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Three Generations of Ongoing Controversies Concerning the Use of Short Acting Beta-Agonist Therapy in Asthma: A Review

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An increase in asthma mortality in 1960s noted by British authors stirred a debate about the use of beta-adrenergic therapy that has persisted in the medical literature. The cause appears to be isoproterenol and fenoterol overuse. A second debate evolved around the possible deleterious, pro-inflammatory effects, of the albuterol distomer. Most clinical studies showed improved bronchodilatation, but limited benefits from using levalbuterol. Recently, genotyping has uncovered a single nucleotide polymorphism at codon 16 that appears to affect the long term response to both regular and as needed use of albuterol, calling for a new genotype based therapeutic approach in asthma.

Keywords asthma, adrenergic beta agonists, receptors, adrenergic, beta, genotype, albuterol enantiomers

INTRODUCTION

The introduction of β agonists was an important milestone in the treatment of asthma. However, since its inception, physicians have been faced with new and difficult problems concerning their use, due to their unintended effects that created new risks for asthmatics and were difficult to explain, stirring a continuous debate. The controversy evolving around the pathophysiologic mechanisms underlying the variable efficacy of the β agonists in asthma, sometimes accompanied by deleterious effects, dated back to the 1960’s (1). Scientific inquiries were centered around three main hypotheses:

(1) the deleterious effects of short acting β2 adrenergic agonists may be due to overuse
(2) the proinflammatory actions of the distomer could impend on the long term asthma control and
(3) the treatment modifying effects of single polymorphisms at codon 16 and/or 27 may affect the long term response to albuterol.

Every line of inquiry started a new generation of controversies and brought a limited insight into the true pathophysiological mechanisms responsible for the unexpected and unintended effects of albuterol treatment in asthma.

THE DELETERIOUS EFFECTS OF OVERUSE

Overuse has more aspects. One aspect is using a short acting beta agonist as needed in excessive amounts, until severe side effects appear. The appearance of life threatening adverse effects depends both on dose and on spacing among the most recent doses. Another aspect may be the regular use; however, agreeing if the regular use is an overuse is more difficult. When as needed use is permitted in addition to regular use, the same problems related to dose and dose spacing appear. When as needed use is not permitted, usually ipratropium is allowed and undetected medicine interactions may modify the results. If too many regular doses are skipped (non compliance) and the total number of doses is less than the amount needed for regular treatment, the medicine may not be truly overused.

At the beginning, the unintended effects were attributed to the overuse of isoproterenol (1), a full agonist at both the β1 and β2 adrenergic receptors (2). The inquiry into isoproterenol as a cause of excess mortality in the 1960’s was thoroughly reviewed by Stolley (3, 4). He compared the international mortality rates from asthma in patients 5 to 34 years old obtained from the vital statistics of 14 countries. A strong positive correlation, explaining approximately 41% of the variation in asthma mortality in epidemic countries like England and Wales, Scotland, Ireland, New Zealand (5), Australia and Norway during the epidemic years (4), was found between excess mortality and the sales volumes of a highly concentrated isoproterenol pressured aerosol, delivering as much as 0.4 mg/dose. The correlation was weaker in the post epidemic period. Interestingly, the United States and Canada had large sales volumes of these pressured aerosols, most of them with isoproterenol 0.08 mg per dose, but did not have the epidemic (3). Stolley concluded that the United States was spared the epidemic due to the fact that the highly concentrated isoproterenol aerosol was not marketed.

A second increase in asthma mortality, described in New Zealand in the 1980’s (5), was studied by Crane (6) in a series of case control studies and it was related to fenoterol, but not to albuterol (7). It was subsequently investigated in Canada in a case-control study based on provincial health records in Saskatchewan and use of fenoterol and albuterol were found to be increased among asthma decedents (8); however, subsequent research performed on the same database and utilizing
long-term information on medication use in the province, concluded that the comparison between inhaled fenoterol and albuterol in the earlier study may have been confounded by indication (9). All asthma deaths occurred in patients not treated with corticosteroids (10, 11).

Generally, scientists agreed that overusing isoproterenol and fenoterol might have been a cause of death from asthma, but the first generation of controversies arose because they were uncertain if the pathophysiologic mechanism leading to death involved either the cardiac or the respiratory system. Initially, the deaths associated with overuse were believed to be due to overstimulation of β1 adrenergic receptors from the heart, leading to cardiac arrhythmias, associated with worsening hypoxemia in severe asthmatics. Another effect of isoproterenol may have been the intramyocardial diversion of coronary blood flow, resulting in subendocardial ischemia (12). Compounding the overuse, the problem with fenoterol in the 1970's may relate to the drug itself, which causes greater adverse extrapulmonary effects than albuterol when inhaled in equal doses by weight (2).

