

Comparison of methods for intestinal histamine application: histamine in enterosoluble capsules or via a duodeno-jejunal tube

Influence of fast and histamine-restrictive diet

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The study was conducted to investigate whether introduction of histamine in enterosoluble capsules produced the same amount of urinary histamine metabolites as that found after application of histamine through a duodeno-jejunal tube. Secondly, to examine whether a histamine-restrictive or a fast diet affected the amount of urinary metabolites. Fifteen healthy subjects were challenged four times with 100 mg of histamine. Results were monitored by the urinary recovery of 1,4-methylimidazole acetic acid (MIAA) from 24 h before to 72 h after challenge. Urine was collected in 24-h samples except on the first day after challenge when separation into 0-2 h-, 2-4 h- and 4-24 h-fractions was made. MIAA was measured by high performance liquid chromatography (HPLC). The results showed that during the first 2 h after challenge the recovery of MIAA was higher with tubes than with capsules. Measurements from all other intervals did not differ significantly between the two challenge regimens. Fast (water only) and histamine-restrictive diet versus non-restrictive diet did not affect the urinary MIAA. MIAA was significantly higher overall during the first 24 h after challenge than in any other fraction. We conclude that oral administration of enterosoluble capsules is an easy and appropriate method for intestinal histamine challenge. Fast and histamine-restrictive diets are not necessary, but subjects should record unexpected responses in a food and symptom diary.

Key words: food allergy; food intolerance; histamine challenge; urinary histamine metabolite.

Accepted for publication 6 September 1990

Bronchial hyperresponsiveness, a common feature of asthma (1), can be assessed by inhalation tests with histamine (4, 7). Hyperresponsiveness of the intestinal tract may be of similar importance in the etiology of food sensitivity (1), and might be determined by local histamine challenge. Administration of histamine via a duodeno-jejunal tube has been reported to reproduce symptoms attributable to foods in some subjects (10). Dietary factors may contribute, since some

foods contain histamine, although the amounts of histamine vary considerably (1, 11). Methods for intestinal challenge with histamine have not been standardized, although food allergy/intolerance remains a major diagnostic problem in allergy clinics all over the world.

The aim of the present methodological study was to investigate whether the troublesome histamine application via a duodeno-jejunal tube could be replaced by oral administration of

enterosoluble histamine capsules, which is a much easier and more comfortable challenge method; and secondly, to evaluate the possible interference of fast and histamine-restrictive diet on the excretion of MIAA.

The methods were compared by measurement of the urinary excretion of a major histamine metabolite, 1,4-methylimidazoleacetic acid (MIAA). MIAA was measured by high performance liquid chromatography (HPLC), (13), and the method was chosen among others (3, 5, 8, 14) because of its efficiency and reliability.

STUDY POPULATION AND METHODS

Participants (12 women and 3 men) selected for the study were volunteers, mean age 34 years (range 18–51); none was pregnant, and they served as their own controls when investigated in further trials. None had received medicine in the week prior to entering the trial, and none had been treated with astemizole.

Throughout the study, 24-h urine collections were sampled in 2,500 ml plastic containers. The collection started 24 h before and lasted until 72 h after the challenge. The first 24 h after histamine challenge the urine was obtained in 0–2 h-, 2–4 h-, and 4–24 h-fractions for monitoring early excretion. Five ml of 6 molar HCl were added to the container before use. The full containers were stored at room temperature until measured. Duplicate samples were aliquoted and frozen in test tubes. The content of MIAA was measured by a reversed phase ion-pair high performance liquid chromatographic method with purified sodium dodecylsulphate as the ion-pairing agent, acetonitrile, and phosphate buffer. A prepacked Merck Hibar RP-18 column was used for chromatography. The sensitivity of the assay was 0.5 µg/ml urine, and the coefficient of variation was 5% or less (13).

A histamine-restrictive diet was obtained by eliminating all histamine-rich foods, i.e. >20 mg of histamine/kg, and histamine-liberating foods 3 days prior to the trials (1, 11). Fast was defined as abstaining from foods and beverages other than plain water, from 12 h before until 2 h after the histamine administration.

