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Compared pharmacological characteristics in humans of racemic cetirizine and levocetirizine, two histamine H_1-receptor antagonists

Jean-Paul Tillement[a,*], Bernard Testa[b], Françoise Brée[a]

[a]*Laboratoire de Pharmacologie, Faculté de Médecine de Paris XII, F-94010 Creteil, France*
[b]*Institut de Chimie Thérapeutique, Ecole de Pharmacie, Université de Lausanne, CH-1015 Lausanne, Switzerland*

This article is dedicated to the memory of Dr. Joachim Mayer (1949–2001), colleague and friend

Abstract

The potent histamine H_1-receptor antagonist cetirizine (Zyrtec®) is a racemic mixture of levocetirizine (now available under the trademark Xyzal®) and dextrocetirizine. In this Commentary, we examine some biological properties of cetirizine and levocetirizine, namely enantioselectivity in pharmacological activity and pharmacokinetic properties, with emphasis on the possibility of racemization, the compared behavior of the two enantiomers, and the potential for interactions with other drugs. Recent data demonstrate that the antihistaminergic activity of the racemate is primarily due to levocetirizine. Levocetirizine is rapidly and extensively absorbed, poorly metabolized, and not subject to racemization. Its pharmacokinetic characteristics are comparable after administration alone or in the racemate. Its apparent volume of distribution is smaller than that of dextrocetirizine (0.41 L kg^{-1} vs. 0.60 L kg^{-1}). Moreover, the non-renal (mostly hepatic) clearance of levocetirizine is also significantly lower than that of dextrocetirizine (11.8 mL min^{-1} vs. 29.2 mL min^{-1}). Our conclusion is that levocetirizine is indeed the eutomer of cetirizine. The evidence reviewed here confirms preclinical findings and offers a rationale for the chiral switch from the racemate to levocetirizine.
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1. Introduction

Cetirizine (Zyrtec®) is a second-generation antihistamine indicated for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria, in adults and children of 6 or more years. Its principal pharmacological effects are mediated through selective inhibition of peripheral histamine H_1-receptors, and its pharmacokinetic properties explain its good tolerability in patients. Indeed, the use of cetirizine is associated with a low incidence of anticholinergic effects such as dry mouth. Furthermore, it causes little sedation and has no cardiac adverse effects unlike highly lipophilic antihistamines [1]. Moreover, it can be safely administered with virtually any other drug, as it does not affect their rate of metabolism. This is due to the fact that it has neither inducing nor inhibiting effects on the major drug-metabolizing enzymes [2].

Cetirizine is a racemate which consists in equal amounts of (*R*)-levocetirizine and (*S*)-dextrocetirizine (Fig. 1). In most medicinal racemates, one of the enantiomers is more active than the other [3], and a number of studies have shown that cetirizine and its enantiomers follow this rule.

As usual with racemates, it is useful to examine whether there is a scientific justification for a chiral switch to the eutomer. This can be done using the decision tree proposed by one of us [4], which consists in comparing the degree of enantioselectivity of the two enantiomers in pharmacodynamic and pharmacokinetic properties, in checking for interactions between enantiomers and with other drugs, and in assessing the absence of interconversion between enantiomers (racemization) [5]. This Commentary covers significant studies published on these aspects.

* Corresponding author. Tel.: +33-1-49-81-36-61; fax: +33-1-49-81-35-94.
E-mail address: tillement@univ-paris12.fr (J.-P. Tillement).

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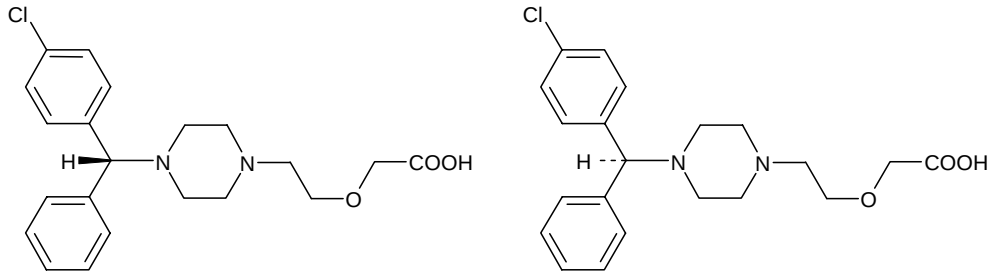

(*R*)-levocetirizine (the eutomer)

(*S*)-dextrocetirizine (the distomer)

Fig. 1. The chemical structure of (*R*)-levocetirizine and (*S*)-dextrocetirizine.

