Single Isomer Versus Racemate: Is There a Difference?

Clinical Comparisons in Allergy and Gastroenterology

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ABSTRACT

Many commonly prescribed drugs exist as a mixture of two distinct chiral isomer forms (enantiomers), each with its own unique chemistry, receptor affinity, and pharmacokinetic profile. Much is unknown concerning the clinical utility of these single enantiomers. This review of the stereoisomers of two commonly used drugs—albuterol for asthma and omeprazole for gastroesophageal reflux disease (GERD) and peptic ulcers—examines the improved efficacy, pharmacokinetics, decreased adverse effects, and fewer drug-drug interactions associated with single enantiomers.

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INTRODUCTION

It has long been recognized that many biologically active molecules exist as two distinct chiral isomers, each with its own unique chemistry, receptor affinity, and pharmacokinetic profile. Although much remains to be learned about the clinical utility of these single enantiomers, recent research suggests they have the potential to offer more predictable pharmacokinetics (and therefore less interpatient variability), improved efficacy, decreased adverse effects, and fewer interactions with other drugs than their racemates. The objective of this paper is to review the clinically relevant differences between stereoisomers of two commonly used drugs: albuterol for bronchial asthma and omeprazole for gastroesophageal reflux disease (GERD) and peptic ulcers.

ALBUTEROL VERSUS LEVALBUTEROL IN ALLERGIC ASTHMA

Albuterol is a short-acting β_2-receptor agonist that exists as a 1:1 mixture of the (*R*)- and (*S*)-enantiomers (Figure 1). Inhaled racemic albuterol acts as a highly effective bronchodilator by relaxing airway smooth muscle, and is the most frequently prescribed compound in its class for the relief and prevention of bronchospasm in patients with bronchial asthma. However, when used on a regular basis, racemic albuterol can produce some degree of subsensitivity or tolerance, which diminishes bronchodilator efficacy by reducing the duration but not the peak of the response. Subsensitivity is especially common when the initial response is measured after a β-agonist washout (a period in which β-agonist use is suspended). Moreover, regular use of racemic albuterol leads to tolerance or impaired ability to protect against challenge with allergen and methacholine (a bronchoconstrictor), and may even worsen trough-level sensitivity to allergens and other bronchoconstricting stimuli (described as airway hyperresponsiveness).[1]

Adverse Effects of (S)-Albuterol: Preclinical and Pharmacokinetic Evidence

Based on preclinical evidence that β_2-agonist enantiomers can have markedly different effects on airway responsiveness, it was proposed that some of the unwanted effects of racemic albuterol might be attributable to (*S*)-albuterol, and that conversely, pure (*R*)-albuterol (levalbuterol) might offer better efficacy than the racemic mix.[1] Unlike levalbuterol, (*S*)-albuterol is not a bronchodilator. It worsens airway hyperresponsiveness to spasmogens such as histamine in animal tissues,[2] and may hamper asthma control by exaggerating airway reactivity. It may also have pro-inflammatory effects on airway eosinophils.[1] In human bronchial smooth muscle, levalbuterol is believed to produce relaxation by reducing intracellular calcium levels. In contrast, (*S*)-albuterol produces a dose-dependent increase in intracellular calcium levels.[3]

Pharmacokinetic studies show that inhalation of the racemic mix results in a 5-fold greater exposure to (*S*)-albuterol due to a much higher peak concentration than levalbuterol.[1,4] While QID dosing of β-agonists results in offsetting blood levels of levalbuterol during the day, at night, levalbuterol may be completely cleared from the system, leaving the effects of (*S*)-albuterol unopposed.

