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ORIGINAL ARTICLE

Intravenous infusion of ascorbic acid decreases serum histamine concentrations in patients with allergic and non-allergic diseases

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Abstract Histamine plays an important role in the development of symptoms in allergic, infectious, neoplastic and other diseases. Empirical findings have suggested beneficial effects of ascorbic acid supplementation in those diseases, and these effects are assumed to be related to a possible decrease in systemic histamine concentration. In the present study, we systematically investigated for the first time the effect of 7.5 g of intravenously administered ascorbic acid on serum histamine levels (as detected by ELISA) in 89 patients (19 with allergic and 70 with infectious diseases). When all patients were grouped together, there was a significant decline in histamine concentration from 0.83 to 0.57 ng/ml×m^2 body surface area (BSA, $p<0.0001$). The decrease in serum histamine concentration in patients with allergic diseases (1.36 to 0.69 ng/ml×m^2 BSA, $p=0.0007$) was greater than that in patients with infectious diseases (0.73 to 0.56 ng/ml×m^2 BSA, $p=0.01$). Furthermore, the decline in histamine concentration after ascorbic acid administration was positively correlated with the basal, i.e. pre-therapeutic, histamine concentration. Intravenous infusion of ascorbic acid clearly reduced histamine concentrations in serum, and may represent a therapeutic option in patients presenting with symptoms and diseases associated with pathologically increased histamine concentration.

Keywords Allergic diseases · Ascorbic acid · Vitamin C · Histamine concentration

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Introduction

The biogenic amine histamine is significantly involved in the pathogenesis of allergic, inflammatory, infectious and neoplastic diseases (Schlueter and Johnston 2011) inducing symptoms such as sneezing, rhinitis, wheezing or bronchial obstruction as well as increased gastric acid secretion and diarrhea. The infusion of ascorbic acid (vitamin C) has been reported to exert to some degree symptom improvement in patients with infectious disease, common cold, bronchial asthma, mastocytosis or malnourished patients (Wilson and Loh 1973; Bucca et al. 1989; Johnston et al. 1992a; Hunt et al. 1994; Douglas et al. 2004; Jarisch 2009; Homann et al. 2010).

In vitro, ascorbic acid breaks up the imidazole ring structure of histamine (Uchida et al. 1989). In vivo, an inverse relationship between plasma ascorbic acid levels and blood histamine concentration was observed (Johnston et al. 1996). In guinea pigs, for which ascorbic acid is an essential vitamin as it is in humans, a supplementation of ascorbic acid led to a decrease in blood histamine concentration (Johnston and Huang 1991). Although supplementation of ascorbic acid as a common treatment option in general practice has gained widespread patients' acceptance, no systematic investigations of ascorbic acid

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infusion on systemic histamine levels have been done so far. Therefore, the aim of the present study was to evaluate the effect of an intravenous high-dose infusion of ascorbic acid on blood histamine concentration in man. In fact, the present data demonstrate that intravenous supplementation of ascorbic acid leads to a decrease in blood histamine concentration. The decreasing effect increased with increasing histamine levels.

Patients and methods

Study population

Between January and June 2011, 89 patients were enrolled in the study. The study was performed according to the Helsinki declaration and was approved by the local Ethic committee. Informed consent was obtained from all participants. Eligible patients were symptomatic outpatients who presented with either allergic or infectious symptoms, took no type of steroids, antihistamines or mast cell stabilizers and did not use ascorbic acid within the last week. In all patients, transaminases, cholestasis parameters and haptoglobin were measured in order to exclude haemolysis as confounding variable. Patients with co-morbidities such as renal or hepatic insufficiency, and hemochromatosis were excluded from this study.

For statistical analysis, the patients were divided into two groups, one with an infectious disease (n=70) and another group with a confirmed allergic disease (n=19). The infectious, non-allergic disease group included patients who presented with upper respiratory tract (n=41) or beginning systemic (viral) infections (n=29), who clinically presented with headache, infectious rhinitis, myalgia, dizziness and subfebrile temperatures. The allergic disease group consisted of patients with previously confirmed allergy (n=4 eosinophilic esophagitis, n=11 allergic rhinoconjunctivitis, n=2 atopic eczema, n=2 bronchial asthma). All patients of the allergic group had either cutaneous or serological signs of IgE sensitization towards pollen, environmental allergens or foodstuffs.

