

DEVELOPMENT OF SAFER MOLECULES THROUGH CHIRALITY

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ABSTRACT

Many of the drugs currently used in medical practice are mixtures of enantiomers (racemates). Many a times, the two enantiomers differ in their pharmacokinetic and pharmacodynamic properties. Replacing existing racemates with single isomers has resulted in improved safety and/or efficacy profile of various racemates. In this review, pharmacokinetic and pharmacodynamic implications of chirality are discussed in brief, followed by an overview of some important chiral switches that have yielded safer alternatives. These include levosalbutamol, S-ketamine, levobupivacaine, S-zopiclone, levocetirizine, S-amlodipine, S-atenolol, S-metoprolol, S-omeprazole, S-pantoprazole and R-ondansetron. Few potential chiral switches under evaluation and some chiral switches that have not been successful are also discussed.

Key words: Chiral switch, enantiomer, racemate, safety

Alternatives to existing molecules are developed with the ultimate objective of increasing efficacy and/or enhancing safety, in view of limitations of modern therapeutic agents. The quest for enhancing the efficacy and safety profile of modern therapeutic agents has made the medical fraternity witness an array of generations of drugs in almost all therapeutic areas. Drugs like thalidomide, cisapride, terfenadine had fallen back due to safety concerns despite their

promising efficacy. From time to time, structural changes in existing drugs had opened up safer alternatives. One of the currently adapted modalities to enhance safety and/or efficacy of existing agents is the 'Chiral Switch.' Switching from existing racemate to one of its isomers has provided safer alternatives to drugs ranging from antihistaminics like cetirizine to anesthetics like ketamine. 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 medical fraternity to be familiar with the newly introduced chiral switches and their rationale. This review discusses basics of chirality, its pharmacokinetic and pharmacodynamic implications and how chirality is used for

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development of safer alternatives to existing racemates.

Basics of chirality^[1-4]

Compounds can be chiral or achiral (non-chiral). Chiral compounds possess the property of handedness, i.e., they may be right-handed or left-handed. These two - left- and right-handed - forms of a chiral compound are identical in their structural formulas but differ in spatial arrangement so that one form is exactly a mirror image of the other but the two forms are not superimposable on one another. This is akin to pair of gloves, socks or hands. An achiral object exists only in one form and there is no possibility of left- or right-handedness. This existence of left- or right-handedness of a compound is referred to as chirality. Chirality or asymmetry can arise in several ways in a molecule but most commonly it is due to the presence of an asymmetric carbon (most common), nitrogen or sulfur in the molecule. An asymmetric carbon atom is one to which four different atoms or groups (ligands) are attached. This carbon atom exists in two different spatial orientations in a manner that ligands in one orientation are not superimposable on ligands of the other. Asymmetric carbon thus imparts left- or right-handedness to the molecule. Figure 1 depicts chiral structure of ibuprofen.

Each form (left- or right-handed) of a chiral compound is called an 'enantiomer' or an 'isomer.' The enantiomers are denoted as R or S according to 'absolute descriptor' convention proposed by Cahn, Prelog and Ingold or they are denoted as dextro (+) or levo (-) depending on clockwise or anticlockwise rotation of plane-polarized light by them respectively. The two systems of

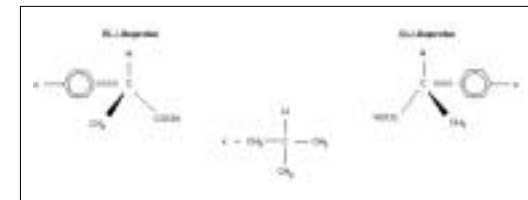


Figure 1: Chiral structure of ibuprofen

nomenclature are mutually exclusive. R enantiomer of one compound may be dextrorotatory, while another compound may have its S enantiomer as dextrorotatory.

A collection containing only one enantiomeric form of a chiral molecule is called an optically pure, chirally pure or enantiomerically pure compound, while collection of equal amounts of the two enantiomeric forms is called a racemate [Figure 2].