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Clinical Evidence

The proposed differences between (*R*)- and (*S*)-albuterol have been confirmed in three clinical studies, two in asthmatic adults and one in asthmatic children. In each of these studies, pure levalbuterol was more effective than an equal amount of levalbuterol administered as a racemic mixture. Taken together, the results suggest that (*S*)-albuterol has a negative effect on both acute bronchodilator response and baseline airway caliber.[1]

Racemic Albuterol Versus Both Enantiomers in Adults

The first study was a double-blind, parallel-group trial of airway sensitivity in 40 asthmatic adults with mild obstruction. The subjects were randomized to receive racemic albuterol (2 mg), levalbuterol (1 mg), (*S*)-albuterol (1 mg), or vehicle. Sensitivity to methacholine was evaluated prior to inhalation, and at 20 minutes and 3 hours thereafter. As shown in Figure 2, (*S*)-albuterol had little effect on airway reactivity at 20 minutes, and actually worsened it at 3 hours (whereas no worsening was observed with placebo). In contrast, both racemic albuterol and levalbuterol significantly improved airway reactivity at 20 minutes. The protection, however, was sustained at 3 hours only with levalbuterol. With racemic albuterol, reactivity deteriorated to placebo levels at this timepoint, presumably because of the counteracting effects of (*S*)-albuterol.[5]

Racemic Albuterol Versus Levalbuterol in Adults

In a subsequent trial, 328 adults with chronic, stable asthma were randomized to receive doses of levalbuterol (0.63 mg or 1.25 mg), racemic albuterol (1.25 mg or 2.50 mg), or placebo TID via nebulizer for 4 weeks. All subjects had regularly used albuterol prior to the study, and all showed moderate to severe airflow limitation when albuterol was withheld for more than 8 hours. All subjects in the active-treatment arms demonstrated an improvement of over 15% in forced expiratory volume in 1 second (FEV_1). As the study was not designed to show a difference between levalbuterol and racemic albuterol, all of the comparisons described are based on post-hoc analysis.[6]

After the first dose, the percent change in FEV_1 was greatest and most prolonged with the high dose of levalbuterol (1.25 mg, Figure 3). Since patients in the 2.5 mg racemic albuterol group received the same amount of levalbuterol (1.25 mg), their weaker response was probably due to the exposure of (*S*)-albuterol. In support of this, the low dose of levalbuterol (0.63 mg) was equal in potency to the high dose of racemic albuterol (2.5 mg) for all FEV_1 analysis.[1,6]

The superiority of levalbuterol over the racemic mix was still apparent after 4 weeks of treatment. The degree and duration of bronchodilation remained greatest with the high dose of levalbuterol, and again, the low dose of levalbuterol was as active as the high dose of racemic

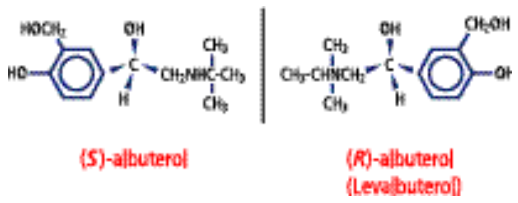

FIGURE 1. RACEMIC ALBUTEROL ISOMERS

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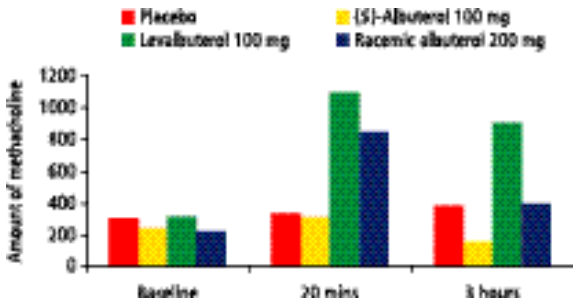

FIGURE 2. AIRWAY REACTIVITY TO METHACHOLINE IN SUBJECTS WITH MILD AIRWAY OBSTRUCTION AT BASELINE, AND AFTER INHALATION OF PLACEBO, (*S*)-ALBUTEROL, LEVALBUTEROL, OR RACEMIC ALBUTEROL

Values represent the mean amount of methacholine needed to produce a 20% decrease in forced expiratory volume in 1 second (FEV_1), hence higher values indicate greater protection against methacholine's bronchoconstricting effects.[5]

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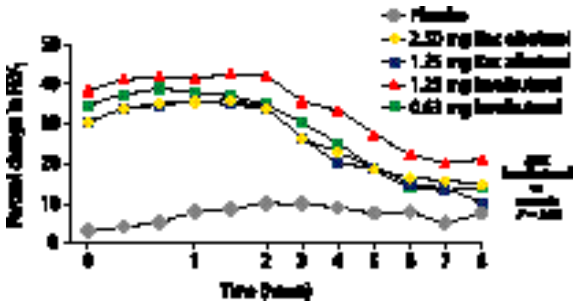

