with cromoglycate before this study. It is likely that withdrawal of anti-inflammatory treatment had resulted in a deterioration of FEV<sub>1</sub>. Another argument for this is that we did not see any further decrease occurring in FEV<sub>1</sub> between four and 22 months (end of the study). The authors also refer to an earlier study by our group<sup>2</sup> that showed a slight increase in airway responsiveness to methacholine in patients receiving regular treatment with terbutaline. Our recent study<sup>1</sup> shows that airway responsiveness to histamine remained unchanged during 22 months on regularly inhaled salbutamol. A review of the literature on the effect of  $\beta$  agonists on airway responsiveness also found no significant changes in airway responsiveness after long term treatment with these drugs.<sup>3</sup>

Our results do not support the recommendation of the authors that regular treatment with short acting  $\beta$  agonists should not be used in combination with inhaled corticosteroid.

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1 Van Essen-Zandvliet EEM, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF, and the Dutch chronic non-specific lung disease study group. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. *Am Rev Respir Dis* 1992;146:547-54.

2 Kerrebijn KF, Van Essen-Zandvliet EEM, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and  $\beta$  agonists on the bronchial responsiveness in children with asthma. *J Allergy Clin Immunol* 1987; 79:653-9.

3 Van Essen-Zandvliet EEM, Kerrebijn KF. The effect of antiasthma drugs on bronchial hyperresponsiveness. *Immunol Allergy Clin NA* 1990;10: 483-501.

**AUTHORS' REPLY** We are grateful to Dr Van Essen-Zandvliet and Professor Kerrebijn for highlighting the results of their important and well executed study. However, neither that investigation nor our own was designed to evaluate the efficacy of combination treatment with inhaled corticosteroids and  $\beta$  agonists, as they seem to suggest. Nevertheless, both offer important and consistent observations regarding the effects of  $\beta$  agonist treatment in chronic asthma.

They comment that after four months of

treatment with regular inhaled salbutamol no further changes in FEV<sub>1</sub> or PC<sub>20</sub> were identified in their asthmatic subjects. On this basis they suggest that long term treatment with the  $\beta$  agonist salbutamol is unlikely to be having an adverse effect. It is important to note that the withdrawal rate due to treatment failure continued unabated throughout the long study period, so that after a median interval of 22 months 45% of patients in the  $\beta$  agonist treated group had required to be withdrawn. This discrepancy between changes in FEV<sub>1</sub> and "asthma control" was also a feature in our own study and is an important one for clinicians to note. Among our own 64 subjects severe exacerbations requiring hospital admission occurred in five and, of these, four occurred during regular fenoterol treatment. Moreover, all of these events occurred after at least 16 weeks of treatment. By contrast, the adverse changes in FEV<sub>1</sub> (mean -0.15 litres) did not alter further after the first four weeks of regular fenoterol treatment. We doubt that subject withdrawal over such a sustained interval is attributable to the washout effects of withdrawing anti-inflammatory therapy. An alternative explanation is that it is due to the adverse effects of regular  $\beta$  agonist treatment.

Secondly, the very high withdrawal rate in the group of patients receiving regular salbutamol will have influenced the results of subsequent PC<sub>20</sub> measurements. Indeed, Dr Van Essen-Zandvliet acknowledges that a low PC<sub>20</sub> at baseline was a predictor for subsequent withdrawal from the study. The impression that the PC<sub>20</sub> did not alter substantially during regular salbutamol treatment is therefore false; only patients with a stable PC<sub>20</sub> were able to continue in the study!

Although we did not specifically conclude that "regular treatment with short acting  $\beta$  agonists should not be used in combination with inhaled corticosteroids", we certainly would agree with that statement. The results of both Dr Van Essen-Zandvliet's study and our own indicate that no demonstrable benefits are obtained when using regular treatment with inhaled  $\beta$  agonists. Although the results of the Dutch study indicate that combined therapy with inhaled corticosteroid and salbutamol was undoubtedly effective, the relative contribution made by inhaled  $\beta$  agonist cannot be ascertained from their results. It may be that inhaled corticosteroids alone (with  $\beta$  agonist used only as needed) would result in benefits which are equal to, or even greater than, those obtained using the combination of treatments. The question of an adverse interaction between inhaled corticosteroids and  $\beta$  agonists has yet to be answered, but is one which requires urgent attention.

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### Respiratory symptoms questionnaire for asthma epidemiology: validity and reproducibility

The validated asthma questionnaire reported by Dr K M Venables and co-workers (March 1993;48:214-9) will also be extremely useful for epidemiological studies of occupational asthma if it is combined in its present form with questions to

elicit a temporal relationship with work.<sup>1</sup>

Such questions might take the form:

1. On holidays, are the problems you answered "YES" to, better, worse or unchanged?
2. On weekends, are the problems you answered "YES" to, better, worse or unchanged?
3. On Mondays, are the problems you answered "YES" to, better, worse or unchanged?

Such a questionnaire could be used with serial peak expiratory flow rate measurements<sup>1</sup> in cross sectional studies to assess the prevalence and rate ratio of occupational asthma in industries where workers are exposed to known causative agents.

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- 1 Burge PS. Diagnosis of occupational asthma. *Clin Exp Allergy* 1989;19:649-52.

### *Chlamydia pneumoniae*

As Dr TJ Marrie mentioned in his editorial (January 1993;48:1-4), we need to confirm the relationship between *Chlamydia pneumoniae* infection and airway irritability, and to find appropriate treatment. Hahn<sup>1</sup> urged asthma researchers to consider the possibility that *C pneumoniae* infection could be one of the underlying (and potentially treatable) causes of adult asthma.

We have recently seen a 39 year old man with cough variant asthma and serologically confirmed *C pneumoniae* infection. Cough variant asthma is an occult form of asthma of which the only sign or symptom is chronic cough.<sup>2</sup> His routine spirometric values were normal, but moderate bronchial hyperresponsiveness to acetylcholine was present. Serum IgE and peripheral blood eosinophils were increased and RAST scores revealed a positive response to grass pollen. Antibody titres of IgG, IgA, and IgM to *C pneumoniae* were 1:1024, 1:32 and <1:8, respectively. On the other hand, antibody titres of IgG to *C psittaci* and *C trachomatis* were 1:32 and <1:32, respectively. The complement fixation test for *Mycoplasma pneumoniae* was negative.

It is well known that macrolides and tetracyclines are effective treatment for chlamydial infections and that bronchodilator therapy is very useful for cough variant asthma. Holmes *et al*<sup>3</sup> recommended that ipratropium bromide inhalation is appropriate in patients with chronic cough following upper respiratory tract infection. Treatment with clarithromycin and inhaled oxitropium bromide for two weeks in our patient was successful. This case indicates that cough variant asthma may be another clinical expression of *C pneumoniae* infection.

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- 1 Hahn DL. *Chlamydia pneumoniae* infection and asthma. *Lancet* 1992;339:1173-4.
- 2 Johnson D, Osborn LM. Cough variant asthma: a review of the clinical literature. *J Asthma* 1991;28:85-90.
- 3 Holmes PW, Barter CE, Pierce RJ. Chronic persistent cough: use of ipratropium bromide in undiagnosed cases following upper respiratory tract infection. *Respir Med* 1992;86:425-9.