Chiral cognisance: a road to safer and more effective medicinal products

ABSTRACT—A quarter of all synthetic medicinal drugs contain a mixture of equal proportions of two molecules that have the same chemical constitution but differ in the spatial arrangement of their constituent atoms such that each is a mirror-image of the other, like the right and left hand. Biologically, receptors which are stereospecific react with only one of the two components of the mixture to produce the desired therapeutic effect, while the other is inactive or may interact with different receptors to cause undesirable, even toxic, effects. Development of syntheses that produce a preponderance of the required form, and efficient separation of mixtures, will result in safer and more effective medicinal products.

Medicinal chemists and pharmacologists have developed highly active and, by implication, selective medicines, yet a quarter of all drugs on the market contain at least 50% of non-therapeutic, potentially harmful chemical ballast. This massive medicinal impurity, the stereoisomeric companion of the therapeutic agent, was already known to Pasteur in 1901. It has been largely and persistently neglected by medicinal chemists, pharmacists and clinical pharmacologists, and is still hardly known to physicians.

When a carbon atom in a molecule is linked to four chemically different groups, its tetrahedric configuration can give rise to a mirror-image asymmetry, a type of stereoisomerism (Fig 1). In solution, the stereoisomers of the molecule are almost identical in their physico-chemical properties, except in their behaviour with regard to polarised light. This is rotated by the isomers in opposite directions, indicated as right (dextro, d) and left (levo, l). A more up-to-date nomenclature is R and S for clockwise and counterclockwise order in which the different groups are located on the carbon atom tetrahedron (Fig 1). When such carbon compounds are synthesised from chemical building stones free in solution, dextro- and levo-rotatory molecules have an equal chance of formation, producing a 1:1 mixture of two mirror-image isomers. They are known as enantiomers and exhibit chirality like the right and left hands (Gk chiros, hand).

The 1:1 mixture itself is called a racemate; it does not change the plane of polarised light because the opposing rotatory effects of the enantiomers are equally balanced.

If hands were to be assembled from a mixture of fingers in the presence of only left-hand gloves as a mould, nothing but left hands would be formed; similarly, chiral molecules can be synthesised in the presence of suitable stereospecific catalysts. In biology, it is enzymes which play the role of (substrate) stereoselective and (product) stereospecific catalysts. Since amino acids and sugars, the major building stones of biological macromolecules, are themselves chiral, the proteins and glycoproteins which constitute enzymes, receptors, carrier molecules etc are also chiral. If the

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Fig 1. Types of stereoisomers. (a) When four different groups are attached to a carbon atom, mirror-image isomers (enantiomers) exist; the order in which the groups occur is specified clockwise (R) or counterclockwise (S). (b) Compounds with a carbon–carbon double bond may occur as cis (Z) and trans (E) isomers.
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The degree of stereospecificity depends on the position of the chiral centre in the molecule. A high degree of stereospecificity means that the chiral centre is in a critical binding area. Location in a non-critical area implies low or no stereospecificity or selectivity in biological properties, i.e. chirality is silent. One and the same chiral centre may be located in a non-critical (silent) position for a particular type of receptor and still be critical for other receptors or enzymes involved in metabolic conversion. The implications of chirality for various aspects of drug action (pharmacodynamics) and drug metabolism (pharmacokinetics) may thus clearly differ. This holds true also for stereoisomers other than enantiomers, such as cis- and trans-(also called Z- and E-) isomers, compounds with a carbon–carbon double bond (Fig 1). For reasons of simplicity we will restrict ourselves here to compounds with only one chiral centre.

Figure 2 presents in a schematic way the distribution of our present therapeutic arsenal based on chirality. In natural and semisynthetic drugs, single-isomer products predominate; most synthetic drugs are either racemic or non-chiral. This underlines the fact that chirality is not a prerequisite for biological activity; whether chirality plays a role depends on the target molecules (receptors, enzymes etc).

Racemic drugs require special consideration. For natural products, a mixture of enantiomers is usually the result of racemisation which may be hard to avoid. In the case of synthetic products, the high percentage of racemic drugs is largely an unhappy inheritance. The presence of 50%, 75% and sometimes even more of the mostly therapeutically useless but potentially toxic isomer(s), the isomeric ballast, has largely been neglected; although that is convenient for the drug industry, it is not good for patients. With few exceptions, the enantiomers in a racemic mixture must be regarded as two fundamentally different compounds, each with its own chemical and biological properties. This has led, in some cases, to marketing the separated, therapeutically effective, enantiomer (Table 1).

An example is the exploitation of the undesirable respiratory depressant in some racemic analgesics narcotics. Separation of the enantiomers showed that analgesic and respiratory (antitussive) action could be parted and the individual enantiomers marketed as different drugs (Table 2).

### Racemic drugs and pharmacological measurements

The terminology ‘active’ and ‘inactive’ enantiomers is misleading. The enantiomer most potent for the desired action is called the eutomer, and the one without such action the distomer. The latter often particularly contributes to undesired actions of drugs, pesticides etc and can never be regarded as completely harmless. The ratio of the activities of eutomer and distomer is called the eudismic ratio. It usually differs for the various components of the desired and undesired actions generated at different receptors. The ratio is specific for a particular racemate in relation to a particular action and is only rarely equal to 1.

The **eudismic proportion** is the proportion of the concentrations of eutomer and distomer in plasma or other body fluids. It is of specific significance in pharmacokinetics. For the racemate itself, the eudismic proportion is 1 by definition. After absorption, stereoselectivity in metabolic conversion will gradually
change the eudismic proportion until a steady state is reached for each of the enantiomers involved. Strictly speaking, no racemate exists in body fluids with the exception of rapid in vivo racemisation. Whether the eutomer or the distomer is preferentially eliminated, ie whether the eudismic proportion changes to values larger or smaller than 1, can only be detected by so-called chiral assays.

