The asthma-like pharmacology and toxicology of (S)-isomers of β agonists

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β_2 agonists were designed to emulate the bronchodilation and mast cell suppression effects of human adrenaline, an endogenous neuromediator. Endogenous adrenaline is produced exclusively as the single enantiomer or isomer, (R)-adrenaline, although all selective β_2 agonists are marketed as racemic drugs, composed of a precise 50:50 mixture of R and S isomers. Isomers are compounds that are nonsuperimposable mirror images. The R isomers of β agonists, essentially all congeners of (R)-adrenaline, exhibit the observed bronchodilation and clinical benefit of the racemate. The S isomers of the racemic β agonists are devoid of clinical benefit, are assumed to be benign, and have not been studied until recently. In contradistinction to their assumed benign status, extensive studies with (S)-albuterol have shown that it opposes the bronchodilation effects of (R)-albuterol (levalbuterol), may be proinflammatory, and exhibits the potential to exacerbate airway reactivity to a variety of spasmogens by enhancing contractile responses. Clinically, (S)-albuterol can increase airway reactivity and, because of its slow metabolism, exists in higher and prolonged plasma concentrations than levalbuterol. The sustained presence of (S)-albuterol may help to explain why racemic β agonists have not demonstrated a significant clinical anti-inflammatory potential. Furthermore, the adverse effects (S)-albuterol may contribute to paradoxic bronchospasm and the occurrence of severe reagenic-like reactions seen with racemic albuterol. These adverse effects of (S)-albuterol are completely avoided with single isomer version of (R)-albuterol (levalbuterol). The removal of (S)-albuterol increased the clinical potency of levalbuterol, such that bronchodilator efficacy is achieved at one-fourth the dose of racemic albuterol, but with marked reduction in side effects. Levalbuterol, a third generation β agonist, retains the clinical benefit of racemic albuterol without the proinflammatory and potentially detrimental effects of (S)-albuterol. (J Allergy Clin Immunol 1999;104:S69-76.)

Key words: *Bronchodilation, anti-inflammatory, (R)-albuterol, levalbuterol, (S)-albuterol, safety*

β_2 agonists have been the main therapeutic treatment of asthma for one half of a century. Rapid and effective in their ability to bronchodilate, they have been structurally enhanced to achieve greater specificity of effect and duration of therapeutic action. They have also been implicated in epidemics of asthma morbidity and deaths since 1939,[1] recognized through clinical observation and epidemiologic studies. Clinical studies have been conducted to examine their potential detrimental effects, the results of which have both exonerated[2,3] and implicated[4,5] β agonists in this regard.

Abbreviation used
EPO: Eosinophil peroxidase

Many theories have been advanced to explain whether β agonists have a causal, casual, or coincidental role in asthma execrations and detrimental effects related to asthma severity.[6] One theory is that the detrimental effects of β agonists relate to their racemic nature. β agonists were developed to emulate the actions of adrenaline, which primarily included bronchodilation and suppression of mast cell activation. However, endogenous adrenaline is always the single-isomer form (R)-adrenaline, although all marketed selective β agonists are racemic, composed of equal amounts of the R isomer and its nonsuperimposable mirror image, the S isomer. Thus although we followed the adrenaline template to generate β agonists, we failed to adhere to the blueprint for single isomers.

From this racemate theory, experimental and clinical studies have delineated an opposing duality of effects of the R and S isomers of β agonists, specifically with (R)- and (S)-albuterol (Fig 1). The results summarized later challenge much of the existing safety information on racemic albuterol, which is in many cases antiquated data generated with obsolete technology that is one quarter of a century old.

