

Prospects for improved therapy in chronic obstructive pulmonary disease by the use of levalbuterol

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Like asthma, chronic obstructive pulmonary disease (COPD) is a chronic disease, the most prominent symptom of which is airway obstruction. Airway inflammation may be pathogenomic in both diseases, but only in COPD does inflammation predominate as a determinant of symptoms to make obstruction largely refractory to treatment. Despite a more limited degree of reversibility than in asthma, β_2 -agonists are used extensively to reduce airway obstruction and to achieve symptomatic improvement, with racemic albuterol being widely favored. In asthma, bronchodilation and bronchoprotection largely account for symptomatic benefit. In COPD, the capacity of racemic albuterol to ameliorate these symptoms is more limited and suppression of edema and of infiltration and activation of leukocytes acquire greater significance. During regular use of racemic albuterol in asthma, bronchoprotection diminishes progressively as hyperresponsiveness becomes increasingly pronounced, a process that is associated with an infiltration and activation of eosinophils. These paradoxical effects of racemic albuterol may be attributed to pharmacologic actions of the distomer, (S)-albuterol. As would be expected, homochiral (R)-albuterol (levalbuterol) is more potent and effective in asthma and may have significant advantages if used in COPD. A substantial (4–8-fold) reduction in the dose of levalbuterol anticipates lesser side effects and diminished risk in patients with cardiovascular disease. Additionally, the increased potency and duration of bronchodilation observed in asthma may extend to COPD. Finally, removal of the proinflammatory actions of (S)-albuterol may eliminate the persisting obstruction and decrease elastance that are associated with enhanced inflammation and may allow levalbuterol to suppress edema and diminish leukocyte activation more effectively. (*J Allergy Clin Immunol* 1999;104:S61-8.)

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Chronic obstructive pulmonary disease (COPD) is a progressive disorder, which occurs almost exclusively in cigarette smokers.¹ Obstruction to airflow is caused by chronic inflammation of the airways (chronic bronchitis) and by emphysema. Inflammation is characterized by a progressive destruction of lung alveolar architecture,

Abbreviations used

cAMP: Cyclic adenosine monophosphate

COPD: Chronic obstructive pulmonary disease

caused by lytic enzymes released from polymorphonuclear neutrophils and from macrophages. As a consequence, there is loss of supportive lung elastic recoil and dynamic airway collapse on expiration.² The airflow obstruction of COPD does not change significantly over a period of several months.

Clinically, a diagnosis of COPD is based on a history of progressively worsening symptoms, including cough, wheeze, and breathlessness with objective laboratory evidence of airflow obstruction that does not improve with treatment.² In older patients, it is sometimes difficult to distinguish between late-onset asthma and COPD, because patients with COPD may have a background of asthma and can show significant improvement on spirometry with inhaled bronchodilators and/or inhaled corticosteroids.³ Clinical features that may help to distinguish between the 2 conditions include a background of heavy smoking and clinical and physiologic evidence of emphysema in patients with COPD (Table I).

The airway obstruction of COPD can be reduced by bronchodilator therapy.⁴ The physiologic consequences of such therapy include a reduction in lung hyperinflation, and because of the shape of the lung pressure/volume curve, this may relieve dyspnea and will reduce the work of breathing.⁵ Additionally, bronchodilators promote slow, deep breathing, which is important in COPD because the improvement in lung emptying will increase maximum ventilation. Because overproduction of mucous is a feature of COPD, additional benefit may arise because of the ability of β -agonists to promote mucociliary clearance.

COPD is overtly inflammatory. Hence the events that comprise acute inflammation largely determine acute exacerbation of symptoms (Fig 1). Thus airway obstruction is determined by summation of several processes. As addition to mucosal edema, there is impaired elimination of an excess of mucus, in which leukocytes and leukocyte debris are incorporated, with contraction of airway smooth muscle by spasmogens generated by inflammatory cells (eg, the peptidoleukotrienes). No less important, however, are the changes in COPD that result from persisting inflammation. Included in these chronic effects is an increase in the volume of bundles of airway

