CHIRAL DRUGS: ONE DRUG OR TWO?

Clinical pharmacology through the looking glass: reflections on the racemate vs enantiomer debate

J. Mifsud

ABSTRACT

Most of the synthetic chiral agents administered as drugs are still marketed as racemic mixtures. Such drug enantiomers can differ substantially in their pharmacological, pharmacokinetic and toxic properties. The development of enantiomerically pure drugs would lead to better therapeutic indices, and less complex interactions. Thus, the re-realisation of the importance of stereochemistry in pharmacology has an important contribution to make to the development and use of safer and more effective medicines. The impact of chirality on drug development and registration policies is discussed.

Keywords: *Chiral, Drugs.*

INTRODUCTION

"Perhaps, looking glass milk isn't good to drink"
- Lewis Carroll in *Alice in Wonderland*

If told by their doctor that they were being prescribed tablets containing 50% of an impurity that is toxic or at best inactive, most patients would no doubt be horrified. This hypothetical state of affairs may seem somewhat bizarre, but the impression that the therapeutic use of drug racemates is harmful, has certainly gained ground in medical circles over the last few years.

Racemates are 50/50 mixtures of the left and right-handed forms or *enantiomers* of compounds, whose molecular structure lack symmetry because the central carbon atoms is surrounded by four different atoms or groups of atoms.

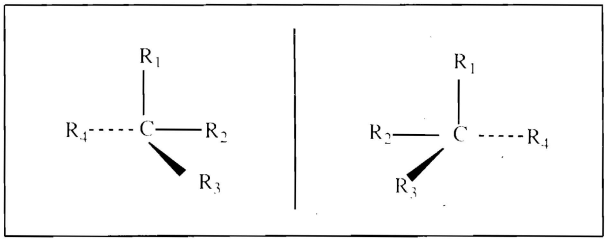

Figure I - The chiral carbon and its two mirror images

This phenomenon is called *chirality* - coming from the greek word "cherios" which refers to handedness i.e. being left or right handed. Enantiomers are mirror images and can be distinguished from the way they rotate polarized light, hence the (+)/(-) or (d)/(l) nomenclature. The accepted nomenclature today is the (R)/(S) system which is related to the Cahn-Ingold-Prelog Convention. Labetolol is just one of a number of chiral drugs and it has two chiral centres.

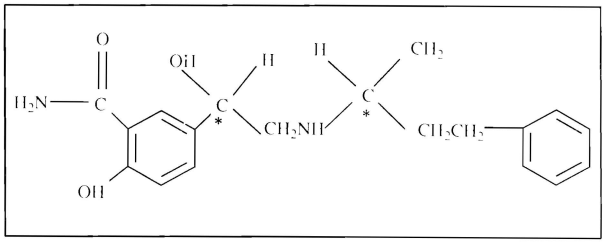

Figure II - The chemical structure of labetolol.
*:chiral centres

Without actually being aware of it, chirality has been with us since the beginning of time. The universe, at its most fundamental level, is *handed*, being made up of molecules, sugars, amino acids whose stereochemistry is absolutely defined. Enantiomers have identical physical and chemical properties in an nonchiral environment,

Janet Mifsud B. Pharm (Hons)

Assistant Lecturer,
Dept of Pharmacy,
Faculty of Medicine and Surgery,
University of Malta,
Msida

however in a chiral environment, such as the human body, their properties differ [1]. It is not therefore surprising, that living organisms are able to discriminate between the two enantiomers, or left and right isomers of a chiral compound, and large differences occur between the biological responses they evoke. Selectivity of action is based on chemical complementariness between the bioactive agents and their specific molecular sites of action which may include enzymes, receptors, carriers[2], just like a right-handed glove which will fit the right hand perfectly but is uncomfortable on the left.

About 40% of synthetic drugs are chiral. Mason[3] has calculated that more than 80% of the synthetic chiral pharmaceuticals which appear in the United States Pharmacopoeia are administered as their racemates i.e. as equal mixtures of relatively *'active'* and *'inactive'* isomers.

