

Time of onset of action of acrivastine in the skin of pollen-allergic subjects

A double-blind, randomized, placebo-controlled comparative study

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The purpose of this study was to assess the time of onset of action of acrivastine in suppressing the wheal response to histamine (10 mg/ml) and allergen (10 000 and 100 000 BU/ml) in the skin prick test. Ten subjects with a well-documented allergy to pollen received single doses of 8 mg of acrivastine and placebo according to a randomized, double-blind, placebo-controlled, crossover treatment design. Duplicate skin prick tests were performed 0, 15, 20, 25, 30, and 60 min after medication. The results demonstrated a statistically significant suppression of the wheal reactions 15–20 min after medication, depending on the reaction producers used. The sum of all three producers showed a statistically significant effect on the wheal reaction 15 min after medication. The upper 95% confidence limit for time lag from dosing of acrivastine until reduction from placebo level commences was 6.5 min. The study substantiates that orally administered acrivastine has a rapid onset of action in the skin of allergic subjects. The results indicate that allergen SPT is a more sensitive tool for studying antihistaminergic activity than histamine SPT.

L. J. Petersen, C. Bindslev-Jensen, L. K. Poulsen, H.-J. Malling

Allergy Unit, Department of Medicine TTA,
National University Hospital, Copenhagen,
Denmark

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Carsten Bindslev-Jensen, MD, PhD
Allergy Unit
Department of Medicine TTA
National University Hospital
Tagensvej 20
DK-2200 Copenhagen N,
Denmark

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Acrivastine, a closely related derivative of the anti-histamine tripolidine, has been shown to be a fast-acting and potent H_1 -antagonist with minimal central nervous system activity (1, 2). Pharmacokinetic studies have shown acrivastine to be rapidly and almost totally absorbed from the gut, reaching peak plasma concentration approximately 90 min after an oral intake of 8 mg (2). Clinical studies have confirmed that acrivastine is a fast-acting antihistamine, as assessed by bronchial and intracutaneous (ICT) histamine challenges (10, 11, 15).

Skin testing with allergens remains one of the most frequently used routines for diagnosing allergy. Although clinical efficacy cannot be directly read from the drug action in the skin under experimental conditions, an effect on the wheal reaction elicited by allergen (causing release of histamine as well as other pre- or newly formed mediators from various cell types) offers more valuable data than those provided by histamine alone.

The aim of the present study was to evaluate the onset of action of acrivastine in suppressing allergen- and histamine-induced wheal reactions after skin prick testing (SPT).

Material and methods

Subjects

Ten subjects (seven women and three men), aged 40 (SD 12.8) years, suffering from well-documented allergy to silver birch and/or grass pollen participated in the study. The subjects had produced specific antibodies against the allergen(s), representing at least a RAST-class 2 (Pharmacia AB, Sweden). The wheal reaction to allergen (100 000 BU/ml) exceeded 3 mm (largest diameter), and the wheal reaction to histamine (histamine hydrochloride 100 mg/ml) exceeded 5 mm. None had any dermatologic, hepatic, or renal diseases. Pregnant women, women of child-bearing potential, subjects suspected of poor compliance, and subjects with hypersensitivity reactions to any components of the test preparations were not included in the study. The protocol was approved by the local ethics committee, and all subjects gave their informed consent.

The subjects had not received systemic steroids within 6 weeks, astemizole within 8 weeks, and other antihistamines within the last 7 days before the study.

Study design

The investigation was performed as a randomized, double-blind, completely balanced, two-period, crossover study. Each subject received acrivastine and placebo according to a computer-generated random code. Half of the subjects received acrivastine-placebo; the other half placebo-acrivastine. Each subject received the medication on the same day of each of 2 consecutive weeks.

Drugs

Acrivastine capsules (Semprex, Wellcome Foundation Ltd, Kent, UK) containing 8 mg of acrivastine and corresponding placebo were used. The placebo medication was identical to the acrivastine capsule except for the content of acrivastine. The medication was taken between 0800 and 1000, after an overnight fast.

