
CME review

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Stereoconfiguration of antiallergic and immunologic drugs

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Objective: To review the concept of chirality and its current role in the pharmacology of antiallergic, antiasthmatic, and immunologic agents.

Data Sources: Ovid MEDLINE and PubMed databases from 1950 to the present time were searched.

Study Selection: Articles that described the pharmacology of chiral antiallergic, antiasthmatic, and immunologic medications were used for this review.

Results: Stereoselectivity affects the pharmacologic profiles of medications in different ways from class to class and within the classes. This summary illustrates that enantiomers differ not only in potency in receptor binding and physiologic effects but also in pharmacokinetic parameters such as volume of distribution, plasma protein binding, metabolism, and clearance. Different enantiomers may produce unrelated pharmacologic effects as well. This review summarizes the variety of possible effects that different stereoisomers may produce and further underlines the importance of the purification and in-depth analysis of chiral compounds.

Conclusion: Chirality plays an important role in pharmacokinetics and pharmacodynamics of various pharmaceutical agents. The importance of stereoisomeric purity in the pharmacologic industry has increased during the past decade as demonstrated by the increased number of studies that examined the in vivo and in vitro effects produced by changes in stereoconfiguration of pharmaceutical agents. This review highlights such effects in certain frequently used medications used in the treatment of asthma and various allergic and immunologic disorders.

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INTRODUCTION

Optic stereoisomerism or chirality describes those compounds that have the same molecular formula and chemical structure but demonstrate a different 3-dimensional configuration around the chiral center, a carbon atom. Different stereoisomers, also known as enantiomers, may have different pharmacologic profiles and physiologic effects. Agents used in medical practice comprise the full spectrum of compounds that include no chiral centers and those that have

chiral centers used in a racemic mixture or as pure stereoisomers. This review concentrates on chiral antiallergic and immunologic medications and pharmacologic differences in their isomers. Certain widely used racemic medications such as albuterol show vast differences between isomers.¹

Classification

Two ways of classifying optical isomers exist: (1) based on their rotation of the plane of polarized light either to the right, referred to as (+), dextro, d, or D isomer, or to the left, referred to as (–), levo, l, or L isomer, and (2) based on the arrangement of the molecules around the chiral center with the atom having the lowest atomic number behind the plane

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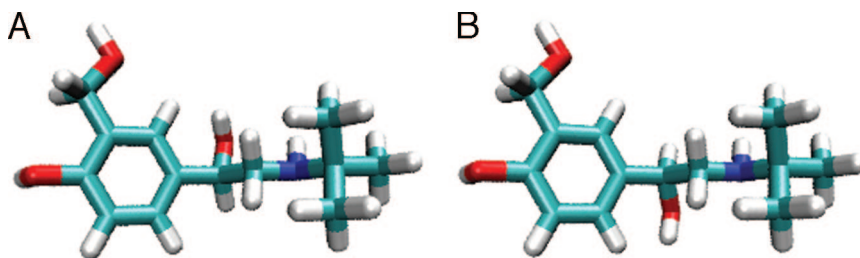


Figure 1. R-albuterol (A) and S-albuterol (B). Cyan color represents carbon; white, hydrogen; red, oxygen; blue, nitrogen. Figure created using University of California Irvine Chemical database (<http://cdb.ics.uci.edu/CHEM/Web/cgibin/ChemicalSearchWeb.py>). Visualization made possible by software VMD 1.8.5 for Microsoft Windows 2000/XL.⁵⁶

of the page and the other atoms in the plane of the page so that their atomic numbers descend either in clockwise or counterclockwise fashion (R is for rectus, Latin for right, and S for sinister, Latin for left). R- or S-isomers can independently rotate the plane of polarized light either to the right or to the left, which means that there is *no* relationship between these classifications. Therefore, the R-isomer may be either levo- or dextro-rotary or vice versa.