2. Is enantioselectivity observed in the pharmacological activity of cetirizine?

In binding assays, levocetirizine has demonstrated a 2-fold higher affinity for the human H_1-receptor compared to cetirizine, and an approximately 30-fold higher affinity than dextrocetirizine [6]. The difference in affinities between the two enantiomers is mostly accounted for by their different dissociation rates from the H_1-receptor, with levocetirizine demonstrating a far longer dissociation half-life than dextrocetirizine (Table 1).

In healthy subjects, levocetirizine inhibited histamine-induced wheal and flare responses to the same extent as cetirizine, with a maximum effect at 6 hr post-dose and a duration of action greater than 24 hr. In contrast, dextrocetirizine was less effective at the same dose [7]. Notably, at 32 hr post-dose the histamine-induced wheal response to levocetirizine was statistically superior to that to cetirizine [7]. Levocetirizine (5 mg) and cetirizine (10 mg) also inhibited histamine-induced increases in nasal airway resistance while dextrocetirizine failed to demonstrate any significant antihistaminergic activity [8]. Thus, the H_1-antagonist activity of cetirizine is primarily due to levocetirizine, which is considered to be the most active enantiomer (i.e. the eutomer), while dextrocetirizine is the least active enantiomer (the distomer).

This can be a first argument to remove the distomer from the racemate and develop the eutomer. However, it is clear that such a decision cannot be based on this single criterion.

Table 1
Binding characteristics of levocetirizine and dextrocetirizine to human H_1-receptors expressed in Chinese hamster ovary (CHO) cells [6]

	k_{+1} (μM^{-1} min^{-1})[a]	k_{-1} (min^{-1})[b]	$t_{1/2}$ (min^{-1})[c]	pK_i[d]
Levocetirizine	2.3 ± 0.4	0.005 ± 0.002	142	8.5 ± 0.1
Dextrocetirizine	1.6 ± 0.7	0.12 ± 0.05	6	7.1 ± 0.1

[a] Association kinetic constant ± SD.
[b] Dissociation kinetic constant ± SD.
[c] Dissociation half-life.
[d] ±SD.

The possibility of adverse reactions caused by the eutomer but not seen with the racemate is a major criterion of decision. It is therefore important to underline here that no serious adverse event was seen in the two clinical studies of levocetirizine discussed below [9,10].

Besides these pharmacodynamic considerations, pharmacokinetic criteria must also be taken into account, e.g. the possibility of racemization of the eutomer, the compared pharmacokinetics of the two enantiomers, and a possible influence of the distomer on the *in vivo* behavior of the eutomer.

3. Is an interconversion between enantiomers (racemization) likely to occur?

Following the oral administration of [^{14}C]levocetirizine dihydrochloride (5 mg) to four subjects, the pharmacokinetic parameters of total radioactivity and levocetirizine were monitored separately [10]. No difference was seen between the respective C_{max}, t_{max} and AUC values, and there was no appearance of dextrocetirizine in human plasma or urine samples following levocetirizine dosing [10]. This is a clear indication that levocetirizine does not racemize in the body, a configurational stability further confirmed when levocetirizine and dextrocetirizine were incubated separately in human plasma.

Similarly, incubation of cetirizine enantiomers in buffer solutions of pH 7.4 at room temperature did not reveal the slightest occurrence of racemization even after days [11]. Thus, there is overwhelming evidence for the great configurational stability of levocetirizine.

