Comparative activity of cetirizine and mizolastine on histamine-induced skin wheal and flare responses at 24 h

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Aims The aim of our study was to compare the activity of cetirizine 10 mg with that of mizolastine 10 mg *vs* placebo at 24 h after intake in healthy volunteers.

Methods This was a double-blind, randomized, placebo controlled, three-way cross-over study with a wash-out period of 7 ± 2 days between each period. The study included 36 healthy volunteers (18–50 years, mean age = 32 years; 9 males). The objective measurement was the cutaneous reactivity to increasing concentrations of histamine (0, 5, 10, 20, 40, 80, 160 mg ml⁻¹) administered by prick tests. The reactivity was evaluated by the wheal and flare areas (mm²). The AUC (area under curves) values of the wheal and flare areas as a function of the log₂ transformed histamine concentration were calculated for each subject and treatment, and compared.

Results A highly significant treatment effect was evidenced both for wheal and flare responses ($P = 0.0001$). This indicates the good activity of both cetirizine 10 mg and mizolastine 10 mg in inhibiting skin wheal and flare reactions to histamine. In addition, the mean AUC values significantly differed between cetirizine and mizolastine (64.8 and 117.8 log₂ (mg ml⁻¹) $\times$ mm² for wheal, and 939.4 and 2340.8 for flare, respectively; $P = 0.0001$), with a superior activity of cetirizine than mizolastine at 24 h after intake both on wheal and flare responses. The tolerance of cetirizine and mizolastine was good. The severity of the adverse events was never more than ‘moderate’, ‘fatigue’ being the most frequent reported symptom [cetirizine (6 subjects), placebo (3), mizolastine (5)], followed by ‘somnolence’ [cetirizine (0), placebo (1), mizolastine (3)]. There was no serious adverse event.

Conclusions This study shows that cetirizine (10 mg) suppresses skin reactivity to histamine more effectively than mizolastine (10 mg) 24 h after intake in healthy volunteers.

Keywords: allergy, antihistamine, cetirizine, mizolastine, prick test, skin

Introduction

Cetirizine, a powerful and well tolerated anti-histamine H₁ drug commercialized in France and numerous other countries, and mizolastine, a recently commercialized anti-H₁ compound, are both active in the treatment of seasonal and perennial allergic rhinitis, and in urticaria at a dose of 10 mg daily. The efficacy of cetirizine has been demonstrated in numerous clinical and pharmacodynamic

studies, in the nose [1–6], as well as in the skin [2, 7–16]. It is rapidly absorbed, and is directly active. In the skin, a significant antihistamine activity is reported after 0.5 h of administration of cetirizine [8, 17, 18].

Mizolastine, more recently commercialized, is a well tolerated antihistamine agent [19–22] with antiallergic properties [23, 24]. Efficacy of mizolastine has been extensively reported in clinical studies in seasonal and perennial allergic rhinitis and rhinoconjunctivitis [25–30] and chronic urticaria [31, 32]. Activity of mizolastine assessed by the wheal and flare reaction induced by histamine shows that it is a powerful and fast-acting anti-H₁ drug at the dose of 10 mg, with a prolonged action [33–37]. Mizolastine absorption is fast with maximal plasma concentration

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at 1.5 h, and an elimination half-life of 8–13 h [33, 38]. Two metabolic pathways are activated for mizolastine, the glucuronoconjugation and the cytochrome P450 3A4 enzymatic system, resulting in the formation of inactive metabolites [38].

A comparison of the activity of cetirizine and mizolastine on the wheal and flare reaction to histamine [34] showed their similar maximal effect at 3–6 h after intake, whereas there was a trend towards a better activity of cetirizine from 8 to 24 h as compared with mizolastine. Our study design was therefore constructed in order to compare powerfully the activity of cetirizine and mizolastine at 24 h after a single intake of a therapeutic dosage of 10 mg each on the cutaneous reactivity to histamine.

Methods

Subjects

This was a double-blind, randomized, placebo controlled, three-way cross-over study. The study included 36 healthy volunteers (27 women, 9 men, aged 18–48 years, mean age 32). They had no personal history of allergy, a negative Phadiatop[®] (Pharmacia & Upjohn, Sweden), sparse family history of atopy or asthma (3 cases of rhinitis, and 1 case of allergy to penicillin and urticaria upon exposure to sunlight in parents or grandparents), and normal laboratory test results at inclusion. All signed a written informed consent to participate into the study, which was approved by the ethics committee of our hospital.