The ‘composition’ of a racemate in body fluids is not only time–but often also route-dependent. Verapamil is an example of a drug with different eudismic proportions in plasma after oral and intravenous administration. The eudismic ratio (R/S) for the negative dromotropic action of this drug on atrioventricular conduction is 10. When taken by mouth, presystemic metabolic (liver or gut) elimination is higher for the eutomer (R) than for the distomer (S), resulting in a low systemic bioavailability for the eutomer. The eudismic proportion in plasma is 0.2 after oral and 0.5 after intravenous administration, ie at equal ‘racemate’ plasma concentrations the eutomer concentration is much lower after oral than after intravenous administration of the drug. Plasma concentrations of a racemate measured by non-chiral assays give information only on the sum of the eutomer and distomer. Since the eudismic proportion is not constant, these concentrations will not be consistently related to the response; in fact, pharmacokinetic constants such as a racemic drug’s half-life, bioavailability, bioequivalence and other pharmacokinetic constants derived from ‘racemate’ concentrations based on non-chiral assays are really meaningless. Further difficulties arise with respect to side-effects, protein binding, active transport, metabolic conversion to bioactive metabolites, etc. Millions of dollars have been and still are wasted on measuring such pseudo-scientific and misleading kinetics of drugs.

**Racemic drugs as a source of medicinal pollution and pseudo-science**

One of the reasons for neglecting the presence of patient-polluting isomeric ballast in drugs has been the contention that clean drugs would be difficult and expensive to produce. Over the past 10 years stereoselective synthesis and enantiomer separation have greatly improved. Costs can now be kept under control, the more so since it is realised that in the production of racemates 50% of the often expensive base materials is wasted in producing risky pollutants.

| Drug               | Eutomer | In use as/for       | Distomer   | Effect of isomeric ballast |
|--------------------|---------|---------------------|------------|----------------------------|
| Levodopa           | l/isomer| Antiparkinsonian    | d/isomer   | Agranulocytosis            |
| Penicillamine      | d/isomer| Antirheumatic, Wilson’s disease | l/isomer   | Neurotoxic, pyridoxine deficiency |

### Table 2. Racemates of which both isomers are marketed as separate drugs

| Pair of isomers | Isomer | Effect    |
|-----------------|--------|-----------|
| Levorphanol     | l      | Analgesic |
| Dextrophan      | d      | Antitussive |
| Dextropropoxyphene | d   | Analgesic |
| Levopropoxyphene | l      | Antitussive |

A simple and effective way to stop polluting the literature with the non-science generated in the study of racemates would be to place an obligation on authors:

‘The composite character of drugs which are mixtures of stereoisomers must be brought to the attention of the reader. The prefixes (RS)- or rac, eg rac-propranolol, in the case of racemates, and (Z/E)- or cis/trans- in the case of that type of isomer, are obligatory. The implications of the composite and chiral nature of the drugs for the interpretation of the data measured and the conclusions drawn must be made explicit’.

An important issue concerning therapeutic racemates is: How are the effects and the side-effects distributed between the enantiomers? Three possibilities exist.

1. The therapeutic effect is stereoselective; the side-effect is non-stereoselective and thus equally divided over the enantiomers. The therapeutic enantiomer is then a hybrid and the therapeutic margin is doubled by eliminating the isomeric ballast.

2. The therapeutic effect and the side-effect are stereoselective. Chances are fifty/fifty that the side-effect can be eliminated by removing the (non-therapeutic) isomeric ballast.

3. If the side-effect and the therapeutic effect are both components of the same pharmacological action, enantiomeric separation works only for independent toxic actions, eg biochemical lesions.

It is highly improbable that the isomeric ballast would be really inert and totally harmless. Its absence is the best guarantee in this respect.

### Role of the regulating authorities

The regulatory authorities have at last agreed to require explicit justification for marketing racemic...
therapeutic agents. They have issued special guidelines for chiral drugs, notably for new racemic mixtures of chemicals presented as medicines; not only the chemical composition of these drugs but also the pharmacology and toxicology of the separate enantiomers are getting attention. But a weak point is that the authorities are still willing to assume that side-effects which are ‘predictable’ from the desirable properties of the drug may be ascribed to the eutomer; the distomer is then assumed to be harmless. In view of the wide range of side-effects and the toxicity related to biochemical lesions, this is an industry-friendly but patient-unfriendly attitude. The first question the physician or pharmacist should ask the medical representative (drug salesman) is: Which of your products are racemic mixtures, and how sure are you that the isomeric ballast is completely harmless? No patient wants to swallow therapeutically useless chemicals even if reassured by the health authorities. Let us at least be honest and announce in bold print on the package of racemic drugs: ‘Contains 50% of therapeutically ineffective, presumably harmless chemical ballast’.

Further reading

1 Ariens EJ, Soudyn W, Timmermans PBMW. Stereochemistry and biological activity of drugs. Oxford: Blackwell Scientific Publications, 1982:1-190.
2 Wainer IW, Drayer DE. Drug stereochemistry, analytical methods and pharmacology. New York: Marcel Dekker, 1988:1–300.
3 Brown C (ed). Chirality and drug design and synthesis. New York: Academic Press, 1990:1–240.
4 Jamali F, Behvar R, Pasutto FM. Enantioselective aspects of drug action and disposition: therapeutic pitfalls. J Pharm Sci 1989;78:695–715.
5 Evans AM. Stereoselective drug disposition: potential for misinterpretation of drug disposition data. Br J Clin Pharmacol 1988;26:771–80.

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