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THERAPEUTIC EFFICACY OF STEREOISOMERS

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ABSTRACT

Stereoisomers are molecules that are identical in atomic constitution and bonding, but differ in the three-dimensional arrangement of the atoms. They are often readily distinguished by biological systems, however, and may have different pharmacokinetic properties (absorption; distribution, biotransformation. and excretion) and quantitatively or qualitatively different pharmacologic or toxicologic effects.Approximately 50% of marketed drugs are chiral having enantiomers and approximately 50% of these are mixtures of enantiomers rather than single enantiomers. One member of the pair may show inactivity or toxicty compared to the other one. E.g. granulocytopenia is related to the d-isomer of levodopa; Vomiting is caused by the d-isomer of levamisole; and myasthenia gravis symptoms were no longer observed when the d-isomer was removed from d,lcarnitine) etc.[1] This review article emphasis on the application of optical isomers in medical research&on issues relating to the study and pharmaceutical activityof individual enantiomers and racemates.

KEYWORDS: enantiomer, optical isomer,pharmokinetic properties,arrangement of atoms.

INTRODUCTION

Structural isomers have the same molecular formula but a different bonding arrangement among the atoms. Stereoisomers have identical molecular formulae and arrangement of atoms they differ from each other only in the spatial orientation of groups in the molecule. Optical isomers (or enantiomers) are stereoisiomers that are non-superimposable mirror images of each other. Different notations are used to distinguish the two enantiomers of a pair: (+) and

(-) refer to the direction in which the plane-polarized light is rotated; (+) symbol for clockwise direction and (-)symbol for anticlockwise rotation. The lower-case letters d-(dextrorotatory) and 1-(Ievorotatory) respectively have traditionally been used as alternatives for this but are becoming obsolete. Confusingly, D- and L- are a different, unrelated notation based on spatial configurations in comparison with the reference molecule glyceraldehyde. This system is widely used in naming many biological molecules such as amino acids and sugars. Other molecules are described by their absolute configuration, usingR (rectus) for right or clockwise and S (sinister) for left or counter-clockwise. The rules for determining the absolute configuration are based on atomic numbers and their masses.

Reactions outside the cell always produce an optically inactive mixture whereas biological activity is specific to one isomer.Drug isomerism have a significant role to play in medical practice as isomers differ in their pharmacokinetic and pharmacodyanmic properties.For some therapeutics, single-enantiomer formulations can provide greater selectivities for their biological targets, improved therapeutic indices, and/or better pharmacokinetics than a mixture of enantiomers. Hence, the subject knowledge can allow drug development of safer and more effective products.

This article reviews the nomenclature for describing stereochemistry and enantiomers, emphasizes the potential biological and pharmacologic differences between the 2 enantiomers of a drug, and highlights the clinical experience with single enantiomers.

Activity of optical isomers on body system and on various drugs.

CARDIOVASCULAR SYSTEM

β_1 selective adrenoreceptor antagonists viz atenolol, acetabutalol,metaprolol etc are levorotary drugs . They are more potent in blocking β-adrenoceptors than their dextrorotary isomers. S(-)verapamil is a calcium channel blocker that exhibit 10-20 times greater than its R(+) isomer which has far less cardiotoxicity and is used in cancer chemotherapy. Similarly for amlodipine which is second most widely used drug for hypertension[17] doesn't cause peripheral edema in it's S form and shows better activity than R-amlodipine.[2] Carvedilol, a non selective third generation beta blocker has proven 2-4 times more potent than propranolol as a beta-receptor blocker in trials conducted testing its efficacy for heart failure.[16] S(-)isomer interacts with adrenoreceptors with 100 times greater potency as β adrenoreceptor blockerthan R(+)isomer also (-)propranolol is 100 times more active as a anti-hypertensive

than R(+)propranolol which can inhibit the conversion of thyroxin (T4) to triiodothyronin (T3).But, Valsartan which is an angiotensin II receptor antagonist showsmore activity in R form than S. Due to better binding activity with the receptor. A new drug Crestor(rovustain calcium) is used for hyperchlorestrolemia is used in RS form.

