

Long-acting β -agonists and inhaled corticosteroids: Is the whole greater than the sum of its parts?

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β -Agonists and inhaled corticosteroids (ICSs) form the cornerstone of asthma therapy. β -Agonists stimulate the Gs α -subunit of the G protein-coupled β_2 -receptor on the airway smooth muscle cell surface, resulting in the stimulation of adenylyl cyclase, which produces cyclic AMP.¹ The resultant airway smooth muscle relaxation and increase in airway caliber mediate the predominant clinical effect of β -agonists as used in asthma pharmacotherapy. However, β_2 -receptors are not only present on the surface of airway smooth muscles but also on other cells, such as mast cells and fibroblasts. *In vitro* stimulation of these receptors results in decreased production of inflammatory mediators in mast cells and decreased extracellular matrix protein release from fibroblasts.^{2,3} Furthermore, some data suggest that β -receptor stimulation can inhibit smooth muscle proliferation.⁴

Although the *in vitro* data mentioned above suggest that β -agonists might produce salutary effects in asthma in addition to their smooth muscle relaxant effects, when evaluated clinically, there is little to suggest that this is the case.⁵ They are therefore classified as reliever medications because they temporarily relieve symptoms but have little effect on long-term asthma control. ICSs, on the other hand, are classified as controller medications because they appear to affect some of the underlying pathobiological processes, such as airway inflammation, that are associated with increased airway reactivity and loss of asthma control.

Long-acting β -agonists (LABAs) produce long-lived stimulation of β -receptors. Considering the mechanisms of action of β -agonists, it is not surprising that adding a LABA to an ICS in patients whose symptoms are not fully controlled with the ICS alone improves asthma symptoms. However, it is unclear whether the benefit provided by the combination is merely an additive one (ie, adding a symptom reliever to a controller) or whether this combination might act synergistically to improve the anti-inflammatory actions of one or both of the components in the combination.

There are a fair amount of *in vitro* data to suggest that ICSs and LABAs might interact synergistically. β -Agonists have been shown to stimulate the glucocorticoid receptor and the CCAAT enhancer-binding protein α .⁶ CCAAT enhancer-binding protein α and the glucocorticoid receptor translocate to the nucleus and inhibit smooth muscle cell proliferation. Glucocorticoid receptor nuclear translocation in epithelial cells collected from sputum increases when β -agonists are administered with ICSs compared with administration of an ICS alone.⁷ Furthermore, addition of β -agonists to corticosteroids has been shown to enhance the antiproliferative effect of the corticosteroid on smooth muscle *in vitro*.⁶

Do these *in vitro* or *ex vivo* interactions change the pathobiological responses of combination therapy in asthma *in vivo*? The study by Kelly et al⁸ is a tentative first step in confirming such a possibility. The team from McMaster University compared sputum indices 7 hours after allergen challenge and airway mucosal biopsy specimens 24 hours after challenge in patients with asthma treated with placebo, an ICS, and an ICS with formoterol. As has been reported by others, LABAs seemed to enhance the eosinophil-suppressing effects of the ICS.⁹ This eosinophil-reducing effect might be mediated through the additive inhibitory effect of LABAs on the production of eotaxin through inhibition of histone H4 acetylation and nuclear factor κ B binding to the eotaxin promoter.¹⁰ What is new is the observation (admittedly *post hoc*) that suggests that LABAs and ICSs might act synergistically to affect the myofibroblast proliferation that occurs in response to the allergen challenge. Myofibroblast proliferation and the presumed increase in smooth muscle mass that might occur as a result of such proliferation has been associated with airway hyperresponsiveness.¹¹ If true, such an observation might explain the unexpected increased in anti-inflammatory effects seen from adding a LABA to an ICS, such as the resultant decrease in exacerbations.¹² This observation would also provide a potential mechanistic explanation for the recently reported surprising improvement in methacholine responsiveness seen when a LABA was added to an ICS in patients who possess the Gly16Gly polymorphism of the β_2 -receptor.¹³

Does this study clearly confirm that LABAs and ICSs interact to produce an effect on myofibroblasts and airway smooth muscle area greater than a simply additive effect? No. A statistical difference between an ICS and the ICS/LABA combination was not achieved in relation to myofibroblasts in the primary analysis. Although a difference between an ICS and the ICS/LABA combination was seen in airway smooth muscle area, this analysis was undertaken *post hoc*. Furthermore, one would have felt more reassured that the effect on airway smooth muscle was truly related to the formoterol/ICS interaction had a formoterol control been included. However, the findings are intriguing enough that they deserve further confirmation.

Why does it make a difference? If the combination is merely additive, then a potential concern relates to the possibility that

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adding β -agonists to ICSs merely raises the threshold for an exacerbation. In certain cases this could result in a patient not seeking additional therapy for worsening asthma because of the fact that the patient's airway caliber has not decreased enough to make him or her adequately symptomatic. Such a mechanism of action would then explain the rare severe asthma exacerbations that apparently occur with use of LABAs and possibly even with LABA/ICS combinations.^{14,15} On the other hand, if the combination is synergistic, such that LABAs increase the anti-inflammatory effects of ICSs, ICSs promote the apparently minor anti-inflammatory effects of LABAs, or both, then these rare and severe asthma deteriorations should be considered idiosyncratic events, and the search for their cause, or those at risk, would be altered.

Where are we left? Kelly et al⁸ have suggested avenues for further investigation and a possible observation that would explain how, in the case of combining an ICS and a LABA, the whole might be greater than the sum of its parts.

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