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Comparative efficacy of levalbuterol and racemic albuterol in the treatment of asthma

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To the Editor:

Levalbuterol (Xopenex), the (R)-enantiomer of racemic albuterol, has been available in the United States since 1999 as inhalation solution for patients 12 years of age and older. The indicated age was lowered to 6 years in February 2002; this decision was based on a clinical trial that had been submitted to the US Food and Drug Administration and was published in this Journal by Milgrom et al.^{[1](#)}

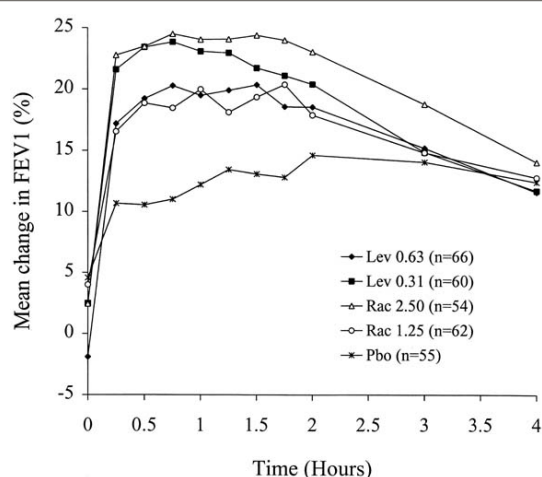
The authors of the trial concluded that a dose of levalbuterol was comparable to a 4- to 8-fold higher dose of racemic albuterol in children. Previously, Nelson et al.^{[2](#)} had reported that a dose of levalbuterol was comparable to a 4-fold higher dose of racemic albuterol in adults and adolescents. Critical analyses of the design and results of these trials do not support the authors' conclusion, which is based partly on comparative efficacy.

These trials were designed to demonstrate the efficacy and safety of levalbuterol in comparison with placebo, not to rigorously compare levalbuterol and racemic albuterol. Racemic albuterol was included to give a sense of relative efficacy and safety, not for

inferential statistical comparison or equivalence analyses with levalbuterol. The trials were conducted in patients with mild-to-moderate asthma, and the drugs were administered as daily scheduled doses. All doses were near the top of the dose-response curves for the study patients, and there were no statistical differences between the doubling doses of each drug or between the 2 drugs.

The protocol-specified objectives of the trial reported by Milgrom et al were to demonstrate comparative efficacy and safety of 0.31 mg and 0.63 mg doses of levalbuterol and 1.25 and 2.5 mg doses of racemic albuterol relative to placebo in children with asthma. In contrast to the title and to the objective stated in the article,¹ the trial was not designed to compare levalbuterol with racemic albuterol. The FEV₁ median peak percent change relative to baseline (primary efficacy variable) showed comparable numerical responses for all active treatments, and there were no statistical differences between the active treatments. The authors cited the comparable responses between the levalbuterol 0.31 mg and racemic albuterol 2.5 mg arms (27.0% vs 26.7% at day 0; 24.9% vs 27.6% at day 21) to support the conclusion that levalbuterol had an 8-fold higher efficacy than racemic albuterol. The same data for day 21, expressed as time-profile FEV₁ curves, are shown in Fig 1 for 6- to 11-year-old patients, the age group for which levalbuterol was recently approved.³

Fig. 1. Mean percent change in timed serial FEV₁ obtained after dosing on day 21, expressed as percent change from baseline. Baseline FEV₁ was obtained before administration of dose on day 1.



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The FEV₁ curves show that the 2 levalbuterol doses had an apparent inverse dose-response. The 0.63-mg levalbuterol dose did not even reach statistical significance in comparison with placebo when ANOVA was used to correct for baseline. Because there were no statistical differences between the active treatment arms, there were no clear dose-response for the active treatments, and even an inverse dose-response for levalbuterol,

conclusions on relative efficacy between levalbuterol and racemic albuterol cannot be drawn from this trial.

Whether levalbuterol has a therapeutic advantage over racemic albuterol is a subject of debate. Some in vitro and animal studies, as well as the clinical trials mentioned above,^{1 2} suggest that levalbuterol might have a therapeutic advantage over racemic albuterol.⁴ In contrast, a cumulative-dose crossover study in patients with mild-to-moderate asthma reported that there was no difference in relative potency between levalbuterol and racemic albuterol,⁵ and an accompanying editorial stated that there are no pharmacologic differences between the 2 drugs.⁶ These conflicting views need to be addressed in well-designed studies. Cumulative-dose studies in the setting of acute severe bronchospasm, such as in patients waking up with nocturnal asthma or with asthma exacerbation, are better suited to test the relative efficacy and safety of levalbuterol and racemic albuterol. These patients are more likely to show a meaningful dose-response between doubling doses that might be more amenable to meaningful statistical comparative analyses.

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Journal of Allergy and Clinical Immunology, The
March 2003, part 2 • Volume 111 • Number 3
Andrea J. Apter, MD, MSc

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6. Asthma

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Reply

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