

CHIRAL SWITCH- AN EMERGING STRATEGY IN THERAPEUTICS

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ABSTRACT:

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 twins of a molecule behave quite differently from each other in a biological environment. This can frequently lead to an improvement in pharmacological and therapeutic profile of the molecule/drug. This understanding of the significance of stereochemistry coupled with advances in chemical technologies and further nudged by regulatory requirements has helped the increase in the development of individual isomers at the expense of racemic mixtures. Apart from the development of novel stereo-selective compounds, a number of racemates have been re-evaluated as potential single enantiomer agents with the possibility of an improved pharmacological/therapeutic profile. These have been termed as Chiral Switches and have resulted in the re-birth of a number of agents as single enantiomers and have provided significant improvements over the racemic drug. Economic considerations are also playing a part with pharmaceutical companies increasingly using chiral switching as a marketing strategy to increase the patent longevity and profitability period of a drug. However, not all these switches have resulted in therapeutic superiority and in many instances, unpredicted adverse reactions have resulted. Before a switch to clinical use of single enantiomers is made, physicians should satisfy themselves from evidence based on well-conducted clinical trials that the chiral switch is cost-effective and improves the outcomes for patients.

Key Words: Chirality, Chiral Switch, Enantiomers

INTRODUCTION:

The ultimate objective of development of newer therapeutic alternatives is to increase efficacy and/or enhance safety. Historically structural changes in existing drugs have given rise to safer alternatives. One of the currently adapted strategy 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'^{1,4} which has provided safer alternatives

to a wide range of drugs. Since the last 20 yrs there has been a steady increase in the number of drugs being used as single enantiomers and sales for single enantiomers were \$225 billion in 2005 which represented 37% of total marketed drugs.² Similar trend is seen in new drug launches where the single enantiomers are steadily picking up at the cost of achiral drugs and racemates as shown below in Fig 1.³

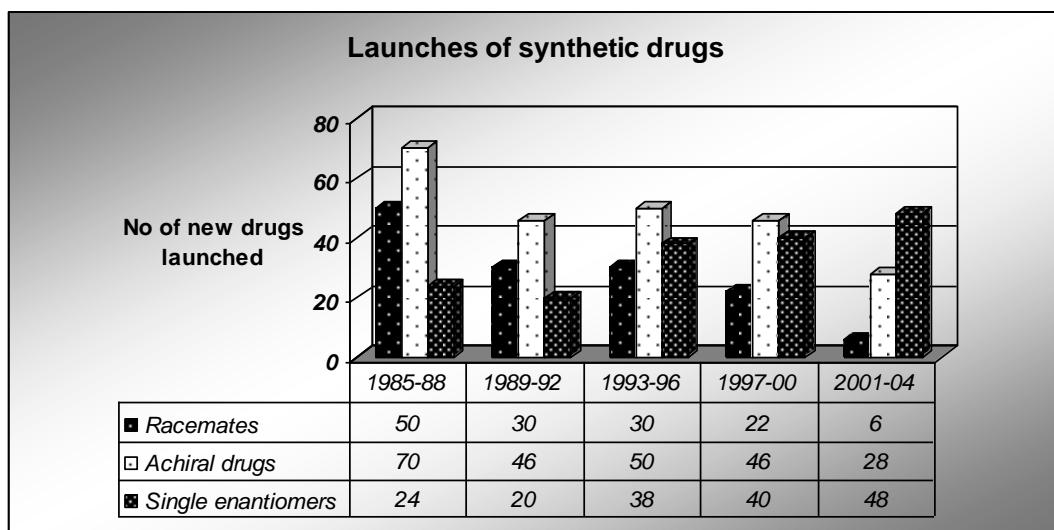


Figure 1

DEFINITIONS AND CHEMISTRY:^{4,5}

Chirality is a property of an object by which the object is not super-imposable on its mirror image. Chiral compounds possess the property of handedness, i.e., they may be right-handed or left-handed. (Cheira in Greek means hand). These two - left- and 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 superimposable on one another. This is similar to a pair of gloves, socks or hands. This existence of left- or right-handedness of a compound is referred to as chirality. The mirror images are termed enantiomers depicted as under in (Fig 2)