THE ASTHMA-LIKE PHARMACOLOGIC AND TOXICOLOGIC FEATURES OF (S)-ALBUTEROL

(S)-albuterol causes activation of human eosinophils

Asthma has a dominant eosinophil component. Accordingly, studies were conducted in human eosinophils, which examine the effects of (R)-, (S)-, and racemic albuterol on stimulation of human eosinophils with 2 different stimuli. In one study, IL-5 stimulated release of superoxide was evaluated[7] and, in the other, ionophore-induced secretion of eosinophil peroxidase (EPO).[8]

These studies showed that (R)-albuterol and racemic albuterol inhibited superoxide generation and EPO release, results consistent with other studies denoting anti-inflammatory effects of racemic β agonists. (S)-albuterol augmented both superoxide (statistically significant) and EPO (dose-trend) responses, indicating that (S)-albuterol might have a potential proinflammatory

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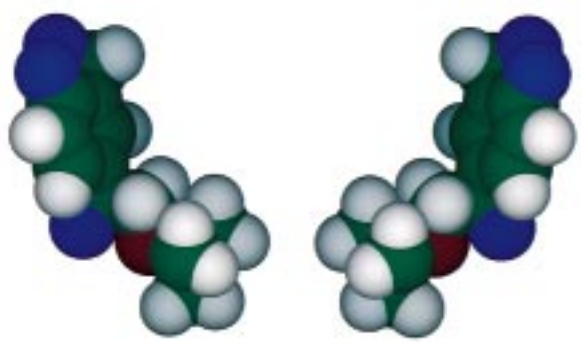

FIG 1. Three-dimensional molecular model of (S)- and (R)-albuterol (levalbuterol).

effect. Even though all β agonists worldwide are racemic, evaluation of the S isomers is rare. For example, although it has been stated that (S)-salmeterol pharmacologic features are not different from that of the racemate,[9] we have been unable to find published reports to confirm this.

(S)-albuterol causes activation of airway smooth muscle cells

Continuous or extensive dosing of β_2 agonists has been implicated with the loss of the protective effect and induction of bronchial hyperreactivity in airway smooth muscle. To evaluate (S)-albuterol for potential adverse effects, single smooth muscle cells were dissociated from bovine trachea, and changes in intracellular free calcium concentration (Ca^{2+}) were assessed in the presence of the individual isomers of albuterol. (R)-albuterol decreased intracellular Ca^{2+}, consistent with its clinical effects of bronchodilation.[10] (S)-albuterol increased Ca^{2+} to a maximal effect at 1 μmol/L, which was unaffected by the β_2 antagonist, ICI 118,551, but consistent with activation of phospholipase C, indicated by an increased (>200%) phospatidyl-inositol turnover. This turnover could be reversed by superfusion of the phospholipase C inhibitor, U73,122, and blocked by an antagonist of L-type Ca^{2+} channels (nimodipine).

Thus (S)-albuterol mobilizes Ca^{2+} by activating phospholipase C, which results in inositol-1,4,5-triphosphate (IP_3)-mediated release from stores and by inducing Ca^{2+} influx through L-type Ca^{2+} channels. Our findings suggest that the effects of (S)-albuterol may augment the contractile effect of spasmogens or compromise the bronchodilation of (R)-albuterol. Because the response to (S)-albuterol could be abolished by atropine (100 nmol/L) or by 4-diphenylacetoxy-N-methylpiperidine, it was suggested that the influx of Ca^{2+} was unrelated to activation of β adrenoceptors but might stem from an interaction between (S)-albuterol and muscarinic (M_2) receptors.[10]

(S)-albuterol augments spasmogen contractions of human bronchus

The effect of (R)- and (S)-albuterol on isolated human bronchus was studied by measuring the contractile responses to different stimuli. Bronchial tissues were obtained from several distinct anatomic sites to avoid area-related differences. (R)-albuterol was found to effectively inhibit a variety of direct and indirect spasmogen-induced contractions of isolated human bronchus,[11] observations consistent with its known receptor binding and pharmacologic features. (S)-albuterol dramatically enhanced the contractile responses to histamine and LTC_4. These pharmacologic actions of (S)-albuterol cannot be attributed to activation of β_2 adrenoceptors, because (S)-albuterol does not bind or block the β_2 receptor. Additional studies on (S)-salmeterol or (S,S)-formoterol are in progress to examine for these counter-productive in vitro effects on human airway tissues.

