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Chiral Chemistry in Pharmacology – A Review

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Abstract

Stereochemistry is a branch of Chemistry involving the study of relative spatial arrangement of atoms within the molecules. Stereoisomers of a same pharmacological agent may show different pharmacological activity on different receptors and on different systems. They are classified as Constitutional Isomers and Stereoisomers. Chirality also influences a lot of Pharmacological Processes ie at both pharmacodynamic level, safety level and also at pharmacokinetic levels. One of the most important advantages of studying Chirality in Pharmacology is removal of unwanted adverse effects, if due to an isomer. Newer interest has developed in studying isomers of already existing drugs as individual drugs, in a quest to find a drug which is highly safe and efficacious as well.

Keywords: *Chiral Chemistry, Stereochemistry, Chirality, Isomers, pharmacology*

Introduction and History:

Stereochemistry is a branch of Chemistry involving the study of relative spatial arrangement of atoms within the molecules. *Chirality* is the property of certain molecules to have the same molecular formula but different structural formula. *Isomers* are molecules with same molecular formula but different structural formula. *Racemicity* is a word derived from the word racemes, which means bunch of grapes. So it is the mix of all the chiralities possible with that particular compound. [1]

In 1815, a chemist Jon Baptiste Biot first thought and postulated the theory of Chirality. Louis Pasteur who is also known as the father of modern medicine first observed the phenomenon of Chirality in 1848. He observed that tartaric acid which is the by product of the wine industry derived from different types of grapes was able to rotate the plane of light differently. Tartaric acid derived from certain variety of grapes used to rotate the plane of light to right whereas some to the entirely opposite direction. Jacob Henricus Van Hoff first defined Chirality and isomerism in 1873. Because of his contribution to this field, he is also called as the father of stereochemistry. In 1898, Lord Kelvin designed the first model of actual measurement of Chirality with the help of microwave radiations. This first model has acted as a development tool form many sophisticated instrument in stereochemistry for measuring and changing the Chirality of a molecule. [2]

Importance to Pharmacology:

Drugs are chemical entities so the property of Chirality is also applicable to drugs. Many isomers of a single drug are possible but the real question is that whether these isomers are chemically stable? But there are certain pharmacological agents who do show the property of Chirality and the isomers of such agents are chemically stable. These stereoisomers of a same pharmacological agent may show different pharmacological activity on different receptors and on different systems. For example D isomer of Amphetamine has got more activity in the CNS where it causes stimulation. L isomer of Amphetamine is CVS specific, where it causes increase in the systolic and diastolic BP.[3]

Rules of Chirality applicable to Pharmacology:

Pfeiffer Rule*:* [4] Sir C.C. Pfeiffer first observed that if a correct isomer is used instead of a racemic mixture, then reduction in dose is possible. This is better explained with 2 examples

a) the dose required of d – Amphetamine to treat attention deficit hyperactivity disorder (ADHD) is much less than the racemic Amphetamine.

b) Rabeprazole a proton pump inhibitor has two isomers, d and l. only d – Rabeprazole has got activity at the proton pumps. The l isomer is inert. So if we use d – rabeprazole (dexrabeprazole) the dose require will be lesser than racemic Rabeprazole.

Cahn Ingold Prelog Rule (CIP rule)*:*[5]

This rule explains the role of chiral centre which is also called as the stereocentre. Chiral centre is the area of the chiral molecule which retains its position in all the possible isomers of that molecule.

For pharmacological agents there are many chiral centres which are present. So many isomers are possible.

Number of isomers α Number of chiral centres present in the compound

But chemical stabitities of such isomers is a question.

Classification: [6]

1. Constitutional Isomers
2. Stereoisomers
3. Diastereomers (geometric isomers)
4. Configuration isomers (cis – trans isomers)
5. Conformational isomers
6. Conformers
7. Rotamers
8. Enantiomers (optical isomers)
9. D/L System of nomenclature
10. R/S System of nomenclature

Constitutional isomers*:* [6]

These isomers differ in the arrangement of single atom in molecule.

For example: Practolol a beta blocker is a Constitutional isomers of Atenolol has been withdrawn from the market due to its eye toxicity. But Atenolol is still used commonly.

Stereoisomers: [6]

These isomers differ in arrangement of entire group in a molecule across the chiral centre.

They are of 2 types.

Diasteriomers or Geometric isomers*:* [6]

These are not mirror images of each other and are not super imposable.

They are further sub classified into 2 types.

1) Configurational Isomers also known as Cis- trans isomers.

2) Conformational Isomers.

Cis - Trans Isomerism or Configurational isomerism [5]

In this isomerism the functional groups if on one side or the same side then they are called as Cis or same side isomer.When the functional groups are on the opposite side they are called as trans or opposite side isomers.Eg : cis – platin or Cisplatin is a antineoplastic chemotherapeutic agent, but trans – platin is inert.