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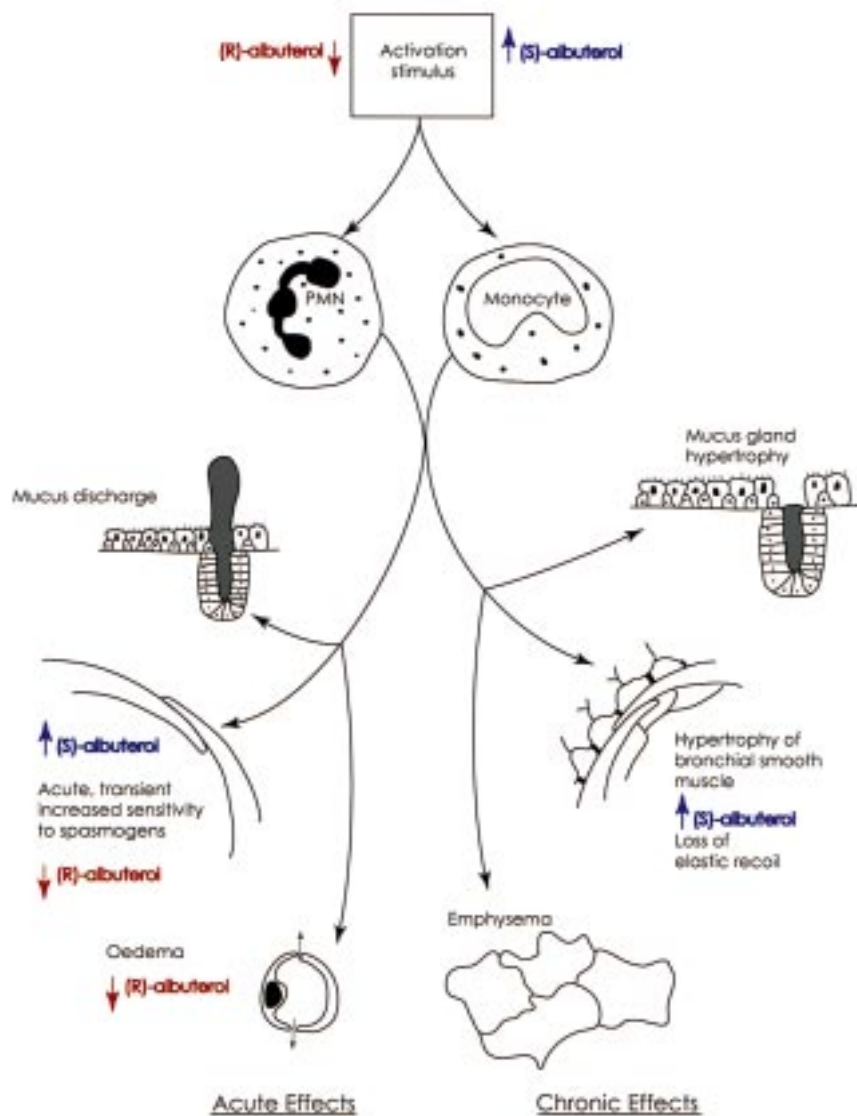


FIG 1. Schematic representation of mechanisms that determine airway obstruction in COPD. Inflammatory stimuli recruit leukocytes into the airways and will activate resident leukocytes to release materials (eg, lipid mediators, enzymes) that produce both acute and chronic effects. Acute effects include mucous discharge, increased vascular permeability, and bronchospasm associated with an increased sensitivity to bronchoconstrictor agents. Chronic effects include hypertrophy of mucous glands and airway smooth muscle and remodeling of the connective tissue matrix of the airways to cause a loss of elastic recoil and a reduction of the surface area available for gas exchange. (S)-albuterol may exaggerate these changes by making airway smooth muscle hyperresponsive and by diminishing elastic recoil to allow airways to close. As has been demonstrated for the eosinophil, (S)-albuterol may augment activation of neutrophils and macrophages, to nullify protective effects of levalbuterol and thereby promote sequelae of airway inflammation. Levalbuterol will diminish increased vessel porosity and, by either spasmolysis or reduction of airway hypersensitivity, will limit the capacity of smooth muscle to effect obstruction. By elevating intracellular cAMP, levalbuterol may inhibit leukocyte activation and thereby diminish both acute and chronic processes that determine the pathologic condition of COPD.

smooth muscle and an increased incidence of mucous glands. This remodeling of the airways causes tissue elements to intrude into the airway lumen and thereby reduce vital capacity. This form of airway obstruction may contribute to the hyperreactivity of the airways that is evident in COPD.^{6,7} However, in this disease, airway hyperreactivity is considerably less pronounced than in

asthma, and it is unlikely that this changed behavior of the airways will contribute to symptoms as prominently as in asthmatic airways.