Pharmacokinetic and pharmacodynamic implications of chirality

All the pharmacokinetic processes, viz, absorption, distribution, metabolism and excretion may be influenced by chirality. Active transport processes may discriminate between the enantiomers, with implications on bioavailability - e.g., esomeprazole is more bioavailable than racemic omeprazole.^[5] The volume of distribution of levocetirizine has been shown to be significantly smaller than that of its dextro enantiomer, which is a positive aspect in terms of both safety and

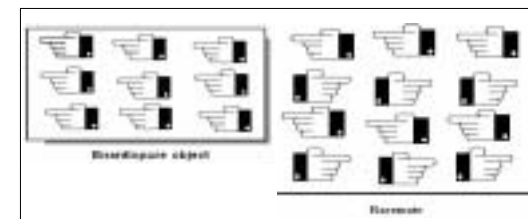


Figure 2: An optically pure compound and a racemate

efficacy.^[6] Drug metabolizing enzyme systems are also subject to stereoselective influences. Two isomers of a drug are often metabolized at different rates. This may result in accumulation of the inactive enantiomer or rapid elimination of the active one and vice versa. Two isomers of a drug also induce or inhibit the cytochrome enzymes stereoselectively.

The phenomenon of 'Chiral Inversion' adds to the complexity. Chiral inversion is conversion of one enantiomer into its mirror image. For example, the S form of ibuprofen is active but significant R (inactive enantiomer) to S inversion takes place in the body.^[7] Therefore, a certain amount of S-ibuprofen is theoretically expected to be less effective than the racemate containing similar amount of S-ibuprofen. Clinical studies have however shown a superior efficacy and enhanced safety with S-enantiomer as compared to that of the racemate containing similar amount of S-ibuprofen.^[8] Harmful intermediates are released during R-to-S conversion upon administration of racemate, whereas administration of S-ibuprofen results in no such release of intermediates as it does not undergo chiral inversion. This is thought to be the reason of enhanced safety of S-ibuprofen over the racemate.^[9] S-thalidomide exhibits teratogenic effect whereas R thalidomide is sedative. However, the individual enantiomers of thalidomide are both inverted rapidly to the racemic mixture in the liver. Hence the claims that R-thalidomide could be safer and that the thalidomide tragedy could have been prevented by using single R-enantiomer of thalidomide are not valid.^[10] Many drugs, however, do not undergo chiral inversion, e.g.,

S-amlodipine.^[11] The single active enantiomers hold promise only if it is proved that they don't undergo chiral inversion to a significant extent.

Pharmacodynamic implications of chirality could be easily understood with the example of a drug-receptor model as depicted in Figure 3. As the two isomers of a drug have different spatial configurations, their complementary binding sites are also expected to be different. One isomer may bind precisely to the target sites (receptor, enzyme, etc.), while the other may have an imprecise binding. This inactive isomer (commonly referred to as 'distomer') may bind precisely to other sites that are not the intended targets. In this way, whenever a drug exists as a racemate, the one isomer may be active while the other isomer may have:

1. No activity.
2. Some activity.
3. Antagonistic activity.
4. A completely separate beneficial activity.
5. A completely separate adverse activity.

Putting chirality to work for drug safety

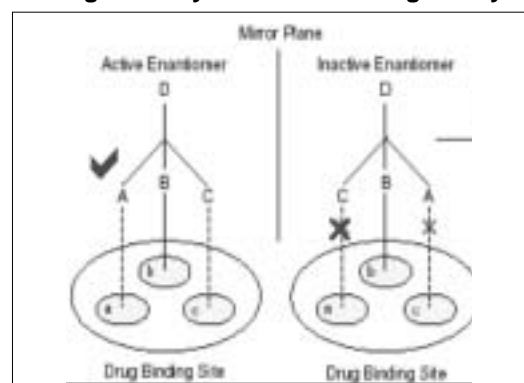


Figure 3: Stereoselective binding of enantiomers (Source: Primary Care Companion J Clin Psychiatry 2003;5:70-73)

Pharmacokinetic differences result in different spectra of interactions for the two isomers. Pharmacokinetic differences may also result in one isomer being retained more in poor metabolizers than its counterpart. Activity at undesired targets is a pharmacodynamic mechanism of adverse effects due to the distomer. The idea of investigating single stereoisomers following the observation of unacceptable adverse effects with the racemate is not new. D-penicillamine, dextromethorphan and levodopa are well-known examples where the other isomer is associated with adverse effects and hence not used. Following are some recent examples where single isomers have enhanced safety profile over the racemate.

