Original article

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A double-blind, single-dose, crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine versus placebo: suppression of histamine-induced wheal and flare response for 24 h in

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Key words: cetirizine; ebastine; epinastine; fexofenadine; histamine; histamine H_1-antagonists; loratadine; skin tests; terfenadine.

Background: New H_1-antagonists have become available, but there has been no comparison of their potency for inhibiting histamine in the skin.
Methods: Cetirizine 10 mg, ebastine 10 mg, epinastine 20 mg, fexofenadine 60 mg, terfenadine 60 mg, loratadine 10 mg, or placebo was given to 14 healthy male volunteers in a double-blind, crossover randomized manner. Inhibition of the wheal and flare response to epicutaneous histamine phosphate (100 mg/ml) challenge was measured at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 h after doses.
Results: Epinastine inhibited the wheal and flare after 30 min. Cetirizine commenced acting at 1 h and was superior to other treatments. Ebastine was no better than placebo until 4 h, but was efficacious thereafter until 24 h. Terfenadine induced potent inhibition after 1 h and was superior to its metabolite fexofenadine. Loratadine was the least potent inhibitor. Inhibition of the flare response paralleled the patterns seen for wheals. The rank order for area under the curve (0–24 h) was cetirizine, epinastine, terfenadine, ebastine, fexofenadine, loratadine, and placebo.
Conclusions: The inhibition of histamine effects in the skin may be useful in predicting the clinical utility of newly introduced antihistamines in treating allergic disorders.

The first H_1-antihistamine was described in 1937 (1); diphenhydramine (2) was introduced in 1946 and remains a popular drug even today. However, the initial products of this class have had major limitations because of affinity for

many other receptors and permeability of the blood–brain barrier, leading to multiple adverse effects (3). A second-generation of H_1-antagonists became available with the discovery of terfenadine (4), and subsequently the introduction of astemizole (5), loratadine (6), and cetirizine (7). The first extensive comparison of the biological properties of the first- and second-generation drugs was performed by Simons et al. (8): they showed that the rank order for inhibition of histamine-induced wheals and flares in the skin was cetirizine, terfenadine, loratadine, astemizole, chlorpheniramine, and placebo. Juhlin et al. (9) have extensively reviewed other studies that have compared the pharmacodynamics of antihistamines as defined by inhibition of the cutaneous response to histamine and allergen challenge. The consensus of approximately 27 investigations was that cetirizine was the most potent drug with regard to cutaneous inhibition. Additional properties attributed to the second-generation antihistamines include inhibition of inflammatory mediator release (10), and, in the case of cetirizine, inhibition of the recruitment of eosinophils into the late-phase response to allergen challenge in the skin (11) and lungs (12).

All of these drugs have been used extensively for management of allergic disorders such as seasonal and perennial allergic rhinitis (13) and urticaria (14). H_1-antihistamines are considered adjunctive drugs for anaphylaxis (15). Although once considered by many clinicians and regulatory authorities to be contraindicated in asthma (16), it is now clear that the second-generation antihistamines are safe in asthma (17). Furthermore, cetirizine was shown to reduce the cardinal symptoms of asthma (18, 19).

Recently, severe tachyarrhythmia and even deaths were reported during terfenadine administration, especially when metabolism of the drug was hindered by administration of other products known to inhibit the hepatic cytochrome P450 enzymes (20). Similar side-effects have been observed with astemizole. In fact, much of the H_1-antagonism observed with terfenadine is due to its acid metabolite. This is currently marketed as fexofenadine and this will soon replace terfenadine as a therapeutic agent (21). Additional new products in this group of drugs include ebastine (22, 23) and epinastine (24).

There have been no comparisons of the additional second-generation antihistamines now available. Using the model of inhibiting histamine-induced cutaneous wheals and flares, we compared the onset, potency, and duration of action of these new H_1-antagonists with those of other second-generation antihistamines currently in clinical usage.

Material and methods

This study was conducted at a major research center, the Covance Clinical Research Unit in Leeds, UK. A double-blind, placebo-controlled, randomized, crossover protocol was used, and the protocol was approved by an independent review board for clinical research. Seven single-dose treatments were administered: cetirizine 10-mg tablets, ebastine 10-mg tablets, epinastine 20-mg tablets, fexofenadine 60-mg capsules, terfenadine 60-mg tablets, loratadine 10-mg tablets, and placebo (lactose) tablets. All test items were obtained from commercial sources. The doses of each product selected were those currently approved and available at the time of the trial. A period of approximately 7 days was chosen between each treatment to eliminate any significant carry-over effect. The study started on 10 March 1997 and the clinical part terminated on 28 May 1997.