CENTRAL NERVOUS SYSTEM

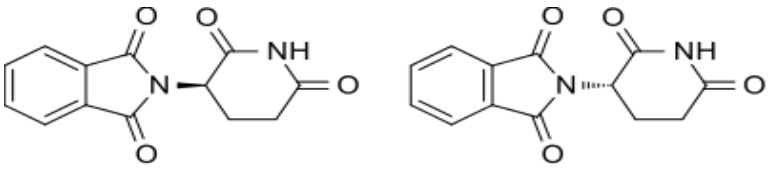
Barbiturates which are used as hypnotics are racemic compounds and only l-isomer is active, the other is either inactive or excitative. For example, S(-)secobarbital is more potent as anesthetics than R(+)secobarbital. Ketamine is administered intravenously due to its potency by virtue of its property. The S(+) isomer is more potent and less toxic than its R(-) antipode which has side effects like agitation, hallucination, restlesness. Isoflurane is used in surgical operations[3] shows more effective in (+) form than (-) isomer at inhibiting currents induced by the bath application of acetylcholine. S(+)citalopram is used as antidepressant and possess 100-fold more potency as a selective serotonin reuptake inhibitor than R(-) enantiomer. Dopa or dihydroxy-3,4 phenylalanine is in Parkinson disease.The l-Dopa(-) form of the drug is widely used in therapeutics as d-form(+) produces toxicity & agranulocytosis. (3-hydroxy-benzodiazepines) oxazepam, lorazepam, temazepametc) are used as tranquilisers. A single chiral center, the (-)enantiomer possesses much greater affinity for binding to the GABA receptors than the antipode. Other drugs likeR(+)5-hydroxy-1-methylhydantoin is useful as a highly-active agent for renal failure whereas the S-form is used as an anticonvulsant[4], Secobarbital enantiomers are equipotent as anticonvulsants, but the S(-)isomer is a more potent anesthetic and is also more toxic than the R(+)isomer.

The D-isomers of Amphetamine and methamphetamine are strong central nervous system (CNS) stimulants, while the L-isomers lack appreciable CNS stimulant effects, but instead stimulate the peripheral nervous system. Methadone, a central-acting analgesic with high affinity for μ-opiod receptors, has been used to treat opiate dependence and cancer pain. In humans, R(-)methadone is about 25-50 fold more potent as an analgesic than its S(+) antipode.[5]

- Pfizer's pain drug Lyrica (pregabalin a 3-isobutylgaba), which saw $5.1bn worth of revenue[20], is a lipophilic analogue of GABA which shows its activity in S(+)3isobutylgaba form.

IMMUNOMODULATORY DRUGS

Thalidomide was earlier given to pregnant women to reduce the effects of morning sickness led to many disabilities in babies and early deaths in many cases. Theoretically, only the inactive S(-) isomer is teratogenic & causes birth defects, while the R enantiomer is effective against morning sickness but practically, both isomers are genotoxic because of its in-vivo interconversion and of its species-dependence.[18,19]



The (-) enantiomer of gossypol possesses higher anticancer potency than racemic gossypol in human breast cancer.[6]

- Emtricitabine and tenofovir alafenamide (F/TAF) by Gilead Sciences and Japan Tobacco.[21] The cis (2R, 5S) isomer of Emtricitabine is found to have profound antiviral activity as a human Immunodeficiency Virus Nucleoside Analog Reverse Transcriptase Inhibitor and is used in HIV-1 infection while the other cis (2S, 5R) isomer and the trans isomers (2S, 5S) and (2R, 5R) have lower therapeutic activity and are found to be of reduced interest in therapeutics.[22]

ENDOCRINE SYSTEM (THYROID GLAND)

Levothyroxine, also known as L-thyroxine, is a synthetic thyroid hormone that is chemically identical to thyroxine (T_4). It is used to treat thyroid hormone deficiency, and occasionally to prevent the recurrence of thyroid cancer. Dextrthyroxine (D-thyroxine) causes cardiac side effects when used as a treatment for hypercholestrolemiaand hence,D Thyronine (T_3) might be of value in the prophylaxis of atherosclerosis in cases of symptomless hypercholesterolaemia.[7]

RESPIRATORY SYSTEM

Albuterol (salbutamol), salmeterol and terbutaline are sympathomimetic drug-selective β_2-adrenoceptor agonists mainly used as bronchodilators in the treatment of asthma. Pharmacologically, only their l-isomer or R(-)isomer is effective and the other inactive d-or S(+)isomer may be responsible for the occasional unpleasant side-effects associated with the drug.

