

Chirality – Today and Tomorrow’s Way of Treatment

P. Bhandari, C. Shah, S. Surwade

Introduction

An object is “chiral” if and only if it is not superimposable on its mirror image.¹ “Chiral” refers to the spatial orientation of objects including molecules. Molecules must interact with receptors, enzymes and binding sites for absorption, distribution, metabolism, excretion and action. This interaction is stereospecific and depends on how closely the three dimensional structure interacts or fits onto the three dimensional receptor or binding site.² Thus similar looking mirror images may not behave in same manner with respect to such binding sites. Just as one would not wear a right shoe on the left foot or a right handed person would not try to write with the left hand, the orientation of molecules is vital for proper pharmacokinetics (what body does to the drug) and pharmacodynamics (what drug does to the body).

In fact, mixtures of enantiomers available as racemate drugs are actually fixed-dose combinations of two different molecules³ (as regards to their action with binding sites), and pose as much irrationality

as many fixed-dose combinations of different drugs we are aware of.

The science of “chirality” includes the synthesis of single enantiomers, their intermediates and chiral “switches”. In a “chiral switch”, the more useful enantiomer is isolated from the mixture (racemate) and presented as an improved single enantiomer chemical entity. The term “*unichiral*” is recommended to be used to specify the stereochemical composition as stereochemically homogeneous, i.e., consisting of a single-enantiomer. The word “homochiral” has also been used to mean “unichiral”.¹

Why chirality is important?

In an analysis of all single enantiomer drugs launched as a percentage of chiral molecules, the ratio increased from 31.6% in 1985-1988 to 89.8% in 2001-2004 (Fig. 1).⁴ It is estimated that sales of unichiral drugs could reach \$200 billion in 2008.² A number of factors have contributed to the introduction and popularity of unichiral products since 1980 and more so 1992 onwards. These are: introduction of enantioselective analytical methods, new synthetic methods for unichiral molecules, chromatographic methods for separation and more importantly US FDA statement in 1992 stating that development of racemates would require justification for inclusion of both the isomers.^{1,3}

Table I : Glossary

Chiral: not superimposable on mirror image

Racemate: mixture of two or more enantiomers

Enantiomer: Single isomer not superimposable on its mirror image. Also called ‘unichiral’.

Eutomer: active isomer

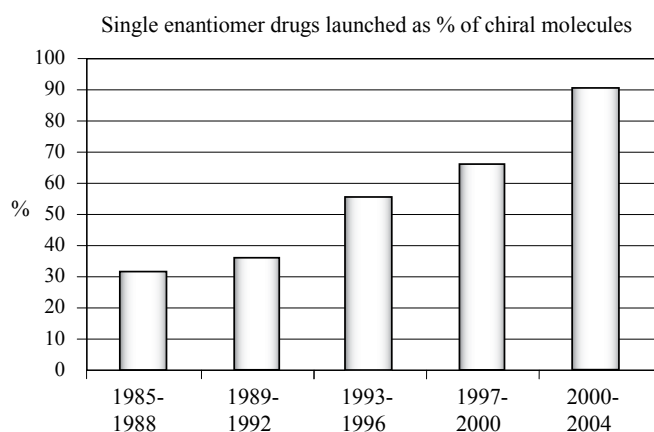
Figure 1 : Nature is chiral

Our hands and feet are chiral - the right is a mirror image of the left and not superimposable.

The fragrance of oranges and lemons is due to S(-) Limonene. R(+) Limonene has a turpentine like odor!

Our bodies can only metabolize (+) glucose and not (-) glucose.

(+) leucine tastes sweet while (-) leucine bitter.

Figure 2: Percentage of single enantiomer drugs against chiral molecules launched from 1985-2004.

Example of how enantiomers differ

An elegant review on the differential properties of different enantiomers of commercially available racemates appears in the Journal of Indian Medical Association.⁵ One recent example of dexrabeprazole is discussed here. The structure of the two enantiomers of rabeprazole (usually present in racemate as 1:1 mixture) is presented in Table 2. Simply stated, the lone pair bond (from the S to the 2 electrons) is either looking towards the reader or away, in three dimension. This alters the spatial configuration of the molecule and hence its interactions with sites controlling absorption, distribution, metabolism

Table 2 : Differential properties of Rabeprazole enantiomers

	Dexrabeprazole	Levorabeprazole
Structure		
Configuration	R	S
Optical rotation	Dextro-rotatory	Levo-rotatory
C-max in healthy volunteers (ng/ml) ¹¹	576.106 ± 50.68	234.52 ± 83.40
AUC _{0-t} in healthy volunteers (ng/ml*hr) ¹¹	1972.18 ± 417.63	460.35 ± 227.56
Half-life in healthy volunteers (hr) ¹¹	2.74 ± 0.11	1.57 ± 0.89
Isomer to racemate ratio of inhibition of ulcers in aspirin-induced ulcers in rat model ¹²	1.93±0.9	1.04±0.2

All values are expressed as mean ± standard deviation

etc. Although in case of PPIs, the final active moiety is an achiral 'sulfenamide', the kinetics of the enantiomer determines the availability of the sulfenamide.⁵ This chirality of PPIs has led to the introduction of esomeprazole, S-pantoprazole and dexrabeprazole.

