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Special Article

Stereochemistry, a Basis for Sophisticated Nonsense in Pharmacokinetics and Clinical Pharmacology

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Summary. The significance of stereochemistry in therapeutic action is outlined and elucidated. Often only one isomer is therapeutically active, but this does not mean that the other is really inactive. It may very well contribute to the side-effects. The therapeutically non-active isomer in a racemate should be regarded as an impurity (50% or more). It is emphasized how in clinical pharmacology, and particularly in pharmacokinetics, neglect of stereoselectivity in action leads to the performance of expensive "highly sophisticated scientific nonsense". This also holds true in the development and marketing of new drugs as exemplified by various "pseudo-hybrid" drugs now reaching the clinic.

Key words: stereoselectivity, drug action; eudismic ratio, isomeric ballast, (in)active isomers, pharmacokinetic nonsense, hybrid drugs, pseudo-hybrid drugs

Biologically active agents, such as neurotransmitters, hormones, drugs, etc. often show a high degree of selectivity in action, related to their discriminatory capacity with regard to their molecular sites of action, the specific receptors or enzymes on which they act. This capacity requires chemical complementarity between the bioactive agent and the sites of action, which accounts for the physicochemical characteristics of particular groups in the molecule that participate in the interaction as well as their spatial arrangement, their steric configuration. Inherent stereoselectivity in action can be accounted for on the basis of as few as three groups in the bioactive molecule participating in the interaction with the receptor. Stereoselectivity is quite common amongst bioactive agents [1, 2, 3, 4, 5].

Of the various types of stereochemistry, such as the occurrence of enantiomers, cis-trans isomers, epimers, etc. the first is of particular significance. It requires the presence in the molecule of a centre of asymmetry, usually related to the presence of four different groups attached to one carbon atom. Enantiomers are characterized by their mirror image relationship. Involvement of three of the groups on the carbon atom, known as a three-point interaction, implies a high degree of complementarity of one of the enantiomers (the most active one, known as the eutomer) with the site of action and is incompatible with a proper fit of the other isomer. The latter will only be poorly active or not active at all, and is known as the distomer. The ratio of the activity of eutomer and distomer, the eudismic ratio [4], is a measure of the stereoselectivity. High activity of the eutomer means a high degree of complementarity with the molecular site of action and thus a correspondingly poor fit for the distomer, with a relatively large eudismic ratio as a result [1, 2, 6]. This ratio decreases, therefore, with the activity of the eutomer, a relationship known as "Pfeiffer's rule" [1, 2, 7, 8]. This holds true if the centre of asymmetry is located in a section of the molecule that participates in the pharmacon – receptor interaction. A centre of asymmetry in a nonrelevant part of the molecule does not count [1, 2, 7, 8].

Since most biochemical processes are stereoselective, natural products are usually obtained in an optically active form. Organic synthesis, however, as a rule results in racemic mixtures containing 50% of each of the isomers. They differ in their rotation of polarised light, one isomer giving right hand (dextro, *d*) and the other left hand (levo, *l*) rotation. The racemic mixture, *dl*, does not rotate polarised light.

Drugs Containing 50% Impurity

In medical practice, although it is often assumed that only one compound is administered, 50:50 mixtures of compounds (stereoisomers) are frequently in-

volved. One must be aware of the fact that stereoisomers definitely are different chemicals, mostly with quite distinct biological properties [2]. Stereoselectivity in drug action implies that in the mixture of isomers only one is therapeutically active. The inactive isomer should be regarded as an impurity (50%); [2]. It does potentially contribute, however, to the side-effects.

For certain types of therapeutic substances, such as β-adrenergic agents, β-adrenergic blockers, antiepileptics and oral anticoagulants, up to 90% of the "compounds" in use are in fact racemic mixtures. For antihistamines and antidepressants this holds true for about 50% of the preparations. On the whole it applies 10 to 15% of all drugs. In certain cases the differences in activity of the isomers, the enantiomers, are scientifically established, but in many cases this knowledge is lacking.

