Stereochemistry in Drug Action

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The importance of stereochemistry in drug action is gaining greater attention in medical practice, and a basic knowledge of the subject will be necessary for clinicians to make informed decisions regarding the use of single-enantiomer drugs. Many of the drugs currently used in psychiatric practice are mixtures of enantiomers. For some therapeutics, single-enantiomer formulations can provide greater selectivities for their biological targets, improved therapeutic indices, and/or better pharmacokinetics than a mixture of enantiomers. This article reviews the nomenclature for describing stereochemistry and enantiomers, emphasizes the potential biological and pharmacologic differences between the 2 enantiomers of a drug, and highlights the clinical experience with single enantiomers of the selective serotonin reuptake inhibitors fluoxetine and citalopram. In some cases, both a mixture of enantiomers and a single-enantiomer formulation of a drug will be available simultaneously. In these cases, familiarity with stereochemistry and its pharmacologic implications will aid the practicing physician to provide optimal pharmacotherapy to his or her patients.

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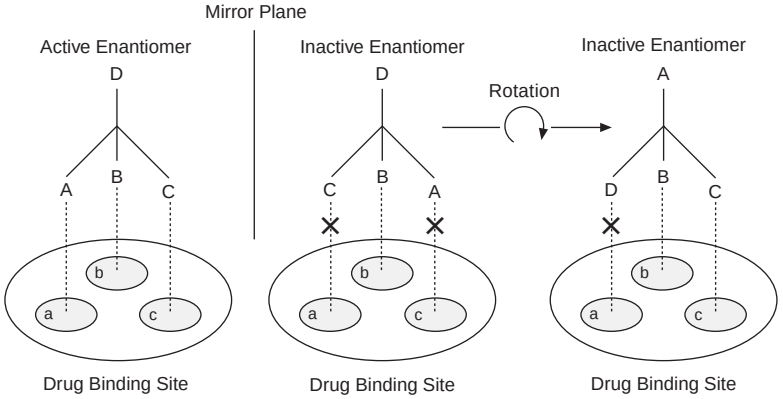
CHIRALITY AND ENANTIOMERS

This section contains the basics needed to understand chiral drugs. Undergraduate textbooks in chemistry are good resources for a more thorough discussion of chirality and enantiomers. The most important point is that chiral drugs have 2 structurally similar forms that can behave very differently in biological systems due to their different shapes in 3-dimensional space. These 2 possible forms are termed *enantiomers*, and the 2 enantiomers of a given chiral drug should be considered 2 different drugs. This topic is discussed further in the next section.

Chirality is formally defined as the geometric property of a rigid object (like a molecule or drug) of not being superimposable with its mirror image. Molecules that can be superimposed on their mirror images are achiral (not chiral). Chirality is a property of matter found throughout biological systems, from the basic building blocks of life such as amino acids, carbohydrates, and lipids to the layout of the human body. Chirality is often illustrated with the idea of left- and right-handedness: a left hand and right hand are mirror images of each other but are not superimposable. The 2 mirror images of a chiral molecule are termed *enantiomers*. Like hands, enantiomers come in pairs. Both molecules of an enantiomer pair have the same chemical composition and can be drawn the same way in 2 dimensions (e.g., a drug structure on a package insert), but in chiral environments such as the receptors and enzymes in the body, they can behave differently. A *racemate* (often called a racemic mixture) is a mixture of equal amounts of both enantiomers of a chiral drug. Chirality in drugs most often arises from a carbon atom attached to 4 different groups, but there can be other sources of chirality as well. Single enantiomers are sometimes referred to as *single isomers* or *stereoisomers*. These terms can also apply to achiral drugs and molecules and do not indicate that a single enantiomer is present. For example, molecules that are isomers of each other share the same stoichiometric molecular formula but may have very different structures. However, many discussions of chiral drugs use the terms *enantiomer*, *single isomer*, and/or *single stereoisomer* interchangeably.

The 2 enantiomers of a chiral drug are best identified on the basis of their absolute configuration or their optical rotation. Other designations such as D and L (note the upper case) are used for sugars and amino acids but are specific to these molecules and are not generally applicable to other compounds. The terms *d*, or *dextro*, and *l*, or *levo*, are considered obsolete and should be avoided. Instead, the *R*/*S* system for absolute configuration and the +/– system for optical rotation should be used. The absolute configuration at a chiral center is designated as *R* or *S* to unambiguously describe the 3-dimensional structure of the molecule. *R* is from the Latin *rectus* and means to the right or clockwise, and *S* is from the Latin *sinister* for to the left or counterclockwise. There are precise rules based on atomic number and mass for determining whether a particular chiral center has an *R* or *S* configuration. A chiral drug may have more than one chiral center, and in such cases it is necessary to assign an absolute configuration to

Figure 1. The Hypothetical Interaction Between the 2 Enantiomers of a Chiral Drug and Its Binding Site[a]



[a]The active enantiomer has a 3-dimensional structure that allows drug domain A to interact with binding site domain a, B to interact with b, and C to interact with c. In contrast, the inactive enantiomer cannot be aligned to bind the same 3 sites simultaneously. The difference in 3-dimensional structure allows the active enantiomer to bind and have a biological effect, whereas the inactive enantiomer cannot.

each chiral center. Optical rotation is often used because it is easier to determine experimentally than absolute configuration, but it does not provide information about the absolute configuration of an enantiomer. For a given enantiomer pair, one enantiomer can be designated (+) and the other as (–) on the basis of the direction they rotate polarized light. Optical rotations have also been described as *dextrorotatory* for (+) and *levorotatory* for (–). Racemates can be designated as (*R*,*S*) or (±).

