Long-acting Inhaled β2-Agonists and the Loss of "Bronchoprotective" Efficacy

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The long-acting β2-agonists, salmeterol and formoterol, are effective bronchodilators with a much longer duration of action than salbutamol or terbutaline (1). They are the first of a new generation of β2-agonists and have been available for clinical use only in the last decade. Both have been shown to be effective as an additive therapy for asthma inadequately controlled by a standard dose of an inhaled corticosteroid (2–4). Salmeterol, the only long-acting β2-agonist currently available in the United States, is positioned in the National Asthma Expert Panel's report for use in moderate to severe persistent asthma in combination with regular use of another long-term controller, like an inhaled corticosteroid (5). The long-acting β2-agonists are usually administered twice daily and are particularly effective for preventing nocturnal asthma and exercise-induced asthma (EIA).

Two of the actions of β2-agonists in the airways are bronchodilation (6) and bronchoprotection; that is, inhibition or prevention of bronchoconstriction induced by some other stimulus, like methacholine (7–9), histamine (10), allergen (11), hyperventilation with cold air (12), or exercise (13). That these actions are distinct is suggested by studies of the effects of repeated dosing with an inhaled β2-agonist over 2 weeks or longer: The acute bronchodilation produced by acute treatment with an inhaled β2-agonist diminishes only slightly (14–17), at least in stable patients. This is not true of the bronchoprotection. With regular use of a β2-agonist, its inhibition of the bronchoconstriction caused by another agent diminishes, even while the acute bronchodilation is maintained (17–22). This loss of the bronchoprotective action of a β2-agonist was shown in the study by Cheung et al (17) of salmeterol's protection against methacholine-induced bronchoconstriction in steroid-naive mild asthmatic patients given 8 weeks of regular treatment with salmeterol. At the beginning of the study, treatment with salmeterol caused a 10-fold shift in the dose-response curve to methacholine given 1 hour later. That is, the dose of methacholine required to cause a 20% fall in FEV_1 was 10-fold greater 1 hour after treatment with salmeterol than it had been on study entry. After 4 weeks of treatment with salmeterol (50 μg twice daily), acute treatment with salmeterol shifted the dose-response to methacholine only twofold (17). Similar findings have come from several studies of salmeterol and formoterol (22–26). A reassuring finding from these otherwise disturbing studies is that the loss of bronchoprotection against methacholine is not progressive and reverses soon after regular β2-agonist therapy is stopped.

Loss of bronchoprotective action has also been demonstrated when exercise is used as the bronchoprovocative stimulus (21). It does not appear that decreasing the frequency of salmeterol use to once daily prevents this development of tolerance. Simons et al (27) showed that a single 50 μg dose of salmeterol inhibited EIA for at least 9 hours but that this effect waned during regular once-daily treatment. A decrease in the bronchoprotective action against the asthmatic response to inhalation of allergen has been shown in adults after as little as 1 week of salmeterol treatment (28,29).

In this issue of the *Journal*, Lipworth et al (30) extend this body of work, providing further evidence of the development of tachyphylaxis to bronchoprotection against methacholine. Specifically, they examined whether changing the dosing regimen of formoterol altered the magnitude of the loss of bronchoprotection and compared the effects of different doses and frequency of formoterol with the effects of a regular use of a short-acting β2-agonist, terbutaline. Their trial was well-designed; it included a placebo arm and a run-in period without β2-agonists to ensure that β2-receptors were not down-regulated to start with. Seventy-two patients with mild to moderate asthma, all taking inhaled corticosteroids, were assigned to four active treatment groups: formoterol 6 μg BID, 24 μg BID, 12 μg QD, and terbutaline 500 μg QID. All groups developed tachyphylaxis to protection against methacholine, without significant differences among the treatments after 2 weeks. In contrast to this demonstrable loss of bronchoprotection, the bronchodilator response (1 hour after inhalation) was still maintained over the 2 weeks study period.

The main finding from this study, therefore, is that 2 weeks of treatment with formoterol leads to a demonstrable loss of bronchoprotection against methacholine chal-

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lenge, irrespective of the dosage level (6 to 24 μg) or regimen (BID or QD). On the basis of these findings, the authors state that patients should be made aware that regular treatment with such long-acting β2-agonists may not confer full protection against a bronchoconstrictor stimulus, and that additional β2-agonist rescue medication may be needed in order to overcome acute bronchoconstriction.

