



What Doesn't Kill May Not Make You Stronger β -Blockers for Asthma

Activation of the β_2 -adrenergic receptors (B2ARs) on the airway smooth muscle by administering β -agonists is the most effective and most commonly used approach to relieve acute bronchospasm in asthma. The B2AR exhibits constitutive signaling even when the receptor is not occupied (1). The fact that administration of β -blockers can produce bronchospasm in patients with asthma suggests that tonic activation of these receptors may be important in preventing airway narrowing in some individuals with asthma. Thus, it came as a surprise that, in a murine model of antigen-induced asthma, B2AR knockout mice experience less airway hyperresponsiveness and, perhaps most surprisingly, less mucus metaplasia and airway eosinophilia than wild-type controls (2). Certain β -blockers act competitively to block activation of the receptor by other ligands, whereas others (inverse agonists) block the constitutive signaling of the receptor (1). The effects seen in the knockout mice were reproduced when wild-type mice were pretreated with β -blockers with inverse agonist properties, but not with β -blockers without such properties (2). The fact that the inverse agonists produced effects similar to knocking out the receptor suggested that the constitutive effects of the receptor might be proinflammatory. Thus, it appeared that although the acute effect of β -blockade might be to produce smooth muscle constriction, blockade of the constitutive effect might be beneficial for asthma in the long run, and this suggested the possibility of a novel approach to the treatment of asthma.

This line of thinking generated even more excitement after Hanania and colleagues, in open-label uncontrolled trials, showed that nadolol, an inverse agonist, could be safely administered to patients with mild asthma (3, 4). They observed that nadolol was associated with a doubling dose improvement in airway hyperresponsiveness to methacholine. The dose had to be titrated up very slowly and carefully, and even so, some patients had to be withdrawn due to acute bronchospasm even at the lowest dose. Encouragingly, even though those who remained in the trial experienced a 5% dose-independent reduction in FEV₁ over the study period, the ability to bronchodilate in response to salbutamol was sustained (4).

In this issue of the *Journal*, Short and colleagues (pp. 1308–1314) describe the results of a randomized, double-blind, placebo-controlled, crossover trial to assess the effects of chronic non-selective β -blockade with propranolol, an inverse agonist, as an add-on to inhaled corticosteroids in individuals with asthma with mild to moderate disease (5). The investigators used the long-acting anticholinergic tiotropium to prevent catastrophic drops in FEV₁. Unfortunately, there was no improvement in the primary or secondary outcomes, which included methacholine and histamine reactivity, asthma control, fractional exhaled nitric oxide, and asthma-related quality of life.

Do the results suggest that inverse agonism has no antiinflammatory effect? Not necessarily. These were individuals with well-controlled asthma on inhaled corticosteroids with a mean Asthma Control Questionnaire score less than 1. Corticosteroids

can up-regulate β -receptors (6) and may have blunted any possible effect of the β -blockade. Additionally, corticosteroids profoundly suppress exhaled nitric oxide (7) and thus may have prevented any detection of a signal in that biomarker.

Nonetheless, the results of the study are disappointing from a therapeutic perspective. It can be argued that inhaled corticosteroids blunted the possible biological effects of β -blockade. However, if β -blockade is unable to improve outcomes in the setting of inhaled corticosteroid use, the prospects are considerably dimmed, considering the difficulty with titration and overcoming the additional bronchospasm, that this form of therapy will be a practical addition to our armamentarium. One can only hope that more selective inverse agonists might produce more encouraging results. One could also argue that perhaps this form of therapy might be more effective in patients not well controlled on inhaled corticosteroids. However, considering the initial bronchospastic effects, this may be a more difficult group to study. For now, in the case of β -blockers in asthma, what doesn't kill you does not appear to make you stronger.

Author disclosures are available with the text of this article at www.atsjournals.org.

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