However, based on the parallel decrease in hospitalizations and deaths for severe asthma after the two inhaled medicines were removed, Sears (13) concluded that the two epidemics of asthma deaths among young people were temporally associated with introduction of potent short-acting beta-agonists (isoproterenol and fenoterol) and appear to be related to the adverse effects of these drugs on airway function and airway hyperresponsiveness rather than to cardiotoxicity. The decrease in hospitalizations for asthma exacerbations following their withdrawal could not be attributed to non-respiratory causes, like cardiac events.

Another conflicting aspect of overuse was the regular treatment,

(a) with the patient also using it when needed, or
(b) without using it as needed.

While some studies undertaken in New Zealand (5, 13) showed a deleterious effect of regular use, Chapman (14) achieved more frequent asthma control with regular than with as needed albuterol use.

(a) Drazen et al. (15) found that the regular use of albuterol (2 puffs four times a day) was neither more beneficial nor more deleterious in asthma patients when compared with as needed use. Regular users required an average of 1.3 extra puffs taken as needed for symptom relief, compared with 1.6 puffs in the as needed group. Compliance with regular use was appreciated at 80%. Since the regular use did not prevent in this group the need for an as-needed use of the same magnitude like in the as-needed group of asthmatics and regular use was associated with the administration of much more drug (9.3 puffs per day compared with 1.6 puffs per day), probably the most important conclusion to be derived from this work was that regular administration did not affect the treatment efficacy and safety, but it only led to a pointless overuse of medication.

(b) By pooling 22 studies of regular β agonist use (both short and long acting racemic drugs) and excluding studies allowing as needed use in the placebo group, a recent meta-analysis (16) showed that the regular use did not change the mean forced expiratory volume in 1 second (FEV1) posttreatment response or the net FEV1 treatment effect, but substantially reduced the peak FEV1 posttreatment response and the FEV1 dose response to subsequent administrations of β2 agonists. A potential mechanism for these adverse effects with regular use of β2 agonists (either or not associated with as-needed use) might be tachyphylaxis to protection against induced bronchospasm (17). The development of tolerance might explain the overuse, followed by a further deterioration of FEV1 after subsequent doses, that may account itself for further increases in use (β2 agonist “addiction”) (16).

**DIFFERENT ACTIONS FROM DIFFERENT ENANTIOMERS MAY IMPED ON LONG TERM ASTHMA CONTROL**

The ambivalent characteristics of the short acting β2 agonists set the stage in the early 1990’s for another set of controversial issues, starting a second line of inquiry into the beta adrenergic controversy. While during the first period the pathogenesis of asthma is centered on the idea of bronchospasm, during the second period the pathogenesis of asthma is centered on the idea of inflammation. Accordingly, the controversy shifts focus to the relationship between beta agonists and airway inflammation.

More intensive exploration of the nonbronchodilator activities of the albuterol enantiomers suggests that albuterol overuse might impact on the long term asthma control, due to the pro-inflammatory actions of the (S)-albuterol. For asthma therapy, (R)-albuterol is considered the eutomer, while (S)-albuterol is seen as the distomer. Racemic albuterol is a medicine with variable treatment effect, due to the opposite effects of enantiomers, owing less predictable pharmacokinetics to ever changing ratios between its (R)- and (S)-enantiomers. Due to the difference in the sulphation rates of the enantiomers (18, 19), leading to different plasma levels, possibly accompanied by an increased retention of the distomer in the lung (20), reliance on racemic albuterol may lead to a five- to seven-fold greater exposure to (S)-albuterol in just a few hours (21) or even higher. Thus, bronchial smooth muscle may be exposed to disproportionately higher concentrations of the potentially toxic (S)-enantiomer, causing the deleterious effects to become more evident.

Recent research performed on human bronchial smooth muscle cells (hBSMC) by Agrawal et al. (22) shows clearly that, in addition to their ratio, the effects of distomer on the proinflammatory pathways also depend on the amount and duration of exposure. At equimolar concentration the enantiomers have opposite effects on the bronchodilatory pathways in bronchial smooth muscle cells (Table 1).

While the eutomer acts through a cascade of signaling events starting at the level of the β2 adrenergic receptor, it seems that the distomer binds to intracellular site(s) present only in selected cell types and unrelated to the β2 adrenoceptors (Table 2).

