

REVIEW ARTICLE

Influence of Stereospecificity on Drug Bioavailability

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ABSTRACT

Chiral compounds contain unique structural design that cannot be superimposed but are with identical molecular formula. Bioavailability assessment of new drug products and formulations require assessing the time course of the active moiety in the systemic circulation. Large numbers of marketed and investigational drugs contain one chiral center and are administered as racemates. In drug development, enantiomeric selection is done to maximize therapeutic effects or alleviate drug toxicity that has yielded both success and failure. Further metabolism of chiral compounds can influence pharmacokinetics, pharmacodynamics, and toxicity. Optically pure pharmaceuticals may go through racemization *in vivo*, opposing single enantiomer benefits or inducing unexpected effects. Enantiomers may possess different carcinogenicity and teratogenicity. Appropriate chiral antidotes should be chosen for therapeutic benefit and to minimize adverse effects. The importance of stereo selective assays in various absorption, distribution, metabolism and excretion processes were studied. Establishment of bioequivalency by nonspecific assay therefore assures the bioequivalency of the active enantiomer, and enantiospecific assays would simply add to the cost of the study and drug development. A brief discussion of some important concepts such as enantiomer inversion, stereospecific first-pass metabolism, enantiospecific absorption and chiral excipients was studied.

Key words: Stereospecificity, racemisation, bioavailability, enantiomers.

INTRODUCTION

A large number of drug substances are not single chemical entities but rather mixtures. Chemical synthesis results in the formation of an optically inactive racemate containing an equal amount of two stereoisomers with identical physicochemical properties but differing in their property to rotate the plane of polarized light: one enantiomer will rotate the plane in the right direction, (dextrorotatory, *d* or *þ*) while its antipode will rotate in the opposite direction with the same magnitude (levorotatory, *l* or *–*). The more active enantiomer is termed the “eutomer,” and the less active the “distomer”. The distomer is often incorrectly viewed as a passive component of the racemate with little pharmacological or pharmacokinetic (PK) significance. However, in some cases, the distomer may act as an agonist or antagonist at the receptor site or compete for drug metabolizing enzymes and binding sites. When two or more chiral centers are present in a molecule, then a mixture of diastereoisomers with different physicochemical and maybe different

pharmacological properties is obtained. While there are limited examples of stereoselective bioavailability and pharmacokinetic studies of diastereoisomers, this group of stereoisomers has the greatest potential for displaying substantial stereospecificity in their pharmacological responses, and therefore a stereoselective assay for diastereoisomers should be considered in bioavailability and PK studies. Bioavailability assessment of new drug products and formulations requires assessing the time course of the active moiety in the systemic circulation. The most common stereoisomers found together in medicines are optical isomers, or compounds for which their structures are mirror images: the drug substance is usually a racemate, a 50:50 mixture of *R* and *S* isomers, some drug substances contain geometric isomers and still others especially proteins of high, molecular weight derived from natural products or through fermentation, may be a mixture of structurally related but chemically distinct compounds. Each chemical entity within

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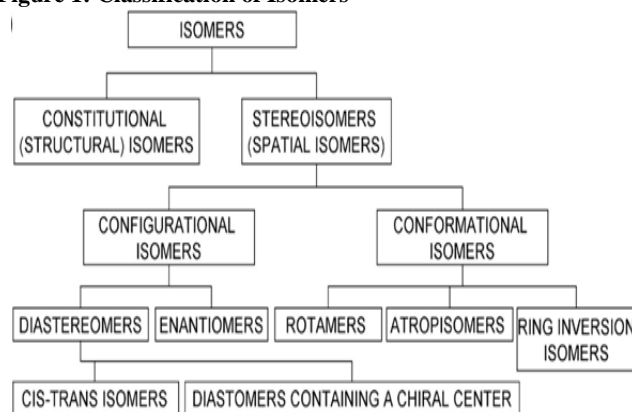
the drug substance can have a different pharmacologic, toxicologic, and pharmacokinetic profile^[1]. For example, dextro amphetamine (S isomer) is a potent central nervous stimulant, whereas the R enantiomer is almost devoid of such activity. Many commonly employed chemical assays do not distinguish between stereoisomers. Obviously, under these circumstances, attempting to quantify the various processes and to relate plasma concentration to response has many problems with no simple solutions. Notwithstanding these problems, specific information about each chemical entity should be studied whenever possible. Increasingly stereoisomers are being produced as single chemical entities, such as S-naproxyn which avoid these problems. In contrast many new protein and polypeptide drugs are being introduced that may in many instances, lack purity. Furthermore, these substances are often measured by assays that lack Specificity^[2].

