

Inhaled β_2 -agonists and airway responses to allergen

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A series of investigations show that the regular use of inhaled β_2 -agonists will increase all aspects of the airway response to allergen. The mechanism of this effect is uncertain; however, it appears to be different from the mechanism that produces tolerance to β_2 -agonist effects. One possibility is that the regular use of β_2 -agonists might induce a mast cell β -receptor dysfunction that might make mast cells more prone to release mediators. As a result β_2 -agonist use plus allergen exposure might cause more mediator release than does allergen exposure alone. The corollary of this is that β_2 -agonist use plus allergen exposure might cause more airway inflammation than does allergen exposure alone. These hypotheses are both testable. I believe that this is a clinically important phenomenon and may well be a major reason for β_2 -agonist-induced worsened asthma control. Further investigations are indicated to identify the mechanism and the clinical relevance of the phenomenon. (*J Allergy Clin Immunol* 1998;102:S96-9)

Inhaled β_2 -agonists are the most potent bronchodilators and functional antagonists available for the management of asthma and are consequently the most widely prescribed asthma medication. However, recent studies linking both asthma morbidity¹ and asthma mortality² with inhaled β_2 -agonist use have raised concerns regarding their safety.

Indirect side effects of inhaled β_2 -agonists are well recognized and noncontroversial. The major indirect side effects are overreliance on a potent symptom-relieving agent, with consequent underuse of antiinflammatories (ie, undertreatment of asthma), and underappreciation of true asthma severity. In addition, these potent bronchodilators/functional antagonists may allow increased allergen exposure, which will further increase airway inflammation.³

Although these indirect effects are undoubtedly important and provide a plausible explanation for association of β_2 -agonist use/abuse with asthma morbidity and mortality, regular use of inhaled β_2 -agonists may also have direct side effects in asthma. Two of these are tolerance to their beneficial effects⁴ and increased airway responsiveness.^{5,6} Alone or together, these could be responsible for the reduced asthma control seen with regular use of inhaled β_2 -agonists.¹ We and others have undertaken a series of investigations to address one aspect of this, namely the

Abbreviations used

AMP: Adenosine monophosphate
EAR: Early asthmatic response
LAR: Late asthmatic response

influence of regular use of inhaled β_2 -agonists on the airway response to allergen. We believe that β_2 -agonist-induced increase in airway responsiveness to allergen is clinically important and may explain β_2 -agonist-induced worsened asthma control.

TERBUTALINE, METHACHOLINE, AND ADENOSINE MONOPHOSPHATE

The article that stimulated our initial investigation was that by O'Connor et al⁷ who, in 1992, reported on tolerance to the nonbronchodilator effects of inhaled β_2 -agonists. They studied airway responsiveness to a direct stimulus, methacholine, which acts directly on the airway smooth muscle, and to an indirect stimulus, adenosine monophosphate (AMP), which causes bronchoconstriction in part by release of mediators from mast cells. Their study involved 12 subjects with mild asthma who had been able to remain off β_2 -agonist therapy for 4 weeks. They did a double-blind, randomized, cross-over trial comparing 1-week treatment periods of placebo 4 times daily and terbutaline 500 μ g 4 times daily. At the start of each treatment, methacholine PC₂₀ and AMP PC₂₀ were determined immediately after administration of the blinded medication. These measurements were repeated a week later on the second to last and last day of treatment, respectively, again immediately after the blinded medication. The postterbutaline PC₂₀ values before regular terbutaline treatment were thus compared with the postplacebo PC₂₀ values before regular placebo treatment, and similar comparisons were made after 1 week of the treatments. The results are shown in the left panel of Fig 1 and include the following.

1. Initially, terbutaline provided significantly greater protection against AMP-induced bronchoconstriction than it did against methacholine-induced bronchoconstriction.
2. After 1 week of treatment, tolerance was evident in that there was a partial loss of the bronchoprotective effect of terbutaline against both stimuli.
3. The tolerance was greater for the inhibition of bronchoconstriction induced by the indirect stimulus AMP.
4. There was no reduction in baseline FEV₁ or in bronchodilation (not shown on the graph).

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Supported by a grant from the Saskatchewan Lung Association.