Translational Pharmacology

Medications that exist as racemic mixtures may have decreased efficacy and a less desirable side effect profile than pure isomers. Stereoisomerism can affect both the pharmacokinetics and pharmacodynamics of these medications. Individual isomers may be differentially and independently absorbed, metabolized, and cleared. Furthermore, as shown in the study by Borgstrom et al.,² pharmacokinetics profile of one enantiomer may be dependent on the presence of the other enantiomer. Studies exist that analyze stereoselectivity of such medicinal pharmacology aspects as binding to the receptor, side effect profiles, metabolism, and disposition of one of the most commonly prescribed drugs for asthma, albuterol.^{1,3} (Figure 1 demonstrates 2 enantiomers of albuterol as mirror images of one another. The apparent topologic difference between the 2 isomers could affect the fit of the molecule with its receptor.) Current knowledge about chirality and the ability to synthesize proper optical isomers allows the avoidance of racemic mixtures when the safety of such mixtures are not proven, whereas the Food and Drug Administration encourages the development of pure isomers rather than racemic mixtures.⁴ Another important aspect of stereoselective pharmacology, the concept of *in vivo* interconversion, also plays a critical role in the manufacture and clinical use of chiral medications.

In nature, chirality is a key concept involved in the basic building blocks of proteins and sugars that are found in living tissues. Most amino acids that comprise naturally occurring proteins are in the L-configuration, whereas most of the naturally occurring sugars have the D-configuration. Interestingly, because of their relative paucity in biological systems, it has been postulated that unique peptides composed of D-amino acids may have certain advantages in medical use,

for example, in maximizing antigen presentation of synthetic vaccines.⁵

Isolation and Manufacture

Stereochemically pure agent manufacture has been limited, which often makes it impractical to market pure products or to monitor isomeric contamination. However, multiple compounds produced by biological systems have been studied and found to be almost optically pure, such as alkaloids. This ability of living organisms to produce pure enantiomers has been used by virtually all industries that deal with medicinal chemistry. In the stereopurifying industry, a popular role has been given to nanotechnology, such as the use of cyclic oligosaccharide molecules, cyclodextrins, which have a carrier capacity via the opening of the ring where pharmaceutical agents can be inserted. Nanotechnology is becoming more widely used in processes where recognition, separation, or protection in an unfavorable environment is required. In stereochemistry, they serve as inclusion complexes for specific stereoisomers, and thus they are able to recognize and separate different enantiomers from racemic mixtures.^{6,7}

METHODS

A search of the Ovid MEDLINE and PubMed databases from 1950 to the present using the keywords *levo*, *s-*, *r-*, *dextro*, *enantiomer*, and *chiral* was performed to identify and summarize articles that investigate *in vivo* and *in vitro* pharmacology of stereoisomers of commonly used antiallergic and immunologic medications. Articles that described the pharmacology of chiral antiallergic, antiasthmatic, and immunologic medications were used for this review. Based on the results of the search, conclusions are made with respect to how the chiral properties of certain agents influence their pharmacology.

RESULTS

The results presented concentrate on the clinical impact on various organ systems, including the immune system, focusing on the generation of an inflammatory response, the respiratory system and bronchodilators, and the allergic response and antihistamines and decongestants.

Immunologic and Inflammatory Response

The inhaled corticosteroid budesonide exists as a racemate, with the R-enantiomer having a 2-fold greater affinity for the glucocorticoid receptor than its S-enantiomer. Although the enantiomers do not interconvert in vivo and the pharmacokinetics of the enantiomers do not appear to vary,⁸ the volume of distribution and plasma clearance of the R-(+)-enantiomer appear to be greater than those of the S-(−)-budesonide and the rate of biotransformation appears to be quicker for R-(−)-budesonide.⁹

