Rediscovering Chirality – Role of S-Metoprolol in Cardiovascular Disease Management

Jagdish C Mohan¹, Siddharth N Shah², Sunny Chinchansurkar³, Arindam Dey³, Rishi Jain³

Abstract

Background: The process of drug discovery and development today encompass a myriad of paths for bringing a new therapeutic molecule that has minimal adverse effects and of optimal use to the patient. Chirality was proposed in the direction of providing a purer and safer form of drug [Ex- cetirizine and levocetirizine]. Decades have passed since the introduction of this concept and numerous chiral molecules are in existence in therapeutics, yet somehow this concept has been ignored. This review aims to rediscover the ignored facts about chirality, its benefits and clear some common myths considering the example of S-Metoprolol in the management of Hypertension and other cardiovascular diseases.

Methods: Relevant articles from Pubmed, Embase, Medline and Google Scholar were searched using the terms “Chiral”, “Chirality”, “Enantiomers”, “Isomers”, “Isomerism”, “Stereo-chemistry”, and “S-Metoprolol”. Out of 103 articles found 17 articles mentioning in general about the concept of chirality and articles on study of S-metoprolol in various cardiovascular diseases were then reviewed.

Results: Many articles mention about the importance of chirality yet the concept has not been highlighted much. Clear benefits with chiral molecules have been documented for various drug molecules few amongst them being anaesthetics, antihypertensives, antidepressants. Benefits of S-metoprolol over racemate are also clear in terms of responder rates, dose of administration and adverse effects profile in various cardiovascular diseases.

Conclusion: Chirality is a good way forward in providing a new drug molecule which is safe with lesser pharmacokinetic and pharmacodynamics variability, lesser side effects and more potent action. S-metoprolol is chirally pure form of racemate metoprolol and has lesser side effects, is safer in patients of COPD and Diabetes who also have hypertension and comparable responder rates at half the doses when compared to racemate.

Introduction

The word Chiral is derived from Greek word ‘KHEIR’ or ‘CHEIR’ which means hand.1,8-10 Chirality is a property of a molecule wherein the mirror images do not superimpose on each other owing to the difference in spatial arrangement of the atoms in the molecule (Figure 1).1

The concept of Chirality originated when Louis Pasteur discovered two hands of sodium ammonium tartrate in 1848 and subsequently it was found that most of the carbohydrates, amino acids, nucleosides were chiral molecules and by extension even hormones, enzymes and DNA are chiral in nature.2-6 Nature also provides evidence of chirality. One such example is the Sweet smell of Oranges which is due to S-limonene whereas R-isomer gives a turpentine odor. Probably one of the best Examples of Chirality is Human hands.7-10

The Importance of chirality has already been established in many therapeutic areas. Most of the antidepressants, anesthetics, antihypertensive drugs are chiral molecules.11 The age old molecules like dextrose, well established molecules like levo-cetirizine have...
already established the benefits of this property. Despite extensive evidences, the concept of chirality is somehow ignored both by the industry and the clinicians. This review focuses on advantages of the property of chirality undertaking S-Metoprolol as an example, its therapeutic applications and the need to provide a purer form of drug for maximal benefit of the patient.

### Heritage of Chirality – The Buried Third Dimension

In medical history the Thalidomide incident that happened in 1961-62 was probably the darkest episode. Thalidomide was introduced in the market in 1958 as a mild sedative which was safe in pregnancy but was soon withdrawn owing to the congenital anomaly that it caused: Phocomelia [Seal Limbs]. It was years later when the concept of chirality was understood much better that the answer was found as to what caused the teratogenicity with thalidomide. It was then established that S-enantiomer of thalidomide caused the anomaly that it caused: Phocomelia [Seal Limbs]. It was years later when the concept of chirality was understood much better that the answer was found as to what caused the teratogenicity with thalidomide. It was then established that S-enantiomer of thalidomide had the maximal adverse effects and that the R-enantiomer contained the desired therapeutic activity.12

R-Thalidomide and its analogs have recently been a subject of numerous studies. In 1998 the USFDA approved R-Thalidomide for use in treating leprosy symptoms and studies indicate some promising results for use in treating symptoms associated with AIDS, Lupus, rheumatoid arthritis, inflammatory bowel disease and Multiple Myeloma.12