The distomer may have an action similar to the triggers of clinical asthma and it produces effects that are very similar to the disease it is treating. However, the ability of the distomer to translate inflammatory signals into airway smooth
muscle contraction is not clearly proven at the clinical level—
detrimental effects were observed only in animals and iso-
lated human cells. As an example, the distomer can intensify
allergic bronchospasm in animals and it has been found to
promote the activation of human eosinophils in vitro (25),
but these deleterious effects have not clearly translated into
clinical effects in man. This discrepancy evolved as one of
the core issues of the β2 adrenergic controversy.

A missed point in this controversy is that albuterol enan-
tomers may influence the global treatment outcome in
asthma by modifying the phenotype. The eosinophilic in-
fammation is used as a marker of severity for distinguishing
among severe asthma phenotypes (26). Medicines like al-
buterol enantiomers are present all the time in the human
smooth muscle cell environment in severe asthma and they
are a major determinant of the number of eosinophils present
at any time in the lungs (27). Thus, the β2 agonist treatment
received has its share in establishing a certain asthma pheno-
type, but its major contribution toward phenotype still goes
unnoticed.

One of the possible ways to explain why an apparent dele-
terious action of (S)-albuterol couldn’t be detected at the clin-
ical level is to look at the difference in magnitude of effects
and in timing, another key point missed by the previous dis-
cussants. The isolated human bronchial smooth muscle cells
are submitted only to the action of the distomer, but not to
triggers (22). By contrast, in clinical settings, the deleteri-
ous effects might be due mainly to asthma triggers and to
a lesser extent to the distomer, because triggers generally
precede the administration of albuterol, start the exacerba-
tion and may have an identical, but stronger action that could
mask the weaker action of the albuterol distomer that comes
with the racemic albuterol given as treatment. Furthermore,
regular corticosteroid use could also mask the deleterious

| TABLE 1.—Opposite effects of albuterol enantiomers at equimolar concentrations. |
|------------------------------------------|-----------------|--------------------------|
| Calcium (22)                             | Decreases the intracellular free calcium concentration after methacholine activation | Increases the intracellular free calcium concentration after methacholine activation |
| Histamine (23)                           | Significantly reduces contractile responses to histamine | Contractile responses to histamine are increased |
| Gs expression (22)                       | No effect | Increased expression |
| Gs−α1 expression (22)                    | Reduced expression | Increased activity |
| p110 protein expression/PI3 kinase activity (22) | Not stated | Strongly increased |
| RII protein expression/NF-κB activation (22) | Distomer significantly inhibits IL-5-induced superoxide production up to 60 min. This inhibition is enhanced by isobutyl methylxanthine (IBMX) | It does not inhibit IL-5-induced superoxide production before 60 min when incubated with IBMX |

| TABLE 2.—Pros and Cons for an Intracellular Binding Site of the Albuterol Distomer. |
|------------------------------------------|-----------------|--------------------------|
| Muscarinic receptors                     | Atropine can block the effect of (S)-albuterol on Ca2+ (28) | Atropine cannot modify the (S)-albuterol stimulated release of granulocyte-macrophage colony stimulating factor (GM-CSF) from the human bronchial smooth muscle cell (hBSMC) (29) |
| Unspecified cholinergic receptors       | Strong specific binding of trinitated (S)-albuterol in intracellular membrane fractions of hBSMC, not displaceable by (R)-albuterol (22) | — |
| Inside the cell, unspecified place       | Very high binding site of trinitated (S)-albuterol in a fraction enriched with endoplasmic reticulum in the hBSMC (31) | — |
| Intracellular membrane fractions         | Stronger specific binding of (H)H(S)-albuterol in the microsomal fraction of hBSMCs, correlated with NADPH-cytochrome c reductase activity (32) | — |
| Endoplasmic reticulum                   | The intracellular receptor for distomer (either for transmembrane transport or the target receptor) may be present in hBSMCs, where the distomer increases the production of GM-CSF (29), but missing in human bronchial epithelial cells, where the distomer does not alter the production of GM-CSF (33) | — |
| Microsomes                               | The intracellular receptor for distomer (either for transmembrane transport or the target receptor) may be present in hBSMCs, where the distomer increases the production of GM-CSF (29), but missing in human bronchial epithelial cells, where the distomer does not alter the production of GM-CSF (33) | — |
| Inside the cell, only in cell types where an unspecified receptor is present | | |
distomer action, coming from the racemate administered as needed.

Most asthma exacerbations are due to an upper respiratory infection and half of them may have the rhinovirus, known to be a potent asthma trigger, as etiologic agent (34). Both the rhinovirus (35) and the distomer act synergistically on the same mechanism: they enhance the production of nuclear factor kappa B (NF κB) (22). Their stimulative action on the production of NF κB can be reversed by corticosteroids, through the inhibition of the transcriptional effects of this nuclear factor (36). The balance point between the amount of NF κB that may be yielded through the action of the triggers and/or the distomer and the amount of corticosteroids needed to counteract their effects remains unexplored (22).