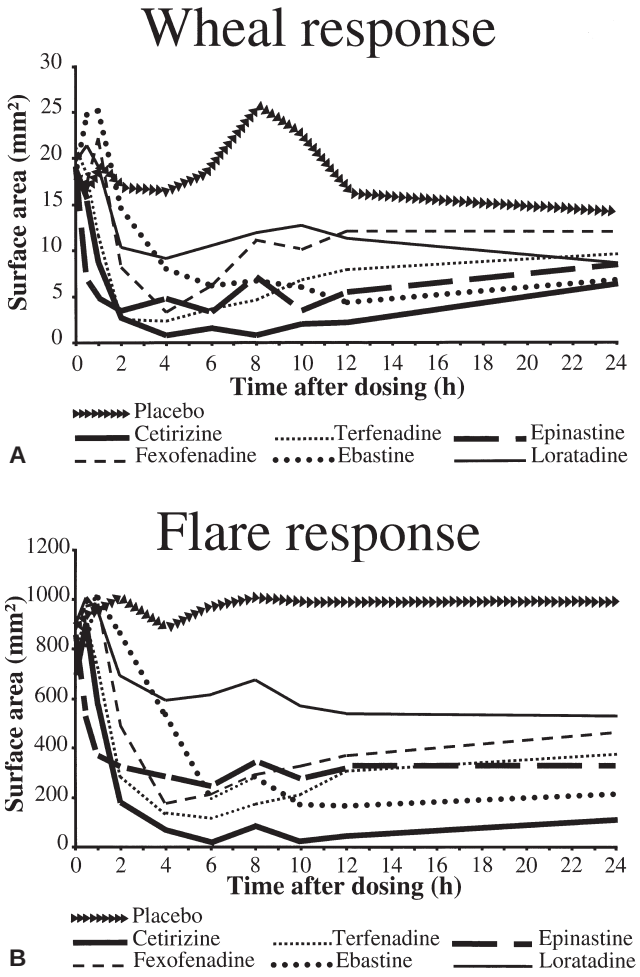

Figure 1. Least-squares mean surface area for wheal (A) and flare (B) responses after epicutaneous histamine (100 mg/ml) challenge, performed before and up to 24 h after single doses of H_1-receptor antagonists and placebo in 14 healthy male adults.

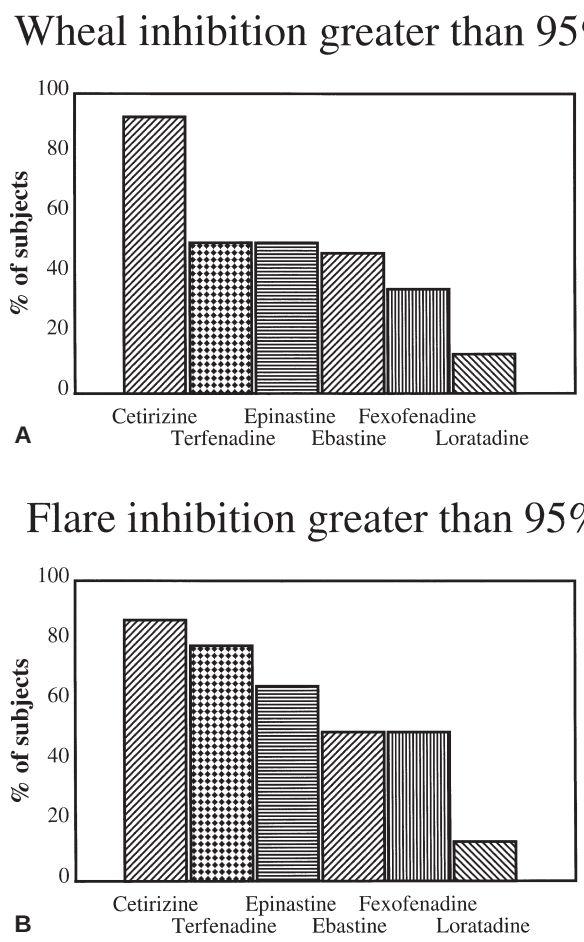

Figure 2. Percentage of subjects with greater than 95% inhibition of wheal (A) and flare (B) surface areas at one time point for each treatment. n=14 for all treatments except ebastine (n=13) for wheal inhibition.

