

Say What, Beta-Blockers for Asthma?

In 1972 Sir James Black received the Noble Prize for the theory of “synoptic antagonism” and the invention of the world’s first beta-receptor and H₂-receptor blockers, propranolol and cimetidine, respectively (1). In his then novel approach to the treatment of cardiovascular disease, Black focused on developing a drug that reduced the demand on the heart by reducing oxygen consumption. In 1964 Inderal was released and revolutionized the treatment of cardiovascular diseases, including hypertension, angina, myocardial infarction, and tachyarrhythmias. During this period of great progress for cardiology, however, beta-blockers were considered to be contraindicated in patients with impaired left ventricular function and got a bad name from pulmonologists by causing acute bronchospasm in individuals with asthma. Ten years ago, however, Packer and colleagues demonstrated that low doses of the beta-blocker carvedilol improved mortality in patients with chronic heart failure and generated an epiphany in the medical community with the realization that chronic beta-receptor stimulation may in part drive progression of congestive heart failure (rather than help it) and that low dose beta-blockade therapy could slow this progression (2). Along a similar line, now a decade later, a similar epiphany may be surfacing regarding the role of the beta-receptor in allergic airway inflammation and the potential role of beta-blockade in the treatment of asthma.

In this issue of the *Journal* (pp. 256–262), Nguyen and colleagues investigated if systemic beta-blockade with two different beta-blockers can modulate the inflammatory response in an ovalbumin model of asthma in mice (3). In previous studies, these authors demonstrated that in contrast to the acute effects of beta-blockers on airway hyperresponsiveness, the chronic administration of these agents significantly improved methacholine responsiveness in a chronic model of asthma (4). In the studies reported herein, the authors extend these findings by demonstrating that, in addition to the effects on airway hyperresponsiveness, chronic beta-blockade reduces eosinophilic inflammation, cytokine elaboration, and mucin content in chronically ovalbumin-challenged mice. Two beta-blockers were used in these studies, one nonselective (nadolol) given orally and one selective for the β_2 receptor (ICI 118,551) given by sub-cutaneous pump. Both agents demonstrated similar effects on inflammatory cells and mucin production, suggesting the effects are mediated primarily via antagonism of the β_2 -receptor. Importantly, to dissect whether the mechanism of this anti-inflammatory effect was occurring during sensitization or challenge, these studies employed three different sensitization/challenge protocols and demonstrated that the modulatory effect of beta-blockade was occurring during the antigen challenge phase of the allergic inflammatory response and not the sensitization phase. The findings were also confirmed in a different laboratory using a slightly different mouse strain and ovalbumin sensitization/challenge protocol supporting the reproducibility of the findings. There are some limitations in these studies. While nadolol reduced cytokine levels in bronchoalveolar lavage, data on the effect of ICI 118,551 on cytokine elaboration is not reported. This information would be helpful in understanding relative contributions of

β_1 and β_2 receptors to the study’s findings. In addition, these studies were inadequate to address the mechanism of the anti-inflammatory effect of beta-blockade. For example, was the modulation of inflammation in the lung due to impaired recruitment to the lung, proliferation of inflammatory cells within the lung, or an increase in cell turnover (apoptosis)? Elucidating these effects could be useful in gaining finer fidelity to develop beta-antagonists with selective “pulmo-protective” effects. Even so, the authors’ conclusion that when taken in moderation beta-blockers might have anti-inflammatory effects in asthma is reasonable.

However, while these results are tantalizing and suggest that we should analogize from studies in heart failure to the beneficial effects of beta-blockade on asthma, we must proceed with caution. Extrapolation from this study’s findings and studies done in patients with chronic heart failure needs to be carefully considered. Indeed, these investigators recently studied the effects of nadolol in a dose escalation trial in 10 subjects with mild asthma (5). Although this small trial demonstrated that individuals with asthma can safely tolerate nadolol and that there was a significant increase in dose of methacholine responsiveness, nadolol caused a significant decrease in FEV₁ independent of dose at the conclusion of the study, and 4 of the 10 patients treated increased their rescue medication use or had decreased lung function. In addition, two recent studies done in patients with chronic obstructive lung disease (COPD) and asthma suggested that beta-blockade, both selective and nonselective agents, have adverse effects when used in the “real world.” Brooks and colleagues performed a large retrospective electronic medical record database review of 11,592 adult patients with asthma and COPD, and demonstrated that patients with asthma with or without COPD that were taking selective or nonselective beta-blockers had an increased risk of hospitalizations and emergency department visits (although the reasons for admissions are not defined) (6). van der Woude and colleagues performed a double-blind, placebo-controlled, randomized crossover study in 35 patients with COPD and airways hyperresponsiveness of treatment with propranolol, metoprolol, celiprolol, or placebo for 4 days. While both propranolol and metoprolol worsened airways hyperresponsiveness and propranolol adversely affected lung function, the cardioselective beta-blocker celiprolol had no effect on pulmonary measurements (7). These studies indicate that using beta-blockade in patients with asthma will require pulmonologists to balance the variables of drug selection, obstructive lung disease phenotype (asthma, COPD, or both), dose, and timing of treatment. A slippery slope, indeed.

It is possible that there is some credence to the concept that beta-blocker treatment will address the long and controversial history that chronic beta-receptor stimulation with short-acting and long-acting beta-agonists may contribute to poor asthma outcomes. It remains unclear if the systemic administration of nonselective beta-blockers will have any effect on patients also taking short-acting and/or long-acting beta-agonists. However, given the preponderance of data, it appears clear that what will ultimately be the determining factor regarding the beta-blockers for asthma “paradigm shift” will be to the right of the decimal point of the risk/benefit ratio. It is likely that in the heterogeneous

environment of human asthma, the benefit will be small, difficult to detect, and may not significantly affect standard clinical outcomes. While the safety and efficacy trial demonstrated that nadolol was relatively safe in individuals with mild asthma, the niche for beta-blockers will likely be in patients with moderate to severe disease, a subset of patients that may be significantly more susceptible to the deleterious effects of acute bronchospasm. Not to mention the potential effects of noncompliance on the acute deleterious and chronic beneficial effects suggested by these findings. Nevertheless, as it is well known that many patients with asthma tolerate beta-blocker therapy for treatment of cardiovascular disease, Nguyen's findings suggest that low-dose chronic beta-blocker treatment may prove useful to reduce inflammation and mucus in a subset of individuals with asthma. Ultimately, future studies will be required to determine if the findings in these studies will translate into improved asthma outcomes in patients.

Conflict of Interest Statement: G.L.C. reports having been a paid speaker for GlaxoSmithKline, Merck, AstraZeneca, and Novartis, and has received grant support from Wyeth Inc., Centocor Inc., Pfizer Inc., and Novartis, Inc.

GEOFFREY L. CHUPP, M.D.
Yale School of Medicine
New Haven, Connecticut

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