Another possible way to explain why an apparent deleterious action of (S)-albuterol couldn’t be detected is to look at enantiomers’ potency. The distomer has a weak action, but there is a matter of controversy if it is either beneficial or deleterious. Some scientists consider that, in asthmatics, it doesn’t have any pharmacological action at all (11).

According to the three point model, the distomer has a weak beneficial action, going in the same direction with the eutomer. The affinity ratio between the eutomer and the distomer at β2 adrenergic receptor level, as described by Lehmann, Rodrigues de Miranda and Ariens (37, 38), which varies in different reports, is known as the eudismic ratio. Its variability might be ascribed, at least partially, to traces of eutomer in the distomer. At an eudismic ratio of over 1:90 in humans (25, 38), contamination with only 1% eutomer apparently may double the activity of a distomer preparation. If the distomer has a weak deleterious action, as shown in cell culture more recently, then minute traces of the eutomer in the distomer preparation can mask it at a great extent. Therefore, in order to calculate the balance point, future research work will need to begin by establishing the results of the eudismic analyses and to use very pure preparations of distomer (38). At present, this kind of information is almost completely unavailable from authors.

In clinical settings, racemic albuterol is often used in conjunction with other drugs and it also continues to be used in clinical studies. However, the results of scientific studies designed to study possible drug interactions are difficult to interpret with racemic albuterol, because it is unclear which enantiomer (or both) is involved. The apparent results will depend on enantiomer concentrations and may vary over time, due to their different rates of metabolism (39). When testing other drugs for interactions, it would thus be prudent to first use the levalbuterol. Follow-up studies with racemic drug could then be done to see if they yield similar results.

The majority of studies comparing the treatment effects of racemic albuterol and levalbuterol (40, 42, 43, 45, 46, 48–50, 55–57, 58), but not all (41, 44, 47, 51–54, 59) suggest that there may be an advantage in using levalbuterol (Table 3), that is reflected by a lower dose of levalbuterol needed to obtain the same efficacy compared to racemic albuterol. This is consistent with the fact that the administration of doses of racemic albuterol less than 2.5 mg may compromise efficacy (42, 43, 48), while lower doses of levalbuterol can be administered without a change in efficacy both in adults (42, 46, 50) and in children (42, 43, 48, 56). Analysis of isomer concentrations in the blood, at entry, reveals an inverse correlation between (S)-albuterol levels and bronchodilation (57), favoring the conclusion that the distomer has a deleterious and opposed effect to the eutomer when they are administered together in racemic form. Some more recent studies performed in the emergency department, where corticosteroids are associated (52, 53), suggest no difference between levalbuterol and racemic albuterol (60). However, in a larger study, where 40 mg of prednisone are administered at entry (57), corticosteroid use prior to admission proves to be a crucial factor, with levalbuterol being more efficacious than racemic albuterol only in patients who do not report corticosteroid use prior to admission.

However, some authors still question the need to use lev-
albuterol, claiming that levalbuterol has no advantage over racemic albuterol (61). Indeed, in mild asthma, where patients use this asthma reliever less than once daily, in average, high concentrations of (S)-albuterol might not occur or might not have clinical significance. However, when mild asthmatics use more albuterol at home to treat an ongoing asthma exacerbation, the result might be an increase in symptoms and a delayed recovery from asthma exacerbations, owing to high distomer concentrations (62). In severe asthma, partly because of lack of long term follow up studies, the use of levalbuterol is debatable in my opinion as a reviewer. Severe asthma patients, who use high amounts of albuterol as needed, are treated concomitantly with inhaled corticosteroids, that counteract the negative effects of high concentrations of distomer. However, at least one study (63) shows that electronically measured adherence to corticosteroids drops to approximately 50% within seven days of hospital discharge, followed by a significant worsening in symptom control. Unopposed by corticosteroids, the proinflammatory activity of the albuterol distomer might be a contributory mechanism for the deleterious effects and increased risk of death from asthma. In conclusion, in dual users levalbuterol may prevent some exacerbations during periods of corticoid underuse, due to noncompliance. In the emergency department it may be better to use levalbuterol, because research shows that the hospitalization rate is higher in patients who are treated with racemic albuterol compared to those who are treated with lev-
albuterol (55, 57). The reason may be that most asthmatics in crisis prove to be noncompliant with their inhaled corticos-
steroid treatment before admission and they come from home with mounting distomer concentrations, after using a high amount of racemic albuterol as needed.

