ESSENCE

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FROM THE EDITORIAL DESK....

Welcome to the Fifth issue of ESSENCE from AIIMS Mangalagiri

During the last decade, Drug Chirality, more specifically the use of single enantiomers versus racemic mixtures has been in the forefront of discussions in scientific forums. This is because the left and right handed enantiomers of a molecule behave quite differently from each other in a biological environment. Structural changes in existing drugs can give rise to safer alternatives. The current issue discusses one of the currently adapted strategies to enhance safety and/or efficacy of existing agents ie switching from existing racemate to one of its optical isomers and is known as 'Chiral Switch'.

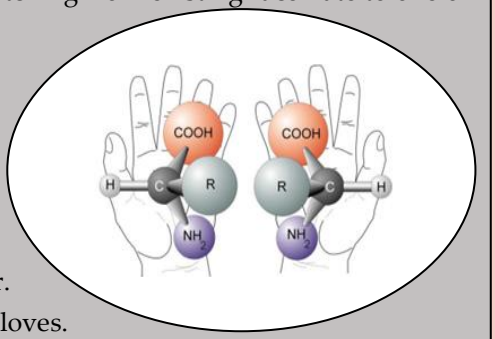
Adverse Drug Reactions (ADRs) continue to remain an important public health issue and among the leading causes of morbidity & mortality. The aim of the Pharmaco-vigilance activities is to collate the data and use the inferences to recommend regulatory interventions, besides communicating risks to healthcare professionals and the public. The current issue highlights the importance of signal generation and detection in identifying the adverse effects of a drug.

The current issue also discusses the recent drug approvals and also safety alerts of various drugs. Finally, the readers can test their knowledge about the stalwarts and scientists in the field of Pharmacology with the cross word puzzle on 'History of Pharmacology'.

Happy Reading and Stay Safe……

Feedback and Suggestions may be sent to Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri (Andhra Pradesh) at email id: pharmacology@aiimsmangalagiri.edu.in

Structural changes in existing drugs can give rise to safer alternatives. One of the currently adapted strategies to enhance safety and/or efficacy of existing agents is switching from existing racemate to one of its optical isomers and is known as 'Chiral Switch'.



Chirality is a property of an object by which it exists in forms. These two left & right-handed forms of a chiral compound are identical in their structural formulae but differ in spatial arrangement so that one form is exactly a mirror image of the other but the two forms are not super imposable on one another. This is similar to a pair of hands (Cheira in Greek means hand) or gloves.

The mirror images are termed 'Enantiomers'. The enantiomers have identical physical and chemical properties and only differ in their three-dimensional spatial configuration. A drug containing equal amounts of both the enantiomeric forms is called a 'Racemate'.

Pharmacological Implications of Chirality

Chirality can dictate the pharmaco-dynamic and pharmaco-kinetic profile of a drug. In a racemate, very often only one enantiomer is responsible for the desired pharmacological effect while the other may be either inactive (silent passenger) at best or responsible for adverse effects at worst. Similarly the pharmacokinetic profile of a drug as racemic or as its enantiomer may be sufficiently different so as to therapeutically beneficial.

Chiral switch in drug development and therapeutics:

Chiral switch is defined as the development of an enantiomer from a previously marketed racemic drug. Very often the single enantiomer developed as a result of chiral switch can have important therapeutic benefits as can be seen from the examples of Chiral switch (Table in next page) that have been done to develop the enantiomer.

Regulatory issues on Chirality & Chiral switch

Underscoring the crucial importance of Chirality, the regulatory authorities in several countries require that a method to discriminate between enantiomers should be investigated and the ratio of the enantiomers in the racemic mixture be determined. The responsibility lies with the drug developer to provide a justification why they are developing a racemate instead of a single enantiomer. Moreover, when single enantiomers are developed from previously marketed racemates, (Chiral switch) the regulatory bodies permit bridging studies between the original and new submission. Because of this encouragement provided by regulatory attitudes, and ably supported by technological developments, since the last 20 yrs there has been a steady increase in the number of drugs being used as single enantiomers and where the single enantiomers are steadily picking up at the cost of racemates.

Economic considerations in Chiral Switches:

The development of chiral switches while certainly may be based on sound pharmacological and therapeutic rationale, economic considerations are also a guiding force behind the exercise. Development of a new drug today is a high risk business and only about one drug discovery project in 100 being successful. Moreover, research and development costs are increasing, with the current cost estimates of bringing a drug to market reported to be $ 1200 million and ever growing. Moreover, drug development time is now so long that the average effective patent life of a "new" agent is only 10-12 years. In this scenario developing an enantiomer from a racemic compound is comparatively easier and obtaining marketing approval usually requires relatively few new studies as has been mentioned above.

