Chiral Switch Drugs for Asthma and Allergies: True Benefit or Marketing Hype

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Enantiomers are one of several possible molecular configurations present in a drug that has at least 1 chiral center. A drug containing 2 or more enantiomers is called a racemic mixture. Enantiomers are being developed from racemic mixtures as drugs in their own right often to extend patent protection of highly popular drugs. However, the therapeutic advantages of single enantiomer drugs developed for respiratory use such as levalbuterol, arformoterol, and levocetirizine over their racemate has been disappointing. In addition, single enantiomer drugs may be several fold more expensive than the racemic drug. New single enantiomer drugs, which are stable (no interconversion back to the racemate) and have fewer adverse effects and a more predictable pharmacodynamic or pharmacokinetic profile would confer a therapeutic advantage and thus would be beneficial for clinical use.

Background

THE DEVELOPMENT OF single enantiomer drugs from established or previously marketed racemates is described as chiral switching.^{1,2} Enantiomers are 2 stereoisomers that are mirror images (thus not superimposable), which have identical physical and chemical properties except in a chiral environment, such as, polarized light and biological systems such as with receptors and enzymes. A chiral center (most often an asymmetric carbon atom) confers different spatial orientation of the enantiomers, and thus often results in differing pharmacologic effects. The nomenclature for enantiomers has varied over the years and was initially based upon the direction of rotation of polarized light and termed (+) or “d” for dextrorotatory (right-handed) and (–) or “l” for levorotatory (left-handed) and although “d” and “l” are considered obsolete, they are still used in the naming of drugs (levalbuterol, levocetirizine). Designations that use “D” or “L” are specific for sugars and amino acids rather than drugs.³ The most accurate nomenclature is based upon the absolute spatial orientation of groups at the chiral center using R/S with the direction of rotation of polarized light, + / –. Thus, an enantiomer may be S(+), S(–), R(+), or R(–). Racemates are equimolar mixtures of enantiomers. Eutomer and distomer refer to the therapeutically active and less active enantiomers, respectively.

The decision to develop a single enantiomer product includes both scientific and economic rationales. A scientific decision tree to inform the development of a eutomer from a racemate⁴ begins with confirmation of stereoselectivity in

receptor recognition and includes *in vivo* efficacy. Importantly, the eutomer must not racemize (interconvert between enantiomers) in any clinically meaningful time frame, have no pharmacodynamic or pharmacokinetic interaction with the distomer, and have no adverse effects not already known for the racemate.⁴ Last, the enantiomer must represent a therapeutic advantage for the patient by having a more selective pharmacodynamic profile, improved therapeutic index, less complex pharmacokinetic profile such as a more direct relationship between the concentration and effect, and reduced potential for drug interactions.²

The economic reasons for developing a single enantiomer from a racemate is most often to extend patent protection (an additional 3 years) for a top selling product that is nearing the end of marketing exclusivity. Before the 1990s, it was estimated that nearly 50% of all drugs used were racemates.⁵ However, the Food and Drug Administration's (FDA's) interest in evaluating each enantiomer in a racemate spurred development of single enantiomer drugs and they now account for 55% of the new molecular entities approved by the FDA.⁶ Montelukast is the lone respiratory drug that has been developed as the enantiomer without a racemate ever being marketed.⁷

Levalbuterol

The (R)-enantiomer of albuterol, levalbuterol, was introduced in the US market in 1999. The scientific criteria described above for developing a therapeutically improved single isomer product is only partially met with levalbuterol.

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The enantiomers are stereoselective at the β_2 -receptor with a 68-fold greater potency for the (R)- than (S)-albuterol⁸ and racemization after administration of either enantiomer is low, at around 6% and is likely due to acid-catalyzed racemization in the acid environment of the stomach from the swallowed fraction of an inhaled dose.^{9,10} There are no pharmacodynamic differences between the racemate and (R)- albuterol as demonstrated in an elegantly designed study in which the racemate, and (R)- and (S)- albuterol were administered in nine, microgram-equivalent, doses for the eutomer at 25-min intervals in a randomized crossover manner.¹¹ A 2:1 potency ratio for (R)-albuterol versus the racemate on the forced expiratory volume in the first second (FEV1) was observed in this study as were similar findings for effects on the heart rate and serum potassium. There are pharmacokinetic differences between the enantiomers such that the (R)- enantiomer is metabolized 12 times faster than the (S)- leading to higher concentrations of (S)-albuterol by all routes of administration and is due largely to the stereoselective metabolism of swallowed drugs.¹⁰

It is this latter finding coupled with early reports of adverse effects of the (S)-albuterol in animal studies that led to the assumption that administration of (R)-albuterol would confer a greater safety profile compared to racemic albuterol.¹² However, clinical studies have failed to convincingly demonstrate a greater efficacy or safety of (R)-albuterol over the racemate. In fact, administration of single doses of (S)-albuterol has little to no effect on airway hyperreactivity measured by methacholine provocation¹² although one study showed a small statistically significant increase in airway hyperreactivity.¹³ To determine if there is a therapeutic advantage of levalbuterol over the racemate, studies conducted in the emergency department or hospitalized patients versus the outpatient setting are most relevant as regular daily use of inhaled β_2 -agonists is not supported by asthma guidelines.^{14,15} Several studies in children in both the emergency department (ED) and hospital have failed to find clinically important advantages that are consistent between studies for levalbuterol versus the racemate.^{16–21} Two studies in children evaluating higher doses of levalbuterol by continuous nebulization in the ED (3.75 mg/h levalbuterol vs. 7.5 mg/h albuterol)²⁰ and hospital (10 mg/h levalbuterol vs. 20 mg/h albuterol)²¹ also measured (S)-albuterol serum concentrations to determine if levels affected outcomes. In both studies, there was no difference in clinical outcomes between levalbuterol and albuterol despite higher (S)-albuterol serum concentrations in the albuterol group.