Study design

The study consisted of three periods, with a wash-out period of 7 ± 2 days between each. For each period, subjects came in between 07.00 and 09.00 h to take medication at random (one capsule of either cetirizine 10 mg, mizolastine 10 mg or placebo, identical in appearance) with a glass of water. Twenty-four hours later, they came in again to undergo a series of skin prick tests to increasing concentrations of histamine (0, 5, 10, 20, 40, 80, 160 mg ml⁻¹) (Prick lancet, Bayer).

Activity

The objective measurement was the cutaneous reactivity to histamine administered by skin prick tests. Activity was evaluated by the measurement of the wheal and flare areas, as previously published for ebastine [12, 13, 39]. Fifteen minutes after histamine skin prick testing, wheals and flares at each histamine concentration were drawn directly on the arm. Tape was applied, removed, and glued onto a transparency, permitting an exact tracing of each area. All areas were calculated after scanning and integration on

a computer program (Adobe Photoshop), and analysed with the public domain NIH Image program (written by W. Rasband at the US National Institutes of Health). Histamine concentration-response curves in function of the wheal and of the flare areas were constructed, and log transformed.

Expression of results and statistical analysis

The efficacy analysis was carried out on the per protocol population (PP), i.e. all the randomized and eligible subjects without any major protocol deviation (36 subjects).

The objective measurement was the cutaneous reaction, i.e. the wheal and the flare areas (mm²), to increasing concentrations of histamine at 24 h after single intake. The areas of wheals and of flares were used to establish the log₂ transformed concentration–mean response to histamine curves.

For statistical analysis, the efficacy variables were the AUC values (area under curve) of the wheal and of the flare areas [curves of wheal and flare areas (mm²) as a function of the log₂ transformed histamine concentration (mg ml⁻¹)] calculated using the trapezoidal rule. Comparisons of the mean AUCs was performed by an analysis of variance for latin square. If the treatment effect was significant, the Newman–Keuls posthoc test was applied to perform a pairwise comparison, principally between the two active treatments. 95% confidence intervals on the difference between the treatment means were calculated.

Results

Wheal areas

The curves of mean wheal areas as a function of log₂ transformed histamine concentrations determined for each treatment are presented on Figure 1. The largest mean wheal area was obtained under placebo, regardless of the histamine concentration, the smallest under cetirizine, and an intermediary under mizolastine. The three curves never crossed.

Overall analysis of the results performed on the AUC values shows a highly significant treatment effect for wheal reactions ($P=0.0001$). Mean AUC values for each of the three treatments significantly differed (*posthoc* tests) between both active treatments and placebo ($P=0.0001$), as well as between cetirizine and mizolastine (AUC values = 64.8 ± 3.9 , 117.8 ± 7.3 and 175.9 ± 7.5 log₂ (mg ml⁻¹) $\times$ mm² for cetirizine, mizolastine and placebo, respectively; $P=0.0001$) (Table 1). The order of activity was cetirizine > mizolastine > placebo. The cutaneous reactivity was therefore more significantly inhibited with

cetirizine than mizolastine, and mizolastine was significantly more effective than placebo.

Flare area

The curves of mean flare areas as a function of log₂ transformed histamine concentration are presented on Figure 2. The largest mean flare area was observed also under placebo, the smallest under cetirizine, and an intermediary under mizolastine. The three curves never crossed.

Overall analysis performed on the AUC values showed a significant difference between the three treatments: 939.4 ± 131.4, 2340.8 ± 203.4 and 4179.3 ± 179.1 log₂

(mg ml⁻¹) × mm² for cetirizine, mizolastine and placebo, respectively (*P* = 0.0001) (Table 1). In addition, the posthoc tests showed that each of the three treatments significantly differed from the other two, with an order of activity of cetirizine > mizolastine > placebo.

Tolerance

An analysis of the safety variables was performed on all randomised subjects (37 volunteers), according to treatment. There was no pretreatment adverse event. The tolerance for cetirizine and mizolastine was good. The severity of the adverse events was never more than 'moderate'. Twenty-one subjects among the 37 randomized volunteers reported at least one adverse event, with a total of 25 adverse events. 'Fatigue' was the most

Figure 1 Concentration–response curves of the wheal areas to log₂ transformed histamine concentration 24 h after administration of cetirizine (open circles), mizolastine (open triangles) or placebo (closed squares). Points are means, and bars are s.e.mean of the areas (mm²) measured in 36 healthy volunteers.

Figure 2 Concentration–response curves of the flare areas to log₂ transformed histamine concentration 24 h after administration of cetirizine (open circles), mizolastine (open triangles) or placebo (closed squares). Points are means, and bars are s.e.mean of the areas (mm²) measured in 36 healthy volunteers.