FIGURE 3. BRONCHODILATOR EFFICACY IN ASTHMATIC PATIENTS TREATED WITH A SINGLE DOSE OF PLACEBO, RACEMIC ALBUTEROL 1.25 OR 2.5 MG, OR LEVALBUTEROL 0.63 OR 1.25 MG[6]

FEV_1=forced expiratory volume in 1 second; Rac=racemic; AUC=area under time curve.

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albuterol (Figure 4). Furthermore, compared with placebo, the need for rescue medication was significantly lower (P=.001) with levalbuterol (1.25 mg). In contrast, the high dose of racemic albuterol was only marginally significantly different (P=.056) from placebo in terms of rescue medication use.[1,6] Again, these results argue for a deleterious effect of some component of the racemic mix, presumably the (*S*)-albuterol.

Another intriguing observation from this study is that after 4 weeks of treatment, baseline (ie, trough drug level) FEV_1 values improved by about 0.1 L (6%) in patients who had received levalbuterol or placebo, but improvement was negligible in those who had received racemic albuterol. The difference was even more striking in the subset of patients who did not use inhaled steroids.[1] This further supports the theory that (*S*)-albuterol has an undesirable impact on pulmonary function: since it is cleared from the system more slowly than levalbuterol, its detrimental effects would be expected to be most pronounced at the end of the dosing cycle, when it is unopposed by the (*R*)-albuterol enantiomer.

As expected, levalbuterol 1.25 mg and racemic albuterol 2.5 mg were comparable in their effects on serum potassium glucose and glucose levels and ventricular beat frequency (these measures reflect activation of β-receptors outside the airways). Similarly, the rates of these adverse effects were also comparable between levalbuterol 0.63 mg and racemic albuterol 1.25 mg. Since the 0.63 mg dose of levalbuterol produced as much bronchodilation as racemic albuterol 2.5 mg, treatment with this dose of levalbuterol might be anticipated to offer equal potency to the 2.5 mg dose of racemic albuterol, with fewer adverse effects. It should be noted that nervousness and tremor were the only adverse effects that were slightly more common with levalbuterol 1.25 mg than with racemic albuterol 2.5 mg.[1,6]

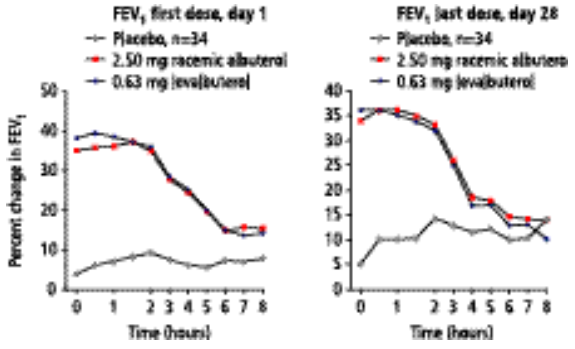

FIGURE 4. BRONCHODILATOR EFFICACY IN ASTHMATIC PATIENTS TREATED WITH PLACEBO, RACEMIC ALBUTEROL 2.5 MG, OR LEVALBUTEROL 0.63 MG

Left panel shows results after the first dose. Right panel shows results after 4 weeks.[6]

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FEV_1=forced expiratory volume in 1 second.

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Racemic Albuterol Versus Levalbuterol in Children

Levalbuterol (0.16, 0.31, 0.63, or 1.25 mg) was compared to racemic albuterol (1.25 and 2.50 mg) in a dose-ranging, crossover study of 28 children between 6 and 11 years of age, with chronic, stable asthma. All subjects had used racemic albuterol regularly prior to enrollment and showed moderate to severe airflow limitation when albuterol was withheld for 8 hours, with reversibility after a 2.5 mg dose.[1,7]