THE TREATMENT MODIFYING EFFECTS OF BETA ADRENERGIC RECEPTOR GENE POLYMORPHISMS

The seminal work of Drazen et al. (15) opened the way to a third line of inquiry, into the genetics of asthma. Research showed that the β2 adrenergic receptor gene is highly polymorphic, with all the non-synonymous single nucleotide polymorphisms resulting in receptors that have distinct characteristics that include ligand binding, functional coupling, and agonist-promoted regulation (64, 65).

Israel et al. (66) genotyped a majority of the mild asthma patients who participated in the Drazen study (15) and then looked at their peak flow responses to regular versus as needed beta agonist treatment. Approximately one sixth of patients were Arginine/Arginine (Arg/Arg) homozygous at
### TABLE 3.—Studies comparing treatment outcomes with racemic albuterol and levalbuterol.

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Number of Patients</th>
<th>Study Design</th>
<th>Comparisons</th>
<th>Improved Outcomes with Levalbuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Perrin-Fayolle et al. (40), 1996</td>
<td>40 patients</td>
<td>Double-blind, placebo-controlled, parallel group study. Duration: single dose.</td>
<td>Hyperresponsiveness to methacholine in asthmatics treated with a single dose of nebulized racemic albuterol (200 µg), levalbuterol (100 µg), (S)-albuterol (100 µg) or placebo (10/group).</td>
<td>Suppression of hyperresponsiveness to methacholine at 180 min only in the levalbuterol group.</td>
</tr>
<tr>
<td>&quot;Cockcroft and Swystun (41), 1997</td>
<td>12 adults</td>
<td>Double blind, randomized, four way, crossover. Duration: 4 single doses, 2–7 days apart.</td>
<td>Levalbuterol 1.25 mg vs. placebo; Racemic albuterol 2.5 mg vs. placebo; (S)-albuterol 1.25 mg vs. placebo.</td>
<td>None.</td>
</tr>
<tr>
<td>&quot;Nelson et al. (42), 1998</td>
<td>362 patients over 12 years of age</td>
<td>Randomized, double-blind, parallel-group trial. Duration: 4 weeks.</td>
<td>Levalbuterol 0.63 mg and 1.25 mg vs. placebo; Racemic albuterol 1.25 mg and 2.5 mg vs. placebo.</td>
<td>1. Morning pre-dose FEV1 at 28 days; 2. Greater bronchodilation after the first dose in combined levalbuterol groups compared to combined racemic albuterol groups; 3. Similar, but lower bronchodilation for the 0.63 mg dose of levalbuterol and the 2.5 mg dose of racemic albuterol.</td>
</tr>
<tr>
<td>&quot;Gawchik et al. (43), 1999</td>
<td>43 children</td>
<td>Randomized, double-blind, single-dose, crossover study. Duration: 4 single doses, 2–8 days apart.</td>
<td>Levalbuterol 0.31, 0.63 mg and 1.25 mg vs. placebo; Racemic albuterol 1.25 mg and 2.5 mg vs. placebo.</td>
<td>1. The FEV1 values over the 8-hour study period after levalbuterol 1.25 mg, but not at other doses; 2. Similar, but lower bronchodilation for the 0.63 mg dose of levalbuterol and the 2.5 mg dose of racemic albuterol; 3. Lower β-mediated side effects for an equipotent dose of levalbuterol, when compared with racemic albuterol; 4. Lower (S)-albuterol blood levels.</td>
</tr>
<tr>
<td>&quot;Cockcroft et al. (44), 1999</td>
<td>11 adults</td>
<td>Double blind, randomized study. Duration: 6 days.</td>
<td>Racemic albuterol 2.5 mg, Levalbuterol 1.25 mg and (S)-albuterol 1.25 mg vs. placebo.</td>
<td>None.</td>
</tr>
<tr>
<td>&quot;Ramsay et al. (45), 1999</td>
<td>33 patients</td>
<td>Double-blind, placebo-controlled, four-way, cross-over study. Duration: 4 single doses, 3–14 days apart.</td>
<td>Spirometry was measured at 30, 60, 90, 120, 150 and 180 min in the methacholine group (n = 10).</td>
<td>At 90 minutes, the mean FEV1 maximal increase was higher in levalbuterol versus racemic albuterol.</td>
</tr>
<tr>
<td>&quot;Handley et al. (46), 2000</td>
<td>20 adults</td>
<td>Randomized, double-blind, dose-ranging, five-way crossover study. Duration: single, nebulized doses.</td>
<td>Levalbuterol 0.31 mg, 0.63 mg and 1.25 mg vs. placebo and vs. Racemic albuterol 2.5 mg.</td>
<td>1. Levalbuterol 1.25 mg provided the greatest increase and duration in FEV1 improvement; 2. Similar, but lower bronchodilation for the 0.63 mg dose of levalbuterol and the 2.5 mg dose of racemic albuterol.</td>
</tr>
<tr>
<td>&quot;Lotvall et al. (47), 2001</td>
<td>20 adults</td>
<td>Crossover study design. Duration: 4 single doses, 3 days apart.</td>
<td>Levalbuterol 0.00625, 0.0125, 0.0250, 0.05, 0.1, 0.2, 0.4, 0.8, and 1.6 mg vs. placebo; Racemic albuterol 0.00625, 0.0125, 0.0250, 0.05, 0.1, 0.2, 0.4, 0.8, and 1.6 mg vs. placebo; Racemic albuterol 0.0125, 0.0250, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6 and 3.2 mg vs. placebo.</td>
<td>None.</td>
</tr>
<tr>
<td>&quot;Milgrom et al. (48), 2001</td>
<td>338 children</td>
<td>Multicenter, randomized, double-blinded study. Duration: 3 weeks.</td>
<td>Levalbuterol 0.31 and 0.63 mg vs. placebo; Racemic albuterol 1.25 mg and 2.5 mg vs. placebo as active control arm. Adverse effects compared.</td>
<td>1. Levalbuterol was clinically comparable to 4- to 8-fold higher doses of racemic albuterol; 2. Levalbuterol demonstrated a more favorable safety profile.</td>
</tr>
<tr>
<td>&quot;Carl et al. (49), 2003</td>
<td>482 children</td>
<td>Randomized, double-blind, controlled trial. Duration: 2 hours. Decisions taken after 2 hours, based on wheezing and air exchange scores.</td>
<td>Hospitalization rate in asthmatics admitted to an emergency department and an inpatient asthma care unit and blindly assigned to either racemic albuterol or levalbuterol treatments.</td>
<td>Significantly lower hospitalization rate in levalbuterol treated patients (36%), compared to racemic albuterol treated patients (45%).</td>
</tr>
<tr>
<td>&quot;Nowak et al. (50), 2004</td>
<td>91 adults</td>
<td>Prospective, open-label, nonrandomized pilot study. Duration: 2 hours. Decision, in patients with FEV1&gt;60%, without accessory muscle use and with absent/diminished wheezing) was made at the emergency medicine physician’s discretion.</td>
<td>Levalbuterol 0.63, 1.25, 2.5, 3.75, or 5.0 mg vs racemic albuterol 2.5 or 5.0 mg every 20 minutes three times, followed by a 60 minutes observation period.</td>
<td>1. Baseline plasma (S)-albuterol levels were negatively correlated with baseline FEV1 and percent change in FEV1; 2. Levalbuterol 1.25 mg produced effective bronchodilation that was greater than both racemic albuterol doses; 3. Reduction in hospitalization rates.</td>
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the B16 locus of the β2 adrenergic receptor gene. The authors found a small decline in the morning peak expiratory flow only in patients homozygous for arginine who used albuterol regularly, magnified during the four weeks run out period, and they hypothesized that the β2 adrenergic receptors were downregulated more steeply than in the homozygous B16 Glycine/Glycine (Gly/Gly) patients, with adverse effects when using a regular albuterol treatment. Their results show that the two variants at the 16th position do not differ in terms of receptor binding characteristics or receptor mediated activation of the adenylyl cyclase second messenger pathway; rather they differ in the extent to which they can be downregulated (66).

