

Correspondence

Inhaled β_2 -agonists and allergen-induced airway responses

To the Editor:

We were interested to read Dr. McFadden's opinions on β_2 -agonist therapy (Rostrum, J ALLERGY CLIN IMMUNOL 1995;95:641-51). Our opinions differ in several areas. We wish, however, to point out an error in McFadden's reanalysis of our data regarding salbutamol-induced increase in the allergen-induced early asthmatic response.¹ Dr. McFadden states that reanalysis of untransformed allergen PC₂₀ data fails to show any significant effects between salbutamol and placebo.

Our investigation was designed to look for reduced functional antagonism of salbutamol versus allergen and was modeled after the study of O'Connor et al.,² substituting allergen as a mast cell stimulus that was more clinically relevant than adenosine monophosphate. We found an unexpected increase in airway response to allergen, almost double, after 2-week treatment with inhaled salbutamol, 200 μ g four times daily, compared with placebo.¹ The untransformed and log-transformed data for the 11 subjects with complete data are shown in Table I. After the 2-week salbutamol treatment, 10 of 11 subjects showed increased airway response to allergen; the change in allergen PC₂₀ was 50% or greater in five. PC₂₀ values are not normally distributed; therefore, it is not appropriate to use parametric statistics on untransformed data. However, contrary to McFadden's claim, the calculations still show significance for untransformed data ($p =$

0.027), as well as for the log-transformed data ($p = 0.0012$) (Table I). Nonparametric tests might be more appropriate to use to analyze these data; we used several nonparametric tests and these all showed significance (p values ranged from 0.007 to 0.04).

Two subsequent studies have confirmed this finding in largely different subjects.^{3,4} Two independent labs have shown that this effect extends to the more clinically relevant late asthmatic response.^{5,6} Similar findings regarding salbutamol and exercise-induced bronchospasm have been observed.⁷

Inhaled allergens are the most important inflammatory stimuli in the pathogenesis of asthma. Enhanced allergen-induced airway responses,^{1,3-6} and possibly enhanced allergen-induced airway inflammation⁶ after regular use of inhaled β_2 -agonists, are almost certainly highly clinically relevant. We believe that this significant effect of regularly used inhaled β_2 -agonists should not be ignored.

D. W. Cockcroft, MD, FRCP(C)

R. Bhagat, MD

S. Kalra, MD

V. A. Swystun, BSc

Division of Respiratory Medicine

Royal University Hospital

University of Saskatchewan

Saskatoon, SK, S7N 0W8

Canada

TABLE I. Allergen PC₂₀ after 2-week treatments with salbutamol and placebo

Subject No.	Allergen PC ₂₀ (PNU/ml)		Log allergen PC ₂₀	
	Placebo	Salbutamol	Placebo	Salbutamol
1	1479	675	3.17	2.83
2	1264	1041	3.10	3.02
3	70	34	1.85	1.53
4	1188	868	3.07	2.94
5	3495	3846	3.54	3.59
6	312	148	2.49	2.17
7	79	38	1.90	1.58
8	625	130	2.80	2.11
9	391	130	2.59	2.11
10	364	244	2.56	2.39
11	1146	718	3.06	2.86
Mean difference		231		0.27
SD		296		0.20
Paired <i>t</i> test		2.59		4.49
<i>p</i> Value		0.027		0.0012

PNU, Protein nitrogen units.

REFERENCES

1. Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;342:833-7.
2. O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled β_2 -agonists in asthma. *N Engl J Med* 1992;327:1204-8.
3. Cockcroft DW, Swystun VA, Bhagat R. Interaction of inhaled β_2 agonist and inhaled corticosteroid on airway responsiveness to allergen and methacholine. *Am J Respir Crit Care Med* 1995 (in press).
4. Bhagat R, Swystun VA, Cockcroft DW. Salbutamol-induced increased airway responsiveness to allergen and reduced protection vs methacholine: dose-response [Abstract]. *J ALLERGY CLIN IMMUNOL* 1995;95:387.
5. Cockcroft DW, O'Byrne PM, Swystun VA, Bhagat R. Regular use of inhaled albuterol and the allergen-induced late asthmatic response. *J ALLERGY CLIN IMMUNOL* 1995;96:44-9.
6. Gauvreau GM, Watson RM, Jordana M, Cockcroft D, O'Byrne PM. The effect of regular inhaled salbutamol on allergen-induced airway responses and inflammatory cells in blood and induced sputum [Abstract]. *Am J Respir Crit Care Med* 1995;151:A39.
7. Inman MD, O'Byrne PM. The effect of regular inhaled salbutamol treatment for 1 week on exercise-induced bronchoconstriction [Abstract]. *Clin Invest Med* 1995 (in press).