Nonsteroidal anti-inflammatory drugs (NSAIDs) with the 2-arylpropionic acid structure, such as ibuprofen, are usually administered as a racemate except for naproxen, which exists in the S-configuration. The anti-inflammatory activity of NSAIDs primarily resides in their S-(+)-enantiomer, with equivalent efficacies between the pure isomer and the racemate mixture, but requires lower dosing. The R-enantiomer undergoes stereoconversion in vivo, thus affecting the accurate measurement of the dose for the active form and influencing the pharmacokinetics of the drug.^{10–12} The stereoselectivity analysis of the deleterious side effects of NSAIDs, such as gastric and intestinal mucosa damage, exhibits conflicting results. Interestingly, animal models have demonstrated that intestinal mucosa ulceration seems to be due to the enhancement of the mucosal toxicity of S-(+)-ketoprofen by R-(−)-enantiomer. This enhancement may be related to the ability of R-(−)-ketoprofen to increase oxidative stress and modify neutrophil migration.¹³ Human endoscopy studies have demonstrated gastroduodenal tolerance for R-flurbiprofen, with patients developing fewer ulcers when compared with R-ketoprofen or its racemate mixture.¹⁴ In the analysis of ketorolac enantioselectivity, R-ketorolac was seen to have less ulcerogenic activity when compared with the S-enantiomer by direct microscopic measurement. The same analysis showed that S- and R-ketorolac appear to have analgesic activity independent of the cyclooxygenase (COX) inhibition mechanism.¹⁵ The R-enantiomer of *etodolac*, although inactive in the usual NSAID role as a COX inhibitor, has been found to have cytotoxic properties.¹⁶

The immunomodulatory agent cyclosporine A has been used in various capacities, from transplantation to control of urticaria to the treatment of tear film dysfunction. This small

polypeptide is thought to cause immunomodulation partly through binding to cytoplasmic cyclophilin, ultimately inhibiting the activation of interleukin-2 (IL-2) transcription. Its chiral counterpart, cyclosporine H, is produced when D-MeVal-11 peptide is substituted for L-MeVal. This simple chiral inversion is associated with a major structural conformation change.¹⁷ Cyclosporine H does not possess the same immunosuppressive properties as cyclosporine A but was found to have certain anti-inflammatory activity mediated by a different mechanism than the cyclophilin signaling pathway. Its anti-inflammatory properties may lie in inhibition of histamine and de novo synthesized inflammatory mediator release from basophils. Such release, when stimulated specifically by the activation of the formyl peptide receptor, was competitively inhibited by cyclosporine H. However, when other receptors involved in basophil activation and histamine release, such as G protein-coupled receptors, were challenged, cyclosporine H did not demonstrate significant activity.¹⁸

Thalidomide (Fig 2), infamous for its teratogenic effects when used as a sedative, is now being explored as a possible anti-inflammatory agent. Its sedative effects were shown to be related to the blood concentration of R-enantiomer, but its anti-inflammatory effects, specifically its ability to inhibit the release of tumor necrosis factor α , has shown stereoselectivity to its S-counterpart.¹⁹ Thalidomide undergoes interconversion in tissues, thus producing some amounts of R- and S-enantiomers, which makes it difficult to avoid the teratogenic side effects. There have been conflicting reports with different conclusions as to which enantiomer is responsible for the teratogenicity. These differences may be attributed to the in vivo interconversion factor.²⁰

Bronchodilators

Albuterol, a first-line medication used for the treatment of acute exacerbation of asthma, is a racemic mixture of S-(+)- and R-(−)-isomers. It has been shown that the levorotary R-isomer levalbuterol is the major contributor to the β_2 -adrenoceptor-mediated bronchodilation, with at least 100-fold greater affinity of R-albuterol to the receptor, whereas S-isomer can actually enhance bronchial reactivity.¹ The effect on heart rate and serum potassium level may also be