Healthy white male subjects between aged 20–40 years and within 15% of their ideal body weight were recruited for this study from a pool of volunteers at the Covance Unit. Their body weights and heights ranged between 58 and 85 kg and 165 and 187 cm, respectively. Each subject gave written informed consent for participation, and was aware of being free to withdraw from the study at any time without prejudice. A medical history, examination, electrocardiogram, electrolytes, panel for liver and renal function, complete blood count, urinalysis, and serologies for hepatitis B and C and HIV were used to confirm their overall good health. Exclusion criteria included any prescribed medication within 2 weeks, any antihistamines within 1 week (no astemizole for 6 weeks), use of any investigational drug for 3 months, history of drug hypersensitivity, clinically significant allergic diseases, excessive use of alcohol or tobacco, use of any recreational drug, any acute illness within 4 weeks, or any subjects judged inappropriate to participate by their personal physician or unit physicians. Drugs known to alter the immunologic or other major organ systems such as systemic corticosteroids, barbiturates, phenothiazines, cimetidine, etc., were not to be used within 4 weeks of study initiation. Volunteers with any other current or prior history of clinically significant medical illness were excluded.

A total of 15 patients were recruited for the study. One patient withdrew after three dosing periods, and he was replaced by another subject. Thus, 14 individuals completed all seven dosing periods and evaluations. Volunteers were admitted to the research unit on the night before drug administration, and remained for at least 24 h after the drug was taken. To control for circadian changes, all drugs were administered beginning at 0830 with a 5-min interval between dosing of individual subjects. Drugs were removed from sealed vials, placed directly into the mouth of each subject, and swallowed along with 200 ml of water while standing. The oral cavity was inspected after dose administration to insure all treatments were swallowed. Subjects remained erect for 2 h after dose administration. Blinding was maintained by administration of each dose by a third party independent of the staff monitoring medical parameters and performing histamine skin testing. The subjects were not familiar with the study medications, and were not permitted to see the products ingested. The order of drugs administered was based on a random order protocol.

Subjects abstained from alcohol for 48 h before each dosing and for the 24-h evaluation period afterward. No caffeine was consumed while on the unit. Subjects fasted after 2200 the night before each dosing until 1200 of the day after drug administration except for water.

The chief outcome variable was the wheal and flare response to epicutaneous histamine challenge. A drop of histamine phosphate (100 mg/ml in normal saline) was placed on the upper back, and a sterile lancet used to break the superficial skin through the drop of solution. After 10 min, skin wheal and flare areas were measured by tracing on the skin with a marker pen and transferring this to a transparent acetate sheet. The surface areas of the wheals and flares were measured by computerized planimetry. Evaluations were made before each drug and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 h after doses. Patients completed a Bond-Lader visual analog scale evaluation of alertness (25) before each dose and at 12 and 24 h. Finally, patients were queried for side-effects by asking the open question, ''How have you been feeling since your were last asked?'' This inquiry was made before each drug and at 3, 12, and 24 h. Laboratory studies were repeated before each dosing and 24 h later.

Statistical analysis was performed by repeated measures analysis of variance with the Greenhouse Geisser adjust-