(S)-albuterol toxicologic features

It has been generally assumed that overt toxicologic features of a racemic drug are associated with the isomer that exhibits the primary pharmacologic features. In the case of racemic albuterol, (R)-albuterol exhibits 100-fold greater affinity for the β-adrenergic receptor over (S)-albuterol and thus would naturally be expected to exhibit far greater acute toxicology than (S)-albuterol (Fig 2). In several toxicology models, the lethal doses for rats by intravenous or oral administration of (S)- and (R)-albuterol were nearly equivalent.[12] Thus (S)-albuterol, which does not bind to the β-adrenergic receptor nor contribute to efficacy, caused acute lethality at doses similar to the racemic drug. In other studies in mice, (S)-albuterol had intravenous toxicity comparable to racemic albuterol. Thus (S)-albuterol is not inert.

The reported data on racemate toxicity is comparable to previously published data for the acute toxicity of racemic albuterol (Proventil, Ventolin) and showed that (R)-albuterol exhibited a safety profile equivalent to racemic albuterol. These combined findings show that (S)-albuterol exhibits acute toxicity that is unrelated to β receptor occupancy or the route of administration.

THE CLINICAL CONSEQUENCES OF (S)-ALBUTEROL

Three decades of paradoxic bronchospasm

β agonists have long been recognized to induce asthma,[13] and in the case of racemic albuterol, such asthma-like side-effects have been seen and witnessed for over 3 decades as paradoxic bronchospasm. Immediate bronchoconstriction after aerosol inhalation probably reflects irritation, whereas delayed bronchoconstriction (after a short period of bronchodilation) is not understood. Racemic albuterol exhibits moderate-to-severe paradoxic bronchospasm (15.4%) in patients,[14] although racemic isoproterenol also shows a high percentage of paradoxic bronchospasm.[14,15]

The paradox denotes the conflict between the observed response (bronchoconstriction) and the expected response (bronchodilation).[16] It is now a further paradox that "paradoxic bronchospasm" has remained so for 30 years. Although it has been shown that excipients,

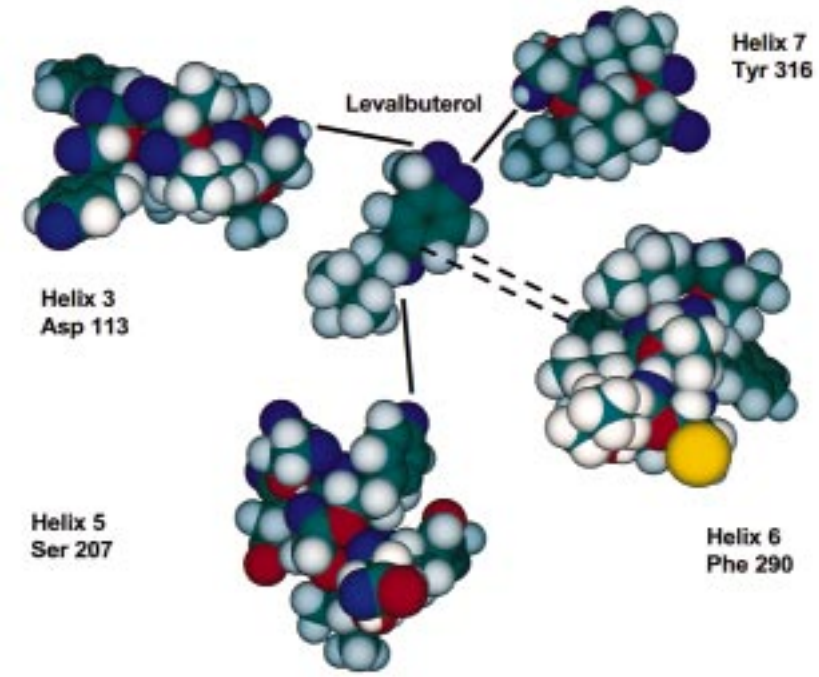

FIG 2. Three-dimensional molecular model of (R)-albuterol (levalbuterol) binding to the key amino acids of the human β_2 receptor.