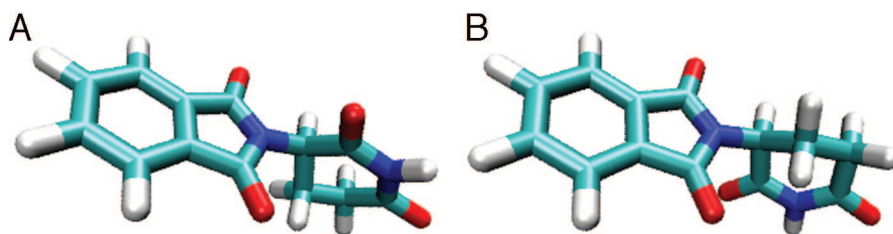


Figure 2. R-thalidomide (A) and S-thalidomide (B)—non-superimposable mirror images of this molecule demonstrate how 3-D geography may differ, affecting the molecule's interaction with a receptor. Cyan color represents carbon; white, hydrogen; red, oxygen; and blue, nitrogen. Figure created using University of California Irvine Chemical database (<http://cdb.ics.uci.edu/CHEM/Web/cgi-bin/ChemicalSearchWeb.py>) and visualization program VMD 1.8.5 for Microsoft Windows 2000/XL.⁵⁶

lower with levalbuterol vs racemic albuterol, although there are conflicting published reports regarding these side effects.²¹⁻²⁴

On a cellular level, R-albuterol causes a dose-dependent decrease in intracellular calcium that may be the mechanism for its clinical relevance, whereas S-albuterol demonstrated cell shortening and an increase in the intracellular concentration of calcium in a model of bovine tracheal smooth muscle cells. This effect was not blocked by the β_2 -receptor antagonist administration but was inhibited by the administration of atropine, implying the involvement of 1 of the muscarinic receptors.²⁵

The well-known phenomenon of paradoxical bronchoconstriction and increased sensitivity to inhaled antigens, increased late-phase allergic reactions, and increased sputum eosinophil counts in response to albuterol inhalation treatment may be attributed to S-albuterol. Handley et al^{1,26} summarized some of the work performed on proinflammatory effects of S-albuterol and described several mechanisms of how this may occur, including eosinophil activation, increased epithelial permeability, and muscarinic M2 receptor activity of S-albuterol compared with R-albuterol. Some examples of proinflammatory effects of S-albuterol and anti-inflammatory effects of R-albuterol were noted in studies of pretreated S-albuterol sheep that had increased histamine-induced endothelial and epithelial permeability, airway protein, neutrophil counts, and IL-8 levels. Studies with S-albuterol-exposed eosinophils have shown exaggerated production of superoxide in response to IL-5, whereas R-albuterol pretreatment of eosinophils has demonstrated inhibition of superoxide production. Peroxidase secretion as a result of eosinophil activation was also studied in the context of albuterol stereoisomerism. Although some reports did not demonstrate any S-albuterol-mediated augmentation of the eosinophil peroxidase release in stimulated eosinophils, they demonstrated the ability of R-albuterol and the albuterol racemate mixture to inhibit such release.²⁷ The proinflammatory ability of S-albuterol reflected by an increase in bronchial hyperreactivity to a given allergen can be alleviated by the R-enantiomer.²⁸

Another commonly used bronchodilator, the long-acting β -agonist formoterol, is used in aerosolized form as a racemate mixture. Interestingly, it has 2 chiral centers, and the RR-enantiomer is 1,000 times more potent at the human β_2 -adrenoceptor than the SS-isomer. RR-formoterol was demonstrated in sensitized guinea pigs to inhibit antigen-induced bronchoconstriction and histamine release, whereas SS-formoterol was found to be inactive. As seen with albuterol, the SS-enantiomer of formoterol, besides being much less active at the β -receptor, also may incur deleterious effects. When the toxicity of formoterol was analyzed, it was found that the minimum lethal intravenous dose of the RR-isomer was twice that of the SS-isomer, suggesting that the toxicity of the SS-isomer may not be related to binding to the β_2 -adrenoceptors.²⁹ The same study suggested that, similar to albuterol, the SS-isomer may be antagonistic to RR-formot-

erol. This finding was demonstrated by the exaggeration of bronchial contraction in response to carbachol challenge after pretreatment with SS-formoterol but not RR-formoterol.

