Reversal of histamine-induced bronchoconstriction by the H₁-receptor antagonist levocabastine: A potential model for efficacy in anaphylaxis

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1 The rate of onset and magnitude of the effect of levocabastine, a potent H₁-receptor antagonist, in reversing histamine-induced bronchoconstriction were determined in a double-blind cross-over trial against saline placebo. Histamine was administered by nebuliser so that forced expiratory volume in 1 second (FEV₁) was reduced to 80–75% of baseline FEV₁ in 10 men with mildly or moderately responsive airways and the effects of intravenous injection of saline or saline + 200 µg levocabastine were studied.

2 The maximum rate of recovery of FEV₁ was 7[2–10]% min⁻¹ (median [range]) in the first 5 min after levocabastine injection, but only 4[1–7]% min⁻¹ after saline alone ($P < 0.05$).

3 The median area under the recovery curve of FEV₁ from 0 to 30 min after injection was 405 [228–498]% basal FEV₁ × min after levocabastine and 301[98–502]% basal FEV₁ × min after saline alone ($P < 0.002$).

4 FEV₁ returned to 90% of baseline within 30 min in all subjects after levocabastine, but not after saline alone ($P < 0.002$).

5 Histamine-induced bronchoconstriction was relieved more quickly by levocabastine than saline alone. This model may have application to the study of drugs used in the treatment of anaphylaxis.

Keywords histamine levocabastine anaphylaxis H₁-receptor antihistamines bronchoconstriction

Introduction

Anaphylaxis, because it is rare, unexpected, sudden and life-threatening, is difficult to study systematically in man, and differences between species make it difficult to extrapolate from animal models. Anaphylaxis is believed to be due to the release of mast-cell mediators, particularly histamine, leukotrienes, prostaglandins, bradykinin and other peptides and chemotactic factors (Austen, 1987; Bach, 1982). The role of histamine was originally suggested by Dale & Laidlaw (1910) who observed that histamine reproduced the pathological changes of anaphylaxis in the guinea-pig lung. Schild *et al.* (1951) showed that high concentrations of antihistamine

(mepyramine) inhibit the constriction of bronchial rings from an asthmatic subject caused by house-dust mite antigen *in vitro*. It has become standard practice to treat anaphylaxis by the administration of an H₁-receptor antagonist such as chlorpheniramine intravenously, as well as intramuscular adrenaline (Editorial, 1981). However, the difficulties of experimental study have thus far precluded validation of this practice. Treatment of anaphylaxis must correct hypotension and bronchoconstriction rapidly to be of value.

We have developed a method to test the magnitude and speed of effects of antihistamine drugs in histamine-induced bronchoconstriction, in

which the degree and rate of reversal of histamine-induced bronchoconstriction was examined in volunteers given a potent antihistamine or saline by intravenous injection. The antihistamine chosen for the study, levocabastine, has the advantages of very high potency and specificity at H_1 -receptors. It has proved of very low toxicity in experimental animals and studies with intravenous doses of 200 μg levocabastine in man have not demonstrated sedation or other ill effects (Awouters *et al.*, 1986). Levocabastine's high potency, specificity and lack of sedative action made it suitable for volunteer studies.

Methods

Ten men, aged 26 (21–49) years, were studied. Seven were healthy medical staff with a history of mild reversible airways obstruction such that they occasionally suffered from wheeze, and three were patients at Newcastle General Hospital Chest Clinic with mild asthma. All were otherwise healthy, and none was receiving any regular therapy. Each subject gave written, informed, consent to participate in the trial, which was approved by the Newcastle Health Authority Ethics Committee.

Each subject was studied at the same time of day on two occasions 1 or 2 weeks apart. On each, baseline FEV_1 was measured three times at 5 min intervals using a dry spirometer (Vitalograph Limited, Buckingham, England). Each measurement was taken as the mean of three successive readings of FEV_1 , defined as the forced expiratory volume in the first second after a maximum inhalation. An 18G cannula ('Venflon', Viggo, Helsingborg) was inserted into a forearm vein under local anaesthesia with 1% plain lignocaine, and the subject rested for 15 min. Histamine acid phosphate dissolved in 0.9% sodium chloride was then administered by an air driven De Vilbiss 646 nebuliser and Johns Hopkins dosimeter, which incorporated a thermistor flow sensor and a valve opened on inspiration (Hendrick *et al.*, 1986). After 5 min, three measurements of FEV_1 were made in succession, and the mean calculated. If mean FEV_1 was above 80% of baseline mean FEV_1 , a further dose of histamine was administered, cumulative dose being 0, 1.5, 3, 6, 12.5, 25, 50, 100, 200, 400, 800 and 1600 μg histamine acid phosphate after the first to the twelfth dose respectively. The cumulative dose of histamine required to provoke a 20% reduction in FEV_1 from the baseline value on each day (PD_{20}) was found by graphical interpolation based on the semilog dose response curve. If mean FEV_1 was below 75% of baseline, it was remeasured until it had