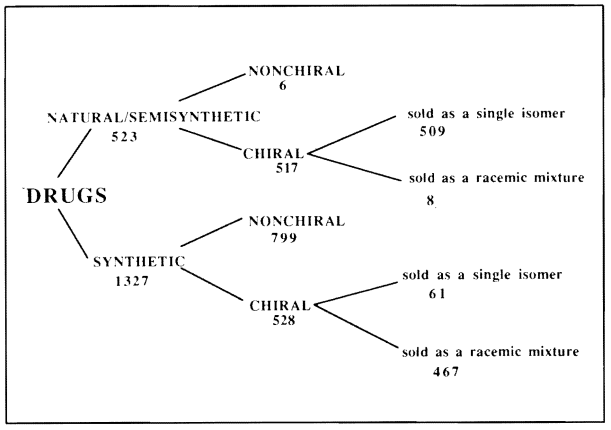

Figure III - Chirality of drugs:
their application as single isomers or racemates [3,24,25]

This may be because it is easier to synthesize mixtures of enantiomers rather than the pure forms themselves. The inactive form, however, may not be a passive component of the drug mixture. It may be an *agonist*, or an *antagonist*, or it may have actions on other receptors, resulting in either unwanted side effects or contributing to overall drug efficacy. In addition, its metabolites may also be active or toxic.

HISTORY

"All artificial bodies and all minerals have superimposable images. Opposed to these are nearly all organic substances which play an important role in plant and animal life. These are asymmetric, and indeed have the kind of symmetry in which the image is not superimposable with the object."

- Louis Pasteur, 1890 [4]

The existence of optical isomerism has been known since the first half of the 19th century. In 1815, Jean-Baptiste Biot discovered optical activity and in 1848, Louis Pasteur isolated, for the first time in history, a pair of non-superimposable mirror-image crystal forms which liberated (d)- and (l)- tartaric acid [4]. In the 1930's, British pharmacologist, Arthur R. Cushing, demonstrated substantial differences between the pharmacological properties of atropine, or racemic hyoscyamine, a cholinergic antagonist, and (l)- hyoscyamine. During the 1950's, the importance of stereochemical considerations in medicinal chemistry and drug design was consistently emphasized by Arnold Beckett and Alan Casey in their classical studies on synthetic opiate type narcotics. However in the 1960's, the addition to the therapeutic armaentarium of novel synthetic drugs was invariably always in the racemic form [5].

Perhaps the most tragic example is *thalidomide*. This drug was marketed during the 1960's as a sedative, and it was widely used by pregnant women, many of whom later gave birth to deformed children. Thalidomide was administered as a racemic mixture of its two optical isomers. Too late, did following research show that it was only the sinistral (-)-isomer, and not the (+)-isomer, which had a teratogenic effect on rat embryos, producing the same birth defect as those of the thalidomide children in the early 1960's [6].

Questions of whether clinical efficacy and safety are greater in one member of a stereoisomeric pair of drugs are now being asked, and terms such as *isomeric ballast*[7] and *composite chiral drugs* (CCDs)[8] have now become commonplace.

TODAY

Present day medical curricula deal with stereochemistry as something to be mentioned only when dealing with the biochemistry of amino acids and sugars. Few teaching and reference books even mention stereochemistry and its significance [2].

In current research, the rapid emergence of published data regarding drug enantiomers is indicating strongly that studies on individual enantiomers should be quantitated individually for a number of reasons:

- the kinetics of drug enantiomers often differ, leading to interindividual variation in the plasma ratio of the enantiomers

- the pharmacological properties of drug enantiomers are often different
- the technology to routinely separate and quantitate drug enantiomers is rapidly advancing [9].