The investigation consisted of four trials with intervals of 1 week. In each trial, all subjects were challenged with 100 mg of histamine. For introduction into the duodeno-jejunal tube, histamine hydrochloride from the State University Hospital pharmacy was administered in a 10 mg/ml solution. Ten ml of the solution was mixed with 10 ml of lukewarm tap water in a 20 ml syringe and injected into the tube for 1 min. The tube was rinsed with 30 ml tap water. The position of the tube near the duodeno-jejunal flexure was verified by X-ray. For enterosoluble administration, the histamine hydrochloride salt was packed in No. 1 gelatine capsules, 80% soluble within 2 h in 0.1 molar hydrochloric acid at 36–38°C (ALK Laboratories, Hørsholm, Denmark). The capsules were coloured with ferrous oxide and swallowed with 50 ml water.

Trial I: the subjects were challenged with histamine through the duodeno-jejunal tube. Urine was collected as described. The individuals were subjected to a histamine-restrictive diet and fast.

Trial II: the subjects were challenged with capsules containing histamine. The subjects collected urine, fasted and observed a histamine-restrictive diet as in trial I.

Trial III: the subjects were rechallenged with histamine in capsules, as in trial II; they did not fast but observed a histamine-restrictive diet.

Trial IV: the subjects were rechallenged with histamine in capsules, as in trials II and III; they observed no histamine-restrictive diet, but fasted.

Statistics

A logarithmic transformation of the measurements of MIAA was necessary to obtain normal distribution and homogeneity of variance. For each trial and for each period (2, 4, 24, 48, and 72 h after challenge), the individual difference between the after-challenge sample and the baseline sample before challenge was determined. For each of the trials I, III, and IV, the differences were then compared with trial II by a two-way analysis of variance classified by trials and subjects.

Six subjects underwent all trials. The comparison between trials, using a two-way analysis

of variance classified by trials and subjects, was therefore performed on the involved subjects only, i.e. the statistical analysis in the comparison between trials II and III involved only eight subjects, and between trials II and IV only six subjects (Table 1).

To describe the kinetics of absorption and excretion, in particular the duration before the return of the MIAA excretion to baseline, the mean difference of all trials for each patient between the 24-h before-challenge sample and the 24-h, 48-h and 72-h after-challenge samples, respectively, was analysed by a two-way analysis of variance classified by periods (24 h, 48 h, 72 h) and subjects. As there was a difference between periods, the daily mean was tested by a Student's *t*-test. A 5% level was accepted as a significant difference.

RESULTS

Method of intestinal application (trial I versus trial II)

The reliability of intestinal application of histamine in enterosoluble capsules was tested

against duodeno-jejunal tube by comparing results from the 15 subjects in trial II (capsule) with the results from the 15 subjects in trial I (tube). The major excretion of urinary MIAA was observed during the first 24 h after challenge, i.e. a steeper slope on the curve was observed only in this period (Fig. 1). The 24-h excretion of MIAA from 24 to 48 h after the challenge did not differ from the 24-h excretion of MIAA in the baseline period (i.e. -24 h to 0). This can be seen from Fig. 1, in which the slope of the curve between 24 and 48 h and further to 72 h does not differ ($P > 0.05$) from the mean slope obtained before challenge. The alteration from baseline MIAA for 2-4 h, 0-24 h, 24-48 h, and 48-72 h was not significantly different between trials I and II. However, the urinary MIAA during the first 2 h after challenge was significantly lower ($P < 0.05$) in trials II, III, and IV than in trial I (Fig. 1).

Influence of fast (trial II versus trial III)

The influence of fast on the excretion of urinary MIAA was tested by comparing trial III (hista-

Table 1.
Mean excretion of MIAA (mg) and range in each time interval

Interval (h)	Trial (mean MIAA (range))			
	I (n = 15)	II (n = 15)	III (n = 8)	IV (n = 6)
-24-0	1.80 (0-3.80)	1.56 (0.00-3.05)	1.43 (0-3.27)	1.79 (0.99-3.93)
0-2	2.57* (0.48-5.12)	0.80 (0.25-2.73)	0.64 (0.17-0.86)	0.77 (0.35-2.28)
2-4	3.49 (1.17-6.56)	2.45 (1.28-5.23)	2.80 (0.73-5.37)	3.00 (1.17-4.25)
4-24	5.66 (2.60-8.22)	6.10 (2.01-11.54)	6.71 (1.66-11.08)	6.48 (2.38-8.62)
24-48	1.79 (0.00-3.60)	2.32 (0-4.60)	2.21 (0-8.87)	2.34 (0-11.52)
48-72	1.80 (0.00-4.85)	1.59 (0-3.78)	1.36 (0-3.48)	1.07 (0-4.01)

Only in the time interval 0-2 h in trial I was a significantly higher increase seen compared with the excretion of MIAA in the same time interval in the other trials. No other significant differences were found. Numerals in parentheses indicate number of subjects in each trial.