propellants,[17] or preservatives[18] account for some of the immediate paradoxic bronchospasm, delayed onset bronchoconstrictive asthma-like reactions often involve systemic reactions and are life-threatening.[19,20] Furthermore, such reactions can be β-agonist specific, where paradoxic bronchospasm is seen with racemic albuterol but not racemic terbutaline.[21]

A pilot study has compared the effect of single doses of nebulized levalbuterol (100 mg), (S)-albuterol (100 mg), racemic albuterol (200 mg), or placebo on responsiveness to methacholine (measured as PC_{20} against methacholine), in patients with asthma.[22] Both levalbuterol and racemic albuterol produced significant protection when subjects were tested for methacholine sensitivity at 20 minutes, whereas neither (S)-albuterol (as expected) nor placebo offered any protection. After 3 hours, protection afforded by levalbuterol was maintained, whereas that afforded by racemic albuterol had been lost, and the subjects who had received (S)-albuterol demonstrated increased airway hyperresponsiveness to methacholine.[22] This study also reveals that levalbuterol can mask the hyperreactive effects of (S)-albuterol when both are present as a racemate.

Patients with asthma who experience β_2 receptor dysfunction such as those described by Liggett[23] might exhibit compromised bronchodilation by levalbuterol in the presence of equivalent effects of (S)-albuterol and could thereby be at risk to exhibit greater propensity for paradoxical bronchospasm.

Many cases of paradoxical bronchospasm to racemic albuterol are life-threatening and have been determined to be independent of route of administration or formulation.[20] Similarly, patients with severe asthma who are treated with racemic salmeterol may exhibit no benefit,[24] although inflammation may be involved. There are many well-established examples of immunologic responses being developed to small molecular weight drugs that would normally not induce immune responses.[25-29] Consistent presentation of xenobiotic substances can lead to the induction of antibody responses, usually by complexing with proteins and the generation of haptenic neoantigens. Development of opsonic or reagenic antibody responses to (S)-albuterol would be manifest as paradoxic bronchospasm.

The failure to achieve clinical anti-inflammatory activity

β agonists inhibit acute inflammatory responses in a variety of cellular or tissue studies.[30] However, after extensive clinical studies, racemic β agonists have failed to significantly inhibit anti-inflammatory activity in wheal and flare responses, late responses, or airway hyperreactivity.[24,31,32] This was thought to reflect insufficient duration of effect seen in the first-generation short-acting β agonists.[9] However, second-generation long-acting β agonists[9,33] have achieved only marginal anti-inflammatory effects.

A valid explanation is that the true evaluation of anti-inflammatory potential will reside in the use of single isomer β agonists, such as levalbuterol, which lack the potential detriments of the S isomer. Because all marketed β agonists worldwide are racemic, the failure of first- and second-generation β agonists to exhibit clinically significant anti-inflammatory effects may reflect the