Confirmational isomerism [5]

Here the rostation of a group is seen with respect to chiral centre.

It differs from Cis trans isomerism by lacking substitution.

They are of 2 types:-

Conformers and Rotamers

The only difference between them is conformers are seen for aliphatic compounds whereas rotamers are for cylical aromatic compounds

Examples: various amino acids have conformers and rotamers

Enantiomers: [6]

This is the most important type of isomerism. As many pharmacological agents show this type of isomerim.

In chemistry this type of isomerism is very popular as it is chemically very stable.

Enantiomers are isomers mirror images of each other. They are superimposable. Enantiomers are also called as optical isomers as they demonstrate optical activity. There are two ways of classifying Enantiomers:

D/L system of Nomenclature :

According to this system the isomers which rotate the plane of light to the right are called as dextrorotatory (+) and the ones which rotate it to the left are called as levorotatory (-). Examples: d – Amphetamine and l – Amphetamine are isomers of Amphetamine.

R/S system of Nomenclature:

This system of nomenclature is independent of the optical activity of the chemical or drug. This system depends on attachment of the functional group to the chiral centre. The compound which has got the

functional group attached to the right side of the chiral centre is the R isomer (rectus). The isomer where the functional group is attached to the left of the chiral centre is the S isomer (sinister). Examples : Esomeprazole is the S isomer of Omeprazole, Escitalopram is the S isomer of Citalopram.

Influence of Chirality on Pharmacological Processes:

- **Pharmacodynamic Processes :**
  Efficacy of the drug: [7]
  The drug receptor interaction can be influenced by Chirality. This can be better explained on the basis of the lock and key model for drug - receptor interaction.

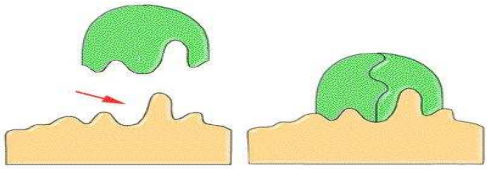

Fig. 1 Drug receptor action

The figure shows that the drug attachment to the receptor. But the isomer of the same drug will not be able to attach to the receptor. Thus the isomer will be lacking the affinity as wellas the intrinsic activity for such receptor.
Example: Dexrabeprazole has the activity at the proton pumps whereas the l isomer of Rabeprazole is inert.

- **Safety of the drug :** [8]
  One isomer may be responsible for adverse effects. The other isomer may be safe to use in such case. Example : Thalidomide, a drug used for motion sickness in late 1950's caused teratogenic effect on the offsprings (Phocomelia). It was later found through animal studies that only the S isomer crossed the blood-placental barrier and was responsible for teratogenicity.
- **Pharmacokinetic Processes :**
  Absorption [9]
  Biotransport of the drug is affected by Chirality. Carrier mediated transport of the drugs across the biological membrane is affected the most.
  Example: S isomer of Hexobarbital shows better plasma levels as the R form.
  Distribution [10]
  Chirality affects distribution as well
  Example: levodopa is the levo isomer of des oxy phenyl alanine or dopa. Levodopa penetrates the blood brain barrier but the dextro isomer of dopa does not.
  Chirality can influence plasma protein binding as well.
  Example: S isomer of warfarin is bound to the plasma proteins 3-5 times more than the R isomer.
  Biotransformation [10]
  Chirality can influence metabolism of drug as well.
  Example: R isomer of Methadone is metabolized by CYP3A4 where as the S isomer by CYP2D6.
  Elimination [12]
  Half life of isomers can be different than the racemic mixture.
  Example : half life of d-Amphetamine is more than l-Amphetamine.

Advantages of studying Chirality in Pharmacology:

- Removal of unwanted adverse effects, if due to an isomer.
- Exposing patient to lower doses of drug with the same therapeutic effect.
- Easier assessment of pathophysiology of the disease and reduction in drug interactions.
- Prevention of isomer-isomer interactions as well.
- Avoids possibility of bioinversion.
- Pharmaceutical Considerations of Chiral Drugs :

Analysis of Drug Chirality*:* [13, 14, 15]
The methods used are

1. HPLC
2. LC-MS
3. Chiral salt rresolution
4. Chiral CE study
5. *Changing Drug Chirality :* [17, 18, 19, 20]
6. The methods used are
7. X – Ray crystallography
8. NMR Method
9. Vibration Circular Dichroism technique
10. Chiral zone electrophoresis

Summary and Conclusion:
Nearly 60% of the drugs used clinically are chiral compounds [21]. But only few of them have been studied as different isomers, as most of these drugs are studied as racemates. Newer interest has developed in studying isomers of already existing drugs as individual drugs, in a quest to find a drug which is highly safe and efficacious as well.

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