4. Is enantioselectivity observed in the pharmacokinetic properties of cetirizine?

The intestinal absorption of H_1-antagonists is usually complete [1,10], and cetirizine and levocetirizine are no exception to this rule. Indeed, with its C_{max} reached within 1 hr, levocetirizine shows the same rapid and extensive

intestinal absorption as cetirizine [12,13]. This is reflected in a total recovery of 98.3% of the dose as determined in the radiolabel study, and a higher value than that the 95% previously measured for cetirizine [14]. Cetirizine, and hence its enantiomers, exist almost exclusively as a zwitterion in the pH region 3.5–7.5 [15]. Due to conformational flexibility and the formation of an internal ionic bond, the positive and the negative charge partly neutralize each other, rendering the molecule more lipophilic and hence better available for passive absorption.

Although the pharmacokinetics of levocetirizine and cetirizine are similar, some differences have been observed. The apparent volume of distribution of levocetirizine is significantly lower than that of dextrocetirizine (Table 2). A low volume of distribution is a valuable property for H_1-antagonists, both in terms of safety and efficacy [16], since it implies a lack of exposure of organs which are not therapeutic targets but where toxic reactions may be elicited. Furthermore, a low volume of distribution reduces the risk of dose-dependent toxicity, individual variations in therapeutic effect, and the potential for drug–drug interactions [1]. The fact that the plasma protein binding of levocetirizine (91.2%) [17] is slightly higher than that of cetirizine (88–90%) may explain the lower distribution volume of the former [18].

5. How extensively are cetirizine enantiomers metabolized?

The non-renal clearance of levocetirizine was found to be significantly lower than that of dextrocetirizine (Table 2). The non-renal clearance (i.e. total minus renal clearance, i.e. 11.8 and 29.2 mL min^{-1} for levocetirizine and dextrocetirizine, respectively) corresponds in fact to the hepatic clearance. Such a difference suggests that more dextrocetirizine than levocetirizine is metabolized in the liver, although biotransformation is low in both cases and probably of no clinical relevance. Indeed, metabolic profiling and quantification have demonstrated that like the racemate, levocetirizine is poorly metabolized [19]. A very low level of biotransformation was also confirmed by the equivalence of pharmacokinetic parameters seen when comparing total radioactivity and unchanged levocetirizine in plasma [10].

This is an important finding since it implies that metabolic interactions with extensively transformed drugs are unlikely for dextrocetirizine and even more so for levocetirizine. In contrast, many other second-generation antihistamines of high lipophilicity are extensively metabolized by hepatic and intestinal cytochromes P450, particularly CYP2D6 and CYP3A4 [14]; the concomitant use of antifungals, macrolides or cimetidine, to cite a few, can dramatically inhibit these enzymes, causing accumulation of unchanged antihistamine and the possible occurrence of overdosage.

6. Are the enantiomers of cetirizine involved in mutual pharmacokinetic interactions?

A recent investigation has answered this question [9]. A two-way randomized, cross-over design was employed with a washout period of 7 days between two treatments, involving either levocetirizine dihydrochloride (10 mg) or cetirizine dihydrochloride (20 mg) dissolved in 50 mL of uncarbonated water, administered to 24 healthy subjects (12 males, 12 females). The plasma and urinary pharmacokinetic parameters of levocetirizine administered alone or in the racemate were compared. The results (Table 2) show clearly that the behavior of levocetirizine was not influenced by the presence of its enantiomer. Compared with the latter, levocetirizine had a higher plasma AUC, a higher C_{max}, a longer terminal half-life ($t_{1/2}$) and a smaller

Table 2
Plasma and urinary pharmacokinetic parameters of levocetirizine and dextrocetirizine following a single dose of levocetirizine or cetirizine [9]