Levosalbutamol: Salbutamol salvaged from its antagonist

The bronchodilator activity of racemic salbutamol resides in its levorotatory R enantiomer and the dextrorotatory S enantiomer has been found to be virtually inactive at therapeutic concentrations.^[12] To add to this, later studies have found that the S enantiomer is not completely inert; it rather induces airway hyper-reactivity, eventually contributing to increased morbidity and mortality in patients with asthma.^[13,14] Clinical studies have shown that it is at least twice as potent as the racemate.^[15,16]

Esketamine: Anesthesia with smoother recovery

In vitro and *in vivo* anesthetic and analgesic pharmacological studies have shown that S-ketamine is two to three times more potent than racemic ketamine.^[17,18] Furthermore, S-

ketamine is eliminated more rapidly as a single enantiomer than as a component of the racemate since R-ketamine inhibits the elimination of S-ketamine.^[19] Thus the recovery time after S-ketamine is shorter than that after the racemate, which is a favorable property for an anesthetic agent. In clinical studies, use of S-ketamine was associated with a remarkably smoother emergence period, a profound postoperative analgesia and a more rapid recovery of cerebral functions. The incidence of psychotomimetic phenomena was negligibly less after S-ketamine in comparison to racemic ketamine.^[20]

Levobupivacaine: The active bupivacaine with less CNS and cardiac toxicity

Bupivacaine has been the most widely used local anesthetic for years. *In vitro* animal studies show that levobupivacaine has less cardiotoxic effects and less toxic effects on the CNS in comparison with both dextrobupivacaine and bupivacaine itself.^[21] Studies in human volunteers confirmed these results. Equal potency of levo- and racemic bupivacaine as determined by MLAC (Minimum Local Anesthetic Concentration) in labor analgesia and reduced toxicity of levobupivacaine provide wider safety margin to levobupivacaine, making it a better alternative in daily clinical practice.^[22] The levorotatory derivative of bupivacaine, ropivacaine, is also a safer alternative to bupivacaine.^[23]

Eszopiclone: Hypnosis with fewer hangovers

Eszopiclone (S-zopiclone), a nonbenzodiazepine hypnotic agent, is the

dextrorotatory enantiomer of racemic zopiclone. Preclinical studies have demonstrated that S-zopiclone is more active than R-zopiclone at the benzodiazepine receptor complex and is responsible for most of the hypnotic activity of the racemic compound.^[24,25] Eszopiclone has a shorter duration of action, which could minimize or prevent residual hangover effects.^[26] Preclinical data also suggest a significantly lower propensity for its anticholinergic effects than that of the R-enantiomer.^[25]

Levocetirizine: Cetirizine made more selective and less sedative

Levocetirizine, the active R-enantiomer of cetirizine - with its smaller volume of distribution, smaller even than that of cetirizine - confers improved safety because of low hemato-encephalic barrier passage and low cerebral receptor binding.^[27-29] Exclusion of the S-enantiomer leads not only to enhanced peripheral receptor binding compared with that of cetirizine but also improves overall selectivity specific to the H₁ receptor.^[30] Gandon JM and Allain H analyzed the effects of single and multiple doses of levocetirizine on CNS using integrated measures of cognitive as well as psychometric performance in 19 healthy male volunteers and concluded that levocetirizine does not produce any deleterious effect on these functions.^[31] Though pharmacokinetic studies indicate improved safety profile of levocetirizine, data on head-to-head comparison of safety of levocetirizine versus the racemate is sparse. A study in 20 healthy volunteers found that both levocetirizine and racemic cetirizine were free from psychomotor and cognitive impairment.^[32] In view of the

inactive nature of the dextro enantiomer and the favorable pharmacokinetics of levocetirizine, the switch from cetirizine to levocetirizine is expected to be safer; large-scale comparative studies are, however, warranted to address the issue.

