Chirality and its Importance in Drug Development

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Chirality and its importance in drug development: what are the issues?
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Many senior medical advisors on regulatory bodies and on advisory bodies have stressed that correct medication should involve the use of single chemical entities, i.e. drugs, rather than combinations of drugs.

The academic leaders of the medical profession have stressed that in general if more than one medication is necessary for the treatment of a patient, each should contain a single drug so that titration of the dose of the different medications to the advantage of the patient can occur. They have opposed strongly the use of fixed drug combinations, except in special cases.

The same purists seem to have been in a land of fantasy, according to the information from those who actively treat many patients; the latter stress they have neither the time nor facilities to titrate patients in the way outlined by the purists. The realities as distinct from the fantasies have not stopped the purist leaders of the medical profession often castigating industry for producing fixed drug combinations which are convenient to both the doctors in practice and their patients.

It seems strange, therefore, that the same leaders have been sometimes using, advocating or condoning the use of fixed drug combinations when chiral centres are present in a drug molecule when the isomers as entities have been in mixtures in the final produced dispensed. They seem to have accepted for decades without demur or complaint that, for instance, when one chiral centre is involved in a drug molecule, that the racemate, i.e., a fixed combination of 1:1 of two chemical entities, can be used, despite the fact that the two enantiomers may have different activities and toxicities. Why is it possible for them to be so indifferent on the use of a single molecular drug entity in a medicine, when it is estimated that about 50% of medicines contain drugs exhibiting chirality and the large proportion of these enantiomeric drugs are used as the racemate, i.e., two entities in a fixed proportion of 1:1? Is this stand taken by them with regard to the pharmaceutical industry making fixed drug combinations a matter of hypocrisy or a matter of ignorance? Surely when they studied chemistry or pharmacology they must have had information about the difference in the activity of isomers. I record some few examples of drugs possessing chiral centres which indicate that they cover many different fields of pharmacological action and medical use.

1. Analgesics: dextropropoxyphene, codeine, hydromorphone, oxycodone, morphine, methadone.
3. Antibiotics: amoxycillin, ampicillin, caphatholin; tetracycline, gentamicin.
5. Antihistamines: brompheniramine, chlorpheniramine, clemastine, promethazine.
7. Sedatives/hypnotics: phenobarbitone, glutethimide.
8. Anticonvulsants: Methylphenobarbitone, methsuximide, phensuximide, ethosuximide.
10. Anaesthetics general: ketamine, methohexitone, etomidate.

The first recorded observations of differences in the biological actions of stereoisomers is attributed to Piutti [1]. He isolated the two enantiomers
of aspartagine in 1886; the (+)-isomer tasted sweet while the (−)-isomer tasted bland. For many decades scientists have stressed the difference in pharmacological activity and toxicity of enantiomers and diastereoisomers, and yet the information has had little effect on the medical leaders. Thirty-five years ago, I personally concentrated some of our research in the analgesic field, where there is a tremendous difference in the activity of enantiomers of the enantiomeric pairs. I reviewed this situation and the importance of stereochemical aspects in biological actions[2, 3]. I ended one article as follows: 'The above examples of stereochemical specificity in biological action serve to indicate the importance of stereochemical investigations of biologically active structurally specific compounds. Although a particular biological response to a compound may be influenced by many factors, studies of the actions of enantiomorphs in which so many properties are identical, enables some of the fine structure of receptor surfaces to be delineated when similar configurations can be established for the more active members of enantiomorph pairs exhibiting a particular biological action. The use of geometrical isomers which are dissymmetric also offers an approach to the elucidation of both the distances, and the orientation of specific receptor areas of the receptor site, if the differences in the physical properties of the geometrical isomers are not great. The combination of such studies with the investigation of the antagonistic action of stereoisomers, and the change in the biological effect upon alterations of the groups necessary for 'combination' at the receptor, has great potentialities in the search to unravel the complexities of the mechanisms by which biological responses are mediated.'

In other articles I stressed the importance of considerations of stereochemistry in the metabolism of drugs[4].

Many times I have argued with the medical purists that the stand they have taken on fixed drug combinations is absolute nonsense in view of the scientific information about the difference in activity and side-effects of enantiomers and diastereoisomers. I failed for decades to produce change, but now matters are changing rapidly.