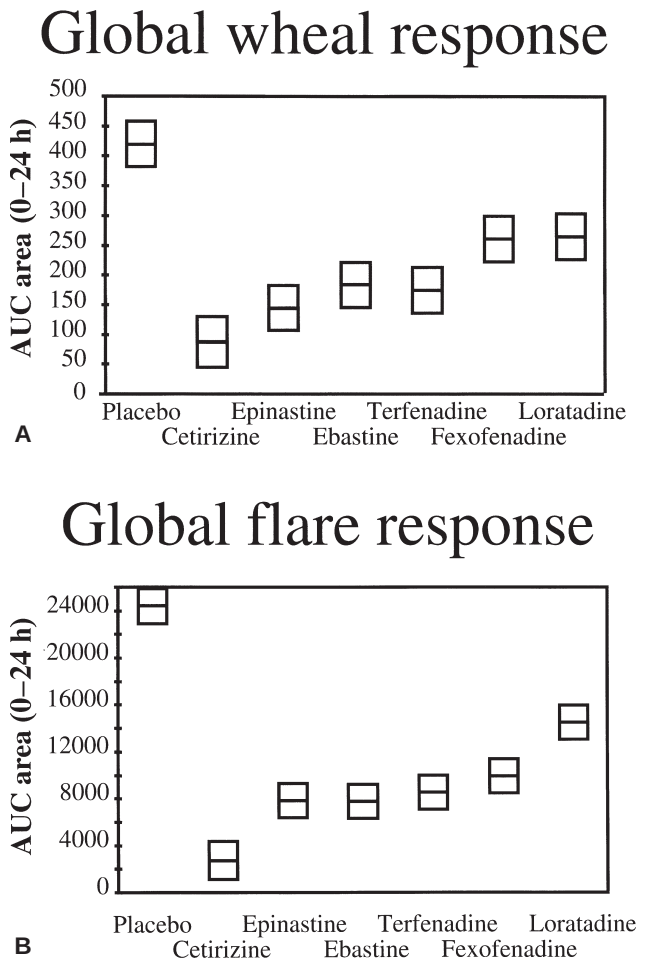

Figure 3. Global wheal (A) and flare (B) mean areas under curve (0–24 h) with 95% confidence intervals for each treatment (n=14).

ment for the surface area data (26). As the inhibition data were not normally distributed and no suitable transformation was available, these data were analyzed by nonparametric methods. The median values for inhibition were compared by the method described by Steinijans & Diletti (27). All tests were two-sided with significance at the 5% level. Global wheal and flare surface areas were calculated as the area under the curve (AUC) between the baseline and the individual area time curves by the trapezoidal rule.

Results

The mean values for the surface area of the wheal and flare responses to epicutaneous histamine challenge for all seven treatments over 24 h are shown in Fig. 1. The values for mean wheal area after placebo were relatively flat except for a slight increase at 8 and 10 h (Fig. 1A). In contrast, a reduction in the wheal size for all six active drugs was seen at various time points. At 4 h after a dose of cetirizine, terfenadine, fexofenadine, epinastine, ebastine, and loratadine, the mean surface area was inhibited by approximately 97, 89, 80, 75, 58, and 53%, respectively, when compared with the pre-dose mean. Thereafter, the wheal size slowly returned toward pre-dose levels, although at 24 h post-dose it remained below 72% of the pre-dose mean for all active treatments.

Administration of cetirizine 10 mg induced a rapid inhibition of the wheal response to histamine, which was most marked between 1 and 12 h, and the effect was significantly different from placebo at 4–12 h post-dose. During most of these time points, the wheal surface area measured after administration of cetirizine was smaller than for any other active treatment. Cetirizine was significantly better than epinastine at 4–8 h post-dose, ebastine at 6–8 h fexofenadine at 6–12 h, terfenadine at 8 h, and loratadine at 4–12 h.

Epinastine 20 mg had the most rapid onset of action, superior to all other treatments at 0.5 h and 1 h after oral administration, and inhibition of wheal surface area was significant *vs* placebo from 0.5 to 10 h. Ebastine had a much slower onset of action, was not significantly better than placebo until 4 h, and continued to be efficacious until the end of evaluation at 24 h. Fexofenadine was slow to inhibit wheal formation and showed a significant inhibition between 4 and 12 h. Terfenadine induced a more marked and rapid inhibition of the wheal response than its metabolite fexofenadine and was significantly superior to placebo between 1 and 12 h post-dose. Terfenadine was superior to fexofenadine from 1 to 2 h and from 6 to 8 h. After dosing with loratadine, inhibition of wheal formation was generally lower than for other active treatments, and it was superior to placebo only at 6 h.

The mean values for the surface area of flares after histamine challenge are shown in Fig. 1B. The values for placebo treatment were near the baseline response from 0.5 to 24 h. The values for active treatments tended to parallel the inhibitory patterns seen for wheal surface areas. In general, there was an increasing effect up to 6 h, and at this time point, the surface areas relative to pre-dose means for cetirizine, terfenadine, fexofenadine, ebastine, epinastine, and loratadine showed inhibitions of 96, 86, 76, 75, 74, and 31%, respectively.