Racemate	Enantiomer as a result of Chiral Switch	Indication	Proposed Therapeutic benefit of enantiomer
Salbutamol & Formoterol	Levosalbutamol & R, Formoterol	Asthma	Reduced potential for airway hyper reactivity
Oxybutynin	S-Oxybutynin	Urinary incontinence	Reduced incidence of anticholinergic side effects
Doxazosin	S-Doxazosin	BPH	Reduction in orthostatic hypotension with subsequent reduction in events of dizziness and fainting
Lansoprazole& Pantoprazole	(*S*)-lansoprazole & (-)-pantoprazole	GERD	Reduction of long term adverse effects like gastric carcinoids and entero-chromaffin like cell hyperplasia.
Zopiclone	Eszopiclone	Insomnia	Lesser incidence of residual hang overs as compared to the racemate.
Amlodipine	(*S*)-amlodipine:	Hypertension	Reduction in side effects including ankle edema.
Ketoprofen	Dexketoprofen.	Pain	More rapid absorption and onset of action and hence has a reduced potential for causing gastric ulceration.
Bupivacaine	Levobupivacaine	Local anaesthesia	Similar clinical profile as racemic bupivacaine with the added benefit of reduction in cardiotoxicity.
Atracurium	Cisatracurium	Muscle relaxant	The dose requirement Cisatracurium is much lower as compared to atracurium thereby reducing the formation of laudanosine, a metabolite implicated in inducing seizures.
Ketamine	Esketamine.	General anaesthesia	A much smoother emergence from anaesthesia, a more intense postoperative analgesia and a more rapid recovery of CNS functions. The incidence of psychotomimetic phenomenon is also significantly reduced.
Cetirizine	Levocetirizine	Allergy	A smaller volume of distribution, passage through the Blood Brain Barrier of the enantiomer is much lesser and also its low cerebral receptor binding makes it more selective and less sedative

Another commercially driven reason for chiral switches is the impending expiry of the patents of some highly successful racemic drugs with estimated market worth of billions. The chiral switch process is increasingly being seen as a strategy to extend the profitable life of a pharmaceutical bestseller, and may result in increasing the patent life times and consequently provide an advantage against generic competition. The single enantiomer can be ready for launch before the patent for the racemate expires and before the marketing of any generics (which tend to substantially drive down the cost of the racemate).

Take Home Message:

Understanding the concept of chirality has provided us with safer alternatives to a wide range of drugs. However, Introduction of a single-enantiomer preparation of a racemic drug should not automatically mean that the single enantiomer should become the standard of care. The health care provider is required to be familiar with the basic characteristics of chiral pharmaceuticals and the decision to use a single enantiomer versus a mixture of enantiomers of a particular drug should be made in the light of the available data from clinical trials and clinical experience.

FDA approves Phexxi vaginal gel for prevention of pregnancy

The US Food and Drug Administration (FDA) has approved Phexx (lactic acid, citric acid and potassium bitartrate) vaginal gel for the prevention of pregnancy in females with reproductive potential. Phexxi is the first non-hormonal, on-demand, vaginal pH regulator contraceptive. It is designed to maintain vaginal pH within the normal range of 3.5 to 4.5, creating an acidic environment that is inhospitable to sperm.

Biocon's drug Itolizumab gets approval to treat Covid-19

Itolizumab is said to be the first new biologic therapy approved globally for the treatment of moderate to severe Covid-19 complications. The approval is for 25mg / 5ml injection solution of the medicine to treat cytokine release syndrome (CRS) in moderate to severe ARDS cases with Covid-19. The drug is an anti-CD6 IgG1 monoclonal antibody introduced in India in 2013 under the brand name ALZUMAb to treat chronic plaque psoriasis. Biocon repurposed the drug for the treatment of CRS associated with Covid-19. It acts via immunomodulation and binds to the CD6 receptor blocking the activation of T lymphocytes. This in turn suppresses the pro-inflammatory cytokines and decreasing the cytokine storm and inflammatory response.

First data for Moderna Covid-19 vaccine show it spurs an immune response

Moderna's Covid-19 vaccine was able to produce antibodies that can neutralize the SARS-Cov-2 , though it caused minor side effects in many patients, according to the first published data from an early-stage trial of the experimental shot. The study, which was run by the National Institutes of Health, showed that volunteers who received the vaccine made more neutralizing antibodies than have been seen in most patients who have recovered from Covid-19.

Adverse Drug Reactions (ADRs) continue to remain an important public health issue and among the leading causes of morbidity & mortality. The Pharmacovigilance Programme (PvPI) of India was initiated by the Government of India with the aim to identify and ADRs at an early stage. The aim of PvPI is to collate the data and use the inferences to recommend regulatory interventions, besides communicating risks to healthcare professionals and the public. This is done through a network of various ADR monitoring centers working in health care establishments across the country.