S-amlodipine: The safer and longer-acting amlodipine

Vasodilating property of amlodipine resides in its S-enantiomer.^[33,34] The R-enantiomer, although inactive as a calcium channel blocker, may not be completely inert. Clinical studies have shown that lower extremity edema associated with amlodipine was resolved in most of the patients when they were shifted to S-amlodipine.^[35,36] Overall incidence of edema with S-amlodipine has been reported to be 1.39% as against the reported incidence ranging from 1.7 to 32% with racemic amlodipine.^[36,37] This indicates that R-amlodipine component of amlodipine is mainly responsible for blunting of precapillary postural vasoconstrictor reflex and for other local changes responsible for peripheral edema due to amlodipine. Plasma half-life of S-amlodipine is also reported to be longer than that of racemic amlodipine. Longer duration of action of S-amlodipine is expected to further reduce the chances of reflex tachycardia.^[11,38] Moreover, the clearance of S-amlodipine is subjected to much less inter-subject variation than R-amlodipine.^[11] S-amlodipine is thus a safer and longer-acting alternative to the existing racemate.

S-atenolol and S-metoprolol: Beta blockers with improved beta-1 selectivity
Although beta blockers are clinically used for their selective beta-1-antagonist effect, the

majority actually appear to have rather poor beta-1/beta-2 selectivity.^[39] Cardiosensitivity of beta blockers is compromised at higher doses, resulting in adverse effects of beta-2 blockade which are particularly of concern in asthmatics, smokers, COPD patients and diabetics.^[40] As with most of the beta blockers, cardiac beta-blocking activity of atenolol and metoprolol resides predominantly in their S-enantiomers.^[41] R-enantiomers of beta blockers have been shown to possess relatively stronger activity in blocking beta-2 receptors.^[42] This higher affinity of R-enantiomer for beta-2 receptors may be a cause of loss of cardiosensitivity at higher doses.

Use of single S-isomers of atenolol and metoprolol is expected to preserve cardiosensitivity even at high doses as the beta-2-blocking R-isomer is absent. Genetic polymorphism in the metoprolol-metabolizing enzyme CYP2D6 increases the chances of loss of cardiosensitivity in poor metabolizers even at normal doses.^[43,44] Interestingly, clearance of R-metoprolol is slower than S-metoprolol in poor metabolizers, resulting in higher concentrations of the non-selective R-enantiomer if a racemate is administered.^[45,46] Use of single S-enantiomer is expected to ensure cardiosensitivity even in poor metabolizers as concentrations of only the beta-1-selective component would be increased. Use of S-metoprolol also avoids some harmful drug-interactions with some drugs like paroxetine, cimetidine, ciprofloxacin and verapamil, which selectively increase the concentrations of non-selective R-metoprolol.^[47-50]

S-atenolol and S-metoprolol have been found to be as effective as double-dosed racemates in reducing blood pressure and heart rate.^[51-54]

Esomeprazole and S-pantoprazole: Safety potentially enhanced through pharmacokinetic consistency

S-enantiomers of omeprazole and pantoprazole are found to be more effective than the corresponding racemates,^[5,55,56] though marked differences have not been observed in the safety profile of the single isomer and racemate preparations. However, R-enantiomers of both the proton pump inhibitors exhibit greater variability than their S-isomers in poor versus extensive metabolizers of CYP2C19 substrates. R-enantiomers of both the drugs are more dependent on CYP2C19, whereas the S-enantiomers could be metabolized by alternative pathways like CYP3A4 and sulfotransferases. This results in the less active R-enantiomer achieving higher concentrations in poor metabolizers, which may in the long term cause adverse effects like gastric carcinoids and enterochromaffin-like cell hyperplasia.^[57,58]

R-ondansetron: Free of QT_c-prolonging potential of racemate

Significant QT_c prolongation has been reported with 5-HT₃ receptor antagonists including ondansetron. Although the recorded QT_c interval is less than that deemed to pose a risk of cardiovascular death, it is reasonable to assume that co-administration of ondansetron with medications that also prolong this interval would produce additive

prolongation of QT_c interval, increasing the risk.^[59] In an experimental study in dogs, it was found that QT_c was very prolonged among animals receiving S-ondansetron and racemic ondansetron and least prolonged among animals receiving R-ondansetron.^[60] Significantly, two of the four dogs receiving S-ondansetron died during or shortly after the experiment, whereas all the dogs receiving the R-stereoisomer or the racemate survived. R-ondansetron was thus shown to have less cardiotoxicity than either S-ondansetron or racemic ondansetron. One more recent study conducted in rats demonstrated that S-enantiomer of ondansetron is responsible for QT_c prolongation and R-ondansetron produced no QT_c prolongation.^[61] It may be noted that R-ondansetron is clinically more potent than the S isomer and clinical studies have found that the effective dose is half of the racemate in treatment of nausea and vomiting.^[62] Thus a switch-over to its single R isomer from racemic ondansetron provides a potentially safer antiemetic alternative.