A general medical practitioner, or even a consultant in a hospital, would find it very difficult to know whether he is prescribing a single isomer or a mixture of isomers of a drug product when he prescribes a product by brand name or generic name because the name used does not, in general, indicate the difference. If he referred to MIMS an answer would not be found. Looking at the British National Formulary this would not provide the information. If Martindale were examined, in some cases the information might be found that a racemic mixture, is involved when a generic name for a drug is used, e.g. chlorpheniramine and brompheniramine (although possibly because one of the isomers, dextro-chlorpheniramine, is marketed separately) and tranilcypromine; but in many cases this would not be so. For instance, for disopyramide or mexiletine, it is not apparent from what is written in Martindale that there is a chiral centre, unless one draws out the drug structure from the chemical name given; yet there are big differences in the activity and side-effects of the isomers. There is no indication under the entry for the following drugs: phenylbarbitone, ibuprofen, ketoprofen or flurbiprofen, that the products are 1:1 mixtures of two enantiomers.

It is important to appreciate the difference between enantiomerism and diastereoisomerism. A structure that is not superimposable on its mirror image, i.e. chiral, can arise in different ways, but most commonly is due to a chiral or asymmetric carbon in the molecule, i.e. a carbon atom to which four different atoms or groups are attached. Two distinct spatial orientations of the substituents of the carbon atom are then possible, one being the non-superimposable mirror image of the other. If one enantiomer aligns three of its groups to interact with three complementary sites in a receptor, its enantiomer can only align two of the groups at any one time to the same receptor. A racemate, i.e. 1:1 ratio of a pair of enantiomers, does not rotate the plane of polarized light. Synthetic routes not involving other molecules with chiral centres in the routes lead to this 1:1 mixture of enantiomers where one chiral centre is in the final molecule. A (+)/(−) or d/l recorded in front of a compound indicates the direction in which the polarized light is rotated by the isomer in solution and gives no indication of the absolute geometry. The d/l system indicates absolute geometry related to (+)-D-glyceraldehyde as a standard or (−)-serine as a standard. This type of designation, however, is not without problems and, consequently, absolute configuration is now usually related to actual orientation in space, i.e. the Cahn–Ingold–Prelog Convention called the Sequence Rule, i.e. the R/S system of nomenclature. The system assigns a priority, based upon atomic numbers to each of four substituents attached directly to the chiral carbon atom. Once the absolute configuration of a compound has been determined the R/S or d/l assignments for a particular
enantiomeric pair can be correlated to the (+)/(-) or d/l information on the enantiomers. Atoms other than carbon can constitute chiral centres, e.g. quaternary nitrogen as in atracurium and phosphorus as in cyclophosphamide.

Diastereoisomers are stereoisomers which are superimposable. This can arise from compounds with multiple chiral centres or geometric isomerism, i.e. cis-trans isomerism. This isomerism does not require chiral centres as multiple activity is not involved. Geometric isomers have the same sequence of atoms in the same order, but the disposition of the groups is different because of the double bond or a single bond with large enough groups to prevent rotation. Geometric isomers have different physicochemical properties and are often recorded under the drug name.

Stereoisomers may differ in their pharmacological activities due to: (a) one isomer being metabolized differently or at a different rate from its related isomer; (b) the isomer being bound to active asymmetric sites differently so that the isomers of the circulating free drug differ to produce differences in concentrations at active sites or in the rates of elimination; or (c) differences in the reaction of the isomers at active sites by which the pharmacological action is mediated.

A range of possibilities for the relative actions of the stereoisomers thus exists.

(1) All of the particular pharmacological action may reside in just one of the isomers, or the isomers may have similar activity, but to different degrees, or the activities may be similar in character and degree. However, these matters can be further complicated by differences in rates of metabolism and distribution of the isomers.

(2) The isomers may have different pharmacological actions because of different selective binding at asymmetric active receptor sites.

(3) The isomers may have different toxicities because of the difference in binding at asymmetric sites via which the toxicities are mediated.

(4) One isomer might react at an active site to produce synergism or antagonism of the action of the other isomer.

Why has it taken so long for the importance of stereochemistry to be realized by the medical profession, when so much evidence has been available for decades?

One reason could be that their education in the more scientific aspects of chemistry, pharmacology and drug metabolism which would have enabled them to appreciate that the right-handed form of a molecule could behave completely differently from the left-handed form, has not been stressed sufficiently.