Ascorbic acid infusion

Ascorbic acid (7.5 g, Pascoe, Giessen, Germany) was dissolved in 250 ml 0.9 % saline solution and infused intravenously over 60 min. We chose a dose of 7.5 g ascorbic acid since this is a widely used dose in the supportive treatment of, e.g. respiratory and infectious diseases in everyday practice. For this purpose, the commercial preparation of the company is provided with 7.5 g ascorbic acid, which is routinely prescribed by general practitioners in Germany. Directly before and 1 h after the end of the infusion, blood was taken to determine serum histamine concentration. Since blood histamine concentrations were measured directly before and 1 h after the infusion, each patient served as its own control for ascorbic acid-induced changes in serum histamine level. We chose intravenous rather than oral dosing because we wanted to determine the acute impact of ascorbic acid supplementation on serum histamine concentration. Moreover, systemic concentration of ascorbic acid after infusion is not disturbed by the variation of the bioavailability of ascorbic acid after oral intake (Bates and Heseher 1994; Levine et al. 1996). The degree of absorption decreases as intake increases. At high intake (1.25 g), fractional human absorption of ascorbic acid may be as low as 33 %; at low intake (<200 mg) the absorption rate can reach up to 98 % (Levine et al. 1996). Besides resorption variations between individual patients, high oral ascorbic acid supplementation sometimes causes gastrointestinal problems, especially in allergic individuals or patients with dyspeptic symptoms; hence, high-dose supplementation cannot be achieved in such susceptible individuals. Therefore, we chose a low rate of intravenous infusion over 60 min. Moreover, at this low infusion rate acute hypotonia which has been observed in rare cases after intravenous application of ascorbic acid should not occur. Finally, we have positive experience with intravenous infusion of ascorbic acid in the emergency treatment of patients with systemic mast cell activation disease (unpublished observation).

Histamine measurement

Serum blood sample tubes (S-Monovette^{R}, Sarstedt, Nümbrecht, Germany) were used, and the blood samples were cooled on ice (4 °C) immediately after being drawn from the vein in order to avoid histamine degradation. Then, the blood samples were centrifuged using a refrigerated centrifuge for 10 min at 4,000 U/min and cooled (4 °C) so that the serum was separated within 20 min after blood drawing. Samples were frozen at –20 °C until the ELISA assay could be performed (IBL Hamburg Histamin Elisa 2006). To avoid false positive results for histamine, we took care that no haemolyzed, icteric or lipemic samples were frozen: when certain concentrations are exceeded (haemoglobin 5 mg/mL, bilirubin 1 mg/mL, triglycerides 30 mg/mL), cross-reactions with methylhistamine and acetylhistamine can occur during the ELISA assay (IBL Hamburg Histamin Elisa 2006). Since heparin and its derivatives might influence the diamine oxidase activity and thereby reduce histamine levels, patients who had already got heparin anticoagulation before admission to the clinics were not included in the study.

Histamine ELISA was carried out in duplicate according to the manufacturer's instructions and standards. The test sensitivity for histamine is 0.05 ng/ml. Coefficients of intra- and interassay variation for more than 20 serum samples were 8.8 and 14.1 %, respectively. For analysis of the data,

GraphPad InStat 3 and GraphPad Prism version 4.00 were used. Non-parametric *U* test for independent samples (Mann–Whitney test) and the Wilcoxon matched pairs test were applied in the statistical analysis of the data. According to Petrovay et al. and the manufacturer's manual (IBL Hamburg Histamin Elisa 2006; Petrovay et al. 2007), the normal range of serum histamine was defined to be 0–1.0 ng/ml. For standardization of the histamine analysis in different patient populations with varying body weights, all histamine concentrations were expressed in nanograms per millilitre × square metre of body surface area (BSA). As we have published in earlier studies (Giera et al. 2008; Raithel et al. 2010 M), expression of mediator levels in relation to body surface area results in reduced interindividual variations of the mediator levels because the amount of tissue mast cells, the length of intestine containing huge amounts of histamine producing and the degrading enzymes, the intestinal immune effector cells and the fat tissue as a source of mast cell activating cytokines are standardized better by incorporating both body weight and height into blood level calculations. The normal range of serum histamine in our department amounts to ≤0.56 ng/ml × m^2 BSA. Data are given as median, 25th and 75th percentiles.