There is in fact a remarkable discrepancy between the "purity" required for chemical agents used as therapeutics, as codified in various pharmacopoeias, and the neglect of 50% (or even more) of impurities in the form of "isomeric ballast". There does not appear to be much concern about administering together with, for example, 50 mg of the compound with the desired therapeutic action, 50 mg of a second compound, the "inactive" isomer, which does not contribute at all to the therapeutic action but can definitely contribute to the risks of the drug. The implications of the use of racemic mixtures are even more spectacular for pesticides. A number of insecticidal organophosphates and various weed killers have a centre of asymmetry and their isomers show a large eudismic ratio [2, 9, 11, 12]. What about the presumably economically and environmentally acceptable application of, say, 500 kg of the active isomer, "the active agent", automatically going hand in hand with the application of 500 kg of a second chemical, the (hopefully) inactive isomer, which does not contribute to the effect, but which must undoubtedly be regarded as an environmental pollutant [2]?

Actions of "Inactive Isomers"

If only one of the enantiomers is responsible for the therapeutic action, there is no reason why the inactive one in this sense might not be active in a different sense. There is a whole spectrum of possibilities in this respect, many of which have been experimentally confirmed.

1. One isomer possesses the therapeutic action and the other contributes to the side-effects, or may even be the main source of them. *d*-Propranolol acts as a β-adrenergic agent, but both isomers contribute to its localanaesthetic and histamine releasing action [13]. *d*-Ketamine is predominantly hypnotic and analgesic, whereas the *l*-isomer is the main source of unwanted side-effects [15].

2. The isomers may have opposite effects. In some barbiturates the *l*-isomer is a depressant and the *d*-isomer is a convulsant [16, 17]. In some cases one isomer acts as a competitive antagonist of the other. Then the racemic mixture, dependent on the affinities of the isomers to their common sites of action, may act as a partial agonist [1]. In the narcotic analgesic picenadol, the *d* form acts as an agonist the *l* as an antagonist, and the racemate *dl* as a partial agonist [18].

Similar relationships have been reported for other agents [1, 19, 20, 21], amongst which are the auxin-type plant growth substances [22]. In the case of the diuretic indacrinone, *d* is diuretic and causes uric acid retention, and *l* acts as an uricosuric. It antagonizes the uric acid retention brought about by the diuretic isomer. The "natural" proportion 1:1 between the isomers is, however, far from optimal. A study of various mixtures shows that a proportion of $2d:8l$ is optimal [23]. A comparable relation has been found for the isomers of the diuretic tienilic acid [24].

3. Particularly interesting is the stereoselective metabolic inversion of the steric configuration of one isomer. In the case of the nonsteroidal anti-inflammatory agent ibuprofen, for instance, the therapeutically inactive *l*-isomer to a large extent is converted metabolically to the active *d*-form in the body [25]. A similar relationship may be expected for the related therapeutics [25a]. There are still good reasons, however, to employ only the eutomer. Conversion of the distomer to the eutomer is only partial and depends on the condition, e.g. liver function, of the patient [25a].

4. Stereoselectivity may be restricted to only one component in the biological action. The β-adrenergic blocking action of the β-blockers is stereoselective, whereas the non-specific cardiodepressant and local anesthetic actions are not. This indicates a difference in the mechanisms of action involved [26]. The actions concerned can then be separated by suitable molecular manipulation. If the eudismic ratio for one, e.g. the therapeutic, action clearly differs or even is inverse to that for other components in the action, this too indicates different mechanisms of action. In the latter case the actions can be separated by resolution of the isomers.

Stereoselectivity in biological activity may, as in the cases mentioned above, be related to the drug-receptor interaction, or to the pharmacodynamics of the agent. It may also be due to differences in pharmacokinetics, e.g. in the rate of metabolic conversion, or even in the pathways involved [27, 28, 29, 30] and in differences in transport processes, including uptake and storage in particular tissues [31, 32]. On

this level mutual interference between isomers is also possible.

What to think of pharmacokinetic studies based on the non-explicit postulate that a mixture of two or even four essentially different chemicals, the stereoisomers, behaves as if only one compound is involved? [10, 14]. Measurement of concentrations of "the" agent and "its" various metabolites without differentiation between the isomers, computerized curve fitting to prove the involvement of a particular multicompartment system, and presentation of, a sometimes extensive, selection of pharmacokinetic constants on basis of such data are all highly debatable.

