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The pharmacokinetics, antihistamine and concentration-effect relationship of ebastine in healthy subjects

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1 The kinetics and effects of ebastine 10 and 50 mg were studied after oral dosing in healthy subjects.
2 The parent drug was extensively metabolised during the first pass to its carboxylic acid derivative, carebastine.
3 The pharmacokinetics of carebastine were linear over the dose range studied and the terminal elimination half-life was 10.6 ± 2.6 and 12.5 ± 1.9 h respectively after 10 and 50 mg of ebastine.
4 Antihistamine (H_1-receptor) activity was examined with intradermal histamine (2μg). Oral ebastine reduced the histamine wheal area for up to 24 h and also reduced subjective local pain.
5 Antihistamine activity correlated well with plasma levels of carebastine in individual subjects.
6 Ebastine appears to have potential as an antihistamine for once a day dosing.

Keywords antihistamine pharmacokinetics histamine wheal concentration effect

Introduction

A limiting factor in the acceptability of most conventional antihistamines is their sedative and anticholinergic effects (Nicholson & Stone, 1982; Paton & Webster, 1985; Levander *et al.*, 1985). Recently, a new generation of antihistamines which do not appear to show sedative properties in their clinically useful antihistamine dose-range, have been introduced. These drugs include terfanadine and astemizole (Nicholson & Stone, 1982; Weiner, 1982). Ebastine (4-diphenylmethoxy - 1 - [3 - (4-terbutylbenzoyl) - propyl]piperidine) (LAS W-090) is another agent which in early clinical trials has been shown to have a long action and appears not to cause sedation in the antihistamine dose range (Roberts *et al.*, 1987). Ebastine itself is extensively metabolised, probably in the liver, to carebastine an active carboxylic acid metabolite which appears to exert most, if not all, of the pharmacological actions associated with the administration of the parent drug. In this study, the pharmacokinetics of carebastine following doses of 10 mg and 50 mg of ebastine were examined. The effect of ebastine 10 mg on an intradermal histamine-induced wheal and pain as well as the relationship between the concentration of the active metabolite and the reduction in wheal size were evaluated.

Methods

Two studies were undertaken. Firstly a study of the pharmacokinetics and tolerance of ebastine in two doses compared with placebo, and a second study in which the effects of ebastine on

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intradermal histamine were examined. The results of the former study on psychomotor responses and autonomic function are reported separately (Vincent *et al.*, 1988).

Healthy normotensive male volunteers aged 19 to 33 years (mean 24.1 ± 5.3 years) and weighing 56–85 kg (mean 67.7 ± 8.4 kg) gave written informed consent. The study was approved by the Research and Ethics Committee of the Greater Glasgow Health Board (Unit North 1). Each subject was judged healthy on the basis of detailed haematological and biochemical investigation and a normal ECG. None of the subjects had any history of allergy and they had not taken any drugs including over-the-counter medication in the 2 weeks before the study. None of the subjects abused alcohol or tobacco. Each subject was advised to abstain from alcohol for at least 48 h and from food, tobacco and caffeine-containing drinks from 22.00 h on the evening preceding each study day.

Pharmacokinetics

In the first study nine subjects received in a randomised order a solution of either ebastine 10 mg or 50 mg diluted in water to a constant volume of 40 ml. Blood samples were obtained from an indwelling venous cannula at intervals of up to 24 h. The plasma was separated and stored at – 20°C until analysed.

Analysis of carebastine

Plasma concentrations of carebastine (LAS X-113) the acid metabolite of ebastine were determined using a h.p.l.c. assay with UV detection. The internal standard was a structurally related analogue, LAS Z-120. 200 μl of LAS Z-120 (60 μg ml^{-1}) was added to 0.5 ml of plasma prior to the extraction procedure. Using a spherisorb 10 μ ODS column (250 × 4 mm) the mobile phase consisted of methanol: 0.02 M sodium acetate: glacial acetic acid: water (380:20:5.5:100). The retention times using this mobile phase and a flow rate of 2 ml min^{-1} were LAS Z-120 – 4.1 min, carebastine – 7.3 min. Aqueous standard curves were run producing satisfactory levels of reproducibility. The assay was found to be linear in the range 50–700 ng ml^{-1} with a limit of detection of 20 ng ml^{-1} (defined as three times baseline noise). Intra-assay variation was determined by replicate assays of six standards at three different concentrations. At 75, 250 and 500 ng ml^{-1}, the coefficient of variation was 7.6, 5.3 and 3.8% respectively.

The drug concentrations were fitted to a hierarchy of models with both first and zero order input using computer assisted non-linear regression analysis. The most appropriate model using extended least squares fitting procedure was a one compartment model with first-order rate constant describing drug absorption.