1/8/66385

Try using binoculars

To the Editor:

In a recent commentary on β_2 -adrenoceptor agonist therapy (*J ALLERGY CLIN IMMUNOL* 1995;95:541-52), increased morbidity and mortality in asthmatic patients is disputed by McFadden, thereby allowing him to conclude that β_2 -agonists are satisfactory drugs for managing acute symptoms of asthma. Contesting the existence of both cause and effect facilitates the conclusion that " β_2 -agonists are the best drugs that we have for managing the acute symptoms of asthma." This approach is disingenuous, for it precludes consideration of deficiencies of existing sympathomimetics, which are *not necessarily* manifest as increased morbidity or mortality. Investigation of such deficiencies has been pursued for over 2 decades and is, at last, offering a prospect of improvement on existing therapy.

Anomalous loss of protection from provocation stimuli during sympathomimetic therapy is not, as McFadden suggested, a poorly substantiated and recent finding, which might account for associations between use of β_2 -adrenoceptor agonists and increased morbidity. Pharmacodynamic deficiencies of β_2 -selective adrenoceptor agonists were quickly recognized by investigators in the United States, who reported that protection from induced airway obstruction had been lost even when bronchodilation was half maximal.¹ This was recognized as important because metered dose inhalers must be used more frequently to maintain symptomatic protection.² Foreshortening of the airway re-

sponse to sympathomimetics as a manifestation of β_2 -adrenoceptor desensitization is an unconvincing explanation, because it is incompatible with the resistance of asthmatic airways to desensitization.³ Instead, demonstration that sympathomimetic drugs induce hyperresponsiveness of the airways, both in animals and asthmatic patients, led to the proposal that this phenomenon underlies the constellation of anomalous responses that have been associated with use of sympathomimetic therapy in asthma.

The first animal study to report increased susceptibility to antigen after regular exposure to epinephrine was published in this journal⁴ and was reinforced by demonstration that increased susceptibility of guinea pigs to histamine followed regular injection of isoproterenol, salbutamol, or terbutaline.⁵ This anomalous effect is explained by the recent finding of hyperresponsiveness of the airways, determined after regular inhalation of fenoterol⁶ or sustained infusion of albuterol,⁷ with indications that disproportionate increased responsiveness to peptidoleukotrienes might explain the vulnerability of sensitized animals exposed to antigen.⁸ Diminished responsiveness to adrenoceptor agonists^{6,7} can be excluded and, for albuterol, may be a manifestation of the actions of the distomer S-albuterol.⁷

Substitution of pure R-albuterol for racemic albuterol is therefore an obvious step, especially because bronchodilator responses to R-albuterol should exceed, in amplitude and duration, the corresponding response to the racemic mixture; and overt hyperresponsiveness should result from exposure to S-albuterol. These predictions were confirmed during initial comparisons of R-, R,S-, and S-albuterol in patients with asthma.⁹ These preclinical and clinical observations anticipate loss of protection from provocation stimuli and provide a mechanism to explain paradoxical bronchospasm.¹ Because stereospecific metabolism causes progressive accumulation of S-albuterol,¹⁰ which has a longer half-life than R-albuterol, S-albuterol can be present in excess of approximately 10-fold.⁹

It is evident that contemporary β_2 -selective sympathomimetics are far from optimal bronchodilators, and we suggest that use of pure preparations of β_2 -adrenoceptor agonists may improve the performance of racemic sympathomimetics. If adverse effects of current sympathomimetics are dependent on occupancy and activation of adrenoceptors (to cause increased penetration of aeroallergens into the lower airways, to diminish secretion of mast cell products, etc.), removal of S-albuterol should not be expected to influence morbidity. If, on the other hand, adverse effects are appreciably determined by actions of S-albuterol, then morbidity will be diminished.

Like a poop deck, the rostrum provides a vantage point from which to detect lights in the darkness. Even so, quite strong lights can be overlooked. It may be recalled that by placing a telescope to his single, blind eye, Admiral Lord Nelson was able to dispute the