Results

The median age of the study population (n=89) was 51.9 years (range, 21–78 years) with 51 women and 38 men. Infusion of 7.5 g ascorbic acid induced a decrease of histamine concentration in 45 of 70 non-allergic patients (64.2 %) and in 14 of 19 allergic patients (73.7 %). One patient out of 89 (1.1 %) reported adverse effects after the ascorbic acid infusion (slight abdominal pain, pruritus, moderate dyspnoea) which subsided after 8 h. In this patient, intolerance to salicylate was diagnosed after further workup. Since the present study was not double-blinded and placebo-controlled, it cannot be excluded that in some patients the infusion procedure has promoted a stress-induced increase in blood histamine level which has contributed to the variation of the effect of ascorbic acid in the patients.

In the whole patient population (n=89), histamine level in blood significantly (p<0.0001) declined by 31.3 % 60 min after the end of the ascorbic acid infusion from 0.83 ng/m^2 BSA (0.47; 1.47) to 0.57 ng/m^2 BSA (0.41; 0.82).

Patients with infectious symptoms in the non-allergic group (n=70, 28–78 years, 42 female, 28 male) presented with a lower basal histamine concentration than patients with allergic diseases (n=19, 21–61 years, 9 female, 10 male) before infusion of ascorbic acid (Fig. 1). In patients with infectious disease, median serum histamine concentration declined from 0.73 ng/m^2 BSA (0.46;1.36) to 0.56 ng/m^2 BSA (0.42; 0.82; p=0.01; Fig. 1); in allergic patients, median

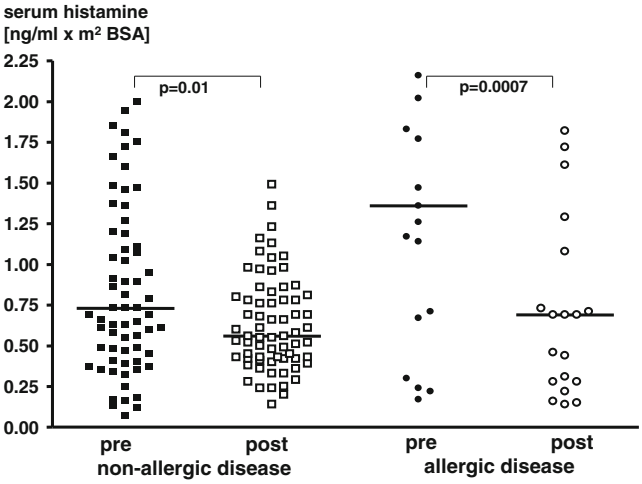

Fig. 1 Distribution of individual serum histamine concentration in patients with infectious disease (non-allergic patients) and allergic disease before (*pre*) and 60 min after the end of the infusion of 7.5 g ascorbic acid (*post*). *BSA* body surface area. p=0.01, p=0.0007—levels of significance for the difference in serum histamine concentration between the respective groups

serum histamine concentration declined from 1.36 ng/m^2 BSA (0.67; 2.16) to 0.69 ng/m^2 BSA (0.28; 1.08; p=0.0007; Fig. 1).

In patients with basal histamine concentrations in the normal range, no reduction of the serum histamine level by ascorbic acid was observed (Fig. 2a). However, in all patients of the infectious disease group with increased serum histamine concentration serum histamine levels were reduced by ascorbic acid: the higher the basal pre-infusion serum histamine concentration was, the greater the reducing effect of ascorbic acid on serum histamine turned out (Fig. 2a). Similar findings were obtained in the allergic patients (Fig. 2a); however, statistical analysis could not be performed because in the allergic group patient numbers in each class were too small.

