

Beta-agonists, airway hyperresponsiveness, and asthma

Donald W. Cockcroft, MD, FRCP (C) *Saskatoon, Saskatchewan, Canada*

Airway hyperresponsiveness to both chemical (e.g., histamine, methacholine) and physical (e.g., exercise, cold air) stimuli is seen consistently in current symptomatic asthma. It correlates with and is likely caused by airway inflammation.^{1, 2} Its measurement provides a sensitive way to identify and quantitate variable airflow obstruction,³ the primary physiologic abnormality in asthma as currently defined. It also correlates modestly with measures of asthma severity.^{4, 5} Accordingly, much interest and research has focused on the effects of asthma therapy on airway hyperresponsiveness. Pharmacologic effects must be differentiated into acute (masking) and chronic (sustained); for a given agent or class of agents these may be opposite. In the short term drugs do not truly alter airway responsiveness, rather they affect its measurement. They may selectively inhibit the stimulus (e.g., H₁ blockers vs histamine,⁶ anticholinergics vs methacholine⁷), interfere with an intermediate pathway (e.g., cromolyn vs exercise,⁸ or cold air⁹), or nonselectively inhibit the response (e.g., bronchodilators^{7, 10}). By contrast, the chronic sustained effects truly alter airway responsiveness; beneficial effects have been hypothesized to be "antiinflammatory."¹¹ The sustained effects can be prophylactic (e.g., environmental control^{12, 13} and cromolyn vs allergen-induced airway hyperresponsiveness both in the laboratory¹⁴ and during allergen seasons¹⁵) or actively antiinflammatory (e.g., inhaled corticosteroids¹⁶).

In this issue of the JOURNAL there are two reports of the effects of β_2 -agonists on measures of airway responsiveness.^{17, 18} Magnussen and Rabe¹⁷ report on the acute effects of inhaled fenoterol, a β_2 -agonist of conventional (4 to 6 hour) duration of action, on the measurement of both methacholine and exercise re-

sponsiveness. Even the low dose of 50 μ g, one eighth of the standard (2 puffs = 400 μ g) dose, inhibited the response to exercise and shifted the dose-response curve to methacholine. The apparent difference between exercise and methacholine may be an artifact of the different ways of measuring responsiveness, that is, dose-response for methacholine versus response to a single dose for exercise. An alternate explanation is that although methacholine is "direct" airway smooth muscle stimulus and will only be modulated by smooth muscle beta receptors,¹⁹ exercise is "indirect" and may be modulated by beta receptors on other cells (e.g., mast cells) as well.¹⁹ Simons et al.¹⁸ demonstrate the acute effect of two doses of salmeterol, a β_2 -agonist of ultralong duration (12 to 24 hour), on measurement of methacholine responsiveness. A large sustained increase in PC₂₀ was seen at both doses lasting for 12 or more hours compared with a duration of 3 or fewer hours for salbutamol. These data confirm that inhaled β_2 -agonists are by far the most potent inhibitors of bronchoconstriction not only against both natural and chemical stimuli used to measure airway responsiveness, but also against other primarily bronchoconstrictor responses (e.g., the early asthmatic response to allergen).¹⁴

This contrasts sharply with the sustained effects of β_2 -agonists on airway responsiveness. The "masking" effects of conventional inhaled β_2 -agonists (albuterol, terbutaline, fenoterol) are short-lived, likely 3 or fewer hours.^{18, 20, 21} At best, inhaled β_2 -agonists exert no sustained effects on airway responsiveness.^{22, 23} Now several studies demonstrate that usual doses (2 puffs 4 times daily or the equivalent) of inhaled albuterol,²⁴ terbutaline,²⁵⁻²⁷ or fenoterol²⁸ actually worsen airway hyperresponsiveness. This "rebound hyperresponsiveness,"²⁷ an increase of approximately one doubling dilution of histamine or methacholine PC₂₀ or PD₂₀,^{25, 26} occurs within the first 4 weeks of introduction,^{25, 26} and does not appear to progress with continued use.²⁶ This effect of β_2 -agonists is likely not simply a measurement artifact, since it is associated with, and perhaps the cause of, worsened asthma control.²⁸ The worsened asthma control that has been demonstrated after use of the nonselective

From the Division of Respiratory Medicine, Department of Medicine, University of Saskatchewan, Saskatoon.

Reprint requests: Donald W. Cockcroft, MD, Division of Respiratory Medicine, University of Saskatchewan, Ellis Hall, 5th Floor, Saskatoon, SK S7N 0X0 CANADA.

β -agonist isuprel^{29, 30} and the selective β_2 -agonist fenoterol²⁸ should be regarded as a class effect until proved otherwise.²⁸

Recent widely publicized reports have demonstrated associations between asthma deaths and the use of a specific inhaled β_2 -agonist or of bronchodilators, particularly inhaled β_2 -agonists in general.³¹⁻³⁴ A causal relationship has not been proved. However, both the acute and sustained effects on airway hyperresponsiveness have been hypothesized to contribute to the relationship between β -agonists and deaths. The potent acute beneficial "masking" effect of inhaled β -agonists leads to excellent symptom control; this may lead in turn to overreliance, a false sense of security, and thus both chronic underuse of and acute delay in receiving appropriate antiinflammatory treatment. This has been suggested as the most important way in which inhaled β_2 -agonists might increase asthma deaths.³⁵ The sustained effects, with worsened asthma control, could obviously enhance both asthma morbidity and mortality rates. Even before inhaled β_2 -agonist-induced deterioration in asthma control was reported, the induced hyperresponsiveness was hypothesized as relevant to increasing asthma mortality rates.³⁶ It was reasoned that a small shift of airway hyperresponsiveness in asthmatic patients would be inconsequential in most, but could cause a marked increase in the small numbers of asthmatic patients with extreme airway hyperresponsiveness, namely those who are likely at greatest risk of dying of asthma.

These data suggest that the new very effective and ultralong acting inhaled β_2 -agonists salmeterol^{18, 37} and formoterol²¹ should be approached with caution. Claims have been made that in addition to being bronchodilators these agents may also be antiinflammatory; however, this may be an artifact of their very long duration (12 to 24 hours) of action. It is important that these agents be demonstrated not to adversely affect airway responsiveness and asthma control.

In conclusion, inhaled β_2 -agonists exhibit opposite beneficial acute and detrimental sustained effects on airway hyperresponsiveness. These may both be relevant to β -agonist-associated increased asthma mortality rates, invoking "overreliance" and "worsened asthma control," respectively. Unfortunately, it is likely that the more potent the β_2 -agonist, the greater the potential risk. For these reasons, we believe inhaled β_2 -agonists should be used "as needed" rather than regularly; a useful goal is to assure that their requirement be limited to less than twice a day.³⁸ This requires focusing on prophylactic "antiinflammatory" treatment such as environmental control, cromolyn, nedocromil, and inhaled corticosteroids.³⁸

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