

Should Regular Use of β Agonists Be Recommended for Patients with Persistent Asthma?

Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. *Ann Intern Med* 2004;140:802-13.

Study Overview

Objective. To assess the effect of regular β_2 -agonist use compared with placebo on pulmonary function and β_2 -receptor function in patients with asthma.

Design. Meta-analysis of randomized, placebo-controlled studies of regular β_2 -agonist use of at least 1-week duration in asthma patients where the placebo arm did not use any β_2 -agonists.

Main outcome measures. Change in mean forced expiratory volume in 1 second (FEV₁) (measured at least 6 hours after administration of the last dose of drug), response to subsequent β_2 agonist after the study period, provocative challenge causing a 20% reduction in FEV₁ (PC₂₀), and in vitro leukocyte β_2 -receptor density.

Main results. Data were available from 22 randomized trials that evaluated 323 participants. Change in mean FEV₁ did not differ between treatment and control groups. Compared with placebo, regular β_2 -agonist treatment reduced peak FEV₁ in response to subsequent β_2 -agonist use (-17.8% [95% confidence interval (CI), -27.2% to -8.5%]), the PC₂₀ to provocative stimuli (-26% [95% CI, -37% to -11%]), and leukocyte β_2 -receptor density (-18.3% [95% CI, -31.6% to -5.1%]).

Conclusion. Regular β_2 -agonist use in patients with asthma resulted in decreased responsiveness to the drug's bronchodilating effects.

Commentary

β_2 Agonists have a clear beneficial role in relieving the acute airway obstruction of asthma. Their role as a regular part of the management for chronic stable asthma is more controversial. An earlier case-control study using pharmacy data suggested that regular β_2 -agonist users developed fatal or near fatal asthma exacerbations more frequently than patients using them less often [1]. Other studies, however, have failed to show a link between regular β_2 -agonist use and worse clinical outcomes [2,3] and suggest that the addition

of a long-acting β_2 agonist for patients already using inhaled corticosteroids provided greater improvement in lung function compared with increasing the dose of inhaled steroid [3]. Findings have led to the manufacture of several fixed dose β_2 agonist/inhaled steroid combinations.

This meta-analysis of multiple small trials of short- and long-acting β_2 agonists where the control group used no β_2 agonists failed to show an improvement in lung function and demonstrated several potentially detrimental effects. How do we reconcile these disparate findings?

First, the outcomes examined in this meta-analysis are physiologic measures only. This study does not provide direct proof that regular usage leads to worse clinical outcomes, such as increased symptoms, emergency department visits, or hospitalizations. Second, the studies included in this meta-analysis did not allow for the use of intermittent β_2 agonists. It is possible that intermittent and scheduled usage lead to similar disease control, while abstinence from β_2 agonist preserves full airway responsiveness to this treatment. Lastly, it also is possible that both sets of findings are true. Asthmatic persons on regular β_2 agonists in addition to an inhaled corticosteroid may have reduced responsiveness to subsequent β_2 -agonist exposure, greater sensitivity to inhaled challenges, and down-regulation of β receptors compared with nonusers. But, these patients still may have better clinical outcomes while they are using the long-acting β_2 agonist because the majority of the bronchodilating effects are still preserved.

Applications for Clinical Practice

Regular β_2 -agonist exposure may reduce some of the beneficial effects of subsequent medication exposure and could potentially increase airway bronchoconstriction provoked by irritant or allergic stimuli. However, it would be premature to completely disregard studies demonstrating the benefits of adding a regular long-acting β_2 agonist to low or moderate doses of inhaled steroids. Additional well-designed studies are needed to define the optimal way to use β_2 agonists for patients with persistent asthma.

—Review by Stephen D. Persell, MD, MPH

References

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