

A review of drug isomerism and its significance

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ABSTRACT

Isomerism finds its importance in the field of clinical pharmacology and pharmacotherapeutics, as isomers differ in their pharmacokinetic and pharmacodynamic properties. Drug isomerism has opened a new era of drug development. Currently, knowledge of isomerism has helped us in introducing safer and more effective drug alternatives of the newer as well as existing drugs. Many existing drugs have gone chiral switch i.e., switching from racemic mixture to one of its isomers. Cetrizine to levocetizine is one of such examples, where effective and safer drug has been made available. In this article, we have attempted to review the basic concepts of stereochemistry and chirality and their significance in pharmacotherapeutics. Various pharmacological aspects such as pharmacokinetic and pharmacodynamic variations resulting out of chirality has been discussed in detail in this article.

Key words: Enantiomer, enantiomorphs, enantiopure

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INTRODUCTION

Stereoisomers are the molecules that are identical in atomic constitution and bonding, but differ in the three-dimensional arrangement of the atoms. An enantiomer is one of two stereoisomers that are mirror images of each other but are nonsuperimposable (not identical), as one's left and right hands, that are the same except for opposite orientation.^[1] Organic compounds that contain an asymmetric (chiral) carbon usually have two nonsuperimposable structures. These two structures are mirror images of each other and are, thus, commonly called enantiomorphs (enantio = opposite, morph = form). Hence, optical isomerism is now commonly referred to as enantiomerism.^[1] Enantiopure compounds refer to samples having, within the limits of detection, molecules of only one chirality.^[2]

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BASIC CONCEPTS

Isomers by definition are the molecules of identical atomic compositions, but with different bonding arrangements of atoms or orientations of their atoms in space i.e., isomers are two or more different substances with the same molecular formula.^[3-5]

Three types of isomerism are possible – Constitutional, Configurational, and Conformational. The terms configuration and conformation are often confused. Configuration refers to the geometric relationship between a given set of atoms, for example, those that distinguish L- from D-amino acids. Interconversion of configurational alternatives requires breaking covalent bonds. Conformation refers to the spatial relationship of every atom in a molecule. Interconversion between conformers occurs without covalent bond rupture, with retention of configuration, and typically via rotation about single bonds.^[4]

Constitutional isomers are also called structural or positional isomers. These are molecules with same atomic composition but different bonding arrangements between atoms. Examples of constitutional isomerism are catechol, resorcinol, and hydroquinone; all of these compounds having the same atomic compositions ($C_6H_6O_2$), but different bonding arrangements of atoms. These are distinct chemical entities with different chemical and physical properties.^[6] Configurational isomers are defined as molecules with identical atomic composition and bonding arrangements but

with different orientation of atoms in the space. These different orientations cannot interconvert freely by bond rotation. Example is d- and s- amphetamine. Conformational isomers are different by relative spatial arrangements of atoms that results from rotation about sigma bonds. Thus, unlike configurational isomers, conformers are interconverting stereoisomers of a single compound.

SEVERAL NEUROLOGIC DISEASES RESULTS FROM ALTERED PROTEIN CONFORMATION

Prions diseases

Prion diseases are fatal neurodegenerative diseases characterized by spongiform changes, astrocytic gliomas, and neuronal loss resulting from the deposition of insoluble protein aggregates in neural cells. They include Creutzfeldt-Jakob disease in humans, scrapie in sheep, and bovine spongiform encephalopathy in cattle.^[3]

Alzheimer's disease

Refolding or misfolding of protein endogenous to human brain tissue, amyloid beta or Abeta-amyloid, is a prominent feature of Alzheimer's disease. In Alzheimer's disease patients, levels of Abeta-amyloid/amyloid beta or become elevated, and this protein undergoes a conformational transformation from a soluble helix-rich state to a state rich in Abeta or amyloid beta sheet and prone to self-aggregation.^[3]

CHIRALITY

A molecule is referred to as chiral if it is not super imposable to its mirror image. The best example of chirality is our hand. Two hands cannot be superimposed identically, despite the fact that our fingers of each hand are connected in the same way. The term chiral was derived from Greek word "cheir" meaning hand and was applied as a description of left and right handedness of crystal structure resulting from molecular asymmetry.^[6] An atom such as carbon, nitrogen, phosphorus, sulphur and silicon forms a tetrahedral structure with four different groups attached to them. They form two nonsuperimposable mirror images. Most optical active drugs are chiral as a result of the presence of asymmetrically tetrahedral carbon atoms. The individual mirror image forms of a chiral molecule are called optical isomers because they rotate the plane of polarized light i.e., they are optically active and differ in structure only in the orientation of atoms. Today, optical isomers are more commonly referred as enantiomers or an enantiomeric pair.^[7,8]

Optical isomers or enantiomers have same physical and chemical properties like identical melting points, pKa,

solubilities, etc. But the important difference between two is that each member rotates the plane of polarized light to the same degree, in opposite directions. Isomerization or enantiomerization is the conversion of one stereo-isomeric form into another (R-ibuprofen to S-ibuprofen). When isomerization occurs by the change of configuration at a single chiral center, the process is called epimerization, and when it leads to the formation of racemes, it is termed racemization.^[3]