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0091-6749/98 \$5.00 + 0 1/0/93903

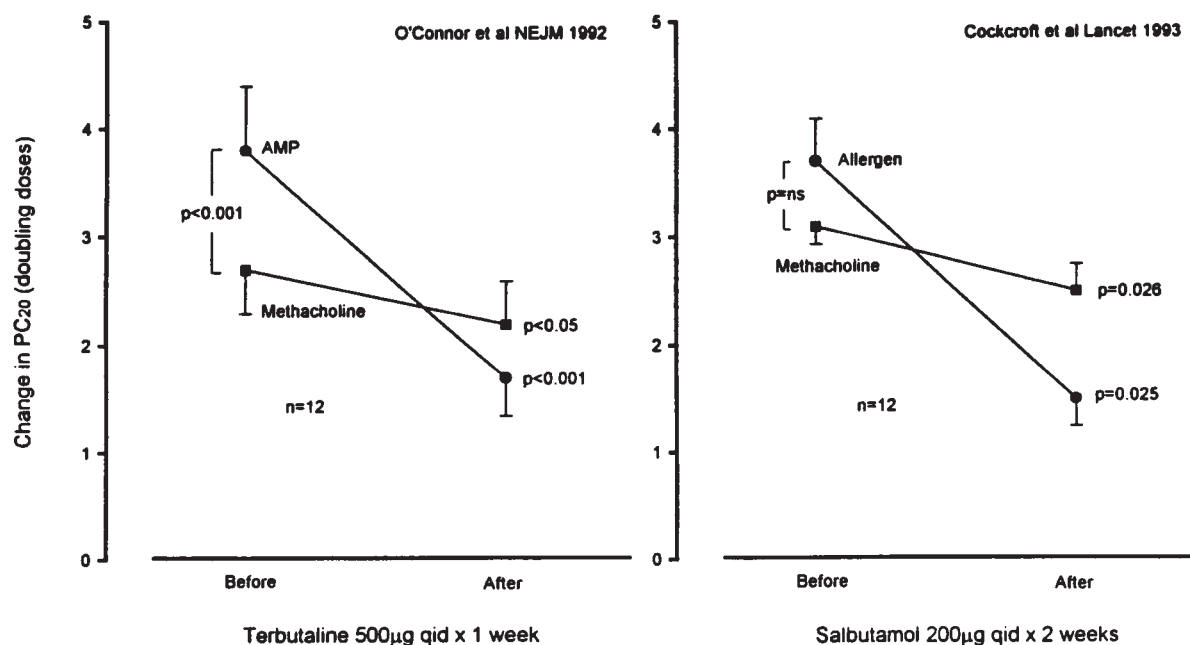


FIG 1. Tolerance to the bronchoprotective effect of inhaled β_2 -agonists. *Left panel* shows tolerance to the bronchoprotective effect of terbutaline versus methacholine and AMP, and *right panel* shows tolerance to the bronchoprotective effect of salbutamol versus methacholine and allergen. The vertical axis represents the bronchoprotection expressed as doubling-dose change in PC₂₀ immediately after administration of the inhaled β_2 -agonist compared with that before. The horizontal axis notes before and after regular 4 times daily use of the β_2 -agonist. (*Left panel* from O'Connor BJ et al. N Engl J Med 1992;327:1204-8.) (*Right panel* modified from Cockcroft DW, et al. Lancet 1993; 342:833-7, Fig 2.)

5. Baseline airway responsiveness to methacholine and AMP was not reassessed after 1 week of treatment and was assumed not to have changed.

This elegant study has a number of messages. This was one of the earliest studies of the many that predictably demonstrate that tolerance to the bronchoprotective effect of inhaled β_2 -agonists occurs easily and rapidly on regular use.⁴ The initially greater protection against AMP-induced bronchoconstriction compared with methacholine-induced bronchoconstriction was explained as follows. The effects of the direct-acting stimulus methacholine are thought to be opposed primarily by terbutaline's stimulation of β_2 -receptors on airway smooth muscle. The greater protection against AMP suggested an additional effect, likely mediated by terbutaline's stimulation of β_2 -receptor on mast cells, which would result in reduced mediator release. The final effect of terbutaline on AMP-induced bronchoconstriction would thus be the sum of the effects on β_2 -receptors on both smooth muscle and mast cells. The final suggestion of these authors was that this additional, and probably mast cell β_2 -receptor, effect appeared to be more susceptible to the development of tolerance.

SALBUTAMOL, METHACHOLINE, AND ALLERGEN (EARLY RESPONSE)

The O'Connor study,⁷ presented 6 months before its publication, stimulated our own series of investigations.

Initially, we designed a study attempting to extend the above observations with 2 important modifications. First, we used salbutamol in place of terbutaline to assess whether this was a class effect rather than a drug-specific effect. Second, we substituted allergen for AMP, reasoning that allergen was a more clinically relevant indirect mast cell-mediated stimulus. We studied only the allergen-induced early asthmatic response (EAR) expressed as the allergen PC₂₀.

