LETTERS TO THE EDITOR

Bronchodilators and bronchial hyperresponsiveness

In a recent editorial (May 1993; 48: 470-3) Drs van Schayck and van Herwaarden present a surprisingly ambivalent account of the effects of β agonist treatment on airway responsiveness. Their conclusion that β agonists have an unimportant effect on responsiveness appears to be based on recent analyses of data from their own study. However, a thorough review of the studies discussed by van Schayck and van Herwaarden1-5 and other relevant studies6-15 ought to prompt different conclusions.

The table shows the results of reported studies of the chronic effects of β agonists on airway responsiveness in asthmatic patients. Single-dose studies have been excluded. We have calculated geometric mean PC20 values for the full treatment period in those studies where sufficient data are given, and in all cases have looked for differences between the "treatment" PC20 (during regular β agonist therapy) and either the baseline PC20 (for parallel group studies) or the control arm (for PRN β agonist) in crossover studies.

We acknowledge that the changes noted are often small and not always statistically significant. Nevertheless, there is a considerable weight of evidence for a negative effect of β agonists on airway hyperresponsiveness. Of the 15 studies listed, 10 showed increased airway responsiveness (lower PC20 or PD20) during regular β agonist therapy, and in five of these the change was statistically significant. In only two studies was decreased responsiveness found (higher PC20 or PD20), of which one was statistically significant. In both of these latter studies6,7 there were substantial withdrawals because of worsening asthma, and although the last measurement of airway responsiveness was carried forward, this may still obscure a deleterious effect on PC20, as those whose asthma deteriorated would be more likely to withdraw from the study.

By taking a neutral position on this important issue, van Schayck and van Herwaarden do not do justice to the data regarding β agonists and airway responsiveness. Although we agree that the mean changes in airway responsiveness during or following regular β agonists is small when considered in relation to the variability of measurement of airway responsiveness in an individual, the effect of a small net increase in mean airway responsiveness in a larger population is much more significant, leading to an increase in severity of asthma - and they have expressed agreement with this view. The mechanism of the adverse effect of regular or frequent β agonist use on asthma is still to be fully explained, but there is little doubt that it exists, and this is reflected in the changes in airway responsiveness which occur in most patients taking these drugs.

D ROBIN TAYLOR
University of Otago Medical School, PO Box 913, Dunedin, New Zealand

MALCOLM R SEARS
McMaster University, Hamilton, Ontario, Canada LBH 4A6


AUTHORS’ REPLY
We thank Drs Taylor and Sears for their recent correspondence. We published the editorial from which they derived that we concluded that β agonists have unimportant effects on bronchial hyperresponsiveness. Our literal conclusion, however, was that "a monotherapy with bronchodilators is not, in general, increase bronchial hyperresponsiveness. In subgroups of patients and with high dosages of a β, adrenergic drug it may have such an effect, although it is small and of doubtful clinical significance.” In the table presented by Sears and Taylor supports this conclusion. Of all 15 available studies (ref 16 has not been published yet) there are only three (refs 5, 7, and 14) that showed a statistically significant increase in bronchial hyperresponsiveness either during or after stopping bronchodilator therapy. There was one study that showed a significant decrease in hyperresponsiveness whilst using a β agonist alone (ref 9). There is one study published on the effect of continuous use of a β agonist in combination with anti-inflammatory drugs (ref 3) which pointed to an increase in bronchial hyperresponsiveness during continuous use of the β agonist. All other studies did not show a significant change in bronchial hyperresponsiveness during or after the use of a β agonist.

If we look more closely at the three studies showing an increase in bronchial hyperresponsiveness during or after stopping monotherapy with bronchodilators, the following remarks should be made. In the study of Kraan et al (ref 5) with 17 asthmatic

Reference | Drug (mg/day) | Design | Weeks | n | Change in airway responsiveness | Direction | Magnitude (baseline, regular) | p |
---|---|---|---|---|---|---|---|---|
1 | Fenoterol 600 | RDB, PLC | 16 | 8 | No change | PC20 16 1 day and 14 1 day | - | < 0.05 |
2 | Fenoterol 1600 | RDB, PLC | 16 | 8 | Increased | PC20 53 1 day and 50 1 day | - | < 0.05 |
3 | Fenoterol 1600 | Open | 16 | 11 | No change | PD20 26 2 day and 29 2 day | - | < 0.05 |
4 | Terbutaline 2000 | RDB, PLC | 4 | 4 | Increased | PD20 4 2 day and 4 2 day | - | < 0.05 |
5 | Terbutaline 1500 | RDB, PLC | 24 | 7 | Increased | PD20 19 3 day and 22 3 day | - | < 0.05 |
6 | Terbutaline 2250 | RDB, PLC | 24 | 5 | Increased | PD20 28 3 day and 30 3 day | - | < 0.05 |
7 | Salbutamol 3000 | RDB, PLC | 2-4 | 12 | Increased | PD20 4 1 day and 4 1 day | - | < 0.05 |
8 | Salbutamol 800 | Open | 4 | 4 | Increased | PD20 10 1 day and 12 1 day | - | < 0.05 |
9 | Salbutamol 1600 | Open | 52 | 15 | Increased | PD20 50 1 day and 60 1 day | - | < 0.05 |
10 | Salbutamol 600 | Open | 96 | 20 | Increased | PD20 24 1 day and 26 1 day | - | < 0.05 |
11 | Salbutamol 600 | PLC | 3 | 11 | Increased | PD20 14 1 day and 17 1 day | - | < 0.05 |