One in four therapeutic agents are marketed and administered to humans as mixtures. These mixtures are not drug combinations in the accepted meaning of the term, i.e., two or more coformulated therapeutic agents, but combinations of isomeric substances, the biological activity of which may vary markedly. The majority of these mixed formulations arise as a result of the use of racemates, an equal parts mixture of enantiomers, of synthetic chiral drugs and, less frequently, mixtures of diastereoisomers. A survey of 1675 drug structures carried out in the 1980s revealed the extent of the problem. Of the 1200 (72%) agents classified as synthetic, 422 (25%), and 58 (3.5%) were marketed as racemates and single enantiomers, respectively.

That the individual enantiomers present in a racemate may exhibit differential biological properties has been known for over a century. However, only relatively recently with advances in the chemical technologies associated with the synthesis, analysis, and preparative scale separation of chiral molecules has the potential significance of stereochemical considerations in pharmacology and therapeutics been appreciated and, in some instances exploited, to a great extent. These new technologies have facilitated both the pharmacological evaluation of single stereoisomers and their production on a commercial scale. Such biological evaluation has resulted in an increased awareness of the potential significance of the differential pharmacodynamic and pharmacokinetic properties of the enantiomers

present in a racemate, particularly with respect to safety issues, and the use of such mixtures has become a cause of concern.

Figure 1: Classification of Isomers



Biological Activity

That enantiomers should be regarded as different compounds, rather than different forms of the same compound and that in some instances, a racemate may be regarded as a “third compound,” is particularly emphasized on examination of their biological properties. The differential pharmacological activity of drug enantiomers was shown in the early years of the last century when the British pharmacologist Cushny demonstrated differences in the activity of (–)-hyoscyamine and atropine (racemic hyoscyamine) and (β)- and (–)-adrenaline. In order to rationalize the observed differences in pharmacological activity between enantiomers Easson and Stedman, in 1933, suggested a “three point fit” model between the more active enantiomer and its receptor. According to the Easson–Stedman model the more potent enantiomer is involved with a minimum of three intermolecular interactions with the receptor surface whereas the less potent isomer may interact at two sites only. Thus the “fit” of the enantiomers to the receptor are different, as are their binding affinities. Similarly, an achiral analog of the drug should also interact at two sites with an affinity and/or activity similar to that of the less potent enantiomer.

The Easson–Stedman model was supported by an examination of the activity of the enantiomers of adrenaline and the achiral desoxy analogue N-methyldopamine. The three functionalities involved in the drug receptor interactions are postulated to be the methylamino group, the catechol ring system, and the secondary alcohol. Only in (–)-(R)-adrenaline (5.31) are these functionalities appropriately configured to take

part in three simultaneous interactions with the receptor. In the case of (S)-adrenaline the hydroxyl group is orientated in an unfavorable position to interact with the receptor and only a two-point interaction is possible. Similarly, N-methyldopamine may interact at two sites, with the result that the activity is similar to that of the S-enantiomer and much less than that of (R)-adrenaline.

Similar data have been obtained for the corresponding enantiomers and achiral derivatives of (R)-noradrenaline (5.30) and (R)-isoprenaline for both α - and β -adrenoceptor activity. On examination of related chiral and desoxy achiral adrenergic agents the Easson–Stedman model was found not to hold always. In some instances the achiral analogues were found to be more active than the “less active” enantiomers. These anomalies were subsequently found to be associated with variable direct and indirect actions of the compounds. The “active” isomers were found to be more potent than their β -enantiomers and achiral analogues in both normal and catecholamine depleted, reserpine-pretreated tissues, whereas the (β)-enantiomers and achiral analogues were equipotent in catecholamine-depleted tissues and of variable potency in normal tissue. These observations resulted in the conclusion that the Easson–Stedman model only applies at sites of direct drug action. Thus, an examination of the stereoselectivity of drug action also provided additional insight into the mechanism of action.

