Pharmacological Importance of Stereochemical Resolution of Enantiomeric Drugs

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Summary

Drug enantiomers have identical properties in an achiral environment, but should be considered as different chemical compounds. This is because they often differ considerably in potency, pharmacological activity and pharmacokinetic profile, since the molecules with which they interact in biological systems are also optically active. Within biological systems, the metabolism of one isomer may be via a different pathway or occur at a different rate from that of the other isomer. Preferential binding of one isomer to plasma proteins may cause differences in circulating free drug and hence alter concentrations at active sites. Interactions of both isomers may differ at the active sites through which pharmacological action is mediated. Actions and levels of activity of the stereoisomers in vivo may also differ. All the pharmacological activity may reside in a single enantiomer, whereas several possibilities exist for the other enantiomer – it may be inactive, have a qualitatively different effect, an antagonistic effect or produce greater toxicity. Two isomers may have nearly identical qualitative pharmacological activity, qualitatively similar pharmacological activity but quantitatively different potency, or qualitatively different pharmacological activity.

To avoid adverse effects and optimise the therapeutic value of enantiomeric drugs, it is necessary that methods for the resolution of racemates be evolved and devolved to determine isomeric purity, establish the effectiveness of isomers of the drug, and detect the presence of an enantiomer with lower therapeutic activity and undesirable adverse effects. Even if a drug is given as a pure enantiomer, methods to discriminate between enantiomers are required because racemisation can occur both in vitro and in vivo. Methods developed for resolution of drug enantiomers should facilitate routine testing of single isomers and their metabolites, studies of pharmacological, toxicological and clinical effectiveness, routine analysis of racemates, pure enantiomers or intermediates in manufacturing processes, and investigation of the potential for inversion of an enantiopure drug substance during the early stages of drug development and therapeutic drug monitoring.
Molecular chirality is a fundamental phenomenon that plays an important role in biological processes. A wide range of biological and physical functions are generated through precise molecular recognition because enzymes, receptors and other natural binding sites within biological systems interact with different enantiomers in decisively different ways. Consequently, pharmaceutical companies and drug regulatory bodies have become aware of the differential efficacy and tolerability of enantiomers of racemic drugs. This has lead some drug companies to develop drugs that comprise single enantiomers. Enantiomeric drugs have become increasingly important over the last 20 to 30 years, since about 56% of drugs currently in use are chiral compounds and 88% of these chiral synthetic drugs are used therapeutically as racemates. The purpose of this review is to highlight the problems of using racemic drugs and to note whether these can be minimised by using pure enantiomers.

1. Pharmacological Importance of Enantiomeric Drugs

Stereoisomeric discrimination is remarkable in biological systems where it is responsible for differences in physiological responses to the individual enantiomers of a given substrate and to the racemate as compared with the corresponding pure enantiomers. The stereoselectivity of a biological system results in between-enantiomer differences in affinity for the active site of receptor systems and enzymes. The degree of stereoselectivity increases with the number of interaction points of the drug with the active site. Drug actions requiring more than 2 points of interaction will have a higher degree of selectivity than a 2-point interaction.

It has become clear that enantiomeric drugs may differ in their pharmacodynamics and pharmacokinetics and both are important in describing the clinical pharmacology of chiral drugs. The following examples highlight how different enantiomers of the same compound may have widely differing physiological activity.

The stereoselectivity of the activity of propranolol (fig. 1) has been investigated for several pharmacological effects and diseases. Racemic propranolol and R-(+)-propranolol shift the haemoglobin-oxygen dissociation curve to the right in vitro. Similar results have been noted in patients being treated with usual doses of racemic propranolol. In hypertensive patients, the same daily doses of racemic propranolol and the non-β-blocking R-(+) isomer inhibited thrombin and arachidonic acid-induced platelet aggregation and thromboxane synthesis. However, only the β-blocking S-(−) enantiomer is effective in treating patients with angina.

Labetalol (fig. 2) is a diastereoisomer commercially available as equal proportions of 4 stereoisomers. Non-specific β1- and β2-blocking activity is predominantly conferred by the R,R isomer, while α1-blocking activity is produced by the S,R isomer. The other 2 isomers S,S and R,S probably contribute to drug activity, but to a much lower extent.

Tocainide (fig. 3) is a new antiarrhythmic racemic drug. In mice, the R-(−) enantiomer is 3 times more potent than S-(+) antipode as an antiarrhythmic drug. Tocainide is an example of a recently approved racemic drug for which negligible information about enantiomeric activity is available.