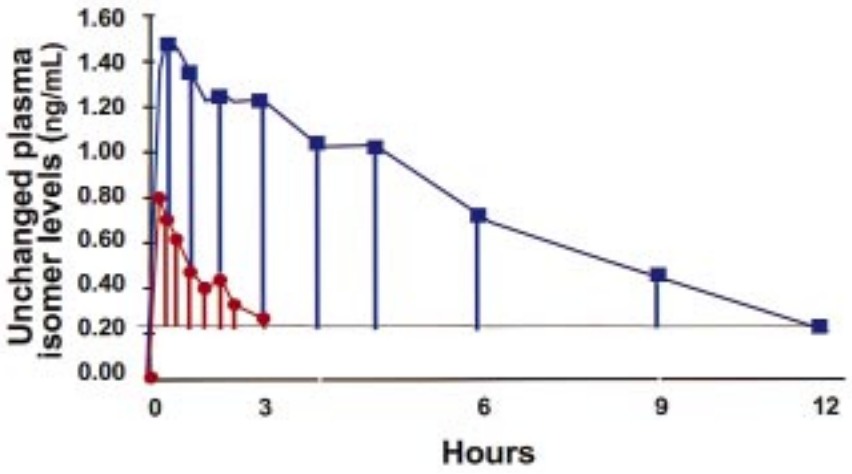

FIG 3. Area under the curve for unchanged drug substance for (R)-albuterol (*red*) and (S)-albuterol (*yellow*) after a single 2.50 mg nebulized dose of racemic albuterol.

detrimental effects of the S isomer rather than a limited duration of activity, as has been proposed.[9] In fact many reports suggest that racemic β agonists may actually worsen airway reactivity and baseline lung function. Because the pharmacologic features of (S)-salmeterol or (S,S)-formoterol are unknown, it is possible that they may also exhibit counter-productive effects on human airway.

(S)-albuterol accumulation may augment pulmonary tolerance

Tolerance is clinically thought to represent a downregulation of the β_2 receptor, with a loss of effect of β agonists. (S)-albuterol shows a protracted presence in the plasma after oral[34] or aerosol[35] dosing, and accordingly patients with asthma will be exposed to sustained and vastly greater amounts of this isomer (Fig 3). Tolerance associated with massive dosing of racemic albuterol may actually represent the (S)-albuterol asthma-like effects noted earlier as the result of the progressive accumulation of (S)-albuterol. Because (S)-albuterol accumulation continues, it could begin to oppose the bronchodilator effect of levalbuterol, which would translate as clinical tachyphylaxis. Because all β agonists are racemic, this effect could occur with any β agonist.

Plasma levels of racemic albuterol do not correlate with bronchodilation

Many studies have commented that plasma levels or half-life of racemic β agonists do not closely relate to the duration of action,[36] are not a useful parameter to adjust dose,[37] and may vary more than 15-fold.[38] The isomer-selective assays developed to quantitate (R)- and (S)-albuterol show that after oral[34,39] or inhalation[35] of racemic albuterol, the area under the curve of (S)-albuterol is 6-fold that of levalbuterol (Fig 3). By definition, because all racemates are 50:50 mixtures of both isomers, the plasma concentrations should be nearly equivalent. However, many tissues such as human lung, liver, platelets, and other cells have been shown to have the preferred capacity to sulfate (R)-adrenaline and levalbuterol,[40] which is an adrenaline analog. However, (S)-albuterol is an antianalog of (R)-adrenaline, and enzymatically it is a poor substrate. Because it is poorly metabolized compared with levalbuterol, the dominant plasma isomer is (S)-albuterol, which does not exhibit bronchodilation. This would explain the lack of correlation between plasma levels of racemic albuterol (which were mostly (S)-albuterol) and the lack of bronchodilation. Although several studies have attempted to correlate in vitro activity with bronchodilatory effects,[41] the failure to consider the racemic nature of β agonists renders such work confounding or inferior.[42] This may explain 2 decades of difficulty in correlating plasma levels with onset or duration of drug action,[35] which is often referred to as "parascience" when failing to evaluate isomers individually.[42]

THE CLINICAL BENEFITS OF REMOVAL OF (S)-ALBUTEROL

Improved efficacy

(S)-albuterol may compromise the clinical effectiveness of racemic albuterol. Accordingly, the single isomer levalbuterol should exhibit greater bronchodilatory effects. In a recent clinical study, 2 doses of the therapeutically active levalbuterol isomer were compared with 2 doses of racemic albuterol to placebo in patients with asthma.[35] Three hundred twenty-eight patients were randomized to receive one of the following nebulization treatments 3 times daily for 4 weeks: 0.63 mg levalbuterol, 1.25 mg levalbuterol, 1.25 mg racemic albuterol, 2.5 mg racemic albuterol, or placebo. Serial pulmonary function testing was performed after the first dose (week 0) and after 2 and 4 weeks of treatment.