In those instances in which mixtures of isomers are studied because of non-availability of the separate stereoisomers, it should at least be mentioned that the data presented concern a mixture of compounds differing in pharmacodynamics and pharmacokinetics. Unless experimental proof is given, one has no right to assume that the therapeutically inactive component in a racemic mixture is free from undesired effects. Can any xenobiotic chemical be considered fully harmless? The presence of a 50% impurity, isomeric ballast, in a drug, even if found to be innocent, should, whenever possible, be avoided.

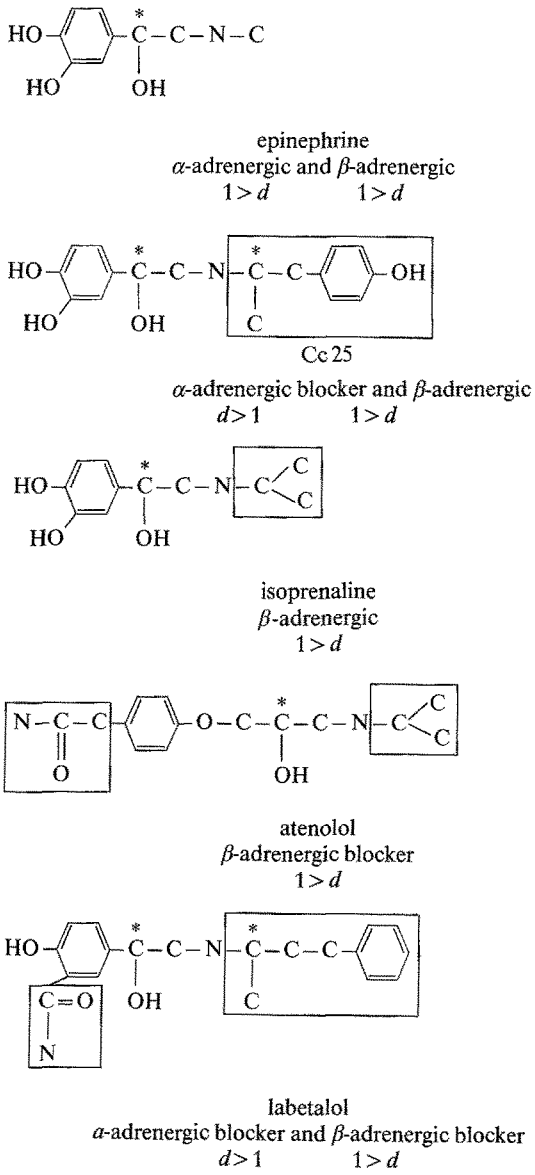
Hybrid Drugs

For reasons hard to understand there is a tendency to develop therapeutic compounds with two or even more types of action, which often differ even in their mechanism of action. In the cardiovascular field, compounds combining an α-adrenergic blocking and a β-adrenergic blocking action are gaining popularity. In such hybrid drugs the proportion of the types of action combined a priori is fixed. Combination in one preparation of an α-adrenergic blocker and a β-adrenergic blocker allows for adaptation and thus optimalization of the fixed dose ratio. Independent dosage allows for adaptation of the therapy from patient to patient.

The hybridization restricts the freedom for chemical manipulation aimed at optimalization of the proportion between the desired actions and at the elimination of undesired actions in the process of drug development.

Pseudo-Hybrid Drugs

Epinephrine has an α-adrenergic as well as a β-adrenergic action; it is a "natural" hybrid drug. By introduction of large substituents, e.g. phenylalkyl groups on the amino function in epinephrine, the α-adrenergic action is converted into an α-adrenergic