Figure 2: The Easson–Stedman model

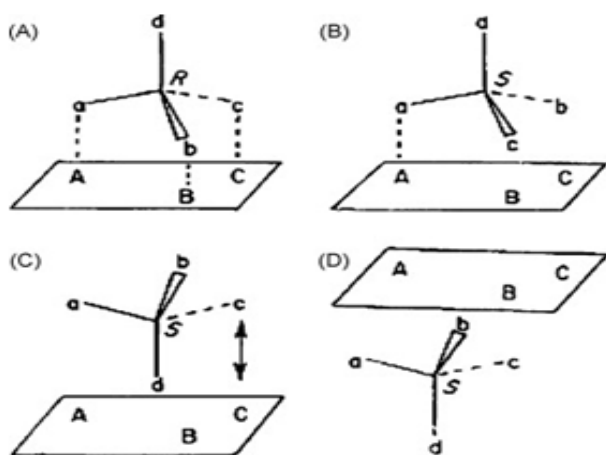


Figure 2 indicates the Easson–Stedman model as proposed originally. For the purpose of making *RS* configurational assignments, it is assumed that the priority sequence is $a > b > c > d$. The binding sites for *a*, *b*, and *c* are represented as A, B, and C. In the Easson–Stedman model (A), the *R*-enantiomer can bind at

all three sites and would be assumed to be the physiologically active material. However, the *S*-enantiomer is limited to a single contact point (B). An alternative possibility (C) for the *S*-enantiomer is ruled out because of steric hindrance by the *d* group. The distances, *a*–A, *b*–B, and *c*–C (indicated by the double arrow) are too large to permit binding. Further, the approach of the *S*-enantiomer from the interior (D) is not allowed.

Pharmacokinetic Considerations

As many of the processes of drug absorption and disposition involve an interaction between the enantiomers of a drug and a chiral biological macromolecule, it is hardly surprising that stereoselectivity is observed during these processes.

Absorption

The most important mechanism of drug absorption is passive diffusion through biological membranes, a process that is dependent upon the physicochemical properties of the molecule, e.g., lipid solubility, *pK_a*, molecular size, etc. If a chiral drug is absorbed by a passive process then differences between enantiomers would not be expected. In contrast, diastereoisomers may show differences in absorption as a result of the differences in their solubility. Stereospecific transport systems are known to exist in the gastrointestinal tract for L-amino acids, dipeptides, and D-carbohydrates, etc. and drugs which are similar in structure to such naturally occurring substrates may be expected to be actively transported. Thus L-dopa, L-penicillamine, and L-methotrexate have been shown to be more rapidly absorbed from the gastrointestinal tract than their D-enantiomers, which are not substrates and are absorbed by passive diffusion. Such active processes may be expected, in theory at least, to increase the rate rather than the extent of absorption. In fact the bioavailability of D-methotrexate is only 2.5% that of the L-isomer.

The drug efflux transporter P-glycoprotein, which participates in drug absorption, distribution, and excretion, is regulated stereospecifically. For example, *R*-cetirizine upregulates P-glycoprotein expression, while *S*-cetirizine down-regulates it. P-glycoprotein is enantioselectively inhibited by the *levo*-isomer of mefloquine, which can affect the transport of P-glycoprotein substrates such as cyclosporine and vinblastin. The human reduced folate carrier is stereospecific for the natural (6*S*) stereoisomer of 5-formyl tetrahydrofolate (leucovorin) and the antifolate

methotrexate. Stereospecific transport contributes to methyl mercury central nervous system (CNS) toxicity. Methyl mercury binds cysteine to generate methyl mercury-cysteine [$\text{CH}_3\text{-Hg-S-CH}_2\text{-CH(NH}_2\text{)COOH}$]. The structure's mimicry of methionine [$\text{CH}_3\text{-S-CH}_2\text{-CH}_2\text{-CH(NH}_2\text{)COOH}$] permits L-type large neutral amino acid carrier-mediated transport across the blood brain barrier. Methyl mercury-L-cysteine uptake significantly exceeds that of methyl mercury-D-cysteine^{3,4}. At certain

concentrations, *S*(-)-bupivacaine has a vasoconstrictor effect absent in the *R*(+)-isomer, which results in drug remaining at the injection site and a longer duration of analgesia. Levobupivacaine (Chirocaine), which did not carry the "black box" warning for cardiotoxicity required of racemic bupivacaine, has been discontinued in the United States.

Distribution

Protein binding

The majority of drugs undergo reversible binding to plasma proteins. In the case of chiral drugs the drug enantiomer-protein complexes are diastereoisomeric and individual enantiomers would be expected to exhibit differences in binding affinity to the circulating proteins. Such differences in binding affinity result in differences between enantiomers in the free, or unbound, fraction that is able to distribute into tissue. The two most important plasma proteins with respect to drug binding are human serum albumin (HSA) and α 1-acid glycoprotein (AGP). In general acidic drugs bind predominantly to HSA, whereas basic drugs bind predominantly to AGP.