Current prices for generic levalbuterol (24 vials of 3 mL 1.25 mg) range from \$56 to \$151, the brand product, Xopenex[®], is approximately \$165, and generic albuterol ranges from \$4 to \$16 (25 vials of 3 mL 2.5 mg), which represents a 14- to 41-fold higher price for levalbuterol compared with albuterol (www.goodrx.com/accessed 7/29/2013). Given the currently available clinical data and the differential price, inclusion of levalbuterol on a hospital or insurance company formulary should be highly discouraged.

Arformoterol

Formoterol has 2 chiral centers and thus can exist in 4 combinations, but only the (R;R) (S;S) racemate is available as the marketed product. As with albuterol, there is stereo-

selectivity at the β_2 -receptor with the (R;R) enantiomer (arformoterol) having a 1000-fold greater potency than the (S;S) form.^{22,23} There is no significant inversion of the 2 individual enantiomers back to the racemate.²⁴ Arformoterol, the (R;R) enantiomer of formoterol was approved by the FDA in 2006 as a solution for inhalation in patients with chronic obstructive pulmonary disease (COPD). There are little pharmacokinetic data for the (R;R)- and (S;S)-enantiomers, but the area under the curve and half-life after single or 14 days of dosing are similar indicating no accumulation of the (S;S) enantiomer.^{25,26} As with levalbuterol and albuterol, there is a 2:1 potency ratio for (R;R)-formoterol versus the racemate on FEV1 and heart rate.²⁷ In a recent pediatric safety study, 3 doses of 7.5 μ g/dose of arformoterol over 1 hour found no clinically important adverse effects.²⁸ Thus, available data indicate there are no clinically important pharmacologic or pharmacokinetic differences between arformoterol and the racemate that would suggest an advantage of the (R;R)-enantiomer. Both arformoterol and formoterol are available as solutions for inhalation and the cost is similar (\$500) for a 30-day supply (www.goodrx.com/accessed 7/29/2013).

Levocetirizine

Cetirizine exists as a racemic mixture of levocetirizine [(R)-enantiomer] and dextrocetirizine [(S)-enantiomer]. Stereoselectivity at the H1 receptor for the histamine-induced wheal and flare response was observed with cetirizine and levocetirizine both inhibiting the size of the wheals and flares with no effect observed for dextrocetirizine in healthy volunteers²⁹ and similar effects were noted for histamine-induced nasal responses.³⁰ Dextrocetirizine appears to be 10-fold less potent than levocetirizine.³¹ Administration of levocetirizine in healthy volunteers does not result in conversion to the racemate for at least 24 hours after a single dose.^{31,32} There are no differences in the pharmacokinetics between cetirizine and levocetirizine and both have a similar volume of distribution suggesting similar penetration through the blood-brain barrier.³² Levocetirizine and cetirizine are largely excreted in the urine (70%–85% recovery) with no significant hepatic metabolism.³³ Renal tubular secretion of dextrocetirizine is 40% greater than levocetirizine, but renal tubular secretion accounts for less than 30% of the total renal clearance, and thus, there is no expected interaction between the enantiomers.³⁴ There is a dearth of published clinical studies comparing levocetirizine with cetirizine, but one 12-week, randomized, double-blind, placebo trial in children with perennial allergic rhinitis demonstrated a better symptom control with cetirizine than levocetirizine.³⁵ In an unblinded study of adults with chronic urticaria, there was no difference between cetirizine and levocetirizine except a better itch response for cetirizine.³⁶ In 2 randomized, placebo controlled, double-blind trials in healthy individuals and patients with perennial allergic rhinitis, there were no differences in the psychomotor performance between levocetirizine and cetirizine.^{37,38} Levocetirizine is available as a generic and costs \$20 to \$50 for a 30-day supply of 5 mg tablets; Xyzal[®], the brand version of levocetirizine, costs approximately \$100, whereas generic cetirizine costs only \$10 (www.goodrx.com/accessed 7/29/2013). Thus, the available clinical evidence coupled with the cost differential, indicates there is no rationale for prescribing levocetirizine in place of cetirizine.

In summary, there are often little clinical data published before marketing a single enantiomer product derived from a currently available racemate. Examining the evidence for relative activity at the therapeutic receptor (which is often published from early biochemical profiling) and the pharmacokinetic data can aid in determining if a new single enantiomer product might confer any clinical advantages. Fexofenadine is a racemic mixture, but has not yet been marketed as its (R)-enantiomer. Thus, it will be important to use the principles described when evaluating this product and other new single enantiomer drugs against their racemates.

Author Disclosure Statement

The authors have no conflicts of interest to report.

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Received for publication August 1, 2013; accepted after revision August 2, 2013.