Signal generation & detection: backbone of pharmacovigilance:

A signal refers to the detection of early warning signs. It is defined as "Reported information on a possible casual relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously." Signals may be generated through four different methods: spontaneous reporting, published case reports, cohort studies and post-marketing clinical trials.

Signal detection involves looking for any new patterns or seemingly significant new findings in the safety database. It may be one or more reports showing particularly strong evidence of a previously unknown ADR for that drug, or involving adverse events that are usually caused by drugs, such as aplastic anaemia or toxic epidermal necrolysis. More often, it is a matter of looking for patterns of cluster of reports that stand out from the background. These clusters may be identified by looking at data tables or using computerized methods involving statistical disproportion.

It is necessary to evaluate the identified potential tentative signals and to check whether they are real or not. In most of the cases, apparent signal can result from the disease that the drug is treating, so if a drug is used in patients for the treatment of high blood pressure (BP), it would not be surprising to find reports of kidney disease, stroke and heart failure, because these are either contributing or complications of high BP.

The identification of signals in the national pharmacovigilance centre's database, requires careful review of individual reports and events. The data in the report(s) need to be of good quality if a signal of a new adverse reaction is to be considered. There should be sufficient data to fully access the relationship of the drug to the event. The strongest signals will have several reports with a "certain" or "probable" relationship. A signal may possible be identified from one very good "certain" report. If there are no "certain" reports, at least three "probable" reports would be necessary for a signal.

The first reports with a "certain" or "probable" relationship are called "index cases". Cases with a "possible" relationship can only provide supporting evidence. A group of unexpected deaths coded as "possible" forms an exception to this general rule and will need to be taken seriously. Cases coded as "unclassified" should not be considered in the investigation of a signal. A group of "unlikely" reports may occasionally produce a signal of an unexpected reaction that was not recognized at the time of clinical assessment.

Methods of Signal Identification

1. **Clinical Assessment of Individual Events**

Careful and standardized clinical assessment of individual reports with alertness to the possibility of a signal, offers the quickest method of identifying signals. The approach should be taken during routine

review of incoming reports. If an assessor identifies an event and thinks that it could be a new type of ADR, a search should be undertaken for records of other similar events to confirm the opinion. First, the database should be checked for other similar reports or clinically related terms. Then the adverse reaction should be checked in appropriate reference sources.

2. **Clinical Review of Collated Events**

All the events in the database for the drug(s) of interest should be reviewed at regular intervals e.g. each month. After review individual event should be coded with a standard term using medical dictionary (e.g. MedDRA). The groups of related events can then be seen clearly. The whole group of events should then be taken into consideration to identify the signal.

3. **Record Linkage**

Record linkage depends on the availability of a unique identifier for patients in the health system or in hospital records. This same identifier must also be recorded with the patient details in the cohort database, in case of cohort studies and cohort event monitoring. It can be used as a tool to gather additional data such as details of hospital admission. The process of record linkage involves matching the patient identifiers in the cohort with patient identifiers in any available databases or registers. The results of the linkage are then reviewed and added to the records of events for the patients in the cohort. An unexpectedly high rate of a particular event may represent a signal.

4. **Automated Signal Detection**

The WHO, Uppsala Monitoring Centre (UMC) at Sweden, regularly scans the WHO database for potential signals using its automated data mining program, the Bayesian Confidence Propagation Neural Network (BCPNN). This produces information Component (IC) values for drug event combinations. These can be plotted as graphs over time to examine any trend. A positive signal will have IC values that become more significant over time as more cases are included.

Identified signals are subjected to hypothesis testing, i.e. processes that determine whether the signal does indeed indicate a new ADR, or whether it is false. Validating a signal is generally a process of gradual strengthening arising from new findings in pharmacovigilance or research.