By way of contrast, the inflammatory component of asthma is more covert, because pronounced and severe cellular inflammation can be manifest in the absence of clinical symptoms (ie, asthma in remission).^{8,9}

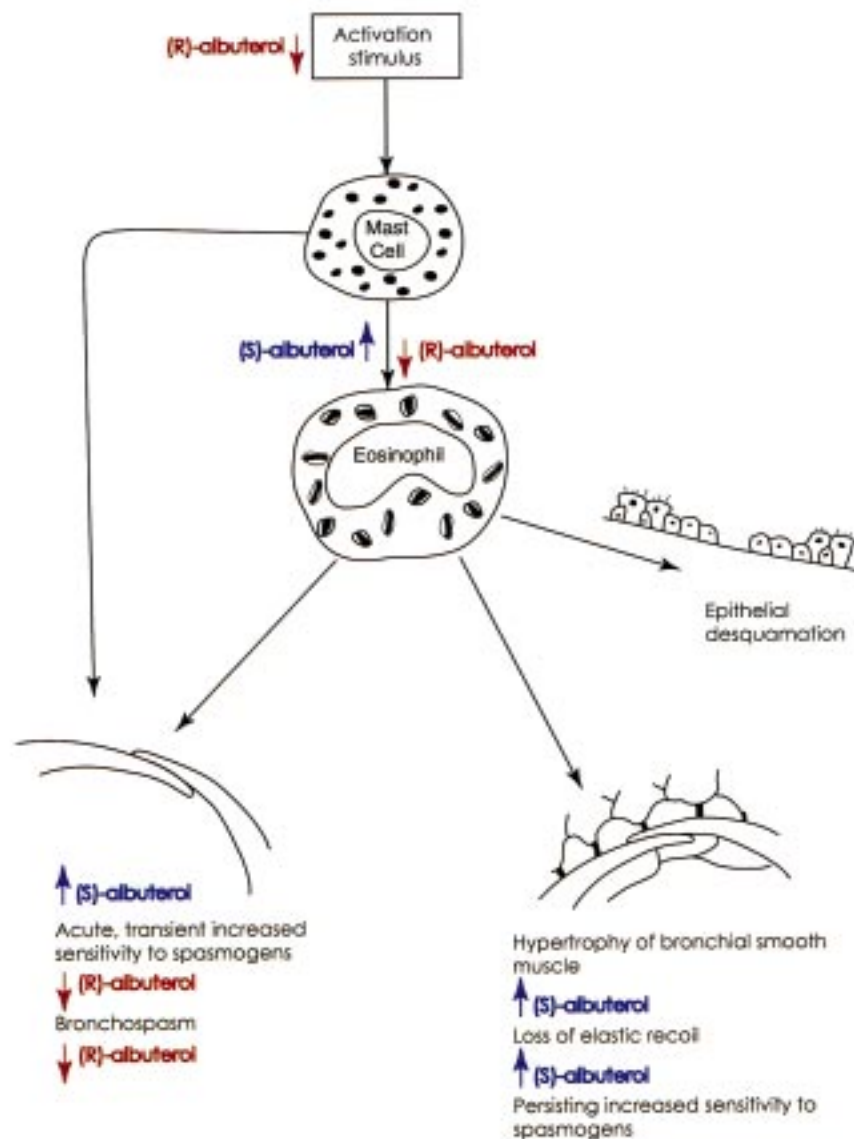


FIG 2. Schematic representation of mechanisms that determine airway obstruction in allergic asthma. Allergen or pseudoallergens will activate mast cells resident in the airways causing release materials (eg, lipid mediators, enzymes) that produce both acute and chronic effects. Acute effects are dominated by bronchospasm that is amplified in hypersensitive airways. Eosinophils have been implicated in causing chronic effects, which include damage to airway epithelium, and remodeling of the connective tissue matrix of the airways to cause a loss of elastic recoil and persisting hypersensitivity. (S)-albuterol may exaggerate these changes by making airway smooth muscle hyperresponsive and by diminishing elastic recoil to allow airways to close more readily. Activation of eosinophils is augmented by (S)-albuterol so that the consequences of airway inflammation are exaggerated. Both by direct spasmolysis and by reduction of airway hypersensitivity, levalbuterol will limit the capacity of smooth muscle to effect obstruction. By elevating intracellular cAMP, levalbuterol will inhibit activation of mast cells and of eosinophils and thereby diminish both acute and chronic processes that determine the pathologic condition of asthma.