At all time points, change in FEV_1 was greatest with the highest dose of levalbuterol (1.25 mg). As in the adult study, the lower doses of levalbuterol (0.63 and 0.31 mg) were equivalent to the higher dose of racemic albuterol (2.5 mg) in efficacy. There was no significant difference between groups in the overall rate of adverse events—side effects related to extrapulmonary β-receptor activation were proportional to the dose of levalbuterol, regardless of whether it was taken as the single isomer or as the racemic mix. This suggests that levalbuterol offers at least a 50% improvement in therapeutic index over the racemate, and again implicates (*S*)-albuterol as the component that undermines pulmonary performance in the racemate.[1,7]

ESOMEPRAZOLE VERSUS OMEPRAZOLE IN GASTRIC ACID SUPPRESSION

Omeprazole was the first proton pump inhibitor (PPI) developed for the treatment of gastroesophageal reflux disease (GERD) and peptic ulcers, and it remains the most commonly used agent in its class.[8,9] Like all other PPIs, omeprazole raises gastric pH by inhibiting gastroparietal cell acid secretion. These agents have a wide therapeutic range, meaning that they can be used at high doses with very little risk of adverse effects. However,

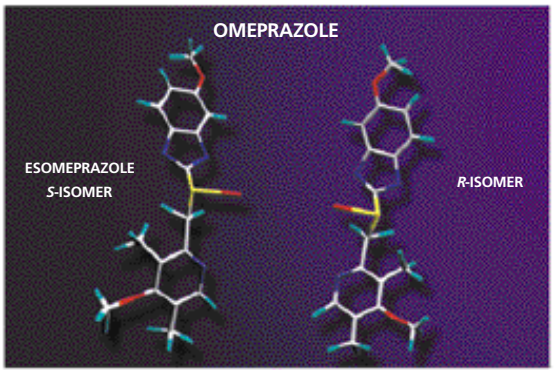

FIGURE 5. RACEMIC OMEPRAZOLE ISOMERS

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all are dependent on the hepatic cytochrome P450 (CYP) system for their metabolism, which can result in drug interactions and marked variability among patients.[9,10] As PPIs exist as enantiomeric mixes of the *R*- and *S*-forms,[8] this has prompted a search for isomers without these drawbacks.

OMEPRAZOLE METABOLISM: IMPACT OF PHARMACOGENETIC VARIABILITY

Racemic omeprazole is metabolized mainly by CYP 2C19, one of the CYP enzymes. A single nucleotide polymorphism in the gene that codes for this enzyme can impair its function, resulting in a "poor metabolizer" genotype-phenotype. Clearance of racemic omeprazole is much slower in poor metabolizers, which complicates the task of finding the optimal dose. The variant CYP 2C19 genotypes can produce a 7-fold increase in drug exposure (measured as the area under the plasma concentration/time curve [AUC]). The impact of the poor metabolizer genotype is similar but somewhat less with other PPIs such as lansoprazole and pantoprazole, but notably less with rabeprazole. Even so, variant CYP 2C19 genotypes can double lansoprazole or pantoprazole AUC, potentially influencing their activity.

Studies using human liver microsomes show that racemic omeprazole is not only a substrate for CYP 2C19, but also a fairly potent inhibitor of it.[12] Clinically, this competitive inhibition can mimic the poor metabolizer phenotype, resulting in excessively prolonged drug exposure to omeprazole or other drugs metabolized by CYP 2C19, such as diazepam.[12,13] The pharmacokinetics of other CYP 2C19 substrates, including some tricyclic antidepressants, nelfinavir, phenytoin, and proguanil, may be significantly altered in patients taking concomitant omeprazole.

Esomeprazole: The (S)-Isomer of Omeprazole

Efforts to find a PPI with more predictable pharmacokinetics have recently focused on omeprazole's *S*-enantiomer, esomeprazole, which is administered in the racemate at a 1:1 ratio with the *R*-isomer (Figure 5). Esomeprazole and the racemic mix are equipotent as inhibitors of the proton pump, but the *S*-isomer offers certain pharmacokinetic advantages, such as a long half-life at the prescribed dose. Whereas racemic omeprazole and its *R*-isomer are metabolized primarily to a hydroxyl form by CYP 2C19, esomeprazole is converted to a sulfone metabolite by a different enzyme, CYP 3A.[10] Rather than being heavily dependent on CYP 2C19, esomeprazole metabolism is principally catalyzed by enzyme CYP 3A, and the clearance rate of esomeprazole was 10-fold lower than that of (*R*)-omeprazole.[10] This indicates that esomeprazole is cleared more slowly than (*R*)-omeprazole.[10] In theory, this chiral-specific metabolism should make esomeprazole less vulnerable to genetic variability at the CYP 2C19 locus, although it does raise the possibility of other drug interactions.[8]