Later on, the same author (67, 68) initiated a prospective, double blind, cross-over, randomized trial, where mild asthmatics, using an average of one puff of albuterol as needed per day as their only asthma treatment, were enrolled by genotyping, using an average of one puff of albuterol as needed. For each asthma treatment, two groups were enrolled: one treated with levalbuterol or racemic albuterol, while the other group received placebo. The primary endpoint was the change in the Pediatric Asthma Questionnaire (PAQ) total score. Asthmatics receiving prednisone and ipratropium bromide were excluded from the study. Duration: 3 weeks. The PAQ scores decreased more in levalbuterol treated patients compared with racemic albuterol or placebo; 1. By week 3, PAQ scores decreased more in levalbuterol treated patients compared with racemic albuterol or placebo; 2. Significant bronchodilation with levalbuterol compared with placebo in children able to perform PEF; 3. Fewer levalbuterol treated patients required admission among those either not previously on steroids or with high plasma (S)-albuterol concentrations at presentation; 4. Fewer adverse effects in the levalbuterol treated group (43.4% vs. 56.4%); 5. No levalbuterol treated patient had a FEV1 response < 10% during the double blind period, vs. 16% in the racemic albuterol treated group.
more severe asthma exacerbations. Analyzing the change in morning peak expiratory flow rate (PEFR) between the beginning and the end of the 16 week treatment period as their primary response variable and the within-genotype difference between the albuterol and placebo treatments as their primary outcome, they noted a long lasting improvement in the morning PEFR after albuterol withdrawal, but only in Arg/Arg patients. They did not find, however, a decline in PEFR when albuterol was initiated. This improvement was seen even after the withdrawal of albuterol as needed. Based on their findings, Israel et al. conclude that alternative treatments should be defined for the Arg/Arg patients, because they can deteriorate when using albuterol in any amount, either regular or as needed. Their study is also important for defining a new genotype based therapeutic approach in asthma.