Skin prick test

All SPTs were performed by the same trained nurse throughout the study. Commercially available pollen (Pharmacia AB, Sweden) and Dome/Hollister-Stier lancets were used. SPT was performed 0, 15, 20, 25, 30, and 60 min after ingestion of either acrivastine or placebo. Duplicate SPT was made through a droplet of allergen (10000 and 100000 BU/ml) and histamine (10 mg/ml), as previously described (9). The wheal response was measured 10 min after SPT. The wheals were outlined and transferred to the patient record form. The wheal areas were determined by a precise and accurate computer-based scanning (14).

Statistical analyses

Repeated measures analysis of variance (ANOVA) on log response ratio (active/placebo) was used with

subject and period as blocking factors, with testing for treatment main effect and treatment effect on time course. If statistically significant courses were found, treatment differences at each time point were tested by standard ANOVA for two-period, crossover studies, followed by construction of 95% confidence intervals. Treatment effects for each reaction producer and the sum of all three types were assessed. *P* values less than 0.05 were considered to be significant.

Results

One SPT area was missing; this observation was calculated by linear interpolation. There was no carry-over effect. For one of the four variables, i.e., the sum of all reaction producers, there was a statistically significant period-by-time effect (*P* = 0.05). This was modeled by a shift model, where the initial wheal areas before dosing were equal for the two periods but after dosing shifted down to about 77%. Since the design was completely counterbalanced, a period effect could not bias the treatment comparison but could only contribute as extraneous noise, making the analysis more conservative; that is, giving less powerful tests and wider confidence intervals.

The wheal areas are shown in Table 1. Acrivastine/placebo ratios (median, 95% confidence interval) are presented in Table 2 together with the results of the statistical analyses. No decrease in wheal areas was seen after placebo medication. After administration of acrivastine, the time courses are similar for both histamine and allergens, showing a smooth fall from about 100% at time 0 to about 30% 60 min after dosing. From the 95% confidence intervals, it appears that, considering the sum of all types of reaction producers, the treatment effect of acrivastine was statistically significant from 15 min after dosing and onwards (upper 95% confidence limit below 100%). If we consider each type separately,

Table 1. Median wheal areas (mm²) after placebo and acrivastine medication. Coefficients of variation are shown in parentheses. Cumulative wheal areas of all reaction producers are expressed in the sum

	0	15	20	25	30	60 min after SPT
Histamine (10 mg/ml)						
Placebo	28.2 (20.7)	29.1 (29.2)	25.8 (31.3)	22.7 (29.3)	30.0 (25.4)	27.6 (41.6)
Acrivastine	30.4 (24.6)	22.3 (36.3)	22.2 (36.0)	13.5 (61.0)	18.4 (53.3)	9.4 (77.1)
Allergen (10000 BU/ml)						
Placebo	17.7 (52.6)	21.2 (51.8)	18.7 (47.2)	19.9 (43.0)	19.3 (44.9)	17.8 (48.7)
Acrivastine	19.4 (41.1)	13.5 (54.2)	13.2 (71.1)	9.4 (78.1)	5.7 (80.3)	4.3 (70.7)
Allergen (100000 BU/ml)						
Placebo	37.0 (64.4)	45.1 (28.8)	41.7 (55.4)	38.3 (48.0)	35.1 (27.3)	36.1 (52.8)
Acrivastine	34.2 (68.6)	36.2 (51.8)	25.4 (49.2)	15.3 (68.6)	16.9 (89.9)	11.6 (53.6)
Sum						
Placebo	87.8 (37.6)	100.2 (15.3)	91.4 (37.2)	84.1 (31.7)	86.3 (21.2)	85.4 (33.6)
Acrivastine	87.4 (38.9)	74.4 (40.3)	63.8 (39.6)	39.4 (59.2)	42.6 (65.5)	26.8 (54.1)