DRUG ISOMERISM AND CHIRALITY

Stereoisomers differ in pharmacokinetic and pharmacodynamic properties. Pharmacokinetic differences resulting out of stereoisomerism can be in absorption like L-Methotrexate is better absorbed than D-Methotrexate, Esomeprazole is more bioavailable than racemic omeprazole; in distribution like S-Warfarin is more extensively bound to albumin than R-Warfarin, hence it has lower volume of distribution.^[5,9] Levocetirizine has smaller volume of distribution than its dextroisomer,^[10] d-Propranolol is more extensively bound to proteins than l-Propranolol; in metabolism like S-Warfarin is more potent and metabolized by ring oxidation while R-Warfarin is less potent and metabolized by side chain reduction, half life of S-Warfarin is 32 hours while it is 54 hours for R-Warfarin.^[5,9]

Pharmacodynamic differences resulting out of stereoisomerism can be in pharmacological activity and potency like l-Propranolol has beta-adrenoceptors blocking action while d-propranolol is inactive; Carvedilol is a racemic mixture, the S(-) isomer is a nonselective beta-adrenoceptor blocker, while both S(-) and R(+) isomers have approximately equally alpha-blocking potency; S-Timolol is more potent alpha-blocker than R-timolol but both are equipotent ocular hypotensive agents; Labetalol is formulated as a racemic mixture of four isomers, two of these isomers - the (S, S)- and (R, S)- isomer are relatively inactive, a third (S, R)- is a potent alpha-blocker and the fourth one (R, R)- is a potent beta-blocker. Labetalol has a 3:1 ratio of beta: Alpha antagonism after oral administration; Sotalol is formulated as a racemic mixture of D- and L-isomers, L-isomer has beta-blocking activity while D-isomer has no beta-blocking activity. The action potential prolonging potential is due to L-isomer; Nebivolol has highly selectively beta-1-blocking effects, while the L-isomers causes vasodilatation; Most beta-2-selective agonist drugs are formulated as a racemic mixture of R- and S- isomers. Only the R-isomer has the beta-2-agonistic activity while S-isomer has no beta-2-agonistic activity, even S-isomer promotes the inflammation. Now a days, Salbutamol is available as a single isomeric preparation of R-isomer as levalbuterol;^[5,9] Ibuprofen is a racemic mixture; S-ibuprofen is active form and R-ibuprofen is inactive. Dexibuprofen, its active enantiomer, is marketed now as single enantiomer with an effective dose of 50% of ibuprofen and fewer side effects;^[11] Halothane, enflurane,

and isoflurane are chiral drugs with different anesthetic potencies;^[5,9] D- (+) 2R,3S propoxyphene is analgesic while (-) 2S,3R propoxyphene has antitussive action.^[12]

Isomerism can lead to different therapeutic uses and adverse drug reactions like Quinine has antimalarial activity while quinidine has an antiarrhythmic property; L-sotalol is alpha-blocker while d-sotalol is antiarrhythmic; Levomethorphan is a potent opioid analgesic while dextromethorphan is a cough suppressant;^[5,9] R-Thalidomide is sedative while S-Thalidomide has been shown teratogenic effects;^[13] R-Naproxen is used for arthralgic pain while S-Naproxen is teratogenic;^[5] D-Ethambutol is antituberculosis drug while L-ethambutol has been found to cause blindness;^[14] (S) (+)-ketamine causes fewer psychotic emergence reactions, less agitated behavior, and better intraoperative amnesia, and analgesia than its enantiomer; L-dopa, used in treatment for Parkinson's disease has an isomer D-dopa which has never been used because it causes deficiency of white blood cells and thus susceptibility to infections.^[5,9]

Two stereoisomers can compete for binding to same receptors like S-methadone antagonizes respiratory depression action of R-methadone. If the two isomers are of agonist and antagonist type, then racemic mixture acts as partial agonist like picendol and sulfinpyrazone inhibits the metabolism of S-Warfarin significantly but not of R-Warfarin.^[5,9]

SINGLE ENANTIOMERS VS. RACEMIC MIXTURES

Single enantiomers have less complex and more selective pharmacodynamic profile as compared to racemic mixture, so have lesser adverse drug reactions, improved therapeutic profile, less chances of drug interactions than racemic mixtures. Single enantiomers seem to be more advantageous over racemic mixtures as - adverse drug reactions occurring due to one enantiomer are avoided, patients are exposed to less amount of drug so body is exposed to the lesser metabolic, renal and hepatic load of drug, there is easier therapeutic drug monitoring of the active pure active enantiomers. A number of drugs are marketed now as single enantiomer like Levosalbutamol, Escitalopram, Naproxen, etc. Many antibiotics have only one enantiomer produced because they are made by fermentation and even the semi-synthetic ones start with the natural fermentation product like quinolones and all penicillins.^[15]

CONCLUSIONS

Research in the field of stereoisomerism has opened the new challenges and the new field avenues in the field of clinical

pharmacology. Currently a large number of clinical trials are going on to compare the efficacy and safety of single enantiomers and the racemic mixture. Many single enantiomer drugs will hopefully flood the market in near future.

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