Newly emerging evidence and the differences in opinions started a fresh area of controversy into this field. Israel considers that a single nucleotide polymorphism at codon 16, with arginine replacing glycine, may be the reason for this decrease in albuterol treatment efficacy (66, 67, 68), while other researchers (69) hypothesize that more complex configurations—the haplotypes—are the cause, and arginine by itself is not causal for a decreased action of albuterol. In a research performed by Cho et al. (69), the bronchodilating response was significantly higher in the homozygous Arg16 subjects, than in the homozygous Gly16 subjects. They further demonstrated that haplotype pairs of the homozygous Arg16Gln27 and of the heterozygous Arg16Gln27/Gly16Glu27 showed the highest bronchodilating responses, and the haplotype pairs of the homozygous Gly16Gln27 the lowest response. As a whole, the bronchodilating response was more positively associated with the combined quantity of Arg16 and Glu27 polymorphisms than with that of Arg16 alone.

However, Taylor et al. (70) have failed to confirm in adults a significant and consistent relationship between the β2-adrenergic receptor haplotype and the magnitude of response to a single inhalation of albuterol. The additional analyses comparing patients who were homozygous for the Arg16 and Gly16 genotypes also failed to confirm a significant relationship between genotype and bronchodilator response.

INQURTSTIONS INTO OTHER PATHOPHYSIOLOGIC MECHANISMS UNDERLYING THE VARIABLE EFFICACY OF THE β2 ADRENERGIC RECEPTORS IN ASTHMA

Even after careful characterization of the pharmacologic action of albuterol enantiomers, there will still be some missing links. Strauss (71) stated that in 34% of patients, albuterol had no effect, but following inpatient therapy for 3.8 ± 0.4 days the patients became asymptomatic and the albuterol effect was presumably restored. Thus, the recent genotype-stratified description of albuterol effectiveness may not account for these cases: Arg/Arg patients would not be expected to increase their sensitivity to albuterol after a few days, because genotype is a permanent feature. Also, failure of self-administered β2 agonists to produce relief from acute episodes of airflow obstruction cannot be interpreted as evidence of primary drug resistance. Perhaps conditions leading to a temporary dysfunction of both β2 adrenergic receptor and underlying stimulatory G protein (Gs) may translate into a break of communication between the eutomer and the relaxation machinery in the cell (72).

A reduction in β2 adrenergic receptor activation in response to eutomer might also take place in connection with various events, like a persistent high-level activation of the β2 adrenergic receptor induced by high albuterol use, which may result in a cross-talk between β2 adrenergic receptors and the constitutive Gαq coupled receptor pathway, augmenting the effects of some bronchoconstrictors (64, 73). They could exaggerate Gs-to-Gi switching and increase the inhibitory G protein (Gi) expression (72), thus inactivating β2 adrenergic receptors, through phosphorylation via protein kinase A (74). Persistent high-level activation may also lead to an increase in phospholipase C-β (PLCβ) expression and consequent airway hyperresponsiveness, as shown by McGraw et al. (64) in genetically engineered mice overexpressing the β2 adrenergic receptor. This might support the hypothesis of Sears (13) about the effects of overuse.

The aggravation of symptoms after albuterol treatment in severe asthma patients (75), (“paradoxical worsening” sometimes associated with continued use) believed to be due to overreliance on albuterol, with increased deleterious effects from the distomer, was not solved through the use of pure eutomer. In these patients, worsening may occur during periods of decreased compliance, associated with inhaled corticosteroids underuse. The aggravation might also depend on a complicated interplay of genetic factors, underlying the level of down-regulation of the β2 adrenergic receptor, in addition to the cross talk. A minority of patients may have a genotype less responsive to albuterol (67). In other cases, a genetic background that makes a patient more susceptible to severe and nocturnal asthma (76) may also make albuterol treatment less efficacious.