EVALUATION OF STEREOPHARMACOLOGICAL VARIATIONS IN SOME DRUG RACEMATES

Various studies have now been reported in the literature about differences in the pharmacokinetic and pharmacological activity of racemic drugs. Some drugs are already being marketed as the pure enantiomer e.g. (-)-naproxen, a non-steriodal anti-inflammatory drug; (+)-timolol, a beta-adrenoreceptor blocking agent; (d)-methyldopa, an antihypertensive and (d)-dextromethorphan, an antitussive.[10]

One of the first examples reported in the literature of stereoselective drug metabolism in man, was that of the hypnotic drug *hexobarbital.* When the separate enantiomers were administered, a very clear central depressant effect was seen after the (S)-hexobarbital, but not the (R)-hexobarbital. The total clearance of (S)-hexobarbital was found to be only about one third of the (R)-hexobarbital, thus plasma concentrations for the (S)-hexobarbital were higher and half-life longer than for the (R)-isomer.[11]

It has been reported that it is (d)-*propranolol* which acts as the beta-adrenoreceptor agent, but both stereoisomers contribute to its local anaesthetic and histamine releasing action.[12] (d)-*Ketamine* is predominantly a hypnotic and an analgesic, whereas the (l)-isomer is the main source of its unwanted side-effects.[13] The therapeutic index of disopyramide could be improved by eliminating the (-)-isomer. This enantiomer is a less potent anti-arrhythmic then the (+)-form, and it is mostly responsible for the heart failure precipitated by administration of the racemic drug, through its marked negative inotropic effect. *Sotalol* is another example of an anti-arrhythmic agent where the use of the racemate is inappropriate. There is excellent animal evidence showing that the (-)-isomer is devoid of beta-blocking activity.[14]

Care must be exerted if decisions are taken to change from a racemate to an isomer. Although the (S)-isomer of *warfarin* is about 3-5 times as potent as its antipode, switching from the racemate to the (S)-isomer, would necessitate a reduction in the dose. There would be no change in therapeutic index and this would precipitate a specific set of potential drug interactions.[15] To the contrary, the greater intrinsic anti-inflammatory potency of (S)-*ibuprofen* is compensated to some extent when using the racemate by metabolic inversion of the less active (R)-form and in fact approximately 60% of an oral dose of (R)-ibuprufen is inverted to the (S)-enantiomer.[16]

After oral administration of *metoprolol*, even though the plasma elimination half-lives of the enantiomers are similar, plasma concentrations of (S)-metroprolol were 67% higher than those of (R)-metoprolol. Clinically, this means that with equal plasma concentrations of metoprolol, a greater degree of beta blockage will be observed in extensive metabolisers than in slower metabolisers.[17] Research has also been carried out on the influence of stereoisomeric factors in the pharmacokinetics of chiral drugs used in the extremes of age such as the elderly.[18]

These are just a few examples of the large number of research papers being published in the specialised journals. A number of excellent reviews and textbooks are now available on the subject of drug chirality.

REGULATIONS

The regulatory authorities are beginning to respond to the scientific and clinical maelstrom concerning the issue of drug racemates and enantiomers.[19] In the United States, the Federal Drug Agency, FDA, has an ongoing discussion with the pharmaceutical industry, which is likely to lead to the promulgation of guidelines and a policy statement has just been published.[20] In Europe, the European Community Committee for Proprietary Medicinal Products has issued a draft guideline statement on isomerism for inclusion in its "Notice to Applicants".[21] If adopted, as looks likely, new submissions for drugs with chiral centres will have to provide information, *interalia*, on the following points:

- isomer ratio and batch to batch consistency;
- a discussion of the toxicological and pharmacological properties of the isomers;
- enantiomer-specific metabolism and kinetics;
- the extrapolation of preclinical data (particularly if species difference occur in the handling of stereoisomers);
- a discussion of possible clinical problems that may arise in relation to stereoisomers.