In case of rabeprazole, in GERD patients with esophagitis, after 28 days of therapy with either the racemate (20 mg) or the R(+) isomer (dexrabeprazole) at half-the racemate dose (i.e. 10 mg), there were fewer patients with residual esophagitis in the dexrabeprazole group compared to the racemate. The absolute risk reduction was 27% with a relative improvement of 42% and number needed to treat (NNT) of only 4. In patients with residual esophagitis, most patients in the dexrabeprazole group showed signs of healing or improvement compared to the rabeprazole group. The absolute risk reduction was 30% with a relative improvement of 46% and

NNT of only 3. The difference was statistically significant ($p=0.036$).⁶

More examples of differential properties of enantiomers

Of the two enantiomers in a racemate, one may be inactive, or more active, or having different action, or opposite actions as illustrated below:

Only one isomer is active, the other is "inactive": Levocetirizine (active), Levofloxacin (active), S-amlodipine (active).²

One isomer is active, the other has "more activity": S-pantoprazole (more potent), Esomeprazole (more potent).⁵

Beneficial effects reside in one enantiomer, the other enantiomer having antagonistic activity: Levo-salbutamol (bronchodilator without pro-inflammatory properties).⁷

Beneficial effects reside in one enantiomer, the other enantiomer having adverse activity: Esketamine (no hallucination/agitation), Levobupivacaine (no cardiotoxicity).²

How single enantiomers may be 'safer' than racemates

Chiral purification has introduced many safer alternatives to existing racemates. Some of the examples⁸ are:

- Levocetirizine - a more selective and less sedative enantiomer
- S-amlodipine – anti-hypertensive isomer with negligible pedal edema
- S-metoprolol – anti-hypertensive without beta-2 blocking R-isomer
- R-ondansetron – free from QTc prolongation of the racemate / S-isomer
- Levosalbutamol- bronchodilator without pro-inflammatory component
- Levobupivacaine – local anesthetic with lesser CNS and cardiac toxicity

- Eszopiclone – hypnosis with fewer hangovers

Some recent unichiral introductions in India

S-amlodipine : This provides the active CCB component only with longer half-life and consistent pharmacokinetics due to less inter-subject variability of S-isomer compared to R-isomer, at half the racemate dose, with less metabolic load. Importantly it prevents accumulation of R-amlodipine in elderly, and causes negligible pedal edema. The average incidence of pedal edema observed in the different SESA trials ($n=5165$) ranged from 0.75% to 1.93% with a mean of 1.36%.⁹

S-atenolol : This enantiomer provides the active beta-1 blocker component only, at half the racemate dose, and lesser side-effects on switch-over from racemate to eutomer (active isomer).⁸

S-metoprolol : This provides the beta-1 blocker component only, at half the racemate dose, avoiding the beta-2 blocking component, and can be administered at high doses without causing beta-2 receptor mediated side effects. It is safer in poor metabolizers of CYP2D6, and avoids many drug-drug interactions.⁷

S-pantoprazole : This provides the more potent and cytoprotective component of pantoprazole, at half the racemate dose, with consistent pharmacokinetics. It does not accumulate in poor metabolizers, and offers lesser potential for drug interactions.⁵

R-ondansetron : This is the clinically more potent component, at half the racemate dose. It does not prolong QTc interval, hence safer in children and elderly, and offers lesser side-effects.⁸

Eszopiclone : The S isomer of zopiclone causes lesser number of anticholinergic side effects as compared to racemic zopiclone.⁸

Dexibuprofen : Active NSAID enantiomer offering higher gastric safety.¹⁰

Critical issues in Chirality

Where enantiomers are involved in opposite actions as in case of beta-blockers, it is not rationale to allow these “fixed-dose combinations” of enantiomers to continue simply because they have existed for a long time as racemates e.g. metoprolol. When enantiomers exist apparently as “inactive” components, the impact of these on the metabolic system and how they compete with or inhibit the action of the metabolizing enzymes need to be assessed. Proper selection of enantiomers may allow matching drugs to poor or extensive metabolizers (e.g. S-metoprolol may be administered to either poor or extensive metabolizers without risk of accumulation of R-isomer in poor metabolizers⁷). The separation of enantiomers in itself does not guarantee introductions of better molecules. Each isomer need to undergo toxicology, pharmacokinetics and clinical evaluation before any benefit can be attributed to the single enantiomer. In some cases enantiomer separation is not required as in with nebivolol or labetolol.

Conclusion

This article has highlighted the growing impact of single enantiomer drugs in therapeutics. Physicians need to reassess the rationality of existing racemates and also determine the clinical value of recent single enantiomer introductions.

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