Drug administered	Levocetirizine dihydrochloride (10 mg)	Cetirizine dihydrochloride (20 mg)	
Drug monitored	Levocetirizine	Levocetirizine	Dextrocetirizine
AUC (μg mL^{-1} hr^{-1}) ± SD	4.14 ± 0.74	4.09 ± 0.65	1.91 ± 0.39
C_{max} (μg mL^{-1}) ± SD	0.51 ± 0.11	0.51 ± 0.10	0.29 ± 0.06
t_{max} (hr) ± SD	0.73 ± 0.33	0.80 ± 0.29	0.82 ± 0.33
$t_{1/2}$ (hr^{-1}) ± SD[a]	7.76 ± 1.59	7.80 ± 1.96	5.52 ± 1.85
Cl/F (mL min^{-1}) ± SD[b]	41.6 ± 7.7	41.7 ± 6.3	90.60 ± 17.16
V_z/F (L kg^{-1}) ± SD[c]	0.41 ± 0.10	0.42 ± 0.11	0.60 ± 0.14
Ae (μg) ± SD[d]	6810 ± 1023	7260 ± 1285	6360 ± 1330
Fe (%) ± SD[e]	68.1 ± 10.2	72.6 ± 12.8	63.6 ± 13.3
CL_R (mL min^{-1}) ± SD[f]	29.8 ± 7.7	32.0 ± 8.3	61.4 ± 17.7

[a] Terminal half-life calculated as $\ln_2/\lambda_z$, where λ_z is the apparent first-order terminal rate constant.
[b] Apparent total body clearance (calculated by dividing the dose administered by the AUC), divided by the bioavailability (F).
[c] Apparent volume of distribution, divided by the bioavailability (F).
[d] Total amount excreted over the entire urine sample collection.
[e] Relative cumulative urinary excretion.
[f] Renal clearance calculated as $Ae/AUC_{(0–48\ hr)}$.

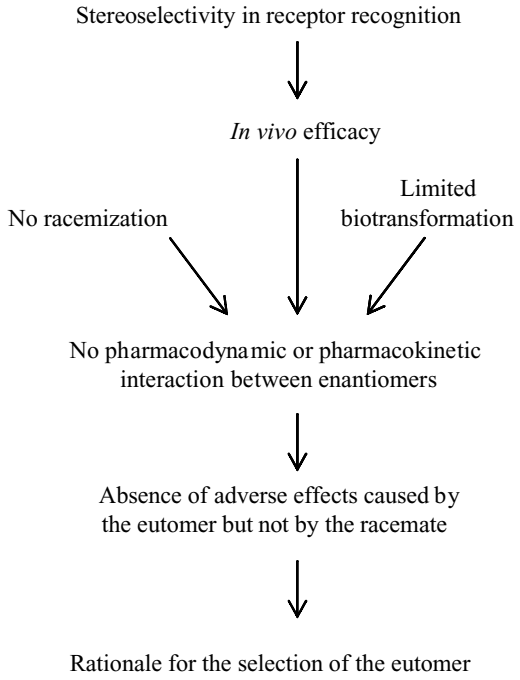

Fig. 2. A sequence of scientific criteria to be applied when choosing between a racemate (this work, cetirizine) and its eutomer (this work, levocetirizine) (simplified from [4]).

volume of distribution (Vd). These results lead to the conclusion that the pharmacokinetic parameters of levocetirizine are not influenced by dextrocetirizine, being neither increased nor decreased.

7. Conclusion: the racemate or the eutomer?

The decision to develop a eutomer rather than a racemate, or to carry through a chiral switch, is based on scientific and commercial criteria. Scientific criteria, the only one of concern to us, can be organized in a decision tree [4], a simplified version of which is shown in Fig. 2.

Applying these successive criteria to cetirizine, it appears indeed that levocetirizine is the eutomer for pharmacodynamic and pharmacokinetic reasons. To summarize, all evidence available indicates that levocetirizine is intrinsically more active and more efficacious than dextrocetirizine, and for a longer duration. Furthermore, its pharmacokinetic behavior appears more favorable due to a lower volume of distribution and a slower renal clearance. Considering the pharmacokinetic–pharmacodynamic model of inhibition of histamine-induced skin reactions by cetirizine [18], the plasma levels achieved by a dose of 5–10 mg of the eutomer are sufficient to reach maximal antihistaminergic effects.

In our view, these findings offer a first rationale for the therapeutic use of the eutomer administered alone.

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