

Diurnal variation of urinary histamine and 1-methylhistamine excretion in healthy children

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In order to establish a noninvasive method of monitoring immediate hypersensitivity reactions in children, we studied the diurnal variation of urinary histamine and 1-methylhistamine excretion and the influence of food intake in a group of 14 healthy nonatopic children (aged 2–16 years). Histamine and 1-methylhistamine in spontaneous urine samples were determined by radioimmunoassay. Mean variation of 2-h intervals was much higher for urinary histamine than for 1-methylhistamine (45% of base-line level versus 24%). There was no circadian rhythm or influence of food intake. The short half-life of histamine released into blood circulation may be the main reason for the higher variation of histamine excretion. In children, urinary 1-methylhistamine is less influenced by diurnal variation and is therefore more suited to monitor immediate hypersensitivity reactions than urinary histamine itself.

Key words: children; histamine; 1-methylhistamine; urinary.

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Histamine (HI) plays an important role in various states of health and disease. It is a mediator of immediate hypersensitivity reactions and a specific indicator of basophil and mast cell activation. Measurements of HI and its metabolites in body fluids (e.g. blood, plasma, urine, cerebrospinal fluid) have been used to assess mediator release under experimental conditions and for diagnostic purposes.

Many studies have used the measurement of HI in plasma as a diagnostic tool to study HI release in asthma (3, 18), anaphylaxis (37), and oral food challenge (1, 2), and as a challenge procedure for the diagnosis of physical and cholinergic urticaria (4). However, plasma HI measurements can be affected by leakage from basophils during blood sampling and separation of plasma. Moreover, plasma HI measurement has been a time-consuming procedure (28, 36). A recently developed, highly sensitive, and specific radioimmunoassay (RIA) has facilitated the determination of HI (23) and is applicable not only to plasma, but also to other fluids, e.g. urine.

As a way of avoiding problems in handling plasma samples, measurement of HI in urine, and more recently of metabolites of HI, e.g. 1-methylhistamine (MH), has been developed as a diagnostic tool to assess the role of HI release *in vivo* (5, 9, 12, 16, 25, 32). Furthermore, urinary measurement of HI and its metabolite MH has the advantage of retrospec-

tive analysis and time-integrated assessment of HI release, e.g. in case of anaphylaxis of unknown origin.

Most of the studies on HI and MH excretion are conducted in adults, with some conflicting results concerning individual variation (8), influence of mealtime, and type of diet (10, 13). There are very few data on urinary HI and MH excretion in children (26, 32).

Since some allergic conditions in children lack objective parameters (e.g. diagnosis of food allergy), monitoring of HI release *in vivo* in immediate hypersensitivity reactions by urinary HI and MH excretion could facilitate the assessment of allergic conditions. Therefore we studied urinary HI and MH excretion in a group of 14 healthy, nonatopic children to elucidate the diurnal variation and the influence of mealtime on urinary HI and MH.

Material and methods

Fourteen healthy children (5 boys, 9 girls) aged 2–16 years participated in this study. The 14 children had no history of atopic disease. In 11/14 children the family history was also inconspicuous concerning allergic diseases; in 3/14 children, siblings, or in one case the mother, suffered from hay fever. All parents gave their consent. Foods containing HI (such as

yogurt, sauerkraut, cheese, and fish) were excluded from diet from 2000 the day before the study day to the end of the study (13, 26).

Urine samples were collected for 24 h, starting with the first morning urine on the study day, including the first morning urine on the following day. The children were asked to drink abundantly. They were instructed to give spontaneous urine samples every 2 h until they went to bed and one last urine sample on the following morning. Urine was collected in 120-ml plastic containers, and aliquots of the samples were stored at -20°C until analyzed. All assays were run in duplicate.

HI was determined by a solid-phase RIA (Immunotech, Marseille, France) (22, 23), in which succinyl glycin is used as a reagent to acylate HI in the sample. The acylated HI competes with 125-I-acylated-histamine-BSA for the binding site of the monoclonal antibody. Samples were diluted 1:11 with a urine diluent buffer, adjusted to a pH of 7. The assay was performed with an intra-assay coefficient of variation of 7.2%, interassay coefficient of variation of 11% in our children. There was no cross-reactivity to MH.

1-Methylhistamine was determined by a double-antibody RIA (Pharmacia, Freiburg, Germany) (9). Urine specimens were diluted 1:51 with phosphate-buffered saline adjusted at pH 7.4. MH in the sample competes with a fixed amount of ^{125}I -labeled-HI albumin complex for the binding sites of monoclonal antibodies. After incubation for 16–20 h at 4°C , bound and free HI is separated by addition of a second antibody, Sepharose[®]-antimouse IgG raised in sheep. Immunoassay is followed by centrifugation and decanting. The assay was performed in our laboratory with a detection limit of 4 nmol per liter. The coefficient of intra-assay variation was 9.4%, interassay coefficient of variation 11.5% in our children. The assay had a crossreactivity to HI of 6%.