Empirically, 1.25 mg of levalbuterol should equal 2.50 mg of racemic if (S)-albuterol was inert. The improvement in FEV_1 for the 0.63 mg dose of levalbuterol was

comparable to 2.50 mg of racemic albuterol, indicating that (S)-albuterol may compromise the clinical efficacy of racemic albuterol. The 0.63 mg dose of levalbuterol was associated with fewer side effects and a less marked effect on heart rate, serum potassium, and glucose compared with the 2.50 mg of racemate.

The greatest increase in FEV_1 was seen after 1.25 mg levalbuterol, especially in subjects with a baseline FEV_1 of 60% or less of predicted ($P < .002$). This was unexpected but predictable, because the patients with the most severe forms of asthma take the greatest amount of racemic β agonists and, accordingly, are exposed to the greatest amount of S isomers. The progressive accumulation of (S)-albuterol and its associated effects may compress the potency and foreshorten the duration of levalbuterol. Because all β agonists are racemates, this thesis may logically be applied to other β agonists. However, there is a paucity of information on the S isomer. For example, it has been stated that (S)-salmeterol pharmacologic features are not different from those of the racemate,[5] there are no published reports to confirm this.

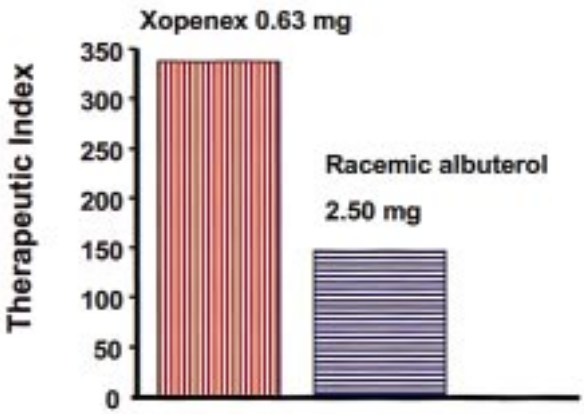

FIG 4. Comparative therapeutic index of levalbuterol (xopenex, 0.63 mg) and racemic albuterol (2.50 mg), defined as bronchodilating benefit over extrapulmonary β-mediated detriments (tremor, nervousness, tachycardia). Levalbuterol at 0.63 mg shows equivalent bronchodilation to 2.50 mg racemic albuterol but marked reduction in side-effects, resulting in a 75% improvement in therapeutic index.

Improved pharmacokinetic to pharmacodynamic correlation

The development of isomer-specific assays had led to the first clinically true correlation of levalbuterol plasma levels to bronchodilation. The development of these assays[43] led to vastly improved accuracy regarding pharmacokinetic/pharmacodynamic effects and also permitted evaluation of the absolute isomeric stability of levalbuterol.

Bronchodilators were designed to achieve rapid relaxation of airways, and this has been achieved with racemic β agonists, with the exception of racemic salmeterol (which, as the result of logical design, does not bronchodilate for 20 minutes). There are known examples of racemates that contain mixed adrenergic effects (labetatol) or exhibit effects on airway resistance independent of β-agonist properties (timolol). If the inactive (S)-salmeterol is preferentially presented to the airways, this may well explain the delayed onset of action of racemic salmeterol. Although slower onset of action was considered "of little clinical importance"[9] and not of "significant difference,"[44] perhaps a pure isomeric version of racemic salmeterol may provide superior therapeutic benefit over (R,S)-salmeterol in terms of onset of action.

Reduction in β-mediated side-effects

The use of β agonists is associated with extrapulmonary adverse effects of decreased potassium, increased glucose, cardiac stimulation, tremor, and nervousness, which were initially assumed to be lack of β_2:β_1 selectivity. These side-effects are well known and disliked by patients with asthma but with no alternative are begrudgingly tolerated. These side-effects are mediated by levalbuterol, whether delivered as a single isomer or as part of a racemate. By removing (S)-albuterol, R-albuterol at 0.63 mg equals the bronchodilation effects of 2.50 mg racemic albuterol. However, there is a marked reduction in β-mediated side effects, such as nervousness, tremor, and tachycardia.[35] There is accordingly a 75% improvement in therapeutic index achieved with levalbuterol (Fig 4).