* centre of asymmetry
1 and *d* ratio of activities of *l*- and *d*-isomers

Fig. 1. Structure and action of epinephrine and derivatives

blocking action, whilst the β-adrenergic action is maintained (Cc 25 Fig. 1) [1, 2, 19, 20, 33, 34]. In epinephrine the α-adrenergic as well as the β-adrenergic actions are located in the *l*-isomer. In the compound Cc 25 obtained after the conversion, the β-adrenergic action remains located in the *l*-isomer, but the α-adrenergic blocking action now is found to be located in the *d*-isomer. In the switch from α-adrenergic to α-adrenergic blocking action, an inversion of the eudismic ratio has taken place (Cc 25 Fig. 1). The "hybrid" compound, the racemate, is a "fixed-ratio" (1:1) "combination" of the α-adrenergic blocking *l*-isomer and the β-adrenergic *d*-isomer. It is a "pseudo-hybrid" drug. The introduction of a phenylalkyl group on the amino group also tends to bring about a

Table 1. The relationship between steric structure and biological activity of labetalol, a drug with a combined β-adrenergic blocking and α-adrenergic blocking action. The α- and β-adrenergic blocking potencies of the stereoisomers are expressed as pA_2

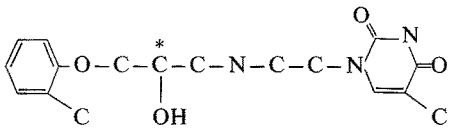
	Rabbit aortic strip (α_1-adrenoceptors)		Guinea-pig left atrium (β_1-adrenoceptors)		Guinea-pig tracheal strip (β_2-adrenoceptors)	
	n	pA_2	n	pA_2	n	pA_2
RR-isomer	3	5.87	6	(8.26)	5	(8.52)
SS-isomer	6	5.98	4	6.43	4	<6.0
RS-isomer	3	5.5	3	6.97	4	6.33
SR-isomer	8	(7.18)	4	6.37	4	<6.0

pA_2 calculated as described by Arunlakshana and Schild see Brittain, Drew and Levy [37]. The α-adrenoreceptor blocking potency rests predominantly in the SR-isomer, the β-adrenoreceptor blocking potency in the RR-isomer. The SS- and RS-isomers, 50% of the compound labetalol, can be regarded as practically inactive

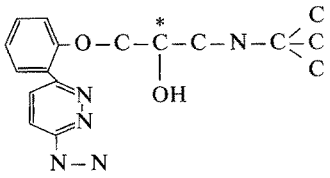
non-stereospecific, musculotropic vasodilator action. The compounds buphenine and isoxsuprine are examples [34, 35].

Replacement of the catechol nucleus in epinephrine or isoprenaline by a suitable substituted ring system results in conversion of the β-adrenergic activity to β-adrenergic blocking action (atenolol Fig. 1). This β-adrenergic blocking action, however, remains located in the *l*-isomer, which corresponds in its structure to the *l*-isomer of epinephrine, in which the β-adrenergic action is also located [2, 31, 36]. As a consequence, in the product obtained by the switch from α-adrenergic to α-adrenergic blocking, as well as from β-adrenergic to β-adrenergic blocking action (labetalol (Fig. 1) is an example) these actions are located in different isomers. This drug is a "pseudo-hybrid", in fact a "fixed-ratio combination". It actually contains two centres of asymmetry, such that it is composed of four isomers. An analysis of the actions of the isomers shows that one isomer is responsible for the β-adrenergic blocking action and one for the α-adrenergic blocking action, while the other two are practically inactive (Table 1); [37, 38, 39]. The situation is further complicated if differentiation between α_1- and α_2- and between β_1- and β_2-receptors, the possibility of ISA (residual Intrinsic Sympathomimetic Activity) and a musculotropic vasodilator action are taken into consideration [2, 37a, 40, 41].

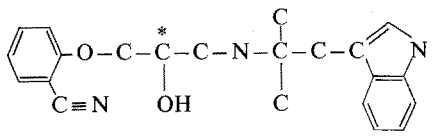
Not uncommon in the field of drug development is the phenomenon that "after one sheep crossed the bridge, many more follow". Examples of various "hybrid" drugs with combined cardiovascular actions on their way to the clinic are illustrated in Fig. 2 [2, 41]. Taking into account that the musculotropic vasodilator action is not stereospecific, and that the