Our study also had 2 other differences. The treatment periods for regular use of salbutamol 4 times daily and placebo 4 times daily were 2 weeks rather than 1 week. In addition, the measurement of the end points was carried out so that both the baseline and postsalbutamol methacholine and allergen PC₂₀ values were measured at the end of each treatment period, allowing us to check for any changes in baseline airway responsiveness to either stimulus, a change we felt at the point of study design that we would not be likely to observe.

When presented in the same format as the O'Connor data (Fig 1, right panel), the results are strikingly similar.⁸ The values for allergen PC₂₀ postsalbutamol dose shift before and after regular use of salbutamol are virtually identical to those for AMP and terbutaline. The methacholine data are shifted upward by about half a doubling dose (more protection with salbutamol), but the curve is parallel. The complete data are shown in Fig 2; this includes the observations on baseline methacholine and allergen PC₂₀ values after each treatment.

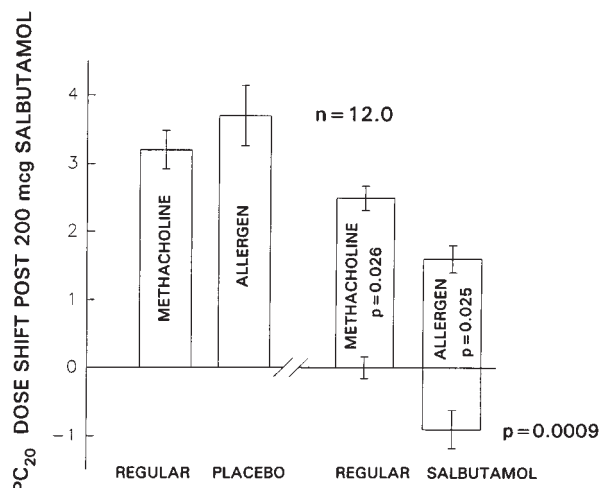


FIG 2. Methacholine PC₂₀ and allergen PC₂₀ before and after 200 µg salbutamol during the 2 treatment periods. Results (n = 12) are expressed as the dose shift (mean ± SEM) calculated as $\Delta \log_{10} PC_{20} \div 0.3$. Baseline PC₂₀ values during placebo treatment period are arbitrarily defined as 0. SE bars at bottom of 2 salbutamol treatment period bars represent dose shift compared with placebo period (methacholine, 0 [0.18]; allergen, 0.91 [0.20]). (From Cockcroft DW et al. *Lancet* 1993;342:833-7).

A summary of the results of our study is as follows. First, salbutamol initially protected better against allergen-induced bronchoconstriction than against methacholine-induced bronchoconstriction. However, this was not significant in our study because of 1 marked outlier in the 12 subjects. Second, tolerance developed to the bronchoprotective effect of salbutamol against both stimuli. Third, there was greater tolerance to the bronchoprotective effect against allergen than against methacholine. Fourth, there was no change in FEV₁ or bronchodilation (not shown on either graph). Fifth, there was no change in baseline methacholine PC₂₀ after 2 weeks of regular salbutamol (Fig 2). Sixth, airway responsiveness to allergen almost doubled; there was a 0.9 doubling dose drop in the allergen PC₂₀ (Fig 2). This was the most consistent and most significant finding in this initial study. Finally, we found that reestablishing allergen PC₂₀ immediately after administration of a β_2 -agonist posed some risks. We began to see systemic allergen-induced side effects; the most concerning event was 1 subject who required emergency intervention for systemic urticaria.

Thus our study confirmed the results of the O'Connor study. We demonstrated that this was indeed likely a class β_2 -agonist effect because salbutamol performed similarly to terbutaline. We also demonstrated that the results were also relevant to allergen, which is recognized as the most important asthma-inducing stimulus. It is appreciated that the allergen-induced EAR is not as clinically important as the late asthmatic response (LAR).⁹ However, we felt that if inhaled β_2 -agonists really do increase airway responsiveness to allergen, this has the likelihood of having important clinical relevance, and thus further investigations were indicated.