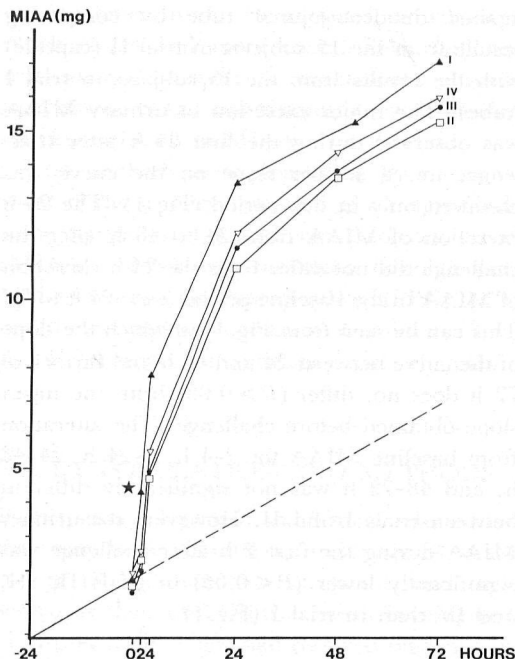


Fig. 1. Accumulated MIAA (mg) excretion in urine from 24 h before intestinal application of histamine until 72 h after application to the intestinal tract. After histamine application (hour 0) a steep increase in the excretion of MIAA was seen in all trials. Only in trial I, was a significantly higher excretion seen during the initial 2 h compared with the other trials (*). After 24 h the slope of the curve was equal to the expected excretion curve (dotted line) indicating that all the histamine has now been excreted. No other difference between trials was observed.

mine-restrictive diet, no fast, capsule) with trial II (histamine-restrictive diet, fast, capsule). The urinary excretion of MIAA during all time periods after challenge did not differ between trials (Fig. 1).

Influence of histamine-restrictive diet (trial II versus trial IV)

The effect of a histamine-restrictive diet on the urinary MIAA excretion was examined by comparing trial IV (no histamine-restrictive diet, fast, capsule) with trial II (histamine-restrictive diet, fast, capsule). The urinary MIAA after challenge showed no significant difference between the trials (Fig. 1).

DISCUSSION

In the present study we aimed at investigating methodological problems connected with developing a method for intestinal histamine challenge. People with food allergy might be hyper-responsive to histamine in their intestinal tract, and after application of histamine in the intestinal tract more symptoms and a higher excretion of MIAA could be expected in patients with food allergy or intolerance compared with normal controls. Further studies are planned to investigate such problems.

This study showed that the excretion of urinary MIAA was significantly higher during the first 2 h after introduction by tube than after application by capsule. The measurements from the rest of the observation period showed no significant difference between the trials. This is consistent with the procedure of application: histamine reached the intestine instantly through the duodeno-jejunal tube. But with the enterosoluble capsule histamine did not reach the intestinal tract until after gastric emptying and dissolution of the enteric coating which takes 1–2 h (11). None of the observations indicated any effect of fast or histamine-restrictive diet on the excretion of MIAA, but the sample was small and a difference might have been overlooked. However, no difference in the pattern of MIAA excretion was observed in any of the subjects investigated, so that an effect of fast or histamine-restricted diet seems unlikely.

The urinary excretion of MIAA was only significantly higher within the first 24 h of challenge. Accordingly, it was concluded that measurement of urinary MIAA was only important during the first 24 h after challenge.

In conclusion, the investigation showed that for intestinal histamine challenge, ingestion of an enterosoluble capsule is just as efficacious as the cumbersome administration via duodeno-jejunal tube. Fast and histamine-restrictive diet produced no differences, but patients should keep a food diary record in case of extreme excretions of MIAA. The repeatability of the test needs to be further investigated, and the test should be applied to patients with known food allergy to see whether any differ-

ence in MIAA excretion and symptoms exists between normals and patients.

ACKNOWLEDGEMENTS

The skilful and dedicated assistance of Lena Baron, laboratory technician, is appreciated. We thank ALK Laboratories, Hørsholm, Denmark, for supplying the capsules; the Augustinus Foundation for supporting the acquisition of the HPLC-equipment; the Danish Medical Research Council for statistical assistance; and the Department of X-ray at the State University Hospital, Copenhagen, Denmark, for its service.

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