CHIRAL DRUGS IN BIOLOGICAL SYSTEMS

Enantiomers of a chiral drug have identical physical and chemical properties in an achiral environment. In a chiral environment, one enantiomer may display different chemical and pharmacologic behavior than the other enantiomer. Because living systems are themselves chiral, each of the enantiomers of a chiral drug can behave very differently in vivo. In other words, the *R*-enantiomer of a drug will not necessarily behave the same way as the *S*-enantiomer of the same drug when taken by a patient. For a given chiral drug, it is appropriate to consider the 2 enantiomers as 2 separate drugs with different properties unless proven otherwise.

The difference between 2 enantiomers of a drug is illustrated in Figure 1 using a hypothetical interaction between a chiral drug and its chiral binding site. In this case, one enantiomer is biologically active while the other enantiomer is not. The portions of the drug labeled A, B, and C must interact with the corresponding regions of the binding site labeled a, b, and c for the drug to have its pharmacologic effect. The active enantiomer of the drug has a 3-dimensional structure that can be aligned with the binding site to allow A to interact with a, B to interact with b, and C to interact with c. In contrast, the inactive enantiomer cannot bind in the same way no matter how it is rotated in space. Although the inactive enantiomer possesses all of the same groups A, B, C, and D as the active enantiomer, they cannot all be simultaneously aligned with the corresponding regions of the binding site.

This difference in 3-dimensional structure prevents the inactive enantiomer from having a biological effect at this binding site. In some cases, the portion of a molecule containing the chiral center(s) may be in a region that does not play a role in the molecule's ability to interact with its target. In these instances, the individual enantiomers may display very similar or even equivalent pharmacology at their target site. Even in these cases, the enantiomers may differ in their metabolic profiles as well as their affinities for other receptors, transporters, or enzymes.

IMPORTANCE OF CHIRALITY IN DRUGS

Approximately 50% of marketed drugs are chiral, and of these approximately 50% are mixtures of enantiomers rather than single enantiomers.[1] In this section, the potential advantages of using single enantiomers of chiral drugs are discussed and some specific examples of single-enantiomer drugs currently on the market are given. Single-enantiomer drugs will become increasingly more available to the practicing physician, and both the single-enantiomer form and the mixture of enantiomers of a given drug may be available at the same time. In these cases, it is critical to distinguish the single enantiomer from the racemic form because they may differ in their dosages, efficacies, side effect profiles, or even indicated use. It is also important to realize that the safety and efficacy data for a drug evaluated as a mixture of enantiomers

Table 1. Selected Racemic Drugs Currently Used in Psychiatric Practice

Bupropion[a]
Citalopram[b]
Fluoxetine
Methylphenidate[b]
Thioridazine (and some other phenothiazines)
Tranylcypromine
Trimipramine
Venlafaxine
Zopiclone[a]

[a]Single-enantiomer formulation under development.
[b]Single-enantiomer form also available.

are still valid. The introduction of a single-enantiomer preparation of a drug previously approved as a mixture of enantiomers does not necessitate that the single enantiomer should become the standard of care. The decision to use a single enantiomer versus a mixture of enantiomers of a particular drug should be made on the basis of the data from clinical trials and clinical experience.

The 2 enantiomers of a chiral drug may differ significantly in their bioavailability, rate of metabolism, metabolites, excretion, potency and selectivity for receptors, transporters and/or enzymes, and toxicity. The use of single-enantiomer drugs can potentially lead to simpler and more selective pharmacologic profiles, improved therapeutic indices, simpler pharmacokinetics due to different rates of metabolism of the different enantiomers, and decreased drug interactions. For example, one enantiomer may be responsible for the therapeutic effects of a drug whereas the other enantiomer is inactive and/or contributes to undesirable effects. In such a case, use of the single enantiomer would provide a superior medication and may be preferred over the racemic form of the drug. Single-enantiomer formulations of (*S*)-albuterol, a β_2-adrenergic receptor agonist for treatment of asthma, and (*S*)-omeprazole, a proton pump inhibitor for treatment of gastroesophageal reflux, have been shown to be superior to their racemic formulations in clinical trials.[2] In other cases, however, both enantiomers of a chiral drug may contribute to the therapeutic effects, and the use of a single enantiomer may be less effective or even less safe than the racemic form. For example, the (–)-enantiomer of sotalol has both β-blocker and antiarrhythmic activity, whereas the (+)-enantiomer has antiarrhythmic properties but lacks β-adrenergic antagonism.[3,4] In addition, the R-enantiomer of fluoxetine, at its highest administered dose, led to statistically significant prolongation of cardiac repolarization in phase II studies; the studies were subsequently stopped.[5]