Although inflammatory events are evident in the absence of symptoms, they can nevertheless contribute to asthma symptoms. However, inflammatory symptoms will be subordinated to the pronounced obstruction of hypersensitive airways that characterizes asthma and that provides a rationale for using β -agonists in asthma therapy. The contribution of inflammatory events is indicated by symptomatic efficacy of steroids

and by the restoration of these symptoms on cessation of steroid therapy.¹⁰ When inflammation is more intense, the relationship between inflammation and symptom exacerbation becomes more obvious, and it is generally accepted that intensification of airway inflammation will herald acute attacks of severe asthma or periods of deteriorating symptom control. The inflammatory features of asthma are broadly similar to those of COPD, except that

TABLE I. Contrasts between clinical and pathologic characteristics of COPD and asthma

Feature	COPD	Asthma
Airway obstruction	Persistent and progressive	Transient and variable
Reduced vital capacity	Pronounced and progressive	Slight and progressive
Decreased elastance	Present	Pronounced
Emphysema	Frequent	Absent
Airway inflammation	Overt	Overt or covert
Inflammatory cell infiltrate	PMN > Eos	Eos > PMN
Hypoxemia	Usual	Infrequent
Mucous secretion	Pronounced and productive	Infrequent
Airway reactivity	Proportional to obstruction	Not related to obstruction
Airway reactivity	Possibly unselective	Strongly selective
Cigarette use	Strongly implicated	Not implicated
Prevalence of allergy	Rare	Circa 50%

Eos, eosinophils.

the most prominent inflammatory cell in asthmatic airways is the eosinophil, rather than PMN (Fig 2). As in COPD, persisting cellular inflammation will lead to chronic changes in airway function such as a progressive loss of vital capacity.¹¹ However, by comparison with COPD, these structural changes may be relatively subtle.¹²

USE OF β -AGONISTS IN COPD

In preclinical research and development, racemic β -agonists have been selected almost exclusively by reference to relaxation of airway smooth muscle, with the express intention of reducing airflow obstruction in clinical asthma. This focus on spasmolysis of airway smooth muscle is well illustrated by studies that sought to differentiate therapeutic actions of (R)-albuterol from (S)-albuterol, when racemic albuterol was being introduced as a therapy for asthma.¹³ Because the use of inhaled racemic β -agonists presumes a reversibility of airway obstruction, it is most appropriately directed toward those patients with a clinical diagnosis of asthma. Nevertheless, use of racemic β -agonists for treatment of COPD has become widespread in clinical practice. This clinical usage is based on empiric control of symptoms, and it is salutary to note that, amongst clinicians, there is no firm agreement concerning objective measurement to establish the efficacy of these drugs in COPD.¹⁴ It is appropriate therefore to consider the potential of levalbuterol (homochiral [R]-albuterol) in COPD, in advance of extensive use in asthma therapy.

Racemic albuterol relaxes airway smooth muscle cells by interacting with adrenoceptors of the β_2 -subtype; of the 2 enantiomers, only (R)-albuterol is responsible for β_2 -adrenoceptor activation. On binding to β_2 -adrenoceptors, (R)-albuterol activates membrane-bound adenylyl cyclase to promote the accumulation of intracellular cyclic 3', 5' adenosine monophosphate (cAMP). The binding of cAMP to the regulatory subunit of cAMP-dependent protein kinase activates a catalytic subunit that phosphorylates substrates to cause a net reduction of intracellular Ca^{2+} .¹⁵

In smooth muscle cells, reduction of intracellular Ca^{2+} induces relaxation, whilst in nerves the release of neurotransmitter is reduced. In mast cells, a reduction of intracellular Ca^{2+} will suppress the release of cytoplasmic granules and the consequent extrusion of histamine, diminishing the formation of peptidoleukotrienes and other lipid mediators. In eosinophils, reduction of intracellular Ca^{2+} will suppress the release of reactive oxygen and will also diminish formation of peptidoleukotrienes. For vascular endothelium, relaxant effects will limit the increased vascular permeability that results from disruption of tight junctions between adjacent endothelial cells. Racemic albuterol is thus able to oppose a range of processes that contribute to airway obstruction in asthma, and it is likely that some of these processes will contribute to the pathologic condition of COPD and be similarly influenced by racemic albuterol (Table I).