Initially, β-adrenoceptor selectivity was determined from relative effects on atria (assumed to have only β_1 receptors) and human or guinea pig bronchus (assumed to have only β_2 receptors). We now realize that these organs contain mixed populations of both β_1 and β_2,[45] which lead to falsely elevated estimations of β_2:β_1 selectivity of 1375:1 for racemic albuterol. Although the β_2:β_1 selectivity of racemic salmeterol was once considered equal to racemic albuterol,[36] marketed elevated β_2:β_1 estimations of 85,000:1 were obtained with these mixed tissues.[9,46] If true, how would salmeterol doses of 200 to 400 μg dramatically increase heart rate (8-16 bpm)[47] and induce tremor, hypokalemia, and hyperglycemia[48] (which are all β_2-mediated responses)?

Studies were performed to determine the binding affinities of various β agonists and respective isomers with specific cloned human β_1- and β_2-adrenergic receptors (Table I).[49] With this contemporary specific system, the β_2:β_1 selectivity of (R)-albuterol is 6.5 and 4.5 for racemic albuterol. (S)-albuterol has neither relevant receptor activity nor selectivity for either β_1 or β_2 subtypes. Although similar claims for (S)-salmeterol have been stated,[46] no experimental evidence has been published to support such statements. Racemic salmeterol has been postulated to exhibit 2 sites of interaction: one is the active site of the β_2 adrenoceptor, and the other is to an adjacent specific site or exosite. Although this theory of an exosite has been proposed in many review articles,[9] this site has never been identified, sequenced, expressed, or cloned and remains speculative.[9,50]

Cloned systems have also identified that (R)- and (S)-salmeterol have activities that vary far less than the 85,000-fold reported in the literature.[46,51] Thus the iso-

TABLE I. Comparison of previous β_2: β_1 selectivity with current reported values where potency based on different tissue responses was determined (9), or with the use of cloned human β adrenoceptors (49).

β agonist	β_1 (atrial)*	β_2 (trachea)*	β_2: β_1*	β_1 (cloned)†	β_2 (cloned)†	β_2: β_1†
(RS)-isoprenaline	1.0	1.0	1.0	41.7	20.1	0.48
(R)-albuterol	NE	NE	NE	1540	236	6.5
(S)-albuterol	NE	NE	NE	111,000	33,600	3.3
(RS)-albuterol	0.0004	0.55	1375	2980	668	4.5
(R)-salmeterol	NE	NE	NE	413	1.5	275
(S)-salmeterol	NE	NE	NE	nc	14.0	nc
(RS)-salmeterol	0.0001	8.5	85,000	784	2.2	356

NE: not evaluated.
Values in nM concentration and nc = not calculable.
*From reference 9.
†From reference 49.

mers of racemic salmeterol do exhibit the characteristic selective β_2 receptor interactions seen with other racemates but may act more as quasi-nonspecific agonist, with very low intrinsic activity and limited oral activity. The lack of isomer-specific binding may also explain why racemic salmeterol shows heterogeneous responses in patients and is reported to be of no benefit to patients with severe asthma.[24]

Potential anti-inflammatory effects of levalbuterol

β agonists were designed to emulate the anti-inflammatory actions of human (R)-adrenaline. In vitro, they inhibit acute inflammatory responses in a variety of cellular or tissue studies.[30] In clinical studies, β agonists are ineffective as anti-inflammatory drugs.[24,31,32] One explanation of this discrepancy is that, in vitro, β agonists are a 50:50 mixture and the R isomer dominates over the S isomer and the anti-inflammatory effect is evident. Clinically, the presentation of racemic albuterol results in 5 to 7-fold more of the proinflammatory S isomer and this could account for the lack of anti-inflammatory activity. Because all β agonists are racemic, the removal of the S isomers may allow for reexamination of the anti-inflammatory effects.