Currently, there is no regulatory mandate in the United States or Europe to develop new drugs exclusively as single enantiomers. The U.S. Food and Drug Administration (FDA) policy regarding single enantiomers was published in 1992. This statement is available at the FDA Web site at www.fda.gov/cder/guidance/stereo.htm. The FDA leaves the decision to pursue a racemic or a single-enantiomer formulation of a new drug to its developers, but the choice of a racemic versus a single-enantiomer formulation must be justified. Although both racemic and single-enantiomer drugs will continue to be developed, a higher proportion of single enantiomers are being submitted for new drug approval.[6]

Although many psychotropic drugs are either achiral (e.g., fluvoxamine, nefazodone) or are already marketed as single enantiomers (e.g., sertraline, paroxetine, escitalopram), a number of antidepressants are currently marketed as racemates, including bupropion, citalopram, fluoxetine, tranylcypromine, trimipramine, and venlafaxine. Other drugs often used in psychiatric practice including zopiclone, methylphenidate, and some phenothiazines are also available as racemates. Of these, single-enantiomer formulations are being developed for bupropion and zopiclone. Dexmethylphenidate (*d*-methylphenidate) has also been introduced recently. Selected racemic drugs used in psychiatric practice are listed in Table 1. An instructive comparison can be made between the development of the single-enantiomer formulations of citalopram and fluoxetine. In both cases, one enantiomer appeared to have superior in vivo properties, and clinical trials were conducted to determine the safety and efficacy of (*S*)-citalopram and (*R*)-fluoxetine.

In the case of citalopram, the *S*-enantiomer is primarily responsible for antagonism of serotonin reuptake while the *R*-enantiomer is 30-fold less potent.[7] In clinical trials, both racemic (*R*,*S*)-citalopram (marketed as Celexa) and (*S*)-citalopram (marketed as Lexapro) were significantly better than placebo for improving depression.[8–11] The early data suggest that (*S*)-citalopram has greater efficacy than (*R*,*S*)-citalopram at doses predicted to be equivalent as well as equal efficacy to (*R*,*S*)-citalopram at a dose that produces fewer side effects.[12,13] Overall, (*S*)-citalopram appears to have advantages over racemic citalopram and is a good example of the potential benefits of single-enantiomer drugs. However, there is currently no evidence that patients with major depression who are responding well to therapy with *R*,*S*-citalopram benefit from switching to *S*-citalopram.

In contrast, the attempt to develop a single-enantiomer formulation of fluoxetine for the treatment of depression was unsuccessful. While (*R*)-fluoxetine and (*S*)-fluoxetine are similarly effective at blocking serotonin reuptake, they are metabolized differently.[5] The use of the *R*-enantiomer was expected to result in less variable plasma levels of fluoxetine and its active metabolites than observed with racemic fluoxetine. Additionally, (*R*)-fluoxetine and its metabolites inhibit CYP2D6, a cytochrome P450 system enzyme, to a lesser extent than (*S*)-fluoxetine and its metabolites.[14] As mentioned, in phase II studies of (*R*)-fluoxetine, the highest dose led to statistically significant prolongation of cardiac repolarization, and the studies were

stopped.[5] Although racemic fluoxetine has been shown to be a safe and effective antidepressant for over 15 years, the (*R*)-enantiomer formulation was not viable due to safety concerns. The experience with (*S*)-citalopram and (*R*)-fluoxetine highlight the potential differences between enantiomers of a given chiral drug and the need to consider single-enantiomer formulations of a previously racemic drug on a case-by-case basis.

SUMMARY

The increasing availability of single-enantiomer drugs promises to provide clinicians with safer, better-tolerated, and more efficacious medications for treating patients. It is incumbent upon the practicing physician to be familiar with the basic characteristics of chiral pharmaceuticals discussed in this article. In particular, each enantiomer of a given chiral drug may have its own particular pharmacologic profile, and a single-enantiomer formulation of a drug may possess different properties than the racemic formulation of the same drug. When both a single-enantiomer and a racemic formulation of a drug are available, the information from clinical trials and clinical experience should be used to decide which formulation is most appropriate.

Drug names: albuterol (Ventolin, Proventil, and others), bupropion (Wellbutrin and others), citalopram (Celexa), dexmethylphenidate (Focalin), escitalopram (Lexapro), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), methylphenidate (Ritalin, Concerta, and others), nefazodone (Serzone), omeprazole (Prilosec and others), paroxetine (Paxil), sertraline (Zoloft), tranylcypromine (Parnate), trimipramine (Surmontil), venlafaxine (Effexor).

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