Terbutaline, a β -agonist commonly used in the intravenous formulation for the treatment of uterine contractions and status asthmaticus, is a chiral drug. Its R-(+)-enantiomer is able to relax tracheal smooth muscle after contraction in response to carbachol, whereas S-(-)-terbutaline had no effect. The enantiomers also were compared in regard to tracheal smooth muscle relaxation after cholinergic and noncholinergic/nonadrenergic excitation with electrical field stimulation, which demonstrated a 1,000 times increased potency of the R-enantiomer, whereas no enhancement of the noncholinergic/nonadrenergic or cholinergic response was observed with the S-enantiomer.³⁰ The 2 enantiomers were found to affect each other's pharmacokinetics in that the S-enantiomer affects the absorption of the R-terbutaline and R-terbutaline influences the elimination of the L-terbutaline.²

Trimetoquinol is a bronchodilator used in Japan for treatment of bronchial asthma and emphysema. The S-(-)-isomer is a much more potent β -adrenergic receptor agonist for each of the 3 receptor subtypes.³¹

Leukotriene Synthesis and Receptor Inhibitors

Montelukast, a chiral leukotriene D4 receptor antagonist, is used clinically in the R-configuration. It has been shown that there is no apparent bioinversion of montelukast to its S-configuration when studied in humans.³² Relative potencies of the S-montelukast as a leukotriene antagonist have not been reported.

Zileuton, an antiasthma medication that inhibits the production of leukotrienes, exhibits the stereoselective plasma protein binding toward R-(+)-enantiomer (96% vs 88%).³³ Relative potencies of the zileuton enantiomers have not been reported.

Antihistamines

Cetirizine (Fig 3), a racemic, longer-acting, second-generation histamine₁ (H₁)-receptor antagonist, is commonly used in the treatment of such disorders as allergic rhinitis and chronic urticaria. Like other second-generation antihistamines, cetirizine exhibits less central nervous system (CNS) penetration, thus producing less sedation when compared with first-generation drugs. There is also a difference in CNS penetration and sedation when the racemic mixture and enantiomers of cetirizine are compared with each other. According to the data published in the prescribing information inserts for levocetirizine and cetirizine, in levocetirizine studies 6% of patients 12 years and older developed somnolence vs 2% in the placebo group, whereas racemic cetirizine had 13.7% somnolence for similar age group vs placebo 7%.^{34,35} Levocetirizine appears to have less CNS effect in part because of increased plasma protein binding, the phenomenon partly controlling the ability for CNS penetration of an agent.³⁶ In a study of cetirizine and its isomers in healthy volunteers exposed to histamine via skin prick, the racemic

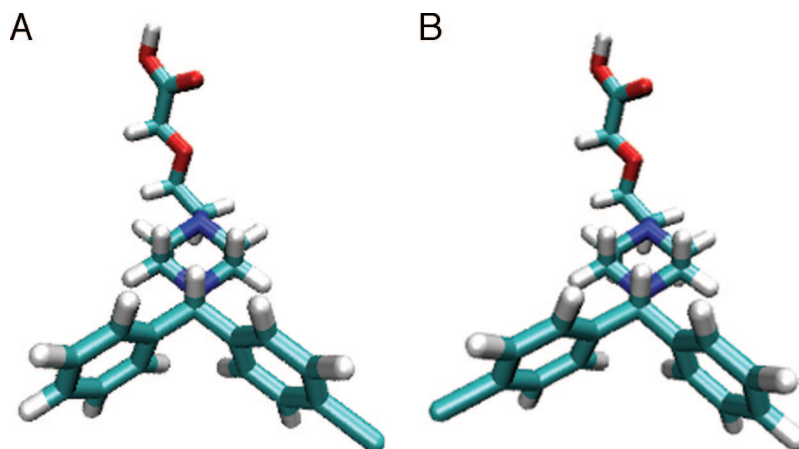


Figure 3. R-(-)-cetirizine (A) and S-(+)-cetirizine (B). Cyan color represents carbon; white, hydrogen; red, oxygen; blue, nitrogen; larger cyan bond on benzene ring represents chlorine. As evident from the image, the enantiomers of cetirizine differ in their spatial arrangement of chlorine. Figure created using University of California Irvine Chemical database (<http://cdb.ics.uci.edu/CHEM/Web/cgibin/ChemicalSearchWeb.py>) and visualization program VMD 1.8.5 for Microsoft Windows 2000/XL.⁵⁶

