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Racemic beta-blockers – fixed combinations of different drugs

K. Stoschitzky, G. Zernig1, W. Lindner2

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, the d- and l-enantiomers of beta-blockers are mirror images [1] (Fig. 2). Although (Fig. 1), resulting in the existence of a d- and l-enantiomer.

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.

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.

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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, i.e., 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 additional 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 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.
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 inhered 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-
It has been shown repeatedly that the beta-blocking effects of propranolol inhibit the conversion of thyroxin (T4) to triiodothyronin (T3) [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 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 T4 to T3 since only d-propranolol [5, 32] or d,l-propranolol [6] decreased plasma concentrations of T3 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 T3 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 remained unaffected (Fig. 5 and 6, lower 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, i.e., the 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.

**Illustration omitted for reasons of copyright.**

**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].
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 have both different pharmacodynamics and different pharmacologic activity of propafenone enantiomers. Circulation 1989; 8: 592–6.


References


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