Mirror, Mirror on the Wall . . . Stereochemistry in Therapeutics

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Steroisomers are molecules that have the same structural formulas but differ in the orientation of their individual atoms in space.1-3 A special form of isomerism occurs when an individual atom, or chiral center (usually a carbon), has four different substituents arranged in a tetrahedral fashion. In this case, two mirror-image orientations, called enantiomers, of these substituents around the chiral center are possible. Enantiomers are identified by the way in which they rotate polarized light: the terms dextrorotatory (d- or [+] -enantiomer) and levorotary (l- or [−]-enantiomer) are used, as is an alternate (and not interchangeable) system in which enantiomers are more rigorously termed R- and S-.1 A number of drugs are prescribed as individual enantiomers: l-timolol and levothyroxine are examples. However, enantiospecific therapy is actually quite rare, and up to half of the drugs prescribed in the United States are racemates, 50-50 mixtures of enantiomers.

The effects of drugs are frequently mediated by binding to specific target receptors, a process that may have strict conformational requirements. Thus, it is not surprising that individual enantiomers, which exist in different spatial orientations, may exert different pharmacological effects. For example, virtually all β-blocker molecules contain a chiral carbon adjacent to an aromatic ring; l-enantiomers are orders of magnitude more potent than d-enantiomers as β-blockers, so the clinical actions of racemic β-blockers are attributable to their l-enantiomers. Moreover, since drug metabolism may also depend on drug binding to specific protein molecules, such as those responsible for hepatic oxidative reactions, it is not surprising that enantiomers may be metabolized or eliminated at different rates.2-3 It has been argued that treatment with racemic drugs in effect constitutes treatment with a fixed combination of drugs with different pharmacological properties and different potentials for toxicity.4-5 Thus, regulatory agencies are considering new guidelines with regard to the preclinical evaluation of racemic drugs,6 and the development of individual enantiomers of existing drugs has been advocated. Kroemer and his colleagues7 now report an interesting and important contribution in this area, using the antiarrhythmic agent propafenone as a model drug.

Propafenone’s major metabolite is 5-hydroxy propafenone, which is roughly equipotent to the parent drug as a sodium channel blocker8-10; the N-desalkyl form is less potent, and its plasma concentrations are relatively low. During long-term therapy, the plasma concentration of 5-hydroxy propafenone may accumulate to levels as high as those of the parent drug, so it is likely that some of the electrophysiological actions of propafenone therapy are mediated by both the parent drug and the metabolite. Importantly, however, the parent molecule is a much more potent β-blocker in vitro than is either metabolite11; as with other β-blockers, one enantiomer, S-(+)-propafenone, is much more potent a β-blocker than the other, R-(−)-propafenone.12,13

Why, then, doesn’t everyone develop evidence of β-blockade during propafenone treatment?14-17 The answer lies in our evolving understanding of the molecular determinants of drug metabolism. Propafenone is 5-hydroxylated by a single hepatic enzyme, called CYP2D6 (or P4502D6). This isozyme is variably expressed in human liver, and mutations and/or abnormalities of alternative splicing of the CYP2D6 gene product lead to the absence of functional protein18,19 in approximately 7% to 10% of whites20,21 and 2% of American blacks.22 The concept of heritable abnormalities of drug-metabolizing enzymes was described in the 1950s23-25; the CYP2D6 polymorphism was first described in the late 1970s, when impaired biotransformation of debrisoquin, an antihypertensive, led to marked hypotension at low drug doses.26 Debrisoquin 4-hydroxylase (CYP2D6) is now known to be a major enzyme in the metabolism of more than 30 drugs, including metoprolol, enacainide, many tricyclic antidepressants, and codeine.21 In “poor metabolizers” (PMs) receiving propafenone, the parent molecule is cleared very slowly, so it accumulates in plasma, and β-blockade is readily demonstrable.11 In fact, side effects during propafenone therapy are significantly more common in PMs than in subjects with the much more common “extensive metabolizer” (EM) phenotype, which may reflect the disproportionately elevated plasma propafenone concentrations observed in PM subjects.27 However, EM subjects are not immune from β-blockade; when they receive other drugs that inhibit CYP2D6, plasma propafenone concentrations rise,28 and β-blockade becomes evident or exaggerated.29 Thus, the apparently “idiiosyncratic” development of an important side effect during drug treatment can now be attributed to genetic factors interacting, in many cases, with polypharmacy. Common drugs that are now known to inhibit CYP2D6 include quinidine and fluoxetine (Prozac).28-31