mixture at the 5-mg oral dose and R-(-)-enantiomer at the 2.5-mg oral dose were analyzed for wheal-and-flare inhibition. Cetirizine and levocetirizine were found to comparably inhibit wheal-and-flare formation by most statistical measurements, with levocetirizine actually having greater inhibitory effect on wheal formation when measured by the percentage of inhibition and analyzed for area under the curve. The S-(+)-enantiomer did not produce such inhibition. A greater inhibitory effect on histamine-induced wheal, observed for levocetirizine, was attributed to the longer pharmacodynamic effect of the levocetirizine than cetirizine.³⁷ Analysis of binding characteristics of cetirizine and the enantiomers demonstrated significantly higher affinity and receptor dissociation half-time of the R-(-)-cetirizine compared with the S-(+)-enantiomer. These differences appear to be related, to some extent, to hindrance caused by the amino acid threonine (Thr) at position 194 and interaction of cetirizine's carboxyl group with lysine (Lys) at position 191 of the fifth transmembrane domain of H₁-receptor. The mutation of Lys 191 into Ala decreased the time to dissociation of levocetirizine by 10-fold, whereas the time to dissociation decreased by 6-fold for the S-(+)-enantiomer. The mutation of Thr 194 into Ala led to decreased stereoselectivity with increased affinity of both stereoisomers but with more pronounced increase in binding for the S-enantiomer.³⁸ Cetirizine stereoselectivity affects not only the receptor binding but pharmacokinetics as well. It has been shown in male Hartley guinea pigs that levocetirizine demonstrated higher plasma protein binding, possibly explaining other findings in pharmacokinetic parameters, such as higher plasma concentration, and lower volume of distribution.³⁹ Levocetirizine does not appear to undergo interconversion to the dextroisomer in vivo, a necessary property for an enantiomerically pure drug.⁴⁰

Fexofenadine, clinically used for the treatment of seasonal allergic rhinitis and urticaria, is a racemic mixture, with its

enantiomers having equal potencies but different pharmacokinetics as demonstrated by the plasma ratio of 1:2 S:R enantiomer.⁴¹

Levocabastine is a potent, selective, second-generation H₁-antihistamine used in topical treatment of allergic conjunctivitis. The L-isomer has been found to be 4 to 90 times more potent than dextrocabastine when studied in guinea pigs at 1 to 24 hours after oral administration.⁴²

Chlorpheniramine, a first-generation antihistamine, is commercially available as a racemic mixture, with the S-(+)-enantiomer displaying higher maximum drug levels and lower clearance and volume of distribution.⁴³ Another study of the pharmacokinetics of chlorpheniramine showed that the S-(+)-enantiomer is more extensively bound to plasma albumin, total plasma proteins, and α -glycoprotein.⁴⁴ No studies were found on the clinical characteristics of enantiomers of chlorpheniramine.

Certain antihistamine medications that may not have a chiral center when chemically modified may create a chiral center with differential potencies of their isomers. For example, the chemically synthesized chiral analog 4-methylebastine, in its levo confirmation, was shown to be 10-fold more potent than the parent compound, ebastine.⁴⁵

Pyranenamine (SK&F 84210) is a potent multiple action antiallergic agent with 2 chiral centers, possibly acting through the mast cell stabilization mechanism, that has been found to be 1,000 times more potent than cromolyn in a rat passive cutaneous anaphylaxis model. The agent was also studied in rat passive ocular anaphylaxis, and it was found that SS-stereoisomer had the more potent inhibitor effect on the allergic response when compared with the RR-isomer. When evaluated by intravenous and topical routes in the rat passive ocular anaphylaxis assay, the (SS) and the achiral forms were found to be more potent antiallergic agents than (RR). Interestingly, the RR-isomer may have a proallergic