Histamine wheal and pain response

In a second study in four further healthy subjects, the response to intradermal histamine induced wheal and pain was assessed after ebastine 10 mg and placebo. In a preliminary dose-response study, histamine (as histamine phosphate) was injected intradermally at the increasing doses of 0.5, 1, 2 and 4 μg in 0.1 ml normal saline while 0.2 ml normal saline was injected into corresponding positions in the opposite arm as a control. The time-course of the change in wheal size was assessed by measuring the wheal size after 10, 20 and 30 min. The dose-dependent increase in histamine wheal area (mean ± s.d.) was linear up to 2 μg (Figure 1) and for subsequent studies, this dose was used. The maximum wheal area was observed after 20 min. For subsequent studies, histamine-induced wheal was measured after 20 min.

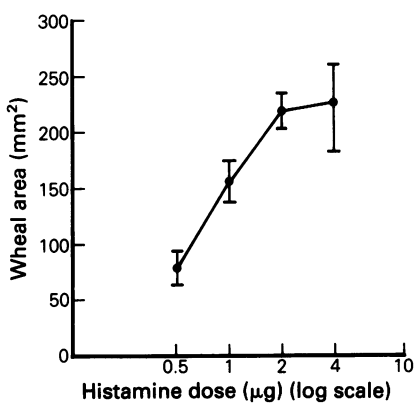

Figure 1 The relationship between increasing doses of intradermal histamine (μg) and wheal area (mm^2) in four normal subjects (mean ± s.d.).

In the definitive study, histamine-induced wheal was evaluated before and at 2, 4, 6, 8 and 24 h after ebastine 10 mg or placebo administration. After the intradermal injection of histamine, the wheal size was dilineated with a ballpoint pen and transferred by means of a transparent tape to a sheet of standard graph paper. The area of the wheal was calculated with the average of the longitudinal and transverse diameters. The percentage decrease in wheal size was calculated from the relationship

$$\frac{\text{Histamine wheal area after treatment} - \text{saline wheal area after treatment}}{\text{Histamine wheal area before treatment} - \text{saline wheal area before treatment}} \times 100$$

The degree of pain perceived was evaluated using a 100 mm visual analogue scale with 'no pain' at one end and 'severe pain' at the 100 mm end. The pain score was assessed separately for right and left arm after histamine and saline on active treatment and following placebo. The pain was expressed as mm from the 'no pain' pole.

Concentration-effect relationship

The relationship between the plasma concentration of the acid metabolite carebastine and the absolute percentage histamine-induced wheal was examined in individual subjects using linear regression analysis. The absolute percentage of histamine induced wheal was calculated from the relationship

$$\frac{\text{Histamine wheal area after ebastine} - \text{saline wheal area after ebastine}}{\text{Histamine wheal area after placebo at the corresponding time} - \text{saline wheal area after placebo at the corresponding time}} \times 100$$

Statistical analysis

Results are expressed as mean ± s.d. Statistical analysis was by means of the repeated measures analysis of variance (ANOVA) for the histamine wheal response and pain scores and by linear regression analysis where necessary.

Results

Pharmacokinetics

These results are summarised in Table 1.

Drug was detected up to 24 h in all subjects. The mean peak concentrations (C_{max}) of carebastine were 99.1 ± 28.6 and 417 ± 54.6 ng ml^{-1} following ebastine 10 and 50 mg respectively. The time to peak plasma concentrations (t_{max}) were comparable with both doses at 3.61 ± 1.06 and 3.70 ± 0.76 h for 10 and 50 mg of ebastine respectively. The elimination half-lives of 10.3 ± 2.6 and 12.5 ± 1.9 h after 10 mg and 50 mg respectively were also comparable and gave no indication of dose related changes in pharmacokinetics. When the area under the concentration-time curve (AUC) and the maximum concentration (C_{max}) were corrected for dose, no significant differences were observed in these parameters at the doses studied (Table 1). A representative plasma concentration-time profile of carebastine after ebastine 10 and 50 mg is shown in Figure 2.

Histamine induced wheal and pain

Ebastine 10 mg significantly ($P < 0.02$) inhibited the histamine-induced wheal for up to 24 h (Figure 3). The individual results of histamine wheal area are shown in Table 2. There were intra-individual differences in wheal area for histamine (Table 2) and saline control (not shown) throughout the 24 h period. Peak reduction in histamine wheal area occurred between

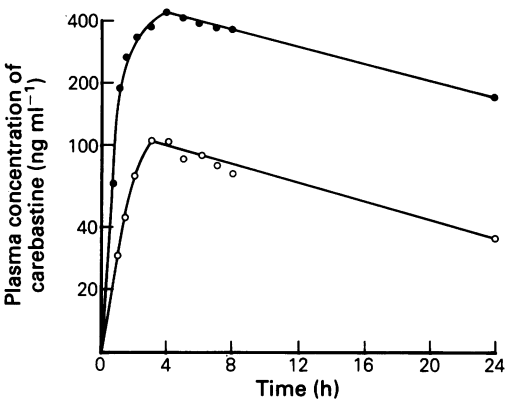

Figure 2 A representative plasma concentration time profile of carebastine after ebastine 10 mg (○——○) and 50 mg (●——●).