Again, epinastine had the most rapid onset of action for inhibiting the flare response, and it was superior to all other treatments at 0.5 and 1 h. This drug was superior to placebo at all time points. Cetirizine had a slightly less rapid onset of action, but the mean surface area of flare was smaller than

for any other treatment from 2 h until the end of the observation period. Cetirizine was superior to placebo from 2–24 h, and to all other treatments at multiple time points. Cetirizine-induced flare inhibition was significantly greater than for ebastine from 2 to 12 h post-dose, for epinastine from 4 to 24 h post-dose, for fexofenadine from 1 to 2 h and 10 to 24 h post-dose, for terfenadine from 10 to 24 h post-dose, and for loratadine from 2 to 24 h post-dose. Ebastine efficacy was not seen until 6 h and remained until 24 h. The values for flare surface area were remarkably similar after ebastine treatment from 6 to 24 h. Fexofenadine-induced flare inhibition slowly increased after dosing, and was superior to placebo only from 4 to 6 h. Terfenadine caused a greater and more rapid inhibition of flare than fexofenadine, but was statistically different only at 2 h post-dose. Terfenadine values for histamine-induced flare surface area were better than after placebo treatment from 2 to 12 h. Loratadine-induced flare inhibition was generally lower than other active treatments and was not significantly different from placebo throughout the 24-h study period.

Fig. 2 illustrates the percentage of individuals who experienced greater than 95% inhibition of wheal (2A) and flare (2B) surface areas at some time point during the day of observation. Thirteen out of 14 subjects had almost complete suppression of whealing after administration of cetirizine. The responses to other antihistamines were considerably less, with just under half the subjects having 95% suppression of wheal area after terfenadine, epinastine, and ebastine therapy. Five subjects receiving fexofenadine had almost complete suppression of the wheal response to histamine, and only two after loratadine.

Inhibition of the flare response to histamine challenge was greater than that of whealing for most treatments (Fig. 2B). Twelve of 14 subjects had more than 95% inhibition at one time after cetirizine. This response was followed by a gradual decline in numbers experiencing near complete suppression of flare in those who took terfenadine and epinastine. Half the treated subjects had 95% inhibition of the flare after ebastine and fexofenadine, and only two after loratadine.

The overall effects of each treatment are illustrated in Fig. 3, which gives AUC and 95% confidence intervals for wheal (3A) and flare (3B) during the 24-h period of study. Regarding the wheal response, all active treatments were significantly lower than placebo with reductions of 79, 66, 59, 56, 38, and 37% for cetirizine, epinastine, terfenadine, ebastine, fexofenadine, and loratadine, respectively. Cetirizine was superior to all other treatments. In addition, terfenadine was superior for wheal inhibition when compared to its metabolite, fexofenadine. We also calculated the global response for the first 12 h for each treatment, and, in general, similar relationships were noted (data not shown).

Considering the overall changes in the flare response *vs* placebo (Fig. 3B), we observed significant decreases for all active treatments: cetirizine: 89%, ebastine and epinastine both: 68%, terfenadine: 65%, fexofenadine: 59%, and loratadine: 41%.

No volunteer had abnormal hematologic parameters or hepatic or renal function studies before, during, or after administration of the drugs. There were no differences in the evaluation of alertness after taking the six antihistamines, as determined by the Bond-Lader visual analog scale before each dose and at 12 and 24 h. No serious adverse events were reported for any treatment in this study. All treatments were well tolerated, and most adverse events were mild in severity, self-limited, and considered to have no relationship or an unlikely relationship to treatments. There were no cases of sedation, or fatigue or tiredness reported for any of the volunteers on any of the treatments.

Discussion

Histamine is a fundamental mediator released during the immediate allergic response from tissue mast cells (3) and during the late-phase response chiefly from recruited basophils (28). Histamine interacts with H_1 receptors to induce smooth-muscle contraction, enhanced capillary permeability, and neuronal stimulation with multiple secondary effects. H_1-receptor antagonists have been widely used for over 50 years, and these drugs have become a mainstay for management of allergic diseases. The second-generation drugs have properties of lower penetration of the blood–brain barrier with a markedly improved safety profile and infrequent adverse reactions. Terfenadine has a high affinity for Ca^{2+} channels (29, 30), and epinastine and loratadine show anti-5-hydroxytryptamine pharmacologic activities (31, 32). In contrast, cetirizine and fexofenadine appear selective for the H_1-receptor (30). Other properties to be considered in evaluating the clinical utility of antihistamines include rapidity of onset of action, potency, duration of action, and regularity of responses.

This study compared for the first time the most widely used drugs of this class as well as newly introduced agents with placebo in terms of inhibition of the cutaneous response to histamine challenge for a day after drug administration. The dosages were chosen according to what was recom-

mended and available at the time the study was conducted (March–May 1997). At that time, fexofenadine was available only as 60-mg capsules and was compared with its parent compound terfenadine at the same dosage.