Another reason could be the method by which products are prescribed, i.e. simply by name, without truly understanding what is meant by that name. The problem is somewhat analogous to the one of prescribing generically, when the regulatory body does not ensure for different products of the same drug that there is comparability in action and relative toxicities. This continues to be the case, despite the fact that there is much evidence that different products containing the correct drug in the correct quantity and of the correct quality, may behave differently. The yellow-card system of reporting by generic name rather than the brand name, manufacturer and batch number of the product, also emphasizes that if a practitioner knows the name of a drug he thinks he knows the characteristics of the product; the medical establishment has done little to sort out this problem and the Medicines Commission has not been particularly helpful.

The third reason is that the information on the different actions and toxicities of isomers was available before the development of methods for analysis of enantiomers in body fluids. In the last two decades, however, the appropriate analytical techniques have become available, chiral gas and liquid chromatography, chiral radio-immuno and radioreceptor assays, chiral n.m.r., etc. In the last decade, dramatic changes have occurred in the perception of the regulatory bodies of the fact that chiral centres can lead to mixtures of products being presented to them for licensing, and that isomeric components may have different activities, toxicities and different rates of elimination. Now that enlightenment has occurred, however, it is important that all involved do not over react because of the previous failures to act correctly.

Clear guidelines must be laid down. For example, if a product with one or more chiral centres has been on the market for many years as a mixture and it has now been found that the desired pharmacological activity resides in one isomer, while the other is inactive and devoid of toxicity, it does not seem reasonable to seek to market the active isomer on the grounds that the inactive one represents 50% of useless ballast. This surely applies if the resolved isomer is to be sold at three or four times the price of the same amount of the active isomer present in the marketed racemic mixture.

However, if the less active isomer exhibits the main toxicity of the mixture there may be thera-
The regulatory body requirements must be clearly defined, because it must be taken into account that the less active, but more toxic, isomer has already been administered to man for many years in a mixture with its less toxic isomer. Obviously the cost/benefit factors must be considered and steps taken to ensure that the costs are not allowed to escalate because of the application of unrealistic demands upon a company seeking to produce evidence to market the active less toxic isomer.

In recent years, there has been an increasing emphasis on the development of medicinal products based on endogenous materials. Often many chiral centres may be present in such molecules. If regulatory bodies demand information on the activity and toxicity of all the possible isomers, then the cost of such studies will increase dramatically the costs of producing a new medicinal agent. However, for new pharmacological agents with one or two chiral centres, it is possible to make out a reasonable case for determining the activity and toxicity of the separate isomers, since such studies might produce a more selective agent with reduced toxicity than would be the case if the mixture as originally synthesized were marketed. Also such studies would improve our knowledge in structure-activity relationships and thus could help in the development of more selective medicinal agents.

It may be that these new demands, when molecules with chiral centres are involved, will cause a synthetic chemist to think carefully of the molecules in a series of compounds he has prepared. He may decide for the detailed pharmacological investigations to choose, in a series, a compound in which there is not a chiral centre, if the activities of a few related compounds possessing chiral centres do not show too much difference in their activities.

Whatever now happens, the stereochemical genie has finally escaped from the medical prison in which it has been confined for too long. Now its good properties and advantages must be harnessed without allowing some of them to be used in a destructive or restrictive fashion. The escape must be utilized to design more selective and safer medicinal agents by keeping under control the escalation of unnecessary demands and requirements which could arise from over zealous regulators who do not have to pay the bill when they make excessive demands and ‘change the goal-posts’ during the course of investigations.


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Chirality and its importance in drug development: a synthetic chemist’s perspective

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Many organic molecules lack both a plane of symmetry and a centre of symmetry. Such chiral molecules exist in two forms, the enantiomers, which are related as an object to its mirror image. The two enantiomers have identical physical properties except for their influence on plane polarized light. The dextro-rotatory (+)-enantiomer will rotate the plane of plane polarized light to the right, the laevo-rotatory (−)-enantiomer will rotate the plane of plane polarized light to the same extent to the left. The two enantiomers will also react differently with other chiral substances, e.g. biological macromolecules such as protein and DNA. Hence, it is not surprising that the two enantiomers of a chiral compound can have different effects on mammalian receptors and enzymes; the process of metabolism in vivo can also be different for the two enantiomers. In view of these facts, there is considerable debate at present as to whether chiral compounds that represent the drug substances of the future should be made and administered as the pure (i.e. chemically and optically pure) biologically active enantiomer.

Abbreviations used: DIBAL, di-isobutylaluminium hydride; LDA, lithium di-isopropylamide; PGF_{2α}, prostaglandin F_{2α}.