GASTRO-INTESTINAL SYSTEM

Proton pump inhibitor Esomeprazole{S(-)enatiomer} of omeprazole is pronounce to reduce stomach acid & is used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease, and Zollinger-Ellison syndrome.

AUTOCOIDS & RELATED DRUGS

- **Non steroidal antiinflammatory drugs & antipyretic activating factors (NSAIDs)** 2-arylpropionate nonsteroidal anti-inflammatory drugs (NSAID), namely ibuprofen, ketoprofen, fenprofen, benoxaprophen, etc show more activity in S-enantiomer i.e. has more analgesic and anti-inflammatory effect than R antipode. Example: S-ibuprofen is over 100-fold more potent as an inhibitor of cyclooxygenase I than (R)-ibuprofen. In the body, only inactive R-enantiomer can undergo chiral inversion by hepatic enzymes into the active S-enantiomer and not vice-versa. Naproxen, the propionic acid class NSAID is used to treat minor aches , pain associated with a common cold and certain symptoms of arthritis and menstrual cramps in S(+) form , but R(-)naproxen causes liver poisoning with no analgesic effect.

- **Histamines & anti-histamines**

Levocetirizine (R enantiomer) of cetirizine, a IInd-generation antihistamine is preferred over other anti- histaminic drugs due to its potency and non-sedative action and better therapeutic index. It has an affinity for H1 receptors approximately 2-fold higher than racemic cetirizine.[8] Thus prescribed in hay fever, allergies, angioedema, and urticaria. Dextrocetirizine (S enantiomer) do not show antihistaminic effects. Dexchlorpheniramine is the D-isomer of chlorphenariramine & used to treat allergic conditions such as hay fever or urticaria.

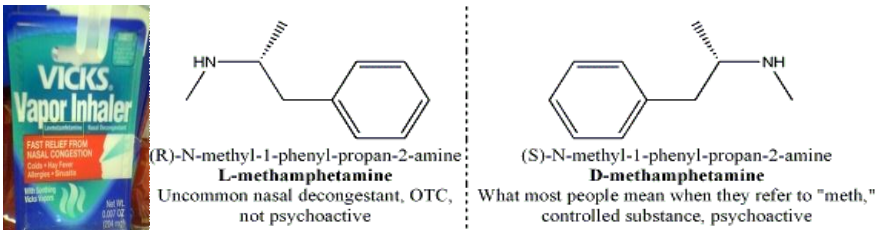
ANTIBACTERIALS (ANTI-TB)

Ethambutol is used widely for thr treatment of tuberculoisis. It shows its activity by inhibition of arabinosyl transferase, an enzyme that polymerizes arabinose into arabinan and then arabinogalactan, a mycobacterial cell wall constituent. This activity is more for its (S,S)-(+)-enantiomer whereas (R,R)-(–)-ethambutol causes blindness. Penicillin's activity is stereodependent. The antibiotic must mimic the D-alanine chains that occur in the cell walls of bacteria in order to react with and subsequently inhibit bacterial transpeptidase enzyme.

SOME WIDELY USED RACEMIC COMPOUNDS

- Glucose: The L form of glucose is a low-calorie sweetener and it is suitable for patients with diabetes mellitus also found to be a laxativebut cannot be used by living organisms as source of energy because it cannot be phosphorylated byhexokinase, the first enzyme in the gylcolysis pathway hence, D glucose is accepted and used widely as a good source of energy to humans and animals.[9]

- Methamphetamine: The L form is available over-the-counter as the active ingredient of the Vicks inhaler and is a metabolite of certain prescription medications whereas the D form is most frequently used as a prescription stimulant and appetite suppressant.[10]



CONCLUSION

Optical isomerism is very common in medicine.Drugs have different enantiomers where one form may be responsible for the successful effects of a drug. whereas the other may be inactive or even harmful. The two forms must be distinguished because they may differ in dosages, effectiveness, side effects, and indicated use. The increasing availability of single-enantiomer drugs promises to provide clinicians with safer, better-tolerated, and more efficacious medications for treating patients. When both a single-enantiomer and a racemic formulation of a drug are available, the information from clinical trials and clinical experience helps to decide the right formulation. Reserach to drug discovery should also be focussed to this direction to achieve high therapeutic relevent results.

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