REMODELLING AND ANOMALOUS AIRWAY HYPERREACTIVITY

It is well established that activation of β_2 -adrenoceptors will influence components of the acute inflammatory and allergic reactions within the airways of subjects with asthma or COPD. No less important are the effects of β_2 -adrenoceptor activation that could mitigate chronic aspects of pathologic condition. In COPD, loss of vital capacity is critically important in determining both morbidity and mortality rates. It is widely accepted that such loss of vital capacity results from airway remodeling, but the cellular basis of this functional defect remains uncertain. An increased volume of bronchial smooth muscle and proliferation of mucous glands are processes that cause airway tissue to intrude into the airway lumen and thereby diminish vital capacity, a process that will be augmented by the loss of elastic recoil that results from tissue destruction of emphysema. This reduction in the cross-sectional area of the airway lumen has been held to account for airway hyperreactivity.¹⁶ Although this concept has become widely accepted, it should be noted that it has yet to be established whether airway hyperreactivity

ity in COPD is indeed nonselective. Although often described as nonselective, airway hyperreactivity in asthma is clearly highly selective so that it should not be presumed that hyperresponsiveness in COPD must be nonselective.¹⁷ Establishing whether hyperreactivity in COPD is, or is not, heterogeneous will allow assessment of the role of structural changes in causing airway obstruction and would greatly assist the evaluation of β -agonist effects in COPD.

Whether racemic albuterol can influence the progression of airway remodeling in either asthma or COPD requires clarification. Quantitative study of asthmatic and normal airways has revealed that it is an increase in the volume of associated connective tissue, rather than myocytes, that determines the enlargement of smooth muscle bundles.¹⁸ It might therefore be expected that actions of inflammatory cells would be central to this process, with proteases derived from neutrophils providing an established mechanism for degradation of laminin, fibronectin, proteoglycans, and various types of collagen.¹² One consequence of this metabolic activity is a decreased elastance of the airways.¹² Decreased elastance allows airway smooth muscle to shorten to a greater extent than can normal airways and hence is critically important in airways that are prone to obstruction. Some insight into the cellular basis of such changes has been provided by defining the pattern of inflammation in animals whose airways have decreased elastance as a consequence of regular exposure to antigen.^{19,20} A particularly intriguing outcome of this study has been the recognition that closely comparable decreased elastance resulted from regular exposure to racemic fenoterol, an observation that had previously been reported for racemic albuterol.²¹ In addition to decreased elastance, the airways of such animals develop hyperreactivity, whether exposed to antigen or to β -agonists, alone or in combination.^{19,21-23} There is a possibility that some aspect of those inflammatory events that determine decreased airway elastance may also determine increased airway reactivity and that effects of endogenous inflammatory processes may be amplified by β -agonists.

The capacity of β_2 -agonists to amplify airway obstruction is not an effect that can be explained or predicted as a consequence of activation of β_2 adrenoceptors. Hence such effects are described as paradoxical because they are in direct conflict with the beneficial effects that these drugs produce in obstructed airways. Paradoxical effects of β -agonists are not restricted to laboratory animals and have been extensively documented in subjects with asthma and can be detected in COPD. Thus several clinical studies have revealed that regular use of β_2 -agonists by patients with asthma will produce hyperresponsiveness, which manifests as loss of bronchoprotection.²⁴ Although most studies have been directed toward asthma, it is apparent that this anomalous property of β -agonists extends also to COPD.²⁵ As yet, there is no evidence to implicate cellular inflammation as a basis for the hyperresponsiveness that follows regular use of β -agonists. On the other hand, an iatrogenic effect cannot yet be dis-

counted because structural differences that have been detected in asthmatic airways rely on tissues from subjects who are unlikely to have escaped exposure to β -agonists. Indeed, it would seem likely that such changes may be determined, at least in part, by regular β -agonist use because clinical trial has revealed that the regular use of β -agonists accelerates the rate of loss of vital capacity by comparison with an equivalent bronchodilator dose of anticholinergic therapy.²⁶