Table 1 Inferential analysis of AUC values for wheal and flare areas.

<i>P</i> value = 0.0001 SNK: CETI>PLAC>MIZO		
Wheal	Difference of means	95% CI for difference of means
CETI-PLAC	– 111	[– 125, – 97]
CETI-MIZO	– 53	[– 66, – 39]
MIZO-PLAC	– 58	[– 72, – 44]
Period effect		<i>P</i> value = 0.3538
Flare		
CETI-PLAC	– 3244	[– 3522, – 2966]
CETI-MIZO	– 1410	[– 1688, – 1131]
MIZO-PLAC	– 1834	[– 2112, – 1556]
Period effect		<i>P</i> value = 0.5178

SNK = Student Newman–Keuls *posthoc* test.

CI: confidence interval.

CETI: cetirizine; PLAC: placebo; MIZO: mizolastine.

frequent symptom (6 under cetirizine, 3 under placebo and 5 under mizolastine), followed by 'somnolence' (0 under cetirizine, 1 under placebo and 3 under mizolastine). There was no serious adverse event.

Discussion

Our study shows a highly significant treatment effect of both cetirizine and mizolastine, administered at a therapeutic dosage of 10 mg each, as compared with placebo, at inhibiting the skin reactivity to histamine 24 h after intake. This result shows the good antihistaminic activity of both cetirizine and mizolastine in the skin at 24 h. In addition, the wheal and flare responses also significantly differed between cetirizine and mizolastine, suggesting a superior antihistaminic activity of cetirizine as compared with mizolastine in the skin at 24 h.

In our study, activity was assessed by the areas of wheal and flare induced by histamine administered by prick test. The ability for H₁-receptor antagonists to inhibit the wheal and flare reaction is a well documented result. The skin prick test technique is one of the most reliable methods for assessing their histamine antagonistic activity in man [12–14, 40]. Study designs lead to compare either their relative efficacy or their time of onset and duration of action [6, 8, 16]. In this study, activity was studied at a given time-point of 24 h, in order to compare the duration of effect of the drugs. A cross-over design was chosen to minimize variability by ensuring a within-subject treatment comparison. This was very well adapted to our purpose, with single-dose intake of each medication, and a 1 week wash-out interval between two treatment periods in order to prevent any carry-over effect.

The significant difference between activity of the two drugs and placebo shows the good efficacy of both cetirizine 10 mg and mizolastine 10 mg in inhibiting skin wheal and flare reactions to histamine at 24 h after intake. This result is in agreement with previous findings of a long lasting activity of cetirizine [8, 14, 36, 38], as well as of mizolastine [33–35] on the wheal and flare areas at 24 h after intake. A similar profile of activity in function of time was observed for all subjects.

In addition, the study clearly shows that the activity of cetirizine is superior to that of mizolastine on both wheal and flare responses 24 h after intake. The superior activity of cetirizine compared with mizolastine on inhibition of the flare reaction is in agreement with previous findings by Rosenzweig *et al.* [34]. In their study, the flare response induced by histamine after treatment with mizolastine and cetirizine did not significantly differ, for the curve as a whole. However, there was a trend towards a better activity of cetirizine from 10 to 24 h as compared with mizolastine [34]. We may then suggest, in view of both their [34] and our results, that their study designed

with 16 volunteers was strong enough to demonstrate a better activity of mizolastine as compared with loratadine, but not strong enough to demonstrate any difference between cetirizine and mizolastine. Our study including 36 volunteers to compare activity of cetirizine to that of mizolastine clearly shows a better activity of cetirizine at 24 h. The different efficacy of both drugs may find its explanation in the biotransformation of mizolastine into inactive metabolites by two different metabolic pathways, the glucuronconjugation and the cytochrome P450 3A4 enzymatic system [38], whereas cetirizine, directly absorbed and active, is also eliminated without any metabolization [41]. Whether a similar profile will occur after multiple dosing, referring to clinical situation with repeated daily intake, will now be interesting to study.

The tolerance for cetirizine and mizolastine was good, with no severe adverse events, always lower than moderate for 'fatigue', followed by 'somnolence'. These adverse events are the mainly reported events with antihistamine agents. However, the levels of spontaneously reported events are here relatively low for both drugs. This is in accordance with the very low incidence of side-effects reported for both drugs [22, 36].

In conclusion, our pharmacodynamic study shows the good activity of both cetirizine and mizolastine at single therapeutic dosage of 10 mg each to suppress skin reactivity to histamine 24 h after intake in healthy volunteers. In addition, the study clearly demonstrates a greater activity of cetirizine as compared with mizolastine on both wheal and flare responses at 24 h.

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