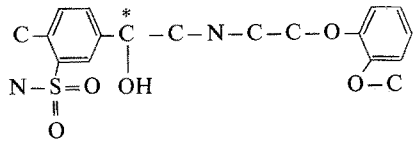
primidolol
β-blocker and α-blocker



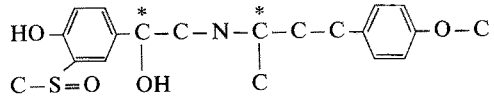
prizidilol
β-blocker and vasodilator



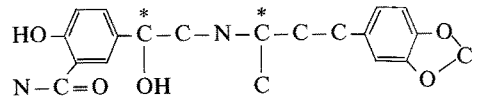
bucindolol
β-blocker, α-blocker and vasodilator



YM-09538
β-blocker and α-blocker



sulfinalol
β-blocker and vasodilator



medroxalol (RMI 81968)
β-blocker, α-blocker and vasodilator

The differentiation between α_1-and α_2- and between β_1- and β_2-adrenergic and adrenergic blocking action has not been taken into consideration. * centre of asymmetry

Fig. 2. "Pseudo-Hybrid" drugs active on the cardiovascular system

α-adrenergic blocking and β-adrenergic blocking actions are located in different isomers it will be clear that in fact the racemates are complex fixed-ratio "combinations" of drugs with different actions, the optical isomers in the mixture. Analysis of the pharmacological actions of the isomers in medroxalol and prizidilol (Fig. 2) shows the presence of isomers with an α-adrenergic blocking and vasodilator ac-

tion, isomers with a β-adrenergic blocking and vasodilator action, and isomers with mainly vasodilator action [37a, 42, 43].

The postulated advantage of "hybrid drugs", drugs with two types of action combined in one compound, namely identity in the pharmacokinetics for the combined actions, does not necessants hold true for the "pseudo-hybrids". Optical isomers often differ in their metabolism [27, 28, 29, 30] and distribution [31, 32]. Further, as indicated above, the proportions of the various isomers, each with its own specific contribution to the therapeutic action, present in the mixtures of isomers may be far from optimal.

Racemic mixtures, though presented as "hybrid" drugs, in fact are "fixed-ratio combinations", and have various disadvantages over classical fixed-ratio combinations of two properly chosen drugs with actions desired to combine. This irrespective of objections against indiscriminate composition and use of the latter combinations [43, 44, 45]. Separation of stereoisomers of drugs and bioactive agents in general, and separate study of the individual isomers, is a requirement for proper biological evaluation.

The development of stereospecific syntheses [46, 47] and methods for the separation of optical isomers, possibly assisted by biotechnology, is a challenge for medicinal chemists and opens perspectives for more selective and safer therapeutics.

The various examples given make it clear that the terms eutomer, distomer and eudismic ratio can be used only in relation to a particular biological action. The enantiomer, i.e. the eutomer for the therapeutic action may, as in the case of ketamine, be the distomer for unwanted actions [15]. For indacrinone the eutomer for the diuretic action is the distomer for the uricosuric action [23]. If the enantiomers have opposite effects, as for certain barbiturates, the eutomer for the depressant action is the distomer for the convulsant action and vice versa [16, 17]. For the "pseudo-hybrid" drugs mentioned, the eutomer for the α-adrenergic blocking action differs from that for the β-adrenergic blocking action.

Conclusions

In the study of drugs it is preferable to use pure compounds with as few impurities as possible. Mixtures of compounds may be the proper object of study, but this should be explicitly states; one may wish, for example, to gain information about an interaction between the components in the mixture. Too often, and even without it being noticed, data in the scientific literature on mixtures of stereoisomers, racemates, are presented as if only one compound were involved. This neglect of stereochemical aspects of drug action, including metabolism, excretion etc. notwithstanding computerized curve fitting, generation of extensive tables with pharmacokinetic constants and postulation of complex multicompartment systems, degrades many pharmacokinetic studies to expensive "highly sophisticated pseudo-scientific nonsense".

This also holds true in the field of drug development and marketing. Scientists in research institutes to a large extent will be aware of stereochemistry and its implications. But there appears to be some kind of an intolerable information gap between science and clinical practice. The development of "hybrid" drugs, presented as a step forward in medicinal chemistry, tends to be a step backward in therapy.

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