HI and MH concentrations are expressed as a ratio of the urinary creatinine excretion (15). Urinary creatinine determination was performed by an autoanalyzer (BIO, Hoffmann La Roche, Switzerland) using the alkaline picrate reaction.

We divided the excretion time curve of each child into 2-h intervals (0900–1100, 1100–1300, 1300–1500, 1500–1700, 1700–1900), using the area under (or over) the curve for comparison of the excretion over the time intervals. The mean of two consecutive morning urine samples served as the individual base-line level for each subject, since the excretion of HI and its metabolites is age-dependent (26). Morning urine samples show good correlation with 24-h urine samples (26). Food intake was recorded to assess mealtime influence on mediator excretion. The physical activity of the children was not restricted, since

it is known that this has no influence on MH excretion rates (8).

Statistical analysis was done for base-line values with the Mann-Whitney U-test, for comparison of mealtime influence with the matched-pair signed rank test, while for differences in excretion intervals the Friedman test, a rank analysis of variance, was used.

Results

Morning urine samples (day 1 compared with day 2) showed no statistically significant differences (Fig. 1).

Histamine

Over the day, the median of HI excretion was not significantly different from overnight base-line values (Figs. 2 and 3). The difference of base-line value expressed as a percentage of individual base-line level indicates the variation of mediator excretion. HI/creatinine excretion, measured in 2-h intervals, showed a mean variation of 45% and standard deviation of 41%.

1-Methylhistamine

There were no significant differences in MH excretion for 0900 to 1900 (Figs. 4 and 5). The mean difference of base-line MH excretion was 24% (SD 20%).

Influence of food intake

Figures 6 and 7 show that there was no significant increase of HI or MH excretion following a meal.

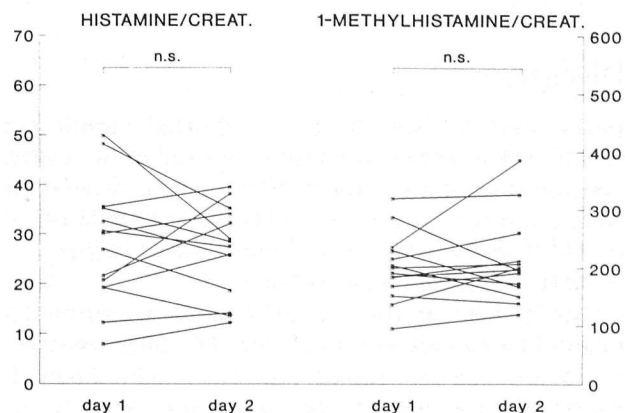


Fig. 1. Comparison of morning urinary HI and MH concentration in $\mu\text{mol/mol}$ creatinine (day 1 to day 2) (n.s. = nonsignificant).

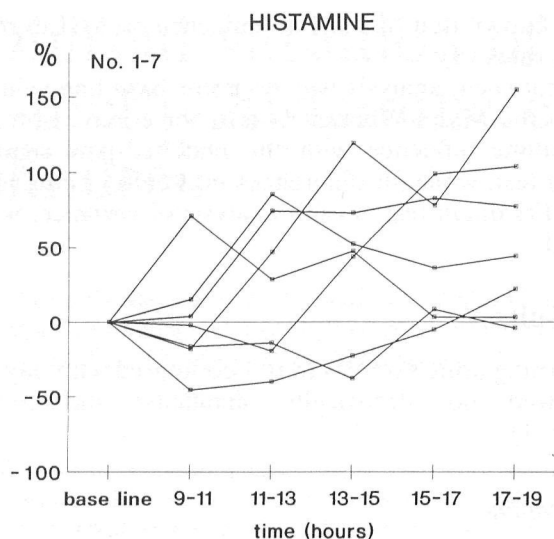


Fig. 2. Diurnal variation of HI excretion in percentage from base line (nos 1-7).

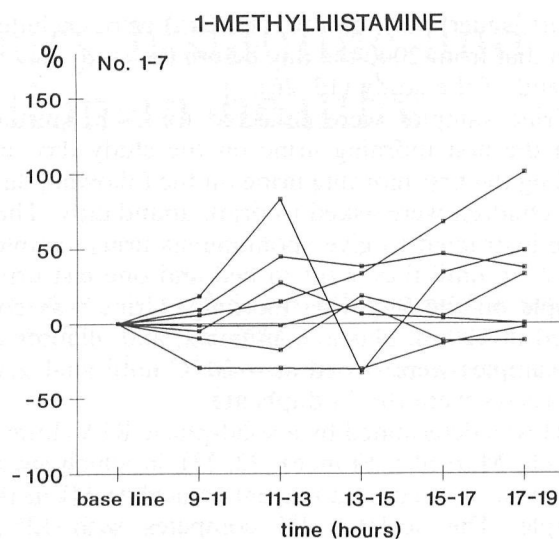


Fig. 4. Diurnal variation of MH excretion in percentage from base line (nos 1-7).