### Nomenclature

Two drugs with the same chemical composition and molecular formula are called as Isomers. There can be two or more isomers of a compound and there is no thumb rule for all isomers being active or of therapeutic value (Figure 2). A mixture of two isomers in equal ratio [50:50] is called a Racemic Mixture or a Racemate. A Molecule may have active Isomers called as EUTOMERS or Inactive isomers called as Distomers or all isomers may get converted to one isomer and such a compound is called as UNICHIRAL compound.13-16

Usually a Carbon atom forms the chiral Center in an isomer however, other than Carbon atom, sulphur, phosphorus can also be the chiral centers for a molecule [Ex- Cyclophosphamide, Sulindac]. Enantiomers may be equipotent [Ex- Cyclophosphamide, flecanide] or one enantiomer may have all the activity [Ex- NSAIDs like ibuprofen and ketoprofen, Beta blockers like timolol and penbutalol]. Some molecules may have both isomers as active form with same spectrum of activity and toxicity [Ex- Warfarin] whereas others may have both active isomers with quantitatively different therapeutic and toxicity profile [Ex- Verapamil].17

All Molecules that are Chiral have different Pharmacokinetic and Dynamic profiles making them separate chemical entities (Table 1). Easson and Stedman designed a model explaining the importance of Pharmacokinetic and pharmacodynamics differences of chiral molecules. Due to the change in their 3D configuration their absorption, distribution, metabolism and excretion varies. The interaction of the Molecules varies with the receptor sites as their absorption, distribution, metabolism and excretion varies. The interaction of the Molecules varies with the receptor sites as their absorption, distribution, metabolism and excretion varies. The interaction of the Molecules varies with the receptor sites as their absorption, distribution, metabolism and excretion varies. The interaction of the Molecules varies with the receptor sites as their absorption, distribution, metabolism and excretion varies. The interaction of the Molecules varies with the receptor sites as their absorption, distribution, metabolism and excretion varies. The interaction of the Molecules varies with the receptor sites as their absorption, distribution, metabolism and excretion varies. The interaction of the Molecules varies with the receptor sites as their absorption, distribution, metabolism and excretion varies. The interaction of the Molecules varies with the receptor sites as.

### Table 1: Definition and examples of various subclass of isomers

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional/Structural</td>
<td>Same molecular formula but different chemical structure due to arrangement of atoms</td>
<td>Ex – Enflurane Vs Isoflurane</td>
</tr>
<tr>
<td>Sterioisomers</td>
<td>Same chemical structure but different spatial/3D arrangement only</td>
<td>Ex- Dextrose, S-metoprolol Vs R-Metoprolol</td>
</tr>
<tr>
<td>Enantiomer</td>
<td>Mirror Images non superimposable on each other</td>
<td>Ex-d- Glucose and l-Sucrose</td>
</tr>
<tr>
<td>Diastereomer</td>
<td>Not mirror images [multiple stereo centers]</td>
<td>Ex-d- Glucose and l-Sucrose</td>
</tr>
<tr>
<td>Optical isomers</td>
<td>In polarimeter – the molecule rotates the plane of polarized light to one particular direction or restricts the movement of light in one particular direction</td>
<td>Ex- d-Sucrose and l-Sucrose</td>
</tr>
<tr>
<td>Spatial arrangement</td>
<td>Based on the spatial arrangement of atoms, a preferred number is given to each side chain considering one chiral center and the molecular weight (highest to lowest), the rotation of the molecule is observed in three dimension – clockwise [Rectus/ R] and anticlockwise [Sinister/S]</td>
<td>Ex- R-Metoprolol and S-Metoprolol</td>
</tr>
<tr>
<td>Geometrical</td>
<td>Without optically active centers [Due to presence of a double bond]</td>
<td>Ex- cis-2-butene and Trans- 2-Butene</td>
</tr>
</tbody>
</table>

### Fig. 2: Isomer classification based on different properties

- **Constitutional/Structural Isomers**
  - Dextro [d]
  - Levo [l]
  - Rectus [R]
  - Sinister [S]
  - Cis
  - Trans

- **Stereoisomers**
  - Enantiomer
  - Diastereomer
  - Optical
  - Spatial
  - Geometrical

- **Table 1: Definition and examples of various subclass of isomers**

- **Class**
  - Constitutional/Structural isomers
  - Sterioisomers
  - Enantiomer
  - Diastereomer
  - Optical isomers
  - Spatial arrangement
  - Geometrical