Given this degree of complexity in propafenone’s clinical pharmacokinetics, one might well ask whether

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this is an example in which therapy with individual enantiomers might be justified. Kroemer and his colleagues have previously reported that R-propafenone inhibits the CYP2D6-mediated metabolism of S-propafenone in vitro. In the present study, they asked whether such an enantiomer/enantiomer interaction occurs in human subjects. In the study reported in this issue of Circulation, they found that, indeed, there is a striking interaction of this type. In seven subjects, all known to have the EM phenotype, plasma concentrations of the β-blocking enantiomer S-propafenone were in fact higher during treatment with 150 mg every 6 hours of the racemate (which contains only 75 mg of S-propafenone) than they were during treatment with 150 mg every 6 hours of S-propafenone alone. Importantly, there was a reasonable correspondence between elevated plasma concentrations of S-propafenone and indexes of β-blockade. They excluded a number of possible potential confounding factors, such as variable absorption or racemization in vivo (a phenomenon whereby administration of a pure enantiomer results in formation of the opposite enantiomer). Thus, it seems likely that, as in vitro, R-propafenone inhibits the CYP2D6-mediated metabolism of S-propafenone.

The findings have somewhat limited implications for whether or not enantiomer-specific therapy should be considered in the case of propafenone. The data indicate that to achieve β-blockade and sodium channel blockade during enantiomer-specific therapy with S-propafenone, much higher dosages than previously anticipated would be required. One could argue that a molecule with multiple actions might be undesirable, so if enantiomer-specific therapy is preferred, it should be with the non-β-blocking R-enantiomer; in fact, this is the rationale underlying current efforts to develop d-sotalol, the very weak β-blocking enantiomer of racemic sotalol, which nevertheless preserves the racemate's other electrophysiological actions. In either case, should β-blockade be desired, a β-blocker could be administered separately.

The study is an important addition to the growing body of knowledge that will be used to set standards about enantiomer-specific therapy. Although the concept does have attractions, there are practical difficulties in its implementation. These include potential difficulties in synthesizing pure enantiomers as well as the possibility of racemization in vivo. The present study also demonstrates that the effects of therapy with a racemate may not necessarily be determined by simply summing the effects of the individual enantiomers.

Thus, programs to develop enantiomer-specific therapy from existing racemates must take cognizance of the phenomenon reported here by Kroemer et al. It is also not far-fetched to speculate that enantiomer/enantiomer interactions may occur not only at drug-metabolizing enzymes but also at other molecules, such as enzymes, receptors, or ion channels, which drugs target. Indeed, an analogous interaction between a parent drug and its metabolite has been described for lidocaine block of the sodium channel. In addition, other mechanisms for enantiomer/enantiomer interactions are possible: for example, the clearance of racemic propranolol is lower than that of d-propranolol, not because of a competitive metabolic interaction but because β-blockade (due to l-propranolol) decreases liver blood flow, which in turn decreases the clearance of the racemate.

A generic problem that the discipline of clinical pharmacology addresses is the definition of the sources of individual variability in response to drug therapy in human beings. Thus, perhaps the most important lesson of the study reported by Kroemer and colleagues is that well-conducted in vitro experimentation can be used both to understand mechanisms of variable responses to drug therapy and to suggest experiments to validate those mechanisms in human beings. With the cloning of individual molecules responsible for drug actions, such as specific P450s, ion channels, receptors, and other proteins, will come the development of new tools that we hope will allow us to make the "idiiosyncratic" drug reaction a relic of our ignorant past.

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