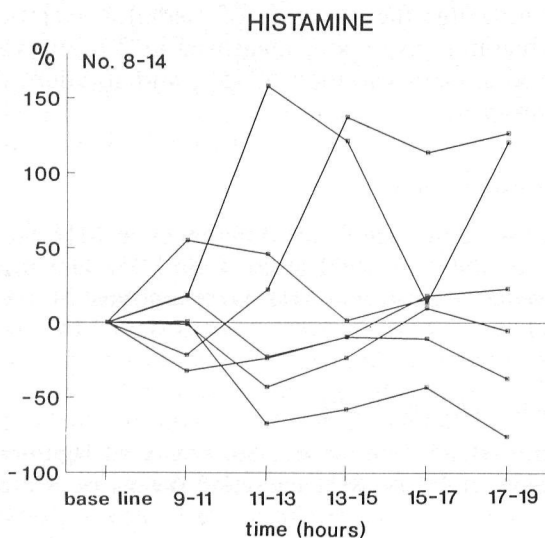


Fig. 3. Diurnal variation of HI excretion in percentage from base line (nos 8-14).

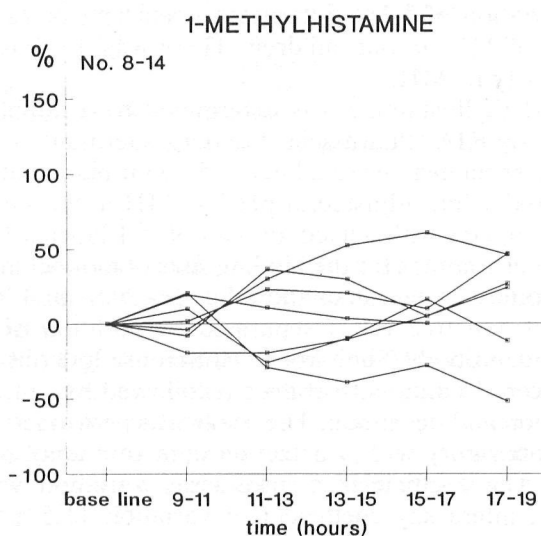


Fig. 5. Diurnal variation of MH excretion in percentage from base line (nos 8-14).

Discussion

In this study we investigated the diurnal variation of urinary HI and MH excretion in a group of 14 healthy nonatopic children. Individual diurnal variations were considerably higher for HI than for MH (45% vs 23%), and no influence of mealtime on urinary HI or MH excretion could be found.

The higher variation of HI excretion can be explained by its very short half-life. HI, once released, is metabolized very rapidly; the half-life in plasma is shorter than 2 min (11). HI excreted in urine is virtually HI which has escaped metabolism, and represents less than 3% of total released HI (6).

Approximately 70% of circulating HI is metabolized to MH (6).

The half-life of MH is much longer than that of HI; after anaphylactoid reactions, MH is still markedly increased in plasma after 30 min (12). MH is excreted in urine in eightfold higher concentration than HI (7) and is representative of the amount of metabolized HI, since HI is the only source of MH in man. Variation of HI concentration in circulation occurs physiologically and is described as a biorhythm with several minima and maxima (30). A more recent study showed a significant decrease of HI at 1600 in plasma and an increased level at 0400 (33).

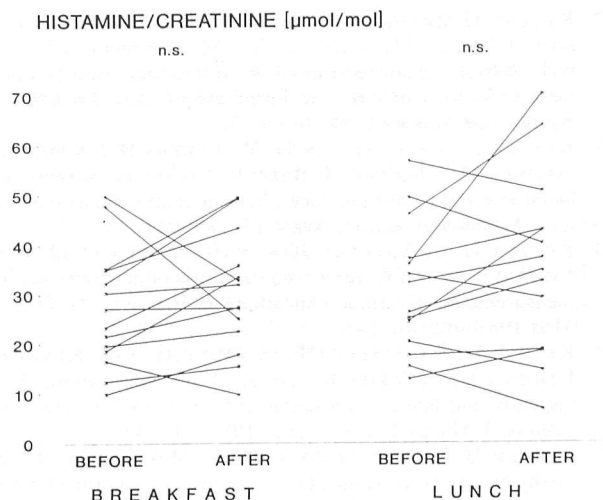


Fig. 6. HI values before and after breakfast and lunch, respectively (in $\mu\text{mol/mol}$ creatinine) (n.s. = nonsignificant).