- **Definition**
  - Same molecular formula but different chemical structure due to arrangement of atoms
  - Same chemical structure but different spatial/3D arrangement only
  - Mirror Images non superimposable on each other
  - Not mirror images [multiple stereo centers]
  - In polarimeter – the molecule rotates the plane of polarized light to one particular direction or restricts the movement of light in one particular direction
  - Based on the spatial arrangement of atoms, a preferred number is given to each side chain considering one chiral center and the molecular weight (highest to lowest), the rotation of the molecule is observed in three dimension – clockwise [Rectus/ R] and anticlockwise [Sinister/S]
  - Without optically active centers [Due to presence of a double bond]

- **Examples**
  - Ex – Enflurane Vs Isoflurane
  - Ex- Dextrose, S-metoprolol Vs R-Metoprolol
  - Ex-d- Glucose and l-Sucrose
  - Ex- d-Sucrose and l-Sucrose
  - Ex- R-Metoprolol and S-Metoprolol
  - Ex- cis-2-butene and Trans- 2-Butene
Chiral Metoprolol

Most beta-blockers like atenolol, acebutalol, metoprolol etc are chiral molecules available as racemates having non superimposable mirror image isomers where in S-Metoprolol is the chirally pure enantiomer. It is known to exhibit greater affinity and higher beta1 receptor blocking activity than the R isomer with S: R activity ratio being 33:1. The beta1 receptor affinity of S-Metoprolol is 50 times greater than that of R-Metoprolol.1

Stoschitzky et al; had Long back stated “it is now unequivocally clear that the d- and l-enantiomers of all beta-blockers that are currently used in research as well as in clinical practice may have both different pharmacodynamics and different pharmacokinetic properties. Therefore, the optically pure enantiomers should be recognized as distinct drugs, thus defining the racemic mixtures as a combination of two different drugs in a fixed 1:1 ratio. Hence the racemate can no longer be regarded as optimal for patients on beta-blocker therapy”.38 Thus by performing a chiral switch one may obtain the purer form of drug that is more potent, efficacious and possessing lesser side effect profile.

Metoprolol is metabolized by CYP2D6 in the body. The main concern is that almost 5% of Indian patients are Poor metabolizers of Metoprolol. Animal studies have shown that, preferential metabolism of R-Metoprolol occurs in extensive metabolizes (EM) resulting in a S:R area under curve (AUC) ratio of 1.37 ± 0.32, this stereoselectivity is reversed in poor metabolizers (PM) (S:R AUC ratio of 0.90 ± 0.06).4 This can lead to accumulation of R-Metoprolol, shifting of beta blockade from beta 1 to beta 2 and loss of cardio selectivity in these patients who receive racemate.1

Many clinicians prefer Levocetrizine [chirally pure form] over cetirizine [racemate] as it causes less sedation; levodopa over dopamine owing to lesser metabolism in plasma, faster and specific action. Similarly S-metoprolol [chirally pure form] can be chosen over racemate which has better pharmacokinetic and pharmacodynamics dynamic profile, more specific action on beta 1 receptors. Following table shows difference between the Metoprolol enantiomers (Table 2).

Many preclinical studies have been carried out which provide the evidence for selective beta 1 activity, antihypertensive efficacy, almost comparable responder rates, improvement in symptoms of angina and heart failure with S-metoprolol. The clinical studies have been summarized in table 3 for a better understanding of the endpoints and benefits of S-Metoprolol.

Table 2: Differences between metoprolol enantiomers

<table>
<thead>
<tr>
<th>S-metoprolol</th>
<th>R-metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta1- selective – blocker (affinity 500 times more)</td>
<td>More selective for beta2- blockade</td>
</tr>
<tr>
<td>Cardio-selective</td>
<td>Not-cardio-selective</td>
</tr>
<tr>
<td>At high doses does not cause b2 blockade</td>
<td>Racemate at high doses causes b2 blockade</td>
</tr>
<tr>
<td>Ratio of S:R = 1:37 in extensive metabolizers</td>
<td>Ratio of R:S = 1:1 in poor metabolizers</td>
</tr>
<tr>
<td>Drug-interactions produce much lesser rise in S enantiomer</td>
<td>Drug-interactions produce 40-50% rise in R enantiomer</td>
</tr>
<tr>
<td>Allows unopposed stimulation of b2-receptors</td>
<td>Blocks b2 especially at higher doses.</td>
</tr>
</tbody>
</table>

Discussion

Chiral molecules are a part of nature and the field of Medicine has seen and understood the importance of chirality viz a viz R-Thalidomide which was reintroduced as therapy molecule for various clinical disorders after it was found that the S-Thalidomide had all the side effects; L-Sucrose being used as sweeteners [no-calorie sugar] as it is only the d-form which gets metabolized in the body. Some other examples include molecules like Dextrose, Levo-dopa, Levocetrizine, Levo-Thyroxine, most of the anesthetics, skeletal muscle relaxants, antihypertensives, and antidepressants. Drugs like statins and amphetamine are available as stereo-chemically pure molecules i.e. they exist in single isomer form in nature hence no purification or chiral switch is required.

Chirally pure drugs seem to be a rational option because chiral switching ensures.38
<table>
<thead>
<tr>
<th>Name of study</th>
<th>Objective</th>
<th>Total no. of patients</th>
<th>Primary and secondary endpoint</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMART trial^1</td>
<td>To compare efficacy, safety and tolerability of S-Metoprolol 50 mg ER Vs racemic Metoprolol 100mg ER in treatment of HT</td>
<td>288</td>
<td>6 weeks</td>
<td>To compare the reduction in SBP and DBP</td>
<td>Responder rate in both group was 96% at 42 weeks [Patients who showed a SBP reduction of ≥20mm Hg or/and DBP reduction ≥10 mm Hg from baseline or those who attained SBP ≤140 mm Hg and DBP ≤ 90 mm Hg on Treatment at 7,14,21,28,35 and 42 weeks]</td>
</tr>
<tr>
<td>SMART COPD^2</td>
<td>To evaluate efficacy, safety and tolerability of S-Metoprolol succinate ER in the treatment of hypertension coexisting with COPD</td>
<td>50</td>
<td>Around 8 weeks [60 days]</td>
<td>Safety and efficacy</td>
<td>Decrease in SBP and DBP and HR in every visit was statistically significant as compared to baseline value</td>
</tr>
<tr>
<td>SMART 2^3</td>
<td>To document efficacy and tolerability of S-Metoprolol 25/50 mg ER in treatment of patients with mild to moderate hypertension</td>
<td>2000</td>
<td>4 Weeks [28 days]</td>
<td>Decrease in SBP and diastolic DBP, reduction in HR; and overall adverse drug reactions (ADR)</td>
<td>The responder rate was 80% at the end of 28 days therapy. [Patients who showed a SBP reduction of ≥20mm Hg or/and DBP reduction ≥10 mm Hg from baseline or those who attained BP ≤140/90 mm Hg]</td>
</tr>
<tr>
<td>Metoprolol ER in Angina^4</td>
<td>To compare the efficacy and safety of a S-Metoprolol ER tablet (50 mg) versus a racemate Metoprolol ER tablet (100 mg) in the management of angina</td>
<td>100</td>
<td>8 weeks</td>
<td>Mean change from baseline in the number of angina attacks. Mean change from baseline in the proportion of patients with no angina attacks, SBP, DBP, HR and proportion of blood pressure responders</td>
<td>Reduction in the number of angina attacks from baseline was significant in both groups with no between-group difference. The response rate (% of patients completely relieved of angina attacks clinically) was greater in the S-Metoprolol (72%) compared to the Metoprolol group (62%). Among hypertensives, response rate in angina was higher in the S-Metoprolol (74%) compared to the Metoprolol group (61%)</td>
</tr>
<tr>
<td>SMART dimension study^5</td>
<td>To Assess safety and efficacy of S-Metoprolol succinate ER tablets in patients with hypertension or angina coexistent with diabetes mellitus.</td>
<td>55</td>
<td>Around 6 Weeks [45 days]</td>
<td>Patients were evaluated for change in SBP, DBP and HR on day 15 and day 45 after starting S-Metoprolol therapy. Evaluation of change in blood sugar level (BSL); fasting (F) and post-prandial (PP) were done at baseline and at day 45 of therapy. Effect on hypoglycemia symptoms/ recovery and other adverse events, if any, were documented during the course of study</td>
<td>The SBP reduced from 161 on day 0 to 141 on day 45 of therapy. The DBP reduced significantly from 97 on day 0 to 87 on day 45. The HR reduced from 87 on day 0 to 83 on day 45 of therapy (expressed as whole numbers after deriving Mean ± SD)</td>
</tr>
</tbody>
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Contd...
Table 3: Summary of clinical trials for s-metoprolol in various cardiovascular diseases