In Japan, the health authorities, in meetings with the pharmaceutical industry, have explained their requirements in the context of the registration of a racemic mixture or optical isomer[22]. Basically, for a racemic mixture, information will be required for its toxicity, pharmacology (efficacy and general), the disposition of each isomer and on the extent of the interconversion between the two isomeric forms. Lastly, information will be required for isomer purity: if one of the isomers constitutes a major "impurity", then this will have to be fully studied in terms of toxicity, pharmacology and disposition [5].

CONCLUSION

Should chiral drugs be used as a single isomer? Perhaps it is wrong to start a witch hunt for racemic drugs which are already marketed[23], but it can be predicted that a full clinical study of the pharmacological and toxicological effects of both enantiomers of any new chiral drug, may be required soon, in order to obtain authorization for marketing the drug as a racemic mixture.

The production of optically active drugs, in place of racemates, does not seem to be a profitable venture. It would increase production costs, and to state bluntly that racemic drugs contain a 50% impurity, is a gross simplification. Many scientific factors such as synthetic pathways, formulation and stability problems, should be taken into account. These factors require a wealth of pharmacokinetic and pharmaco-dynamic information which is not always available. Decisions on whether the racemate or enantiomer is developed for marketing should, in one's opinion, be taken on a case by case basis, maintaining proper ethical and scientific attitudes.

Arguments for marketing drugs as pure enantiomers

- Improved less complex and more selective pharmacological profile
- Better therapeutic index
- Less complex pharmacokinetics
- Less complex plasma concentration-response relationships particularly in relation to therapeutic drug monitoring

Arguments against marketing drugs as pure enantiomers

- Cost of development
- Cost of production

Figure IV - Enantiomers or racemates? [26]

Other factors have to be taken into account. These include feasibility and cost of stereospecific enantiomer synthesis or separation and the quality control of isomeric purity. All in all, this probably argues for some sort of 'decision tree' approach to the issue.

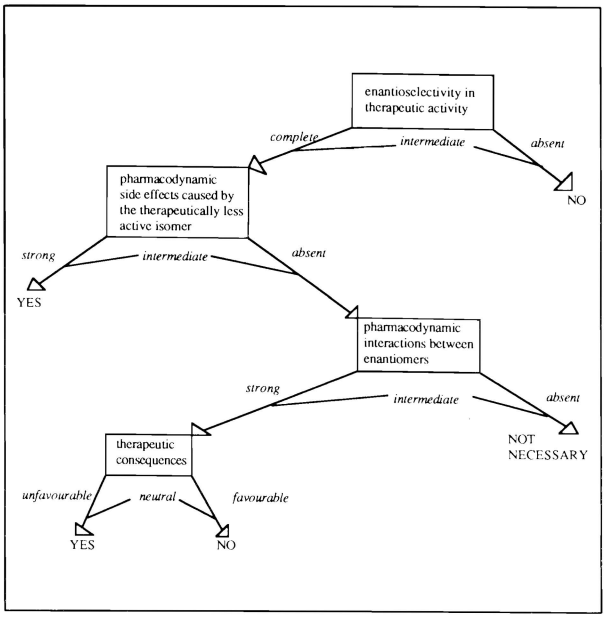

Figure V - Proposed logical scheme addressing the question: should chiral drugs be used as a single isomer? [23]

This would incorporate factors such as pharmacological and toxicological properties of the enantiomers, pharmacokinetic properties, interactive potential, feasibility and cost of production, quality control criteria and 'marketing edge' [5]. Some drugs are already being developed as the pure enantiomers from existing composite chiral drugs with still valid patents. These include (S)-atenolol, (R)-salbutamol and (S)-fluriprofen [8].

Some in the medical community may find all this somewhat daunting and have accused the pharmaceutical industry of stereophobia [14]. Nevertheless, the re-realization of the importance of stereochemistry in pharmacology has an important contribution to make to the development and use of safer and more effective medicines. Drug therapy can only gain from such fruitful discussions from the continual assessment of 'looking glass drugs' and it is useful to remember that a basic rule in science is "non capability or impossibility to do things the proper way is no excuse to do them the wrong way" [2].

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