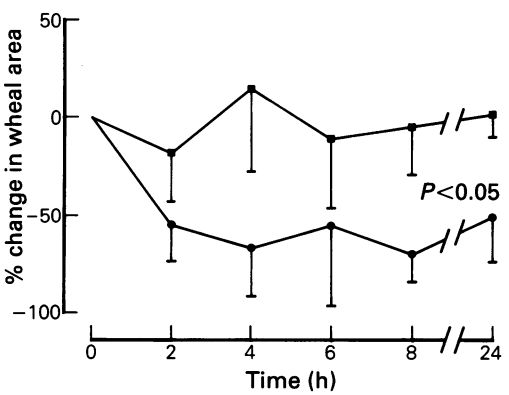

Figure 3 Percentage change (mean ± s.d., $n = 4$) in histamine-induced wheal area-time profile after placebo (■) and ebastine 10 mg (●).

Table 1 Derived pharmacokinetic parameters of carebastine in nine subjects following a dose of ebastine

Ebastine 10 mg *Subject*	*AUC (ng ml^{-1}h)*	ket$_{½}$ *(h)*	C_{max} *(ng ml^{-1})*	t_{max} *(h)*
1	1367	10.8	75.6	2.46
2	1136	10.4	68.3	1.75
3	1914	11.6	94.5	3.91
4	2495	11.1	126.5	4.09
5	2506	11.7	125.7	3.35
6	878	5.2	85.2	4.29
7	1613	13.1	74.3	3.13
8	1822	6.6	150.8	4.21
9	2060	12.0	90.8	5.27
Mean ± s.d.	1755 ± 565	10.3 ± 2.6	99.1 ± 28.6	3.61 ± 1.06
Ebastine 50 mg				
1	9811	11.6	472.5	3.95
2	10366	12.7	449.2	4.51
3	10126	14.1	416.1	4.19
4	7648	12.3	369.8	3.43
5	10003	14.1	420.4	3.79
6	8193	15.1	331.5	2.97
7	9056	9.7	492.8	4.64
8	5717	9.6	361.3	2.24
9	10096	13.6	439.3	3.57
Mean ± s.d.	9002 ± 1552	12.5 ± 1.9	417.0 ± 53.6	3.70 ± 0.76

2–6 h. The mean maximum inhibition of the histamine wheal (by about 70%) occurred at 4 hours after dosing and at 24 h inhibition was still 50% of control. The mean concentrations of carebastine at the corresponding times were 86 and 32 ng ml^{-1}. Subjective pain sensation was moderately but significantly ($P < 0.05$ by ANOVA) reduced (Table 2).

Concentration-effect relationship

The peak concentration of carebastine corresponded with the maximum wheal inhibition. There was a significant linear correlation between plasma concentration of the acid metabolite, carebastine, and the absolute percentage wheal area as shown in the representative subject

Table 2 Area of histamine (2 μg) wheal on the forearm of intradermal subjects at intervals after placebo or ebastine 10 mg orally (mm^2)

Subject number	*Treatment*	*Before treatment*	*Time (h)* 2	4	6	8	24
	Placebo	165	132	228	143	132	165
1	Ebastine	227	123	71	176	78	78
	Placebo	214	283	268	314	329	330
2	Ebastine	227	133	201	165	113	133
	Placebo	201	254	362	189	226	240
3	Ebastine	254	133	156	113	143	113
	Placebo	240	165	177	189	214	177
4	Ebastine	254	189	95	71	87	113