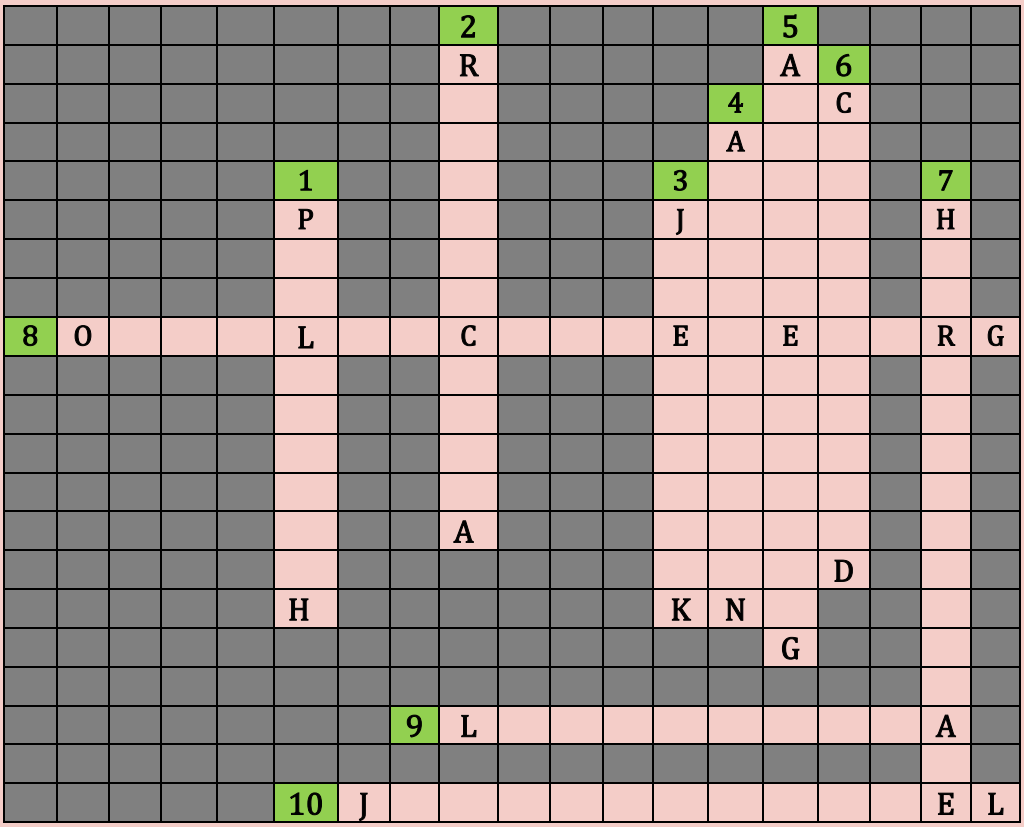
Be Cautious…..Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Allopurinol	Aseptic Meningitis
2.	Fluoroquinolones	Aortic Aneurysm and Dissection
3.	Rotigotine	Rhabdomyolysis
4.	Montelukast	Serious Behaviour and Mood-related changes
5.	Ulipristal acetate	Hepatic Injury
6.	Ferric carboxy-maltose	Hypophosphataemia

S. No.	Drug	Pharmacological Class	Indication	Dosage
1.	Capmatinib	Kinase Inhibitor	Metastatic Non-Small Cell Lung Cancer (NSCLC)	400 mg Oral-BID
2.	Fostemsavir	gp120 Attachment Inhibitor	HIV	600 mg Oral-BID
3.	Remimazolam	Ultra-Short Acting Benzodiazepine	Procedural Sedation	5- 20 mg IV
4.	Metoclopramide Nasal Spray	Prokinetic Agent	Acute and Recurrent Diabetic Gastroparesis	15mg/spray
5.	Selpercatinib	RET Kinase Inhibitor	Lung and Thyroid Cancer	120-160 mg Oral BID
6.	Inebilizumab-cdon	CD19-Directed Monoclonal Antibody	Neuromyelitis Optica Spectrum Disorder (NMOSD)	100 mg IV
7.	Lurbinectedin	DNA Alkylating Agent	Metastatic Small Cell Lung Cancer	3.2 mg/m2-every 21 days
8.	Ripretinib	Pan-KIT and PDGFRα Kinase Inhibitor	Advanced Gastrointestinal-Stromal Tumors	150 mg oral per day
9.	Triheptanoin	Medium-Chain Triglyceride	Long-chain Fatty Acid Oxidation Disorders	35% of the patient prescribed daily caloric intake
10.	Fenfluramine	Amphetamine	Dravet Syndrome	12-17 mg/day

Crossword Puzzle…

History of Pharmacology



Downward	Across
1. Father of Modern Chemotherapy (12) 2. Father of Indian Pharmacology (13) 3. Scottish pharmacologist developed the Beta blocker (Propranolol) (11) 4. American pharmacologist and biochemist, discovered G-protein (13) 5. Scottish biologist and pharmacologist who discovered the Penicillin (16) 6. Father of Modern Experimental Medicine; Established the existence of vasomotor system (13) 7. British physiologist and pharmacologist discovered the chemical transmission of nerve impulses, Histamine actions and isolated the acetylcholine (16)	8. Father of Modern Pharmacology; Discovered glucuronic acid as a conjugation partner in drug metabolism (18) 9. Father of Clinical Pharmacology; Well known for his groundbreaking 1954 article on "**The placebo effect**" in the *American Journal of Medicine (10)* 10. Father of American Pharmacology; Isolated Epinephrine, Amino acids and Insulin (13)

Answers:

Downward

1. Paul Ehrlich
2. Ramnath Chopra
3. Jamesh Black
4. Alfred G. Gilman
5. Alexander Fleming
6. Claude Bernard
7. Henry Hallett Dale

Across

8. Oswald Schmiedeberg
9. Lou Lasagna
10. John Jacob Abel