For the whole study population, the individual change in serum histamine level was negatively correlated to each patient's pre-infusion basal histamine concentration (Fig. 2b; r=−0.803, p=0.0001), confirming above mentioned results made for the corresponding disease groups.

Discussion

Ascorbic acid is empirically used as a therapeutic agent since a long time in several diseases such as common cold, respiratory tract infections, airway hyperresponsiveness, seasickness and histamine intolerance (Wilson and Loh 1973; Bucca et al. 1989; Johnston et al. 1992a; Jarisch 2009). Its deficiency has been linked with scurvy, hyperemesis gravidarum and capillary fragility (Johnston et al. 1992a; Clemetson 2004). In addition to its property

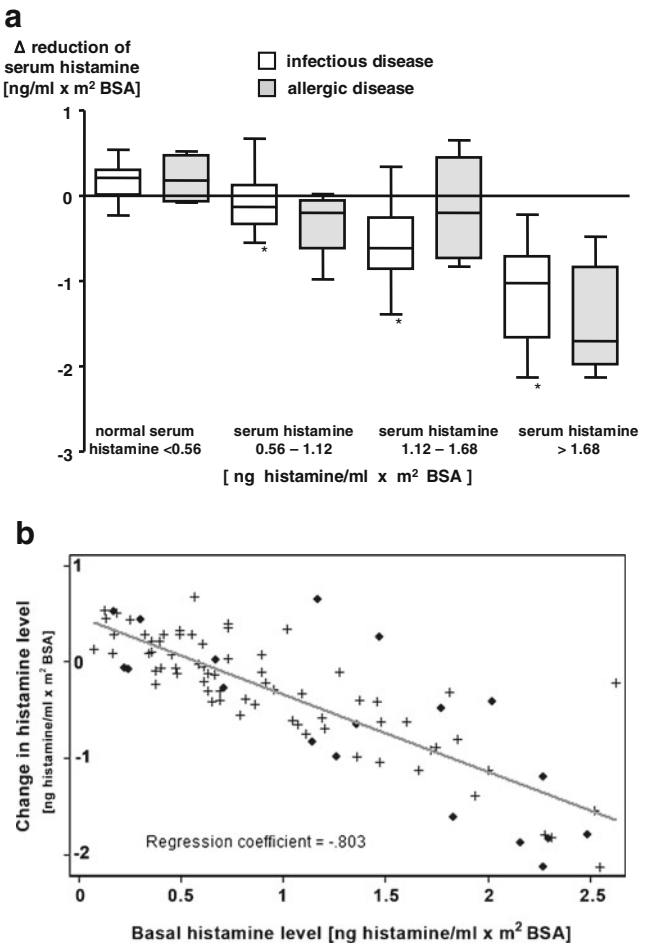

Fig. 2 **a** Histamine-lowering effect of ascorbic acid in relation to the basal serum histamine concentration. The change of the serum histamine concentration (Δ histamine, median and 25th–75th percentile) was calculated from its concentration 60 min after ascorbic acid infusion minus its basal concentration. Basal serum histamine concentration of the patients is divided into four classes (0–0.56 normal histamine concentration, 0.56–1.12 slight elevation, 1.12–1.68 moderate elevation and >1.68 ng/ml×m^2 BSA severe histamine elevation). * In the group of patients with infectious disease the lowering effect of ascorbic acid on serum histamine concentration in subgroups with increased basal histamine concentration was significantly different from that with normal basal serum histamine (0–0.56ng/ml×m^2 BSA; $p<0.002$). In the group of allergic patients, the numbers in each subgroup were too small for statistical analysis. **b** Negative correlation ($r=-0.803$, $p=0.0001$) between the change in histamine level and its basal level before infusion of ascorbic acid (number of patients $n=89$). This relationship did not differ between the groups of patients with allergy (*black diamonds*) and non-allergic (*plus sign*) diseases ($p=0.454$). *BSA* body surface area

as a potent radical scavenger, an effect of ascorbic acid on the important biogenic amine histamine has been assumed to be substantially involved in its clinical effects (Clemetson 1980; Johnston et al. 1992b; Douglas et al. 2004; