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## Racemic beta-blockers – fixed combinations of different drugs

K. Stoschitzky, G. Zernig<sup>1</sup>, W. Lindner<sup>2</sup>

Beta-blockers were introduced in clinical practice in the 1960s as racemic mixtures consisting of d- and l-enantiomers in a fixed 1:1 ratio. Little has changed on this issue although it has been clearly shown *in vitro* as well as in human studies that only the l-enantiomers exert beta-blockade when clinical doses of the racemic drugs are used, the d-enantiomers not contributing to this effect. In recent years numerous specific as well as non-specific effects of d-enantiomers of beta-blockers have been reported. Therefore, these non beta-blocking d-enantiomers may increase or even cause serious side effects on their own. In addition, pharmacokinetic properties of the l- and d-enantiomers vary widely even when they are given in the fixed 1:1 ratio of a racemic drug, particularly when exercise is performed.

In conclusion, the data actually available on this issue demonstrate profound and clinically significant differences between the d- and l-enantiomers of beta-blockers. Therefore, the d- and l-enantiomers of beta-blocking drugs should be recognized and used as individual drugs on their own. We suggest that the so called 'chiral switch' be performed, ie, replace the currently used racemic mixtures with the optically pure l-enantiomers since the best available beta-blocking drugs should not be withheld from patients receiving beta-blockers. Such a procedure is further supported by the facts that the l-enantiomers can nowadays be provided easily and at low cost, and that the pure enantiomers give the full effect at half the dose of the currently used racemic mixtures. *J Clin Bas Cardiol 1998; 1: 14–8.*

**Key words:** Beta-blockers, enantiomers, stereoselectivity, chirality

All beta-blockers that are currently available possess an amino-alkanol side chain with an asymmetric carbon atom (Fig. 1), resulting in the existence of a d- and l-enantiomer which are mirror images [1] (Fig. 2). Although *in vitro* studies showed in the 1960s that the l-enantiomers are orders of magnitude more potent than the respective d-forms [2], most beta-blockers are still used as racemates in research as well as in clinical practice as though they were pure drugs. Within this context, it has been argued over a long period of time that "the limited experience from studies where these isomers had been used separately even suggests that they have no adverse effects at all. Based upon these considerations and in view of the sometimes cumbersome and expensive separation of the isomers, most beta-receptor blocking agents are now used as racemates [3]". Indeed, specific effects of the non beta-blocking d-enantiomers of beta-blockers were unknown at this time. However, during recent years a number of studies have been published reporting highly specific effects of the d-enantiomers of beta-blockers such as antiarrhythmic class-1 effects [4] and inhibition of the conversion of thyroxin to triiodothyronin by d-propranolol [5, 6], or antiarrhythmic class-3 effects of d-sotalol [7]. In addition, there are marked pharmacokinetic differences between the d- and l-enantiomers of most beta-blockers, particularly under exercise [8] and when extensive and poor metabolisers are compared [9, 10]. Nevertheless, the potential clinical impact of these findings still remained doubtful. However, the SWORD study [11] showed that optically pure d-sotalol increased mortality in patients with myocardial infarction by 65 % compared with placebo. Thus, the first clinical trial investigating the effects of an optically pure d-enantiomer, d-sotalol, emphasised the potential harm that may be caused by a non beta-blocking d-enantiomer of a currently used racemic beta-blocker.

The objective of the present review is to highlight the present state-of-the-art in chiral aspects of beta-adrenoceptor antagonists.

### Nomenclature of stereoisomers

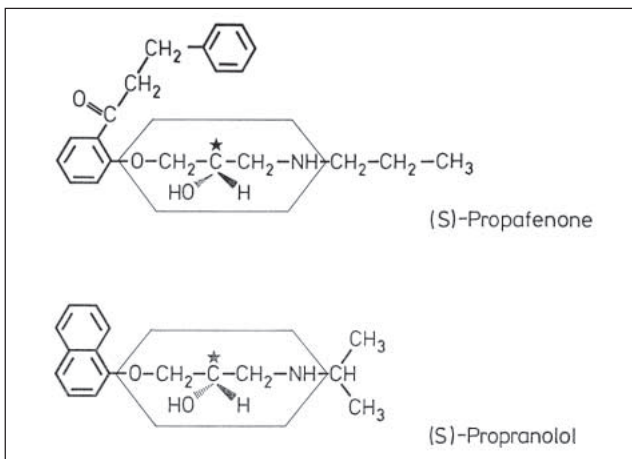
The (R)- and (S)-nomenclature according to Cahn, Ingold and Prelog (CIP) priority rules [12] defines the absolute configuration of a stereogenic centre, in the present case a tetra-coordinated carbon atom substituted by four different ligands. On the other hand, the prefixes d- and l- as well as the (+)- and (-)-nomenclature give information according to the rotation of polarised light to the right or to the left, and therefore, merely describe these physicochemical properties of the enantiomers. All beta-blockers that are currently used in clinical practice contain an asymmetric carbon atom. In the aryloxypropranolamine type compounds the d-enantiomers show the (R)-configuration, and the l-enantiomers show the (S)-configuration. (S)-enantiomers usually are orders of magnitude more potent in blocking adrenergic beta-adrenoceptors than the respective (R)-forms. An exception is sotalol where the asymmetric carbon atom is located in an ethanolamine type side chain. In this case, the priority of the four substituents changes according to the CIP rules [12] so that (R)-sotalol (equivalent to l-sotalol) is much more effective as a beta-blocker than (S)-sotalol (equivalent to d-sotalol).

In order to offer a homogenous nomenclature for all beta-blocking drugs throughout the article, we predominantly use the d- and l-nomenclature (for the hydrochloride salts of the beta-blocking substances, when applicable, dissolved in water) where the l-enantiomers exert beta-blockade whereas the d-enantiomers do not whenever clinical doses of a beta-blocker are used. However, it should be stated again, from a stereochemical point of view, that only the CIP nomenclature is configurationally descriptive according to the spatial arrangement of the substituents of an asymmetric centre in a three-dimensional space. When no prefixes are used at all this implies that the racemic mixture is used.

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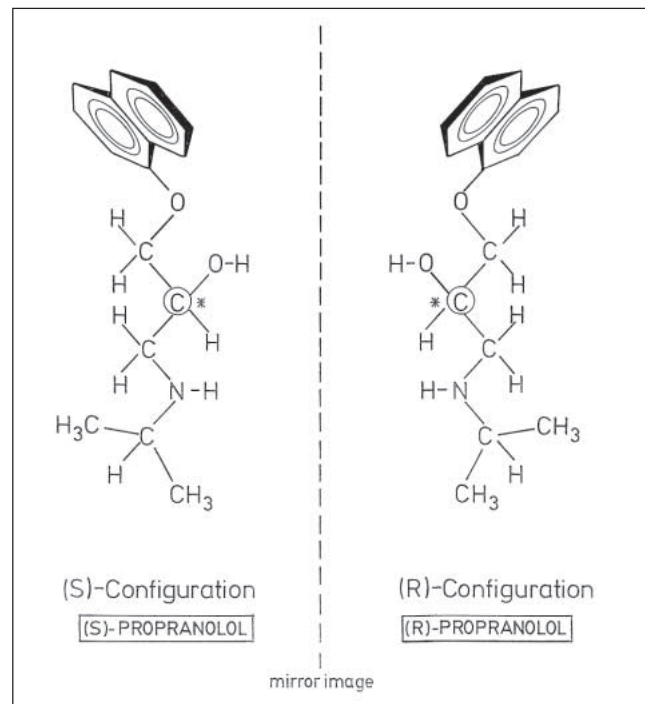
**Figure 1:** Structural similarity of (S)-propranolol and (S)-propafenone. The framed part shows the aminoalkanol chain that is common to all beta-blockers currently used in clinical practice (except sotalol). Hence, the asymmetric carbon atom (marked by an asterisk) is a common feature of all beta-adrenoceptor antagonists.

### Principles of stereoselectivity in beta-adrenoceptor antagonists

All beta-blockers that are currently used in research as well as in clinical practice are structurally related to the beta-agonists epinephrine and norepinephrine. As a common feature, these catecholamines and all beta-blockers possess an asymmetric carbon atom. Effects of agonists as well as of antagonists on adrenergic beta-receptors are highly stereoselective with the l-enantiomers being markedly more potent than the respective d-forms. Therefore, and in clear contrast to the racemic beta-blockers widely used in therapeutics, the human organism stereoselectively synthesises and uses the active enantiomers, ie, l-epinephrine and l-norepinephrine. Hence, it is not surprising that the l-enantiomers of all beta-blockers are orders of magnitude more potent in blocking beta-adrenoceptors than the respective d-forms [13]. Figure 4 shows the markedly different affinities of the d- and l-enantiomers of propranolol, atenolol and propafenone to beta-adrenoceptors *in vitro* [14–16], Figure 3 depicts the effects of d-, l- and d,l-atenolol and placebo on heart rate in humans emphasising that half the dose of l-atenolol is equally as effective as racemic d,l-atenolol suggesting that the full beta-blocking efficacy of the racemic drug resides in its l-enantiomer [15]. On the other hand, both d-atenolol and placebo show no effect [15]. However, it should be noted that propafenone, which is mainly used as a class 1c antiarrhythmic agent, also exerts weak beta-blocking effects due to its structural resemblance to beta-adrenoceptor antagonists (Fig. 1 and 4) [16].

When beta-blocking effects of the d- and l-enantiomers have been compared, the results were similar both in *in vitro* and in human studies, revealing that the l-enantiomers are markedly more effective than the respective d-forms. This has been shown for a variety of beta-blockers such as propranolol [2, 6, 14], atenolol [15], metoprolol [17], sotalol [7], carvedilol [18, 19], propafenone [16, 20] and others.

In addition to the beta-blocking effect that resides predominantly in the l-enantiomers, beta-adrenoceptor antagonists may show further non-specific as well as specific effects which may be completely independent from beta-blockade. These additional effects may or may not be stereoselective, and either enantiomer – the beta-blocking as well as the non-beta-blocking one – may be the dominant one. Such addi-



**Figure 2:** Structural formula of the (R)- and (S)-enantiomers of propranolol which behave like mirror images. The asymmetric carbon atom is marked by an asterisk.

nal effects may be used for particular therapeutic indications, or they can merely contribute to and therefore worsen (specific or non specific) side effects of (racemic) beta-blockers.

Other non-specific effects, formerly also termed membrane stabilizing activity (MSA), particularly occur in lipophilic rather than in hydrophilic beta-blockers. They usually only show either weak or no stereoselectivity. Thus, side effects of racemic beta-blockers caused by such unspecific effects equally reside in both the d- and l-enantiomers and might therefore be reduced by approximately 50 % by omitting the non-beta-blocking d-enantiomers from the currently used racemic drugs.

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**Figure 3:** Heart rate during 4 min of exercise and the following 5 min of recovery 3 hours after oral administration of placebo, 50 mg (R)-atenolol, 50 mg (S)-atenolol or 100 mg (R,S)-atenolol, obtained in a randomised, double-blind, cross-over study (n = 12) [15]. Compared with placebo, (R)-atenolol has no effect at all, whereas racemic (R,S)-atenolol and half the dose of optically pure (S)-atenolol are equally effective (–25 %, p < 0.01 in both cases).

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**Figure 4:** Inhibition of (-)-[<sup>125</sup>I]-iodocyanopindolol binding to beta-receptors: Upper panel: (S)-propranolol is 179 times more potent than (R)-propranolol [14]. Middle panel: (S)-atenolol is 46 times more potent than (R)-atenolol [15]. Lower panel: (S)-propafenone is 2.6 times more potent than (R,S)-propafenone and 54 times more potent than (R)-propafenone [16].

**Figure 5:** Plasma concentrations of (R)-propranolol and (S)-propranolol at rest, at the end of 10 min of exercise, and at the end of 15 min of recovery, obtained 4 hours after oral administration of 80 mg racemic (R,S)-propranolol (upper panel), or 40 mg (R)-propranolol and 40 mg (S)-propranolol (lower panel): plasma concentrations of (S)-propranolol are higher than those of (R)-propranolol ( $p < 0.01$  in all cases). Plasma concentrations of both (R)-propranolol and (S)-propranolol are increased during exercise ( $p < 0.01$ ) and return to baseline after 15 min of recovery after administration of the racemic compound (upper panel). In contrast, only plasma concentrations of (S)-propranolol are increased during exercise ( $p < 0.01$ ) and return to baseline after 15 min of recovery after administration of the optically pure enantiomers whereas those of (R)-propranolol remain completely unaffected (lower panel). All data obtained in a randomised, double-blind, cross-over study ( $n = 12$ ) [8].

### Antiarrhythmic class-3 effects

Recently, SWORD [11] was published as the first clinical trial to investigate the influence of the d-enantiomer of a currently used racemic beta-blocker, namely sotalol, on mortality. The results were disappointing: Bare of beta-blocking effects that reside stereoselectively in the l-enantiomer, optically pure d-sotalol increased mortality by 65 % compared with placebo [11]. In view of these new data, an increase of fatal arrhythmias caused by d-sotalol might presumably be the reason why d,l-sotalol was the only beta-blocker that failed to reduce mortality compared with placebo in a large trial in patients with myocardial infarction [21] whereas other beta-adrenoceptor antagonists such as timolol [22], propranolol [23], metoprolol [24] and atenolol [25] markedly decreased mortality. Thus, SWORD emphasised for the first time the potential hazard that might be inherited in the d-enantiomer of a racemic beta-blocker. Bearing in mind that beta-blockers are generally established as the most effective drugs for the prevention of sudden cardiac death [26] and that racemic d,l-sotalol was shown to be more effective than other antiarrhythmic drugs

in preventing death from any cause [27] although it consists of 50 % of a drug which is now known to be potentially harmful, namely d-sotalol [11], one may assume that optically pure l-sotalol might possibly be more effective in preventing death after myocardial infarction than the racemic mixture d,l-sotalol [21]. Accordingly, it might appear more reasonable to investigate the beta-blocking l-enantiomer rather than d-sotalol which lacks a beta-blocking effect. This might be true for all beta-adrenoceptor antagonists that are marketed and used as racemates since their d-enantiomers have never been shown not to cause harm in similar way to that of d-sotalol.

### Antiarrhythmic class-1 effects

It is well known that propafenone is an effective class-1 antiarrhythmic agent although its chemical structure is that of a typical beta-adrenoceptor antagonist (Fig. 1). Although the antiarrhythmic class-1 effects of d- and l-propafenone are quite similar [16] a recent study revealed some mild differences between the antiarrhythmic class-1 effects of propafenone [28]. Similar to propafenone, both enantiomers of the lipo-

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**Figure 6:** Plasma concentrations of (R)-atenolol and (S)-atenolol at rest, at the end of 10 min of exercise, and at the end of 15 min of recovery, obtained 4 hours after oral administration of 100 mg racemic (R,S)-atenolol (upper panel), or 50 mg (R)-atenolol and 50 mg (S)-atenolol (lower panel): plasma concentrations of both (R)-atenolol and (S)-atenolol are increased during exercise ( $p < 0.01$ ) and return to baseline after 15 min of recovery after administration of the racemic compound (upper panel). In contrast, only plasma concentrations of (S)-atenolol are increased during exercise ( $p < 0.01$ ) and return to baseline after 15 min of recovery after administration of the optically pure enantiomers whereas those of (R)-atenolol remain completely unaffected (lower panel). All data obtained in a randomised, double-blind, cross-over study ( $n = 12$ ) [8].

philic beta-adrenoceptor antagonist propranolol exert antiarrhythmic class-1 effects to the same extent [4].

According to our present knowledge, not only d-sotalol but also d-propranolol might potentially put patients at risk since it possesses antiarrhythmic class-1 effects [4] similar to those of encainide and flecainide which increased mortality in the CAST trial [29]. This might also be true for all other beta-blockers that are used as racemates since their d-enantiomers have never been shown not to cause harm in similar way to that of d-sotalol.

### Inhibition of the conversion of thyroxin to triiodothyronin

It is well known that propranolol inhibits the conversion of thyroxin ( $T_4$ ) to triiodothyronin ( $T_3$ ) [30, 31]. However, these studies were performed with racemic d,l-propranolol without considering stereoselective aspects.

It has been shown repeatedly that the beta-blocking effects of l-propranolol are markedly higher than those of d-propranolol [2, 6, 14]. On the other hand, opposite stereoselectivity has been reported for the influence of d- and l-propranolol on the conversion of  $T_4$  to  $T_3$  since only d-proprano-

lol [5, 32] or d,l-propranolol [6] decreased plasma concentrations of  $T_3$  whereas the optically pure l-enantiomer had no effect [5, 6, 32].

Therefore, optically pure d-propranolol might be useful as a specific therapeutic agent without beta-blocking effects to reduce plasma concentrations of  $T_3$  particularly in patients suffering from hyperthyroidism in which racemic propranolol cannot be administered because of contraindications for beta-blocking drugs.

### Stereoselectivity in pharmacokinetics

Although any racemic beta-blocker consists of its d- and l-enantiomers in a 1:1 ratio, plasma concentrations of these d- and l-enantiomers usually differ significantly and in wide ranges when the racemic mixture is administered orally or intravenously. For example, plasma concentrations of the l-enantiomers are higher than those of the d-enantiomers following administration of d,l-propranolol [6, 8, 14] d,l-metoprolol (extensive metabolisers only) [10] or d,l-propafenone [20]. In contrast, plasma concentrations of the d- are higher than those of the l-enantiomers after administration of d,l-atenolol [15] or d,l-carvedilol [34]. On the other hand, no significant differences between plasma concentrations of the d- and l-enantiomers were found when d,l-celiprolol [35] or d,l-bisoprolol [36] was given.

In addition, pharmacokinetic interactions between the d- and l-enantiomers have been described with propranolol [6], metoprolol [37] and propafenone [33] which may influence plasma concentrations as well as the effects of the respective drugs. Furthermore, plasma concentrations and actions of beta-blockers may be influenced stereoselectively by a number of different factors as emphasised by Walle and co-workers [38].

Due to their structural relationship to epinephrine and norepinephrine, beta-blockers are taken up into, stored in and released from adrenergic nerves together with these catecholamines [39–44]. Recently, it has been shown that the release of beta-blockers from adrenergic nerve endings may markedly influence plasma concentrations of these drugs. However, substantial stereoselective differences have been described.

When single oral doses of the optically pure enantiomers of propranolol or atenolol were given, plasma concentrations of the l-enantiomers increased during exercise and returned to baseline after 15 min of recovery whereas those of the d-enantiomers remained unaffected (Fig. 5 and 6, lower panels) [8]. However, plasma concentrations of both the d- and l-enantiomers increase during exercise to the same extent and returned to baseline after 15 min of recovery following oral administration of the racemic mixture (Fig. 5 and 6, upper panels) [8]. In patients with long-term treatment with d,l-atenolol exercise stereoselectively increased plasma concentrations of l-atenolol [45]. In contrast, in patients chronically treated with d,l-propranolol, exercise increased plasma concentrations of both enantiomers to the same extent [46]. Thus, plasma concentrations obviously do not reflect the concentrations of the effective parts of the racemic drugs, ie, the l-enantiomers, at their sites of action in the synaptic gaps. These findings might explain the poor correlation between plasma concentrations and effects of beta-adrenoceptor antagonists particularly during exercise, and why beta-blockers may still be effective after withdrawal of therapy even when they are no longer detectable in plasma. In addition, these data emphasise first that blood samples should be taken strictly at rest whenever plasma concentrations of beta-blockers are to be determined, and second that stereoselective aspects should not be neglected.

## Conclusions

In the light the facts mentioned above 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 recognised as distinct drugs, thus defining the racemic mixtures as a combination of two different drugs in a fixed 1:1 ratio. Hence the racemates can no longer be regarded as optimal for patients on beta-blocker therapy. In addition to the potentially fatal effects mentioned above, the needless administration of the non beta-blocking d-enantiomers that make up 50 % of every racemic beta-blocker may contribute to an increase of side effects as well as drug interactions [13].

Thus, it would make sense to perform the so called chiral switch, ie, to replace the currently used racemic beta-blockers by the optically pure l-enantiomers in order to avoid potential harm to patients that might be derived from the non beta-blocking d-enantiomers [11, 47] the more so as the synthesis of the optically pure d- and l-enantiomers of any beta-blocking drug is easily feasible today, even on an industrial scale and at low costs, and that only half the dose of the optically pure l-enantiomers is need to obtain the full effect of the currently used racemic mixtures.

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