Table 1. Agents Grouped According to the General Impact Stereoconfiguration Change Had on Their Pharmacology

Unrelated effects and different pathways	Antagonistic effects	Different potency or effect without selectivity ^a	Decreased potency	No potency
Thalidomide, NSAIDs, trimetoquinol, cyclosporine	Albuterol, formoterol, pyranenamine	Phenylpropanolamine, ketorolac, etodolac, mequitamium	Budesonide, trimetoquinol, cabastine	Cetirizine, terbutaline

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

^a Enantiomers of these medications have different potencies at the established pharmaceutical action but were found to have nonstereoselective effects at other sites of action (see text for detail).

effect because it was found to promote the release of allergy mediators instead of inhibiting them.⁴²

Mequitamium iodide, an experimental antihistaminic agent, is a chiral compound, with the S-(+)-enantiomer displaying a 10-fold increase as a histamine receptor antagonist than the R-(−)-enantiomer; however, both enantiomers demonstrated similar antimuscarinic activity.⁴⁶

Decongestants

Pseudoephedrine has 2 chiral centers, producing 4 enantiomers: (1R,2S), (1S,2R), (1R,2R), and (1S,2S). Compounds with the configuration (1R,2S) and (1S,2R) are designated ephedrine, whereas (1R,2R) and (1S,2S) enantiomers are designated pseudoephedrine. The commercially used pseudoephedrine enantiomer is (1S,2S)-(+)-pseudoephedrine (dextrorotary). Pseudoephedrine is used as a nasal decongestant, and it has been shown to possess antitussive properties of central and peripheral action in guinea pigs.⁴⁷

Phenylpropanolamine has 2 chiral centers, with 2 enantiomeric pairs: one pair is called norephedrine and the other is

norpseudoephedrine. Norpseudoephedrine actually is the active metabolite of pseudoephedrine; however, it is not commercially used as a decongestant.⁴⁸ Only the pair of (+)- and (−)-norephedrine had been commercially used as decongestant. The compound exists as a racemic mixture, but its vasoactive properties are attributed to the (−)-enantiomer, which has an α_1 -adrenoreceptor agonist activity.⁴⁹ Interestingly, it has been shown that both enantiomers of this decongestant also have appetite suppressant activity.⁵⁰

Unlike the other 2 decongestants, phenylephrine has only 1 chiral center, and it is commercially used as the (−)-enantiomer.⁴⁸

DISCUSSION

Chirality describes asymmetric molecules that have the same molecular formula and chemical structure but are mirror images of each other, each being termed *enantiomers* or *stereoisomers*. Many medications exist as a racemic mixture of 2 different stereoisomers, and some may have more than 1

Table 2. Common Chiral Medications and Their Properties

Drug	Isomers	Isomer with higher activity	Site of primary difference in action	Effect
Thalidomide	R, S	R- S-	Possibly inhibition of TNF- α release	Sedation
NSAIDs	R-(−) S-(+)	S-(+)-	COX inhibition	Anti-inflammatory
Budesonide	R-(+) S-(−)	R > S	Glucocorticoid receptor	Anti-inflammatory
Cyclosporin	(−), (+)	(−)	In part by inhibiting IL-2 transcription	Immunosuppressant
Albuterol	R-(−) S-(+)	R-(−)-	β -Adrenergic receptor agonist	Bronchodilation
Formoterol	RR, SS RS, SR	RR >> SS	β -Adrenergic receptor agonist	Bronchodilation
Terbutaline	R-(+) S-(−)	R-(+)-	β -Adrenergic receptor agonist	Bronchodilation
Trimetoquinol	S-(−) R-(+)	S > R	β -Adrenergic receptor agonist	Bronchodilation
Zileuton	R-(+) S-(−)	Possibly both	Plasma protein binding R > S	Leukotriene production inhibition, anti-inflammatory

Abbreviations: COX, cyclooxygenase; IL-2, interleukin 2; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF- α , tumor necrosis factor α .

chiral center with multiple enantiomers with similar or antagonistic pharmacologic effects. This review examined published findings on pharmacologic agents commonly used by allergists/immunologists in relation to their chiral nature and provided a summary of possible ways chirality affects the pharmacologic activity of several agents. Many more agents that are clinically important have not been fully investigated as to their chiral properties. This review adds to the recent emphasis on the importance of the investigation of stereoisomeric purity in the development of clinically used agents.