SALBUTAMOL AND THE ALLERGEN-INDUCED EAR

We have done 2 further studies addressing the allergen-induced EAR after regular use of salbutamol. The first study¹⁰ addressed the most frequently asked question regarding our initial data, namely "What about real asthmatic subjects who would surely be using inhaled corticosteroids?" We carried out a double-blind, double-dummy, randomized, 4-way, cross-over study again in 13 subjects who were off β_2 -agonist therapy for at least 4 weeks. We compared salbutamol 200 µg, budesonide 400 µg, both active drugs administered together, and double placebos; each treatment was administered 4 times daily for 1 week. The inhaled corticosteroid significantly improved the allergen PC₁₅ and the methacholine PC₂₀ (the former to a slightly greater extent). The budesonide, however, did not prevent development of tolerance to the bronchoprotective effect of salbutamol against methacholine. Also, budesonide did not prevent the fall in the allergen PC₁₅ from its new improved baseline. The best (highest) results for allergen PC₁₅ were achieved with budesonide alone, and the worst (lowest) results with salbutamol alone; intermediate results were seen with placebo and the combination.

The second additional study addressing the EAR was one designed to determine at what daily dose these effects occurred.¹¹ Once again, we used a 4-way, cross-over study design examining placebo and 3 daily doses of salbutamol (200, 400, and 800 µg) in 10 asthmatic subjects. Tolerance and increased airway response to allergen demonstrated different dose-response patterns. Tolerance to the bronchoprotective effect of salbutamol against methacholine occurred equally at all doses, even at 2 puffs (200 µg) once a day for a week. By contrast, the 2 lower doses, although showing a slight trend, did not significantly enhance the airway response to allergen, whereas airway responsiveness to allergen increased significantly after 1 week of salbutamol at 800 µg per day.

SALBUTAMOL AND THE ALLERGEN-INDUCED LAR

The second most commonly asked question after our first study was published was "What about the more clinically relevant LAR?" Two studies of almost identical design, done in 2 different labs with 2 different groups of subjects, have shown remarkably similar results.^{12,13} Studies addressing the allergen-induced LAR must have, of necessity, a different study design. In both studies the identical dose of allergen was administered approximately 10 to 12 hours after completing treatment courses of salbutamol 200 µg 4 times daily and placebo 4 times daily administered in a double-blind, randomized, cross-over fashion for 1 week with a 1-week washout period. The results of the airways physiology were similar. Both studies showed that after salbutamol the EAR was larger but not significantly so than after placebo. The LAR increased significantly ($P =$

.003 in both studies) almost 2-fold after salbutamol compared with placebo. The allergen-induced fall in methacholine PC₂₀ was also greater after salbutamol but of only borderline significance in one study¹² and not statistically significant in the other study.¹³ The second study, that done in Dr O'Byrne's lab, also demonstrated significantly more sputum eosinophils induced by allergen after a week's regular use of salbutamol when compared with placebo.¹³

The results of these investigations show that regular inhaled β_2 -agonists also enhance the more clinically relevant allergen-induced LAR and that this might well be because of an enhanced allergen-induced inflammatory response.

SALMETEROL AND THE ALLERGEN-INDUCED EAR

Salmeterol induces a more marked tolerance to its bronchoprotective effect against methacholine,¹⁴ and we have shown this to occur very early (at 24 hours) both in subjects who do not require inhaled corticosteroids¹⁵ and in those who do.¹⁶ Because this tolerance is greater than that seen with the short-acting β -agonists, we were concerned that salmeterol might cause more disturbance in allergen-induced airway responses. Designing studies with such a long-acting drug is difficult. We finally settled on examining the allergen-induced EAR 36 hours after completing a 1-week course of salmeterol 50 μ g twice daily compared with placebo.¹⁷ The results were at least partially reassuring. In the 14 subjects, we demonstrated a significant approximately half doubling-dose increase in airway response to allergen after salmeterol when compared with placebo. The change in allergen responsiveness was no larger than that seen after salbutamol; in fact, it was on the low side when compared with our other studies.

There are also some interesting data regarding the inhibition of the EAR. In a double-blind, cross-over study performed by Giannini et al,¹⁸ 8 subjects underwent a *same dose* allergen challenge after the first and last dose of both placebo and salmeterol administered twice daily for a week. Although the initial dose of salmeterol virtually completely inhibited the allergen-induced EAR (4% FEV₁ fall vs 31% for placebo), the last dose of salmeterol no longer significantly inhibited the EAR (24% FEV₁ fall vs 30% for placebo).

These 2 studies taken together further suggest different dose-response characteristics for tolerance and for increased airway responsiveness to allergen. These studies suggest that salmeterol causes a slight increase in air-

way responsiveness to allergen but a very large tolerance to the bronchoprotective effect versus allergen.

I thank Jacquie Bramley for assisting in the preparation of this manuscript.

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