Table 2. Time course of wheal sizes (mm²) after administration of acrivastine. Median ratio of acrivastine/placebo wheal sizes and 95% confidence intervals are presented. Cumulative effect on all reaction producers is expressed in the sum

	0	15	20	25	30	60 min after SPT
Histamine (10 mg/ml)	108 (97–120)	77 (63–93)*	86 (65–114)	59 (41–86)*	61 (50–75)***	34 (25–47)***
Allergen (10000 BU/ml)	110 (81–149)	64 (41–98)*	70 (44–112)	47 (31–72)**	30 (16–55)**	24 (13–43)***
Allergen (100000 BU/ml)	92 (62–138)	80 (51–126)	61 (43–86)*	40 (25–65)**	48 (29–80)*	32 (24–43)***
Sum	100 (78–127)	74 (57–97)*	70 (51–95)*	47 (31–72)**	49 (34–71)**	31 (23–43)***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

the random fluctuations are higher, resulting in wider confidence intervals which mask the effect apparent from the sum, so that for all three types the levels are not simultaneously statistically significantly below 100% at 15 and 20 min, respectively. Since the sum accumulates the information for each of the three types, this does not contradict the conclusion that the effect of acrivastine is recognized from 15 min and onwards in spite of the lack of statistical significance at 15 and 20 min for some of the types.

Since the decline in wheal sizes follows an exponential course, the half-times are 40, 32, 26, and 33 min for histamine, allergen 100000 BU/ml, allergen 10000 BU/ml, and the sum, respectively. If we assume a time lag after dosing of acrivastine until reduction from placebo level commences, a point estimate of mean time lag is negative with a one-sided upper 95% confidence limit of 6.5 min. Thus, the effect of acrivastine on reduction of wheal area after SPT most probably starts immediately after dosing, and probably not later than 6.5 min after dosing.

Discussion

In this double-blind, crossover, placebo-controlled comparative trial, the nonsedating antihistamine acrivastine was assessed with regard to the time of onset of action in the skin of pollen-allergic subjects. Skin prick tests were used to evaluate the biologic effect. The sensitivity, specificity, and reproducibility of skin prick tests are widely acknowledged (3, 9).

The results showed that orally administered acrivastine potently and quickly suppressed histamine and allergen SPT-induced wheal reactions in subjects suffering from pollinosis. A statistically significant wheal suppression was seen 15–20 min after dosing, depending on the reaction producer used. The sum of all three producers showed the same trend, demonstrating a statistically significant effect on the wheal size 15 min after medication.

Our results demonstrated a quicker suppression of the wheal response, as compared with histamine ICT (10, 11). These studies demonstrated a significant effect on the wheal reaction 25–30 min after an oral intake of 8 mg of acrivastine. Also the maximum

effect 60 min after dosing (about 70% wheal suppression) is similar to values obtained 120 min after histamine ICT (11). Whether further wheal suppression could be obtained could not be told, since SPT was not performed beyond 60 min after medication.

The time course for wheal suppression did not differ between histamine and the two allergen solutions. However, the relative magnitude of the wheal suppression seemed to be greater for allergens than histamine. This indicates that allergen SPT is a more sensitive tool for the study of antihistaminergic activity than histamine SPT.

Acrivastine has been evaluated clinically in several disorders, including seasonal allergic rhinitis (4, 5, 12), cholinergic urticaria (8), cold urticaria (13), and chronic idiopathic urticaria (6, 7, 16). In these studies, acrivastine has been shown to be a potent antihistamine with minimal sedative effect.

In conclusion, according to our data, acrivastine is a fast-acting and potent antihistamine, as assessed by skin prick tests in allergic subjects. Its clinical efficacy after chronic administration is well documented. Therefore, acrivastine seems to be very suitable for conventional antihistaminergic therapy as well as patient-initiated, "when-needed" therapy when immediate relief of symptoms is required. The last statement should, however, be supported by supplementary clinical studies on the onset of action in the relevant target organ.

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