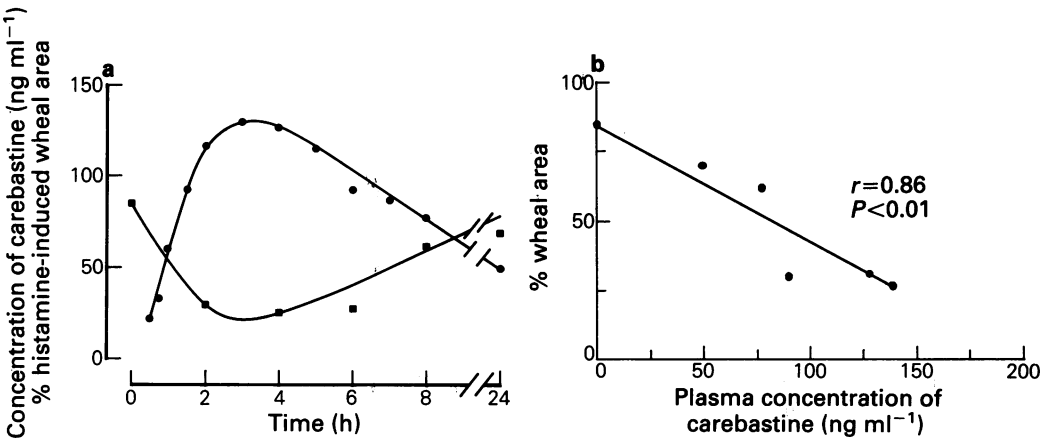

Figure 4 a) Relationship between concentration of carebastine (•) and the percentage histamine-induced wheal area (■) and time in a representative subject. b) Relationship between plasma concentration of carebastine and the percentage histamine wheal area in a representative subject.

shown in Figure 4. In this subject, the plasma concentration of LAS-X-113c was 127 ng ml^{-1} at 4 h when the maximum wheal inhibition was observed and declined to 49 ng ml^{-1} at 24 h.

Discussion

The terminal elimination half life of carebastine after ebastine 10 mg was 10.3 ± 2.6 h. This was not different from that observed after ebastine 50 mg. The peak plasma concentrations were also proportional to the doses indicating that there was no saturation of metabolism. Since there were no differences in the derived pharmacokinetic parameters following both doses, ebastine showed linear kinetics within the dose range studied. A definitive assessment of the pharmacokinetics must await the administration of an intravenous formulation of drug or metabolite. In this study, ebastine appeared to be completely metabolised into one or more active metabolites, similar to cyproheptadine (Hintze *et al.*, 1975; Porter *et al.*, 1975).

We have found that ebastine 10 mg did not significantly impair psychomotor performance and had no effect on autonomic or cardiovascular effects in man (Vincent *et al.*, 1988). This dose significantly ($P < 0.02$) inhibited the intradermal histamine-induced wheal for up to 24 h and the pain perception after histamine was also significantly ($P < 0.05$) reduced. The attenuation of the pain sensation parallels the inhibition of the histamine wheal response and suggests that both the wheal and pain are related by histamine. Histamine-induced wheal is a standard test for assessing the antihistamine effect of drugs (Huther *et al.*, 1977; Carruthers *et al.*, 1978; Bateman *et al.*, 1983; Cohen *et al.*, 1985; Levander *et al.*, 1985). The inhibition of skin wheal appears to be a quantitative index for assessing both drug concentration and the time-course of drug action. Thus, our results suggest that ebastine has a significant antihistamine effect at 10 mg. This dose does not appear to impair psychomotor performance (Vincent *et al.*, 1988). In this respect, ebastine is similar to terfanadine and astemizole (Nicholson & Stone, 1982). The significant inhibition of the histamine wheal for up to 24 h could permit once daily dosing and is consistent with the long terminal elimination half-life of carebastine.

The arbitrary choice of a histamine dose for intradermal injection does not take into account individual variability in response (Bain, 1949; Huther *et al.*, 1977). In this study, the choice of 2 μg histamine and the time of wheal measurements were based on a preliminary dose-ranging study in these volunteers. A circadian rhythm in the histamine wheal response has been described (Reinberg *et al.*, 1965; Peck *et al.*, 1975). Our study was placebo controlled in an attempt to reduce such confounding factors.

A fraction of the wheal caused by intradermal histamine is caused by the vehicle. The absolute percentage wheal area of histamine was therefore calculated as the histamine wheal area after ebastine minus the saline wheal area after ebastine divided by the histamine wheal area after placebo at the corresponding time minus the saline wheal area after placebo at the same time. This procedure also helps to eliminate any time-related changes in histamine response.

Using this approach, there was a significant linear correlation between plasma concentration of the acid metabolite, carebastine, and the absolute percentage wheal area of histamine in some but not all subjects. The disparity in the individual correlations is not clear but could result from variability in responsiveness to histamine (Bain, 1949; Huther *et al.*, 1977), the presence of other active metabolites in varying concentrations in different individuals which could influence concentration-effect relationships (Paton & Webster, 1985), variability in the metabolism of ebastine by the liver (Brodie *et al.*, 1981) or a combination of these factors. A similar significant correlation had been described for astemizole (Richards *et al.*, 1984) and diphenhydramine (Bilzer *et al.*, 1974; Carruthers *et al.*, 1978).

In conclusion, the pharmacokinetics of ebastine were linear over the dose range studied. The significant inhibition of the histamine induced pain and wheal response for up to 24 h is consistent with its long terminal elimination half-life and justifies further evaluation of ebastine as a once daily regimen.

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