A number of agents show enantiomeric selectivity in several aspects related to the pharmacokinetics and pharmacodynamics. Change in stereoconfiguration of a molecule may affect its pharmacology in several ways (Table 1). Two enantiomers may be antagonistic or differ in potency in one action but show no stereoselectivity in another action of the drug. Different enantiomeric potencies have been noted when one enantiomer, by virtue of the stereoconfiguration, exerts a certain action, whereas another enantiomer is less potent or does not show any interaction with the action-producing receptor. Enantiomeric antagonism has been noted where agents are found to produce antagonistic effects between their enantiomers. The antagonism may not necessarily be at the same receptor but may act via another receptor that produces the opposite effect, as demonstrated by albuterol. Another example of a stereoselectivity effect is enantiomeric agonism via a different pathway such as ketorolac, where the S-enantiomer produces its effects and side effects through the COX enzyme inhibition, whereas the R-enantiomer leads to similar end point results, probably via a different, not yet established pathway (Table 2). It should be kept in mind that as more actions of a particular agent are identified, the more ways there will be for the stereoselectivity to play a role.

One important aspect of the chiral pharmacology that requires more investigation is in vivo interconversion of the stereoactive agents. Some agents, such as thalidomide, are known to interconvert in vivo, making the creation of a pure isomer less practical. Other agents, used as racemic mixtures, may not have been extensively studied yet as to their ability to interconvert. Because regulatory agencies such as the Food and Drug Administration may apply pressure for production of stereopure agents, investigation of in vivo interconversion will become increasingly important when evaluating a certain agent for a possible clinical use.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

CME Examination

1–5, Bielory L. 2008;100:1–9.

CME Test Questions

1. Of the listed nonsteroidal anti-inflammatory drugs, one manufactured as a pure enantiomer is:
 - a. ketoprofen
 - b. naproxen
 - c. ibuprofen
 - d. etodolac
 - e. ketorolac
2. S-albuterol was postulated to act as a proinflammatory agent by:
 - a. increase in eosinophil activation
 - b. increase in epithelial permeability
 - c. activity at muscarinic receptors
 - d. all of the above
 - e. none of the above

-
3. What aspect of the pharmacology is unique to a chiral agent?
- volume of distribution
 - in vivo stereointerconversion
 - rate of absorption
 - clearance rate
 - plasma protein binding
4. The teratogenicity side effect of thalidomide is due to which of the following?
- S-enantiomer
 - R-enantiomer
 - due to in vivo stereointerconversion, it is unclear which enantiomer is responsible for teratogenicity
 - neither
 - there are no teratogenicity side effects to thalidomide
5. Use of inhaled ipratropium bromide along with albuterol is occasionally used in the management of an acute asthma exacerbation. One possibility why this anticholinergic agent may augment bronchodilation is that:
- it stimulates secretions inside the bronchial tree
 - it also acts as the β -adrenergic receptor agonist
 - it may prevent S-enantiomer of albuterol from producing muscarinic receptor-mediated increase in intracellular calcium
 - it serves as anti-inflammatory agent through the corticosteroid pathway
 - it inhibits leukotriene production
6. Levocetirizine and levocabastine exhibit which of the following?
- different enantiomeric potencies
 - enantiomers exhibit unrelated physiological effects via different pathways
 - enantiomeric antagonism
 - enantiomeric agonism
 - none of the above
- Answers found on page 36.**
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