CONCLUSIONS

The introduction of pure albuterol eutomer in the treatment of asthma did not solve most of the issues related to the variable effect of the racemic compound. The compendium of signals evoked by activated β2 adrenergic receptors is not well defined (77). The structural basis of agonist efficacy in G-protein-coupled receptors is poorly understood and the basic pathophysiologic mechanisms underlying the variable efficacy of the β2 agonists in asthma have yet to be discovered. The share of each enantiomer to the adverse effects of racemic albuterol still remains unclear.

There is considerable debate regarding the results of the clinical trial data. The difference in potency between levalbuterol and racemic albuterol has not been universally agreed upon. Conclusions on the relative efficacy of levalbuterol versus racemic albuterol cannot be made due to the lack of statistical power to assess superiority and the lack of a clear dose-response relationship in the active treatment arms (60). For those who don’t acknowledge a significant difference in potency and efficacy, the price considerations get more importance (61, 78).

Researchers from the field of clinical pharmacology have looked for actions of the albuterol distomer at other sites inside the cell, without finding any receptor protein to couple the distomer and to enable its action, while showing little interest in its action at the β2 adrenergic receptor site, where (S)-albuterol may be an intrinsically weak stimulant. By contrast, they showed little interest in defining other sites of eutomer action outside the β2 adrenergic receptor. Little is known about non-Gs-mediated effects of the β2 adrenergic
receptor activation, and about how they could negatively impact the function of airway smooth muscle in asthma (73).

Recent research suggests the importance of genotyping in asthma treatment, also illuminating some interrelations between albuterol and ipratropium across genotypes, but the combined potential of enantiomers and genotypes for increasing adverse effects of short acting beta agonists is not yet studied. However, the results of both genotyping and albuterol enantiomers research point to a non-β2 adrenergic receptor mediated mechanism of action for the slow deterioration in asthma control with albuterol use and to a possible relationship between the muscarinic receptor and the β2 adrenergic receptor (22, 30, 66, 67). The finding that the β2 receptors are less responsive in the Arg/Arg patients, while the muscarinic receptors remain available for bronchodilation, shows that airway smooth muscle cells are able to overcome the effects of the inhibition of a bronchodilatory pathway because they retain the capacity to maintain active another bronchodilatory pathway (79).

The contribution of β2 adrenergic receptor polymorphisms to asthma appears to be of a disease modifying rather than a disease causing nature (79). It is still unclear if the treatment modifying effect is due either to a specific single nucleotide polymorphism (SNP) or to a certain combination of SNPs, termed a haplotype. The strong linkage disequilibrium between the B16 and B27 loci pleads for a treatment modifying role of haplotype.

By affecting the expression of inflammatory and/or remodeling genes expressed by the human airway smooth muscle cells, and the tachyphylactic effect of regular exogenous exposure to β agonists, these functional polymorphisms in treatment response genes (66, 67) may account for interindividual variability in treatment efficacy, leading to overuse that may increase the airway inflammation and responsiveness, followed by more severe asthma, with more frequent exacerbations, subsequent hospitalizations and deaths from asthma. Therefore, it will be very important to characterize the asthmatic patient’s genotype and the related phenotypic pattern, in order to predict the individual therapeutic outcome and to select cases suitable for an alternate therapy.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>β</td>
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<tr>
<td>FEV1</td>
<td>mean forced expiratory volume in 1 second</td>
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<td>hBSMC</td>
<td>human bronchial smooth muscle cells</td>
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<tr>
<td>IBMX</td>
<td>isobutyl methylxanthine</td>
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<tr>
<td>Ca2+</td>
<td>Calcium ion</td>
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<tr>
<td>GM-CSF</td>
<td>granulocyte-macrophage colony stimulating factor</td>
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<td>Arg16</td>
<td>arginine16</td>
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<tr>
<td>NADPH</td>
<td>the reduced form of the nicotinamide adenine dinucleotide phosphate-oxidase</td>
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<td>NFκB</td>
<td>nuclear factor kappa B</td>
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<tr>
<td>PEFR</td>
<td>peak expiratory flow rate</td>
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<td>Gly16</td>
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<td>glutamine27</td>
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<td>Glu27</td>
<td>glutamic acid 27</td>
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<td>Gs</td>
<td>stimulatory G protein</td>
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<td>Gi</td>
<td>inhibitory G protein</td>
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<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
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**REFERENCES**


32. Johnson M. Molecular Mechanisms of β2-adrenergic receptor function.