In addition, esomeprazole appears to inhibit its own metabolism to an even greater degree than racemic omeprazole does, resulting in higher plasma levels after repeated dosing than after the first dose.[9] The result of this auto-inhibition is that esomeprazole's AUC is 70% higher than omeprazole's at the same dose, and after repeated administration, mean AUC values can be twice as high with the enantiomer as with the racemate.[8]

Esomeprazole Versus Omeprazole in GERD

The *S*-enantiomer of omeprazole was recently compared to the racemate in a clinical study of 36 patients with GERD. The subjects were randomized to receive the standard dose of omeprazole 20 mg or esomeprazole 20 mg or 40 mg. Outcome was measured in terms of 24-hour intragastric pH and drug AUC, which are the parameters most predictive of clinical efficacy.[14]

The pharmacokinetic advantages of differences noted with esomeprazole were shown to have clear clinical correlates. For example, 20 mg of esomeprazole maintained intragastric pH above 4 for a mean of 12.7 hours, compared with only 10.5 hours for the same dose of the racemate ($P<.01$). Furthermore, 24-hour median intragastric pH was statistically significantly greater with 20 mg of esomeprazole than with the same dose of omeprazole (4.1 versus 3.6, respectively, $P<.01$). Most importantly, there was less interpatient variability in intragastric pH and AUC with esomeprazole than with the racemic mix, suggesting that it would be far easier to provide a dynamically consistent dose in clinical practice (see Table).[14]

TABLE. ESOMEPRAZOLE VERSUS OMEPRAZOLE[14]

- 20 mg esomeprazole kept intragastric pH >4 for 12.7 hours
- 20 mg omeprazole kept intragastric pH >4 for 10.5 hours*
- 24-hour median intragastric pH was greater with 20 mg esomeprazole (4.1) versus 20 mg omeprazole (3.6)*
  - Interpatient variability in intragastric pH and AUC was less with esomeprazole than with omeprazole
  - More effective acid control with less patient variability

*$P<.01$. AUC=area under plasma concentration/time curve.

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CONCLUSION

The studies outlined here show that single isomers can have biochemical and pharmacokinetic differences from their racemic "parents" that result in important clinical benefits. In patients with allergic asthma, pure levalbuterol offers greater and longer-lasting bronchodilation than the same amount of levalbuterol delivered in a racemic formulation. The removal of (*S*)-albuterol offers a persuasive explanation for this difference, based on the fact that it activates human eosinophils, enhances airway reactivity, and induces hyperreactivity in isolated tissues. The activity of (*S*)-albuterol may well explain the paradoxical phenomena of airway hyperresponsiveness and worsened airway obstruction seen with long-term use of

racemic albuterol, and suggests that (*S*)-albuterol may be limiting levalbuterol's anti-inflammatory and anti-allergy potential.[1] These findings suggest that pure levalbuterol may be preferable to racemic albuterol as emergency maintenance therapy for asthma.

In patients with GERD or other acid-related conditions, preliminary data suggest that pure esomeprazole can offer more effective acid control than racemic omeprazole, with less interpatient variability. This may be due to the fact that esomeprazole is primarily metabolized by a different CYP enzyme than racemic omeprazole, so it is not as strongly affected by genetic differences among patients in hepatic enzyme activity. If esomeprazole's improved pharmacodynamic profile is borne out in further research, it should simplify dosing choices for physicians, while presumably exposing patients to fewer adverse effects. With asthma, GERD, and depression, where so much is still unknown about underlying disease mechanisms, the improved safety and tolerability of single isomers will represent a key therapeutic advance. CNS

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