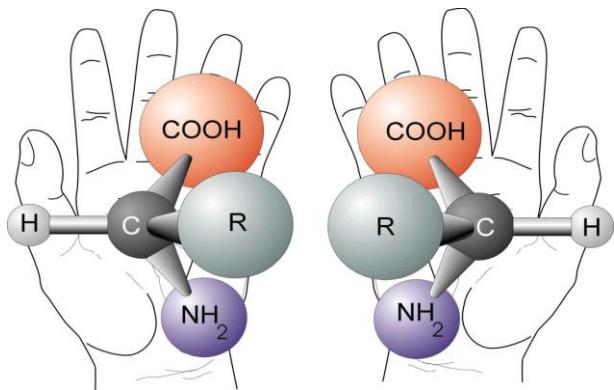


Figure 2

Enantiomers have identical physical and chemical properties such as molecular weight, solubility and melting point. They only differ in their three-dimensional spatial configuration. A collection containing only one isomeric form of a chiral compound is termed a chirally pure, optically pure, or enantiomerically pure compound, while a collection of equal amounts of the two enantiomeric forms is called a racemate

PHARMACOLOGICAL IMPLICATIONS OF CHIRALITY

Chirality has wide ranging pharmacological implications and can dictate the pharmacodynamic and pharmacokinetic profile of a drug.^{4,5} 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 antagonist and 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 significant.

CHIRAL SWITCH

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 has similar profile and indications as the parent racemate but can have important therapeutic benefits that could be as under.⁵

- Increase in Selectivity and more predictable Pharmacodynamic profile
- More predictable and less complex concentration- effect curve
- Improved therapeutic index and safety
- Less complex pharmacokinetic profile
- Reduced potential for drug interactions

Chiral separation techniques:⁶

Apart from the understanding of the pharmacological implications of chirality, the advances in technologies involved in the pharmaceutical processes of synthesis, separation and analysis have supported the cause of enantiomers. The development of methods for analytical and preparative chiral separation have considerably improved over the last two decades. Methods using chromatographic such as gas chromatography, high-performance liquid chromatography, supercritical fluid chromatography (SFC) and thin layer chromatography have been developed which use different principles for chiral separation. More recently, capillary electrophoresis and capillary electro-chromatography are also been widely used. For the separation of enantiomers on preparative scale liquid chromatography (LC) has become increasingly attractive.

Some clinically important chiral switches:

The chiral switch process has given rise to a number of agents that have been developed as enantiomer products. A list of representative chiral switches is tabulated in Table 1 as follows.

Table 1: A list of representative chiral switches

Racemate	Enantiomer developed as a result of Chiral Switch	Indication	Proposed Therapeutic benefit of enantiomer
Salbutamol & Formoterol	Levosalbutamol & RR, Formoterol	Asthma	Reduced potential for airway hyper reactivity ⁷
Oxybutynin	S-Oxybutynin	Urinary incontinence	reduced incidence of anticholinergic side effects ⁸
Doxazosin	S-Doxazosin	Benign Prostatic Hyperplasia	Reduction in orthostatic hypotension with subsequent reduction in events of dizziness and fainting ⁹
Lansoprazole & Pantoprazole	(S)-lansoprazole & (-)-pantoprazole	GERD	Reduction of long term adverse effects like gastric carcinoids and entero-chromaffin like cell hyperplasia. ¹⁰
Cisapride	Norcisapride	Nocturnal heartburn	Minimal interaction with azoles/macrolides and a reduced occurrence of cardiotoxicity. ¹¹
Zopiclone	Eszopiclone	Insomnia	Lesser incidence of residual hang overs as compared to the raceme. ¹²
Amlodipine	(S)-amlodipine:	Hypertension	Reduction in side effects including ankle edema ¹³ .
Fluoxetine	(S)-fluoxetine	Prophylaxis of migraine.	An earlier and greater reduction in attack frequency ¹⁴
Ketoprofen	Dexketoprofen.	Management of pain	More rapid absorption and onset of action and hence has a reduced potential for causing gastric ulceration. ¹⁵

Bupivacaine	Levobupivacaine	Local anaesthesia	The single levo-enantiomer results in a similar clinical profile as racemic bupivacaine with the added benefit of reduction in cardiotoxicity. ¹⁶
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. ¹⁷
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 less after S-ketamine as compared to racemic ketamine. ^{18, 19}
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 ^{20, 21}
Atenolol and Metoprolol	S-atenolol and S-metoprolol:	Hypertension	S-isomers of atenolol and metoprolol retain their cardioselectivity even at high doses as the beta-2-blocking R-isomer is absent ²² . Particularly of importance in asthmatics, smokers, COPD patients and diabetics.