R = randomized; DB = double blind; PC = placebo controlled; PLC = parallel groups; X = crossover; dd = doubling dose.
subjects there was an increase in bronchial hyperresponsiveness only during the first two weeks of the study, but by the end of four weeks this increase had disappeared. In the study of Vathenen et al (ref 7) with eight asthmatic subjects it was observed that a (rebound) increase in hyperresponsiveness occurred, not whilst using the β agonist but afterwards. In our own study (ref 14) an increase in hyperresponsiveness was observed when using a β agonist in a selected group of 15 patients. These 15 patients were selected on the condition that they had used any β agonists or β blockers for one year before the start of the study. They were part of a much larger group of 144 patients who, on average, did not show an increase in bronchial hyperresponsiveness during the use of the β agonist (ref 1, not presented in the table). Looking at the presented table, it seems that the more patients involved in these studies the less clear is the adverse prognosis of bronchial hyperresponsiveness during the continuous use of a bronchodilator. This underlines our conclusion that only in subgroups of patients might the continuous use of a β, adrenergic drug have an adverse effect on bronchial hyperresponsiveness. The only exception seems to be the study of Sears and Taylor themselves (ref 3) with a relatively large number of 64 patients. However, this is the only study in which patients were allowed to use anti-inflammatory drugs as well as their bronchodilator drugs.

As Sears and Taylor have already acknowledged, the observed changes in hyperresponsiveness are small. They are, all between 0·5 and 1·5 doubling doses of the challenge test, which is virtually similar to the repeatability of the challenge test and is therefore of doubtful clinical significance.

The purpose of writing our editorial was not to present a neutral position in this important issue but to show that the general fear that exists among doctors and patients about the chronic use of bronchodilators does not have to be justified by the data available at this moment. We did not, and not, doubt that bronchodilators probably have a (small) negative influence on the long term prognosis of bronchial hyperresponsiveness in certain groups of asthmatic patients. Subgroup analyses of our own data have shown that especially allergic hyperresponsive asthmatic patients seem to have an increased progression of asthma with continuous use of a β agonist.1 Another important issue which still has to be settled is what additional bronchodilator drug should be used (and in what dose) when the patient receives a combination of an anti-inflammatory drug and a bronchodilator.

C P VAN SCHAYCK C L A VAN HERWAARDEN
Departments of General Practice and Pulmonary Medicine, Nijmegen University, PO Box 9101, 6500 HB Nijmegen, The Netherlands


Extrapulmonary effects of fenoterol and salbutamol in normal subjects

Newnham et al have attempted the difficult task of trying to dissect relative β1 and β2 mediated cardiovascular responses to large doses of salbutamol and fenoterol in normal subjects with a low dose of atenolol (June 1993;48:656–8). There are two issues: firstly, the comparative responses to similar doses of these agents by inhalation and, secondly, their selectivity at the β2-adrenoceptor.

Newnham et al showed that salbutamol and fenoterol in doses of 1 mg and 3 mg from metered dose inhalers led to similar increases in heart rate, stroke distance, and tremor, with fenoterol causing a slightly greater fall in serum potassium concentration and a greater rise in systolic blood pressure than salbutamol. Their findings suggest smaller differences between higher doses of salbuta-mol and fenoterol and extrapulmonary effects than other studies, whether the comparisons have been made in vitro, in vivo, or in different species.2 Invariably fenoterol has been found to be more potent in large doses than salbutamol. These intravenous preparations have found a 2–4 times greater effect on heart rate with fenoterol, and this has led to a tenfold difference in the concentra tion of intravenous solutions used rout inely (500 μg/ml salbutamol compared with 5 μg/ml fenoterol). For the different findings of Newnham et al are unclear.

The attempts by the authors to dissect relative β1 and β2 effects have failed as they have shown that atenolol significantly attenuates the β2 mediated effect on heart rate, tremor, and serum potassium concentration. Other designs based on studies by Wellstein et al or Hall et al may enable such relative β2 receptor specificity to be shown.

J CRANE B CURGESS R BEASLEY
Department of Medicine, Wellington School of Medicine, Wellington, New Zealand

C WONG
Department of Medicine, University of Otago, Dunedin, New Zealand


Bronchodilators and bronchial hyperresponsiveness.

D R Taylor and M R Sears

Thorax 1994 49: 190-191
doi: 10.1136/thx.49.2.190

Updated information and services can be found at:
http://thorax.bmj.com/content/49/2/190.1.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/