recovered to 80–75% of baseline, when 2 ml 0.9% sodium chloride alone or with 200 μg levocabastine was given by rapid intravenous injection. The injections were administered in randomised order and double blind fashion. After the injection, three measurements of FEV_1 were made one after the other, and measurements repeated every minute for 5 min, then every 5 min for a further 25 min.

Analysis

Results are expressed as the median and range, as several of the variates followed non-Gaussian distributions. The rapidity of recovery was assessed by calculating the maximum rate of increase in FEV_1 in 1 min during the first 5 min after injection $(\text{FEV}_1/t)_{\text{max}}$, and by estimating the time taken for FEV_1 to recover to 90% of baseline. $(\text{FEV}_1/t)_{\text{max}}$ was found from the largest difference between successive values of FEV_1 during the first 5 min, when FEV_1 was expressed as % FEV_1 . The extent of recovery during the 30 min after injection was quantified by the area under the curve of % basal FEV_1 against time in units of '% basal $\text{FEV}_1 \times \text{min}$ '. Areas were calculated by the trapezoid rule. Results after saline placebo and levocabastine treatment were compared by the Wilcoxon matched pairs rank-sign test. Results were taken to be statistically significant if $P < 0.05$ (two-tailed test).

Results

No adverse events were observed after the administration of either levocabastine or saline. Baseline FEV_1 was 4.16 [3.20–5.82] l before levocabastine and 4.13 [3.20–5.76] l before placebo ($P < 0.05$). The PD_{20} histamine was 160 [20–1600] μg before levocabastine and 190 [17–600] μg before placebo ($P < 0.05$). The time course of recovery from histamine-induced bronchospasm in the presence or absence of levocabastine is shown in Figure 1. The maximum rate of recovery in the first 5 min after injection, $(\text{FEV}_1/t)_{\text{max}}$ was greater after levocabastine than placebo (Figure 2). The median difference was 3% basal $\text{FEV}_1 \text{ min}^{-1}$, $P < 0.05$. Subjects also reached 90% baseline FEV_1 more rapidly after levocabastine than placebo ($P < 0.002$). Three subjects failed to reach 90% of baseline FEV_1 in the 30 min after placebo injection, though all had done so by 20 min after levocabastine injection. The area under the curve from 0 to 30 min post-injection was greater in eight out of 10 subjects after levocabastine than after placebo; median difference 125% basal $\text{FEV}_1 \times \text{min}$, $P < 0.002$ (Figure 3, Table 1).

Figure 1 The time course for recovery of FEV_1 from 80–75% of baseline FEV_1 when saline placebo ($\circ$) or levocabastine ($\bullet$) injection was given to 10 mildly asthmatic men. The time (in minutes) after injection is shown on the abscissa, and the FEV_1 (as a percentage of baseline FEV_1) on the ordinate. Points represent mean and bars show standard errors.

Figure 2 The maximum rate of recovery of FEV_1 from 80–75% of baseline FEV_1 in nine mildly asthmatic men in the first 5 min after the administration of saline placebo or levocabastine injection. The rate of recovery is shown on the vertical axis in units of % baseline $FEV_1 \text{ min}^{-1}$.

Discussion

Since anaphylaxis is rare, sudden, and life-threatening, a prospective clinical trial of its treatment would be difficult. The potential lethality of anaphylaxis provoked in the labora-

Figure 3 The area under the curve (AUC) of FEV_1 vs time from injection for recovery from 80–75% of baseline FEV_1 in 10 mildly asthmatic men. The AUC is shown on the vertical axis in units of % baseline $FEV_1 \times \text{min}$.

tory, for instance by the administration of penicillin to penicillin hypersensitive subjects, precludes this method of study. Possible models for the effects of histamine include hypotension from intravenous histamine infusion, which is unpleasant and may be dangerous, and weal and flare reactions from intradermal histamine (Batesman *et al.*, 1983), which do not follow the same time course or have the same life-threatening potential as the hypotension. Histamine-induced bronchoconstriction is an important part of anaphylaxis. It can be induced reliably and reproducibly under experimental conditions, and the rate of recovery from it may be measured straightforwardly.