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Objective</th>
<th>Total no. of patients</th>
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<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMART HF6</td>
<td>Efficacy and safety of S-Metoprolol succinate ER tablet in the management of congestive heart failure.</td>
<td>31</td>
<td>Patients were observed for change in BP, HR and improvement in symptoms of Heart failure- evident by improvement in NYHA class</td>
<td>Significant reduction from baseline SBP, DBP and HR was observed after 1 month of therapy which decreased further on continuing the therapy till three months. Symptoms of CHF improved in all patients as evident by improvement in NYHA class.</td>
<td>S-Metoprolol succinate ER is effective in reducing the BP, HR and improving symptoms in hypertensive patients of CHF (on a background of routine heart failure therapy).</td>
</tr>
<tr>
<td>SMART SESA7</td>
<td>Efficacy and safety of a FDC of S-Amlodipine 2.5 mg + S-Metoprolol 25 mg vs FDC of Amlodipine 5 mg + Metoprolol 50 mg and FDC of Amlodipine 5 mg + Atenolol 50 mg in the treatment of hypertensive patients with angina.</td>
<td>107</td>
<td>BP responder rates (patients who achieved reduction of ≥20 mm Hg in systolic and ≥10 mm Hg in diastolic blood pressure from baseline or achieve a goal BP of &lt;140/90 mm Hg. Angina responder rates (defined as proportion of patients who were completely relieved of angina attacks within 56 days of therapy)</td>
<td>A higher responder rate, lesser use of rescue antianginals and better safety profile including lesser incidence of edema was seen with FDC of S-Amlodipine + S-Metoprolol compared to racemate Amlodipine + Metoprolol</td>
<td>The FDC tablet of S-Amlodipine 2.5 mg + S-Metoprolol 25 mg was effective and well tolerated in reducing BP and angina episodes in hypertensive patients with history of angina with or without coexisting diabetes and/or hyperlipidemia; FDC of S-Amlodipine + S-Metoprolol had a significantly lesser incidence of AE including pedal edema compared to Amlodipine + Metoprolol.</td>
</tr>
</tbody>
</table>

a. Change in the duration of action, half-life [longer or shorter] owing to the pharmacokinetic considerations resulting in more appropriate dosing frequency
b. Increased receptor selectivity, potency and reduced adverse effects leading to improved safety margin [Therapeutic Index]
c. Decreased potential for drug interactions
d. Decreased inter-individual variability in response due to polymorphisms.

In context of beta blockers, Racemate metoprolol has poor action on beta 1 receptors leading to lesser therapeutic effects and more adverse reactions. As evidently pointed out in various studies mentioned above S-metoprolol is better than racemate in terms of action at half the doses, and safety. Many studies of racemate in similar indications and combinations as that of S-metoprolol were also reviewed and were found to have no different results than S-metoprolol. In controlled clinical trials in hypertension, angina and heart failure racemate metoprolol was found to have efficacy, reduction in symptoms of angina and improvement in Symptoms of HF comparable to S-metoprolol.

The US FDA policy regarding single enantiomers was published in 1992 noting the fact that if the toxicity of significant concern gets eliminated by development of single isomer with the desired pharmacological effect, it would in general be desirable to do so. Although racemic drugs continue to flood the market a higher number of single enantiomers are being submitted for New Drug approval.40

Conclusion

The Concept of Chirality is simple, feasible accurate method to derive a purer form of drug. Though the concept is well known to mankind since long yet it is neglected a lot. Chiral Separation Technologies and their applications can have profound consequence for development of new pharmaceutical entity and can aid in the drug development process by reducing toxicology workload.

Racemate beta blockers are irrational combinations of two enantiomers. Similarly in case of Metoprolol, racemate form is the inactive form having less or no therapeutic activity [beta 1 blockade] and more adverse effects whereas S-Metoprolol is the active enantiomer bearing all the pharmacological activities and less pharmacokinetic variability making it a SMARTer choice amongst the two.

References

4. Rentsch KM. The importance of stereoselective determination of drugs in the clinical laboratory. Journal of