This study also draws attention to the development of tachyphylaxis to the bronchoprotective effects of formoterol or terbutaline despite concomitant administration of inhaled corticosteroid therapy. Several earlier studies have substantiated this finding (23,31,32), but Lipworth's group has itself shown that the administration of systemic corticosteroids reduces formoterol-induced subsensitivity of β2-adrenoreceptors, as assessed by the response to inhaled salbutamol (33,34). The mechanism of this effect of corticosteroids may involve an increase in β2-adrenoceptor gene transcription (35) or a reversal of internalization of receptors from the cell surface (36).

Both in vitro (37) and in vivo (38) studies show that loss of responsiveness to β2-agonist stimulation from repeated agonist exposure is likely mediated by receptor uncoupling (destabilization of the high-affinity state of the receptor) and receptor down-regulation (39). These studies do not explain, however, why either mechanism should lead to a greater loss of β2-agonist-mediated inhibition of airway smooth muscle contraction in response to an agonist than of β2-agonist mediated relaxation. Another explanation is suggested by the observation that the loss of bronchoprotection appears to be greater for indirect stimuli, such as exercise and allergen challenge, than for more direct stimuli such as histamine and methacholine (19,20). It may be that the loss of responsiveness to β2-agonists is of less importance in airway smooth muscle cells than it is in the cells—like mast cells—that are stimulated by exercise or allergen challenge to release the mediators that directly provoke bronchoconstriction.

Whatever the mechanisms responsible, the concern over long-acting β2-agonists stimulated by studies like the one reported in this issue of the *Journal* is that their prolonged occupancy of β-receptors—the feature that accounts for their prolonged duration of action—might more likely produce subsensitivity and down-regulation than does intermittent use of shorter-acting β2-agonists, potentially leading to diminished asthma control in some common situations, as on exposure to an allergen or to an irritating pollutant like sulfur dioxide or on exercising.

Viewed historically, this concern is simply another in a long history of concerns over the possible dangers of regular use of inhaled β2-agonists. Even a cursory review of this long-running, sometimes acrimonious debate is beyond the scope of this editorial. What does seem clear is that in patients with mild asthma, taking inhaled albuterol regularly confers no benefit over taking albuterol only when needed for relief of symptoms, but does not worsen asthma control or cause more frequent or severe asthma exacerbations (40). It also seems clear that in patients with asthma severe enough to require regular treatment with an inhaled corticosteroid, the addition of a long-acting inhaled β2-agonist reduces symptoms, improves peak flow, and reduces the frequency and severity of exacerbations (2–4). There does seem to be some validity, however, to the idea that efficacy of β2-agonists in producing bronchodilation may play a negative role by masking on-going underlying airway inflammation, so that neither patient nor physician recognizes the need for additional therapy. Several studies have shown that in patients with persistent asthma, the maximal improvement achieved from even prolonged treatment with an inhaled corticosteroid diminished when its introduction was delayed for 6 months or longer (41–43). In children with mild to moderate asthma, regular treatment with an inhaled corticosteroid was shown to be more effective than regular treatment with salmeterol, as judged by changes in peak flow, symptoms, bronchial reactivity, and frequency of exacerbations, but to cause a modest reduction in growth (44).

What this all distills down to is that the clinical relevance of the loss of bronchoprotective efficacy of inhaled β2-agonists when a long-acting preparation is taken regularly is still unclear. On the one hand, no study has clearly shown an association of this form of tolerance to these agents with a change in asthma morbidity or mortality. It is also difficult to relate what has been shown in a research setting to what occurs in the natural environment, where so many other variables and confounding factors come into play (eg, use of other medications, time of day, comorbid conditions, etc). On the other hand, the studies that have examined changes in bronchoprotection against provocative stimuli when β2-agonists are taken regularly are remarkably consistent in their findings. In the end, the position taken in the recent revision of the National Asthma Expert Panel's guidelines for the diagnosis and management of asthma seems sensible: Long-acting β2-agonists should be reserved for patients with moderate to severe asthma whose asthma is suboptimally controlled despite regular anti-inflammatory therapy (5). These drugs should not replace inhaled corticosteroids, but may enable lower doses to be used. They may also be used to control nocturnal or exercise-induced symptoms that persist despite standard doses of an inhaled corticosteroid. This may well prove to be only an interim recommendation. The final position of long-acting inhaled β2-agonists in clinical practice has yet to be fully established.

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