This study demonstrated that intravenous injection of levocabastine after histamine challenge reverses the histamine-induced bronchoconstriction faster than injection of saline alone. It is the first experimental demonstration by a randomised, double-blind controlled trial that H_1 -receptor antagonists are effective in reversing one of the potentially lethal actions of a postulated mediator of anaphylaxis. An occasional difficulty with the experimental procedure was that a subject's FEV_1 might fall from above 80% to below 75% of basal FEV_1 after an increased dose of histamine, and it was then necessary to wait a few minutes for FEV_1 to recover to within the required range. The method was otherwise straightforward. In six out of nine subjects the maximum rate of recovery in any 1 min during

Table 1 Effects of saline alone or levocabastine on recovery from histamine challenge

Subject	Basal FEV ₁ ^a (l)		Minimum FEV ₁ ^b (% basal FEV ₁)		(FEV ₁ /t) max ^c (% basal FEV ₁ min ⁻¹)		Time to 90% basal FEV ₁ ^d (min)		AUC ^e (% FEV ₁ × min)	
	S ^f	L ^g	S	L	S	L	S	L	S	L
1	3.91	4.05	73	79	2	7	15	5	308	430
2	3.76	4.16	72	68	4	8	10	3	503	498
3	3.20	3.20	77	79	2	2	>30	15	148	318
4	5.18	5.82	75	74	6	7	15	5	390	500
5	4.03	4.67	76	80	7	10	>30	20	98	228
6	5.76	5.61	74	71	5	5	>30	4	158	335
7	4.22	4.13	77	78	1	5	10	3	325	453
8	3.20	3.40	79	72	4	4	15	10	368	475
9	4.65	4.60	80	80	5	3	20	10	245	380
10	4.39	4.15	77	80	2	7	15	10	295	320
Median difference (L-S)	0.07		1		3		-10 or less		125	
P ^h	>0.05		>0.05		<0.05		<0.002		<0.002	

^a The forced expiratory volume in the first second, measured before histamine challenge.^b The lowest recorded FEV₁ after histamine challenge.^c The maximum rate of recovery of FEV₁ after injection of saline or 200 µg levocabastine when the FEV₁ was within the range 75–80% of basal FEV₁.^d Time from injection to first recorded mean FEV₁ greater than or equal to 90% of basal FEV₁.^e Area under the curve of FEV₁ against time from injection to 30 min after injection.^f Day on which saline was injected intravenously.^g Day on which 200 µg levocabastine was injected intravenously.^h Probability that the observed results were due to chance (paired tests).

the first 5 min after levocabastine injection was faster; the group median value was nearly twice as fast with active treatment. Since recovery in the first few minutes of anaphylaxis may determine outcome, this is of considerable practical importance. The inter-subject variability might be due to difficulties in measurement or to variability in response to the experimental dose of levocabastine.

The time to recovery to 90% basal FEV₁ and the extent of recovery in 30 min judged by area under the recovery curve, also showed a significant benefit in favour of the antihistamine. Whilst the present work demonstrates that levocabastine

is effective in relieving histamine-induced bronchospasm, it does not set out to define the optimal dose of drug, nor its efficacy relative to other antihistamines. In the context of anaphylaxis, death is imminent and the appropriate dose of a drug may be the greatest that can be given without itself causing acute toxicity. Experimental studies at high doses pose major practical problems. There is no evidence that levocabastine has any effect on bronchoconstriction induced by acetylcholine or serotonin in guinea pigs, nor that it interacts with acetylcholine, dopamine, serotonin, noradrenaline or opiates in the rat (Awouters *et al.*, 1986), so it

seems likely that the effects are due to direct and rapid inhibition of H₁-histamine-receptor binding. Unfortunately, validation of the model proposed here would require systematic studies in anaphylaxis, but as has been explained such studies are not possible because of the very nature of the

disease. Instead, histamine induced bronchoconstriction provides a practical alternative to histamine-induced hypotension as a readily quantified measure of the effects of H₁-receptor antagonists and demonstrates the potential usefulness of levocabastine.

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