USE OF RACEMIC ALBUTEROL IN COPD

Currently, racemic albuterol is used extensively in COPD. The rationale is the empiric test of bronchodilator efficacy, which reveals that this drug is effective acutely in populations with COPD. Whether any contribution to efficacy stems from an action on concurrent asthma in individuals within these populations is not clear. It will be apparent therefore that the use of racemic albuterol in COPD does not stem from some pharmacologic insight. Indeed, bronchodilation would seem an improbable therapeutic objective in COPD because atropine-like drugs, which have a very circumscribed basis for bronchodilation, typically effect a degree of bronchodilation in COPD that is not matched by racemic albuterol, which should readily suppress any spasmogenic actions of acetylcholine.²⁷ In addition to this discrepancy, the slow progression to maximal bronchodilation that is typical of atropine-like drugs in COPD is inconsistent with mere smooth muscle relaxation. Suppression of hyperreactivity would be a plausible alternative, especially if changed smooth muscle behavior is the basis for hyperreactivity in COPD and has a different pattern of heterogeneity to that established for asthma.¹⁷ However, no study has yet addressed this issue. Impaired secretion is an alternative for which there is also no experimental verification.

In dogs, formoterol is a potent stimulant of mucociliary clearance, being approximately 100-fold more potent than terbutaline.²⁸ This does not establish that β -agonists can diminish obstruction as the result of mucous accumulation in COPD but merely implies that improved clearance might be considered a response index when responses of subjects with COPD to racemic albuterol are being assessed. Accumulation and activation of inflammatory cells might also merit consideration were it not for the evidence that accumulation of leukocytes may be stimulated, rather than inhibited, by regular use of β -agonists both in animals and in man.^{19,29-31}

LIMITATIONS OF RACEMIC ALBUTEROL IN COPD

Racemic albuterol is used extensively in COPD. However, the basis for the use of this drug is pragmatic and simply reflects a need to oppose airway obstruction. In the absence of any effort to develop drugs specifically for treatment of COPD, it is perhaps inevitable that use will have been of drugs that have been registered for use as bron-

TABLE II. Responses to therapeutic agents in patients with COPD contrasted with corresponding responses in patients with asthma

Therapeutic agent	COPD	Asthma	Ranking
Sympathomimetics	Slight	Pronounced	COPD < asthma
Glucocorticosteroids	Slight	Pronounced	COPD < asthma
Cromones	Ineffective	Often effective	COPD < asthma
Histamine antagonists	Ineffective	Modestly effective	COPD < asthma
Peptidoleukotriene antagonists	Not effective	Modestly effective	COPD < asthma
Theophylline	Modestly effective	Modestly effective	COPD = asthma
Antibiotics	Often effective	Ineffective	COPD > asthma
Parasympatholytics	Usually effective	Less effective	COPD > asthma
LTB ₄ inhibitors	Modestly effective	Poorly effective	COPD > asthma

chodilators in asthma (Table II). Not surprisingly therefore, benefit may be more modest than in asthma so that it becomes important to give greater consideration to adverse effects and to intrinsic limitations than is usual in asthma.

The most notable adverse effects are those that affect the heart. It has long been recognized that racemic epinephrine and racemic isoprenaline can induce necrotic changes in cardiac cells. For these drugs, there is evidence that such necrosis is due to oxidative metabolites and lipid peroxidation, processes that favor calcium overload in cultured myocytes.³² Considerations arising from cell culture studies have been reinforced by the demonstration that hypoxia could sensitize cardiac tissue in dogs to adverse effects of low doses of isoprenaline.³³ Because the patients with COPD in which these drugs will be used are almost all smokers and from an older age group who may have hypoxemia and coexistent ischemic heart disease, perhaps cessation in their use is warranted. There are, however, few clinical data to suggest that in stable COPD there are very special dangers, although there should be careful attention to cardiac symptoms, especially those suggestive of dysrhythmias.³⁴