We observed that all of the antihistamines tested proved to be effective in inhibiting the wheal and flare response to epicutaneous histamine challenge. Epinastine had the most rapid onset of action, and was significantly better than all other treatments and placebo at 30 and 60 min after administration of the drug (Fig. 1). Its effect persisted for 24 h. Cetirizine produced significant inhibition of wheal and flare at 2–4 h, an effect that persisted for 24 h. Overall, cetirizine was the most potent drug (Figs. 1–3). Cetirizine was superior to all other treatments at several time points. In most subjects, cetirizine achieved greater than 95% inhibition of the wheal and flare response at one time point, whereas this degree of inhibition was seen for fewer subjects with other drugs (Fig. 2). Ebastine had a slow onset of action, but showed extremely stable inhibition of the wheal and flare response from about 6 to 24 h. Terfenadine was a potent inhibitor of both wheal and flare responses and was second to cetirizine in reduction in the wheal from 4 to 8 h. Fexofenadine, the natural metabolite of terfenadine, was less potent than its parent compound. Loratadine proved the least potent inhibitor of both wheal and flare response to histamine challenge.

Our findings regarding the relative inhibitory properties of cetirizine, terfenadine, and loratadine are very similar to the observations of Simons et al. (8). Juhlin et al. (9) have reviewed approximately 27 other studies and confirmed this order of potency. Adamus et al. (33) first observed the rapid onset of inhibition by epinastine on the wheal response. Schilling et al. (34) observed that epinastine 20 mg was a potent inhibitor as early as 1 h after dosing, and was superior to terfenadine 60 mg from 1 to 12 h with similar effects noted at 24 h. de la Cuadra et al. (35) demonstrated that ebastine had a slower onset of action than cetirizine in terms of reducing the wheal and flare response to the histamine prick test. Frossard et al. (36) compared the cutaneous dose response of histamine challenge 4 h after administration of 10 mg of either cetirizine or ebastine. They observed that cetirizine was more potent. Furthermore, the variability of the inhibitory response among volunteers to ebastine was considerably greater than for cetirizine. Recently, Simons & Simons (37) compared fexofenadine and loratadine and concluded that the former had a more rapid onset of inhibition for cutaneous whealing after histamine challenge. In summary, these reports are in agreement with the relative potencies we have observed in the present comparison of six drugs.

It is interesting to note that we found the major metabolite of terfenadine, fexofenadine, to be less potent than its parent compound. In a study submitted as part of the FDA filing for fexofenadine (38), it was observed that 80 mg of fexofenadine orally was required to produce the same plasma concentration of fexofenadine as 60 mg of terfenadine taken orally. The suppression of histamine-induced wheal response was compared between subjects receiving either fexofenadine 60 mg b.i.d. or terfenadine 60 mg b.i.d. orally until steady state was reached at 8 days. The AUC for 0–12 h showed a 30% greater suppression of histamine-induced wheals with terfenadine. Finally, in a study in guinea pigs (39), oral terfenadine was 1.5–2.5 times more potent than fexofenadine in blocking the histamine wheal response.

The rapid onset of action of epinastine found in this study is clearly superior to other available drugs. This finding would predict that epinastine will achieve rapid relief of allergic symptoms in patients. Obviously, this is a major expectation of the allergic individual. The delay in onset of the effects of ebastine may be related to the fact that this drug undergoes substantial metabolism to carebastine. Simons et al. (40) speculated that the chief antihistaminic properties of ebastine could be attributed to the efficacy of its metabolite, carebastine, rather than to the parent compound. A similar phenomenon is true for terfenadine, but it should be stressed that the metabolism of terfenadine is extremely rapid when compared to ebastine.

Histamine H_1-receptor antagonists are presently undergoing the most careful scrutiny of their individual characteristics regarding their relative strengths and weaknesses. Therefore, an initial and logical first step would appear to be to define as precisely as possible their respective pharmacodynamic profiles. This particular study makes a direct and head-to-head comparison of six of these compounds that belong to the second generation of these widely used medications. Further evaluations should comprise the definition of their safety profiles (central nervous system characteristics, cardiac properties, and drug–drug interactions, etc.); in essence, those that are most relevant to the widespread and everyday usage of these compounds. Clinical trials must be designed so as to reflect the conditions of everyday usage and must be capable of detecting the differences between individual compounds in terms of efficacy and safety. The best choice for therapy, with an optimal risk-benefit ratio, must be determined after consideration of all these factors.

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