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.[1] However, a thorough review of the studies discussed by van Schayck and van Herwaarden[2 3 5–9 11 14] and other relevant studies[4 10 12 13 15 16] 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 PC_{20} 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" PC_{20} (during regular β agonist therapy) and either the baseline PC_{20} (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 airways responsiveness (lower PC_{20} or PD_{20}) during regular β agonist therapy, and in five of these the change was statistically significant. In only two studies was decreased responsiveness found (higher PC_{20} or PD_{20}), of which one was statistically significant. In both of these latter studies[9 11] 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 PC_{20}, 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 are 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.

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AUTHORS' REPLY We thank Drs Taylor and Sears for their reaction to our recently published 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 does not, in general, increase bronchial hyperresponsiveness. In subgroups of patients and with high dosages of a β_2 adrenergic drug it may have such an effect, although it is small and of doubtful clinical relevance." In fact, 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 during or after stopping a monotherapy with bronchodilators. 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 11 studies did not show a significant change in bronchial hyperresponsiveness during or after the use of a β agonist.

If we look in more detail 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 (μg/day)*	*Design*	*Weeks*	*n*	*Change in airway responsiveness*		
					Direction	*Magnitude (baseline, regular)*	*p*
2	Fenoterol 600	R,DB,PL	16	8	No change	PD_{20} 16·3, 16·9	–
3	Fenoterol 1600	R,DB,PC,X	24	64	Increased	PC_{20} 1·53, 1·03	<0·05
4	Fenoterol 1600	Open	16	11	No change	PD_{20} 0·26, 0·29	–
5	Terbutaline 2000	R,DB,X	4	17	Increased	PD_{20} 4·7, 3·4	<0·05
6	Terbutaline 1500	R,DB,PL	24	7	Increased	PD_{20} 43, 25	–
7	Terbutaline 2250	R,DB,PC,X	2	8	Increased	PD_{20} decreased 0·84 dd	<0·05
8	Terbutaline 2000	R,DB,PL	4	15	Increased	PC_{20} 0·89, 0·66	–
9	Terbutaline 750	R,DB,PL	2 years	53	Decreased	PC_{15} increased 0·5 dd	<0·01
10	Terbutaline 2000	R,DB,X,PC	1	12	Increased	PC_{20} 0·85, 0·51	–
11	Terbutaline 2000	R,DB,PL	24	91	Decreased	PC_{20} increased 0·15 dd	–
12	Terbutaline 3000	R,DB,PC,PL	2–4	10	No change	No change in PD_{20}	–
13	Salbutamol 800	Open	4	8	Increased	PC_{20} 0·84, 0·74	–
14	Salbutamol 1600	Open	52	15	Increased	PC_{20} 13·2, 9·0	<0·001
15	Salbutamol 600	R,DB,PL	96	58	Increased	PD_{20} decreased 0·42 dd at 4 months	–
16	Salbutamol 600	R,DB,PC,X	3	11	Increased	PD_{20} decreased 1·47 dd	<0·01

R = randomised; DB = double blind; PC = placebo controlled; PL = 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 not 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_2 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[1] 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 seem to be justified by the data available at this moment. We did not, and do 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.[2] 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.

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Extrapulmonary effects of fenoterol and salbutamol in normal subjects

Newnham *et al* have attempted the difficult task of trying to dissect relative β_1 and β_2 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 β receptor.

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 salbutamol and fenoterol on extrapulmonary effects than other studies, whether the comparisons have been made in vitro, in vivo, or in different species.[1,2] Invariably fenoterol has been found to be more potent in large doses than salbutamol. Studies using 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 concentration of intravenous solutions used routinely (500 μg/ml salbutamol compared with 50 μg/ml fenoterol). The reasons for the different findings of Newnham *et al* are unclear.

The attempts by the authors to dissect relative β_1 and β_2 effects have failed as they have shown that atenolol significantly attenuates the β_2 mediated effect on heart rate, tremor, and serum potassium concentration. Other designs based on studies by Wellstein *et al*[3] or Hall *et al*[4] may enable such relative β receptor specificity to be shown.

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AUTHORS' REPLY In reply to the letter of Crane *et al* there are some fundamental issues which, although discussed in the paper, require further clarification.

The purpose of our study was not to assess the relative potency of fenoterol and salbutamol, which requires dose-response curves in asthmatic subjects to ascertain relative bronchodilator and systemic β_2 receptor activity. The 25 mg dose of atenolol in our study was chosen on the basis of it producing relatively selective β_1 blockade. It is, however, well documented that atenolol displays dose related β_2 blockade,[1,2] and so it is not, perhaps, surprising that even a 25 mg dose produced a degree of β_2 antagonism. The important point is that a comparable degree of attenuation occurred with heart rate and potassium responses, both of which have been shown to be β_2 mediated.[1-3] Indeed, this occurred to the same extent with both fenoterol and salbutamol.

If fenoterol had stimulated cardiac β_1 receptors to a greater degree than salbutamol, one would have predicted atenolol to have antagonised the chronotropic response to fenoterol more than salbutamol. This was clearly not the case, with the percentage attenuation by atenolol at the 4 mg dose being 14% for fenoterol and 16% for salbutamol. The percentage attenuation of the systolic blood pressure was also comparable for both fenoterol (10%) and salbutamol (8%). Thus, whilst fenoterol may exhibit greater β_2 potency, there is no evidence for it being less selective in terms of relative cardiac β_1/β_2 receptor stimulation. It is also worth pointing out that in a study from Windom *et al*[4] in asthmatic subjects there was no difference in either chronotropic or systolic blood pressure responses to fenoterol and salbutamol, in contrast with isoprenaline which produced greater effects, presumably β_1 adrenoceptor mediated.[5]

Our in vivo data are indeed supported by in vitro data in human right atria,[6] showing that the relative pA_2 values for practolol (β_1 antagonist) and ICI 18 551 (β_2 antagonist) were 5·47 and 8·24 respectively, for antagonism of the inotropic response to fenoterol. Taken together we believe that the body of evidence supports the hypothesis that the effects of fenoterol on the human heart are predominantly caused by stimulation of cardiac β_2 receptors.

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