DOES TURNING CHIRAL ALWAYS BENEFIT?

Not all of the Chiral switches led to a superior substitute. Some chiral switching has resulted in unpredicted toxicity leading to halt in the development of the enantiomer or even its withdrawal from the market.²³ Fenfluramine is a racemic drug which was used as an appetite suppressant. The combination of fenfluramine and the achiral anti-obesity drug phentermine 'Fen-phen,' was at one time widely used for weight loss. When dexfenfluramine, the S-enantiomer, came to the market in 1996, widespread replacement of this new compound was done in the belief that the dextro isomer would be safer. However as realised later, the cardiac adverse effects of fenfluramine were retained in the dextro isomer leading consequently, to the withdrawal of both fenfluramine and dexfenfluramine in 1997.²⁴ Similarly the S-isomer of sotalol increased mortality in patients with myocardial infarction as compared to the racemate and investigations were prematurely terminated.²⁵ Development of single beta-blocking R,R-stereoisomer, named dilevalol, of labetalol was halted due to hepatotoxic adverse effect.²⁶ During the Phase II trials, the R enantiomer of fluoxetine, showed a statistically significant prolongation of cardiac repolarization which led to a halt in the development of the enantiomer.²⁷

REGULATORY ISSUES ON CHIRALITY

At present none of the major regulatory authorities have an absolute requirement for the development of single enantiomer drugs and the decision regarding the stereoisomeric form, i.e. single enantiomer or racemic mixture, to be developed is left to the sponsor/innovator of the compound. However this decision should be a conscious and a deliberate one and should incorporate detailed scientific justification based on quality, safety and efficacy, together with the risk-benefit ratio. The FDA (USA) and the EMEA mandate that the properties of each enantiomer in a racemic molecule, should be studied separately before a decision is taken to market the drug as one of the enantiomers or as a mixture^{28,29}. Rather than using chiral synthetic drugs as racemates in

the first instance, the activities and toxicities of the enantiomers require to be tested individually. Similarly the regulatory authorities in Japan require that a method to discriminate between enantiomers should be investigated and the ratio of the enantiomers in the racemic mixture be determined³⁰. The responsibility lies with the drug developer to provide a justification based on scientific evidence if a racemate is sought to be developed instead of a single enantiomer. When single enantiomers are developed from previously marketed racemates 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, the number of new chiral chemical entities as single stereoisomers submitted for approval to regulatory bodies has increased as compared to the racemic mixtures.

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 50 managing to reach its goal of putting a new drug on the market.³¹ Not surprisingly, the rate of development of new agents is declining, for example the US FDA approved only 29 new chemical entities in 2008³² which is one of the lowest number in the last 30 years. The situation is compounded by the fact that research and development costs are increasing, having doubled over the last fifteen years, with the cost estimates of bringing a drug to market reported to be \$ 802 million and ever growing.³³ 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.

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 billions³³. 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 competition³⁴. 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).

CONCLUSION

Drug development is becoming longer and more complex, while marketing is increasingly competitive. Differences between single enantiomers and racemates are bound to reach the centre stage in the fight to

promote the 'new improved' entity (read isomer). The use of single enantiomers have to be in line with using drugs rationally³⁵ without unduly increasing the inventory of the hospital pharmacy which may have far reaching implications on cost of health care. Nevertheless the increasing availability of single-enantiomer drugs promises to provide clinicians with safer, better-tolerated, and more efficacious medications for treating patients. However when both a single enantiomer and a racemic formulation of a drug are available, the information from clinical trials and clinical experience should be used to decide which formulation is most appropriate. 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.

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