Chirality may influence the basic pharmacological property of protein binding. Albumin has species-specific, stereo-specific binding preferences⁵. Despite diazepam's rapid interconversion, its *M*-form prevails when bound to albumin. Bilirubin, which is achiral in solution due to rapid interconversion of its *M*- and *P*-forms, binds albumin in the *P*-form. Human albumin prefers the active *S*-enantiomer of ketoprofen and has stereoselectivity to other non-steroidal anti-inflammatory drugs (NSAIDs). Human albumin also displays stereoselective binding to warfarin^[6]. Albumin binds *S*(+)-chloroquine more avidly than *R*(-)-chloroquine, whereas α 1-acid glycoprotein binds the *R*-enantiomer more tightly^{7,8}. α 1-acid glycoprotein has stereospecific affinity for *R*(-)-disopyramide, *S*(-)-verapamil, and *R*(+)-

propranolol, and preferably binds the *P*-conformer of diazepam.

Differences between enantiomers in plasma protein binding may be relatively small and in some cases less than 1%. However, such low stereoselectivity in binding may result in much larger differences in the enantiomeric composition of the free, or unbound, fraction particularly for highly protein-bound drugs. For example, the free fractions of (*l*)-*R*- and (*d*)-*S*-indacinone are 0.9% and 0.3%, respectively, i.e., a threefold difference.

Tissue distribution

The extent of tissue distribution of a drug depends on both its lipid solubility and relative plasma to tissue protein binding. In a number of instances differences in calculated volumes of distribution between enantiomers are lost when plasma protein binding is taken into account and unbound volumes of distribution are compared. Similarly, apparent stereoselective distribution of some drugs into various tissues and fluids may be rationalized by differences between enantiomers in protein binding, e.g., the stereoselective distribution of (*S*)-ibuprofen into synovial fluid may be explained by differences in protein binding. Lipid solubility is obviously an important factor for drug transfer across biological membranes and it would appear that lipophilicity is of greater significance than chiral drug-lipid interactions.

However, recent evidence has indicated that some basic drugs preferentially accumulate in tissues containing acidic phospholipids, e.g., phosphatidylserine. Stereoselective interactions, assumed to be electrostatic, between phosphatidylserine and morphine have been reported and there is evidence that other basic chiral drugs, e.g., disopyramide and verapamil, undergo preferential and stereoselective distribution in tissues containing a high content of phosphatidylserine.

Metabolism

In contrast to other processes involved in drug absorption and disposition, drug metabolism frequently exhibits marked stereoselectivity. Stereoselectivity in metabolism may be associated with the binding of the substrate to the enzyme, and therefore associated with the chirality of the enzyme-binding site. Alternatively, selectivity may be associated with catalysis due to differential reactivity and/or orientation of potential target groups with respect to the enzyme catalytic site. The biotransformation reactions

(e.g., hydrolysis, reduction, oxidation, and conjugation) may demonstrate isomeric preference. (*S,S*)-hydroxybupropion is stereoselectively active at dopamine transporters, norepinephrine transporters, and nicotinic acetylcholine receptors. At therapeutic concentrations, CYP2B6-mediated hydroxylation of (*S*)-bupropion to metabolically active (*S,S*)-hydroxybupropion is significantly greater than (*R*)-bupropion, leading to greater apparent oral clearance and lower plasma concentrations^[9]. (*S,S*)-hydroxybupropion is formation-rate-limited, whereas (*R,R*)-hydroxybupropion and racemic hydroxybupropion are elimination-rate-limited. Thus, CYP2B6 phenotypic variability, inhibition or induction, or overdose might alter the clinical consequences of bupropion ingestion. Hepatic, jejunal mucosa, and platelet sulfation of *R*(-)-salbutamol (albuterol) is approximately ten times greater than the *S*(+)-isomer^[10]. The (*S*)-enantiomer of carvedilol undergoes stereoselective oxidation by cytochrome P450 (CYP) 2D6 and CYP1A2 in liver and stereoselective glucuronidation in liver and intestine, which is at least partly responsible for stereoselective presystemic clearance. CYP2C19 preferential metabolism of *S*(-)-lansoprazole is further influenced by polymorphism status (homozygous and heterozygous extensive metabolizers, and poor metabolizers)^[11]. Similarly, systemic *R/S* enantiomer exposures to fluoxetine, metoprolol, pantoprazole, and trimipramine are altered according to CYP2D6 or CYP2C19 status^[12]. CYP2D6 stereoselectively catalyses the *O*-demethylation of (*R*)-venlafaxine. Stereoselective drug metabolism and elimination has been reported for a numerous other compounds: ketamine, whose *R*(-)-ketamine inhibits the more rapidly clearing *S*(+)-ketamine; (*S*)-pentoxifylline conversion to its M1 metabolite; tramadol *N*-demethylation to *S*(-)-*O*-demethyltramadol; renal tubular secretion of *dextro*-cetirizine; and clearance of verapamil isomers^[13-15].