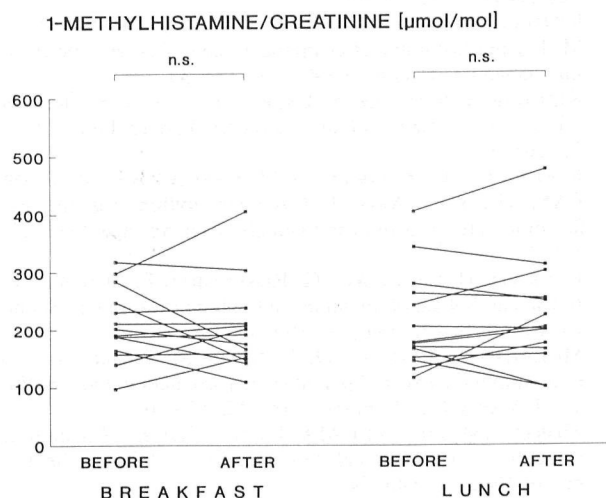


Fig. 7. MH values before and after breakfast and lunch, respectively (in $\mu\text{mol/mol}$ creatinine) (n.s. = nonsignificant).

We chose HI and MH and not methylimidazole acetic acid (MIAA), as urinary parameters, because MIAA failed to be a sensitive marker of histamine-mia caused by bronchial allergen provocation tests (34). Besides, MIAA has to be determined by high-performance liquid chromatography (HPLC), which is a much less convenient assay system than RIA.

Urinary HI and MH excretion may be influenced by HI which is produced by gastric mucosal mast cells and endocrine cells in the oxyntic mucosa (21, 34). One author found two- to fourfold increase in HI and MH excretion, peaking approximately 2 h after intake of food containing no HI or protein (10). Our results (Figs. 4a and 4b) did not show a significant increase in urinary HI and MH excretion after breakfast or lunch. Accordingly, plasma levels of HI were not found to be increased after food consump-

tion (30). Our data suggest that HI released from gastric mucosal cells by endocrine stimuli after a meal has no appreciable impact on urinary HI and MH excretion rates in children.

Several more influences are reported. One of the best-known factors is the increase of HI after a meal of food containing HI (15, 24). Our children avoided HI-rich food for 12 h before the study, as recently suggested (26).

A question of concern is the duration of sampling periods. In 6-h intervals, MH excretion was found to have a maximum increase of 12–41%, as compared with the average values, in children 6–16 years of age (32). We found a mean variation in HI excretion of 45% and in MH excretion of 23% at the 2-h intervals, as compared with base-line values. Maximum variation was considerably higher in some patients. In monitoring mediator excretion, the intervals of urine collection should be as short as possible, because of the short half-life of the mediators, particularly HI. In our experience an interval of 2 h seems to be appropriate for practical purposes.

Conflicting results in the literature concerning variation may derive from the use of different assay systems. However, our results obtained by RIA were in good accordance with normal values obtained by stable isotope dilution fragmentographic methods, as recently published by Oosting (27).

Variation of urinary creatinine excretion can affect the mediator to creatinine ratio measured in urine. Urinary creatinine is, however, reported to be influenced by diurnal variations because of protein intake, for example, during the day (29). In healthy children an acrophase of urinary creatinine at 0500 has been described (19). A more recently published study found no evidence of a circadian rhythm of urinary creatinine excretion (20). In five of our children in whom we could investigate the absolute amounts of creatinine, HI, and MH, we found a stable creatinine excretion during the day.

In the literature a phenomenon of extremely high values in HI excretion is reported, and explained by the presence of commensal bacteria in the urinary tract or vagina which are able to produce HI but not MH (14, 17). We excluded from calculation one girl showing an extremely high HI morning value. We tried to minimize the problem of bacterial contamination by immediate cooling of the samples and freezing within 1 h.

Another possible pool of urinary HI and MH may originate from the kidneys, which are known to be capable of HI production. There may be interactions between renal blood flow and glomerular HI production (35).

Psychological stress may influence mediator release into circulation: therefore, noninvasive urinary sampling – instead of venepuncture – should be the

preferable sampling method, especially in children. In an interesting trial it could be shown that psychological stress during dental therapy could lead to HI release into circulation (31). Physical exercise seems not to influence HI release (8).

We conclude from our results that because of its smaller variations urinary MH is a more reliable parameter than urinary HI for monitoring immediate hypersensitivity reactions in children caused by histaminemia. For interpreting results of, for example, challenge procedures, each patient should be assessed by comparison with a control day. In our view a significant urinary mediator increase is given when it exceeds two standard deviations of control-day excretion.

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