Adverse effects on other cell types also merit consideration, especially when consideration is given to the relative contribution of individual enantiomers of albuterol. Thus it has long been appreciated that the capacity of β -agonists to elevate cAMP within inflammatory cells should be manifest as suppression of the secretion of inflammatory mediators.³⁵ Despite great promise in isolated cell preparations, β -agonists have not become established as anti-inflammatory agents. Rather, it has become evident that their net effect can be proinflammatory when used regularly.^{19,29-31} An explanation for this anomaly can now be suggested, based on the divergent properties of the enantiomers of albuterol. Thus it has recently been shown that, whereas levalbuterol will inhibit activation of eosinophils, (S)-albuterol will promote activation of these cells.³⁵ These conflicting actions will be biased toward a proinflammatory profile for 2 reasons. First, the capacity of (R)-albuterol to impair activation of inflammatory cells will diminish quite rapidly on regular use because β_2 adrenoceptors on these cells are readily lost by downregulation.³⁶ Second, regular administration of racemic albuterol will result in a progressively increasing proportion of (S)-albuterol being retained in tissue fluids so that

the concentration of (S)-albuterol becomes several fold greater than levalbuterol.³⁷ In these circumstances, the effects of (S)-albuterol will overwhelm the anti-inflammatory action of levalbuterol so that activation of inflammatory cells predominates.

Similar considerations apply to hyperresponsiveness. Whereas levalbuterol impairs the expression of hyperresponsiveness, (S)-albuterol initiates or augments this process.³⁸ The response of airway smooth muscle to β_2 -adrenoceptor activation is well maintained and subject to little or no receptor tachyphylaxis.³⁹ Despite this, the protective action of racemic albuterol is blunted on regular use.⁴⁰ This may now be accounted for because the relative accumulation of (S)-albuterol and the increase activation of inflammatory cells, possibly with attendant formation of peptidoleukotrienes, will promote hyperresponsiveness and oppose the protective action of levalbuterol, without necessarily having a comparable effect on bronchospasmolysis. When there is substantial hyperreactivity, bronchodilation may also be diminished.

FUTURE PROSPECTS FOR LEVALBUTEROL IN COPD

Initial studies with regularly nebulized levalbuterol, in both adults and children, have revealed that the removal of the (S)-isomer effectively quadrupled the potency of levalbuterol, by comparison with levalbuterol administered as a racemate.⁴¹ If the distomer were entirely lacking in biologic activity, removal would be expected to give no more than a 2-fold increase of potency. However, in the 4-week studies so far completed, the potency increase has been at least 4-fold. In a single dose pediatric trial, an 8-fold increase in potency was observed.⁴² Such notional increased potency of levalbuterol can only be accounted for removal of pharmacologic activity that would oppose the actions of levalbuterol. The implication of these findings is that the regular use of racemic albuterol may have produced responses that are less than can be achieved with pure levalbuterol. In clinical practice, this deficiency of racemic albuterol has been circumvented empirically by the increase of the dose of racemic albuterol. In accord with this interpretation, proportionately larger doses of racemic albuterol are required to

achieve benefits that are matched by much lower doses of levalbuterol. This can be illustrated by contrasting the effect of regular nebulized racemic albuterol (1.25 mg), which provided inadequate bronchodilation and rising basal airway resistance, with an equivalent dose of levalbuterol (0.63 mg), which was more effective and closely matched the effect of 2.50 mg of racemic albuterol and had the added advantage of not producing increased basal resistance when used regularly.⁴¹

CONCLUSION

Doses of racemic albuterol that are used in COPD are maximal or supramaximal (ie, doses that produce plateau bronchodilation). Against this clinical need for maximal relief of airway obstruction should be offset possible adverse effects of therapy including not only cardiac effects, but also a possible intensification of inflammation. It is generally accepted that the distomer, (S)-albuterol, makes no contribution to the therapeutic efficacy of racemic albuterol, and there is increasing evidence that this material contributes to undesirable properties of racemic albuterol. It seems likely that removal of (S)-albuterol would allow substantially lower doses of levalbuterol to be used during therapy of COPD, when the risk of cardiac side effects as the result of actions of levalbuterol would be diminished. Additionally, there would be a reduced likelihood of anomalous events in the airways, including not only acute events such as paradoxical hyperresponsiveness and bronchospasm but also those inflammatory events, that determine an accelerated loss of vital capacity and that would foreshorten life expectancy in patients with COPD.

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