Excretion

Renal excretion is the net result of glomerular filtration, active secretion, and passive and active reabsorption. Since glomerular filtration is a passive process differences between enantiomers would not be expected. However, apparent stereoselectivity in renal clearance may arise as a consequence of stereoselectivity in protein binding. Stereoselectivity in renal clearance may be observed as a result of active secretion;

however, active reabsorption and renal metabolism may also be significant. Active renal tubular secretion is thought to be responsible for the differential clearance of the enantiomers of a number of basic drugs with stereoselectivities in the range of 1.1 to 3.0. The renal clearance of quinidine has been reported to be four times greater than that of its diastereoisomer quinine. The renal clearance of the diastereoisomeric glucuronide conjugates of both ketoprofen and propranolol has also been reported to show stereoselectivity. In both cases renal clearance is selective for the *S*-enantiomer conjugate of the drug with selectivities of 3.2- and 1.3-fold for propranolol and ketoprofen, respectively.

Large numbers of marketed and investigational drugs contain one chiral center and are administered as racemates^[16,17]. The use of stereoselective assays in comparative bioavailability studies, however, remains controversial^[18,19]. Those arguing in favor of the stereoselective assays reason that with advances in analytical methodologies, enantiospecific assays are now widely available and should be used if the predominant pharmacological activity (or toxicity) of the racemate drug is associated with one enantiomer. Those against the use of stereoselective assays reason that such assays are not necessary because the administered racemate contains the same proportion of each enantiomer, and in bioequivalency studies one compares the rate and extent of the drug availability under identical conditions in the same subject. Establishment of bioequivalency by nonspecific assay therefore assures the bioequivalency of the active enantiomer, and enantiospecific assays would simply add to the cost of the study and drug development.

Enantiomer Interconversion

In vitro prostaglandin synthetase inhibition with some NSAIDs is related to the *S*-isomer, administration of separate isomers or racemates produce similar *in vivo* activities. This anomalous finding is due to the thioester-mediated conversion of the inactive *R*-isomer to the active *S*-isomer^[20]. The conversion of the active *S*- to inactive *R*-isomer is not possible owing to the inability of the *S*-isomer to form the thioester. Ibuprofen, fenoprofen, and benoxaprofen undergo extensive enantiomer conversion, while flurbiprofen, indoprofen, flunoxaprofen, and tiaprofenic acid undergo limited enantiomer conversion²¹. Since the *R*-isomer of NSAIDs may be considered inactive, it is possible that with

those NSAIDs exhibiting little enantiomer interconversion, equal therapeutic effects can be obtained by administering only the S-isomer at lower doses than that required for the racemic drug, leading to possible reduction in NSAIDs-related gastrointestinal (GI) adverse effects.

Stereoselective First-Pass Metabolism

Many beta-blockers and calcium channel blockers are administered orally as racemates, and they have high oral absorption but low systemic availability of the active moiety owing to high hepatic first-pass metabolism. If there is high enantioselective first-pass metabolism, and if the enantiomers have different pharmacological characteristics, then the PK/PD study to evaluate the relationship between plasma concentration and response, when a nonspecific assay is used, will depend on the route of drug administration. When both enantiomers have very high hepatic extraction ratios following i.v. administration, they will have similar total body clearance, which will approach hepatic plasma or blood flow. Owing to this flow limited clearance, differences in intrinsic hepatic clearances of enantiomers may not be evident from their clearance values obtained after i.v. dosing. After oral administration, however, intrinsic clearance differences may lead to large variations in the enantiomer systemic availabilities.

Enantiospecific Absorption And Chiral Excipients

Some racemic drugs, such as methotrexate, leucovorin, L-dopa, cephalixin and terbutaline exhibit enantioselectivity in absorption. Also, many of the excipients used in the oral dosage forms, such as sugars, cellulose, alginate, and cyclodextrins, are chiral themselves some of these materials are even used in racemic chromatographic separations. Overall, various factors are known to affect the systemic absorption of orally administered drugs; so the PK/PD characteristics of each racemic drug should be considered individually when deciding whether an enantiospecific assay is necessary in comparative bioavailability studies.

CONCLUSION

Evaluation of chiral compounds must take into account three-dimensional structure-activity relationships, which may take on varied importance at different receptor types. Chiral considerations are relevant to diverse aspects of pharmacology and pharmacokinetics.

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