Safer single-isomer alternatives under evaluation

S-doxazosin

Dizziness and fainting due to hypotensive episodes are adverse effects of doxazosin, an alpha-1 adrenoceptor antagonist used for treatment of benign prostatic hyperplasia. S-doxazosin is thought to be selective for prostate receptors and at the same time expected to have lower incidence of hypotension.

S-oxybutynin

Racemic oxybutynin is used clinically to treat urinary incontinence and reportedly

undergoes N-deethylation to metabolites R- and/or S-desethyloxybutynin. RS- and R-oxybutynin and RS- and R-desethyloxybutynin exhibit high antimuscarinic activity relative to their antispasmodic activity, while S-oxybutynin and S-desethyloxybutynin exhibit relatively weak antimuscarinic activity. S-oxybutynin deserves consideration for development as a single-enantiomer drug for the treatment of urinary incontinence with a lower incidence of antimuscarinic side effects.^[63]

Dexnorcisapride

The dextrorotatory enantiomer of norcisapride, an active metabolite of cisapride, is a potentially safer alternative to cisapride, as preliminary studies have indicated that the former is devoid of various adverse effects seen with cisapride.^[64]

Examples where the chiral switch was no safer

Fenfluramine is a racemic drug used as an appetite suppressant. 'Fen-phen,' the combination of fenfluramine and the achiral anti-obesity drug phentermine, was widely used for weight loss. When dexfenfluramine, the S-enantiomer, came to the U.S. market in 1996, Fen-phen also came to mean the combination of dexfenfluramine and phentermine. Vigorous prescription of this new compound with the belief that the dextro isomer would be safer concealed the fatal adverse effects of fenfluramine which were retained in the dextro isomer. Both fenfluramine and dexfenfluramine were withdrawn from the market in 1997.^[65]

The single S-isomer of sotalol increased

mortality in patients with myocardial infarction. It should however be noted that S-isomer of sotalol is the non-beta-blocking isomer possessing class II anti-arrhythmic activity.^[66]

Development of single beta-blocking R,R-stereoisomer, named dilevalol, of labetalol was terminated due to adverse effects associated with hepatotoxicity.^[67] However, there are two chiral centers and hence four isomers in labetalol.

Pharmaceutical industry's role in chiral switches

Pharmaceutical companies are in the forefront of pharmaceutical research and are responsible for providing chirally pure products for clinical use. However, the acceptance of any molecule (including chiral switches) would depend solely on its advantages vis-à-vis already existing products. Launching of chirally pure products from the racemate that has been already promoted requires considerable amount of time and monetary investments on its chemical separation and clinical evaluation. Obviously, industry would ensure its returns on investments. Successful emergence of a safer and more efficacious chiral switch is a welcome innovation in the health care system and merits incentives in the form of patents.

CONCLUSION

Clinical use of racemic mixtures has been the accepted practice since years. This has been partly caused by an early general ignorance about the role of chirality in pharmacology

and later by the expense required to separate the stereoisomers on a large scale. With increasing knowledge about advantages of stereoselectivity, better methods have been developed to simplify the separation and preparation of stereoisomers. This has coincided with the regulatory authorities, like US-FDA, encouraging the development of single isomers.^[68] Rather than using chiral synthetic drugs as racemates in the first instance, the activities and toxicities of the enantiomers now need to be tested individually. It is now the responsibility of the innovator to show why a drug should not be used as the single active enantiomer by comparing its efficacy and toxicity with the racemate. Some recent chiral switches discussed above have provided safer and/or more effective alternatives to the existing racemates. Putting chirality to work for development of safer molecules has yielded successful results. Several more chiral switches are expected to replace the racemates with safer options, making drug therapy more effective and safer.

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Source of Support: Nil, **Conflict of Interest:** None declared.