Therefore the true evaluation of the anti-inflammatory potential of racemic β agonists may require single isomer versions of β agonists, such as levalbuterol, which lack the potential detriments of the S isomer. The first evidence of this potential was evident in patients with severe asthma (FEV_1 < 60% of predicted) who were not undergoing steroid therapy. After 4 weeks of treatment (3 times daily) with 1.25 mg of levalbuterol, there was a 0.31-L improvement in lung function.[35] Similar improvements in lung function have been reported for budesonide,[52,53] 0.23 L for 10 mg montelukast for 6 weeks,[54] and 0.37 L for 200 μg (twice daily) beclomethasone for 6 weeks.[55]

Furthermore, 1.25 mg levalbuterol (3 times daily) resulted in a reduction of rescue metered dose inhaler racemic albuterol of 2.20 puffs per day.[35] This compares favorably to the reduction of rescue metered dose inhaler racemic albuterol of 1.44 puffs per day for 10 of mg per day montelukast,[54] and 1.24 puffs for 1.6 mg (4 times daily) cromolyn,[54] 1.98 puffs for 42 μg (twice daily) racemic salmeterol,[56] 0.9 puffs for 2.50 mg racemic albuterol,[35] and 1.12 puffs for 20 mg (twice daily) zafirlukast.[57]

These collective advantages of levalbuterol (effective bronchodilation, improvement in lung function, fewer β-mediated side-effects at equivalent doses, reduction in rescue medicine) suggests that a re-examination of the anti-inflammatory attributes of β agonists might be warranted with the development of single-isomer versions of racemic β agonists. To date, no new racemic β agonists are in development; this therapeutic field is effete. The use of single-isomer versions of β agonists may provide additional advantages not seen with racemic drugs.

Although steroids could suppress the detrimental effects of (S)-albuterol, the effects of other anti-inflammatory drugs such as cromolyn are unknown. The common use of cromolyn (Intal) for pediatric asthma might result in worsening as the result of the detrimental effects of racemic β agonists, evident in the increase in asthma severity and classification.

CONCLUSIONS

The detrimental and proasthmatic nature of (S)-albuterol can help explain delayed paradoxic bronchospasm, the lack of clinical anti-inflammatory effects of racemic albuterol, the development of tachyphylaxis in a β_2 receptor independent manner (ie, accumulation of [S]-albuterol), and the difficult correlation between pharmacokinetics and pharmacodynamics. The removal of (S)-albuterol best explains the 2-fold increase in bronchodilator efficacy seen with levalbuterol clinically.[22,35]

In general, humans are single-isomer creatures in physiologic processes,[57] and the use of racemates violates this natural order. The 1992 Food and Drug Administration guidelines now recognize racemic drugs as combination drugs and require both isomers to be evaluated experimentally, clinically, and toxicologically.[58] The FDA guidelines, which encourage single-isomer drugs over racemic mixtures,[58] have also been included in similar guidelines from Europe, Canada, and Japan.[59]

We are reminded that racemic drugs can have unpredictable effects, such as racemic thalidomide, in which the R isomer was the effective sedative and the S isomer was the teratogen that caused catastrophic birth defects

worldwide. The divergent effects of (R)- and (S)-albuterol should not be seen as a stand-alone phenomenon, because all β agonists are racemates, in which 50% of the clinical dose is the S isomer. Although a constant within the class, these S isomers are virtually unstudied, are of no clinical value, and would be inappropriate to administer as a single-isomeric substance. It would be difficult to develop and market racemates, although racemates developed outside the United States before the 1992 guidelines may be allowed (ie, formoterol) today. In a field that has no new compounds in development and in which the leading drug is a racemic compound developed over 3 decades ago, the introduction of single-isomer versions of racemic β agonists represents a product of contemporary technology to achieve continuous improvement toward therapeutic advances.

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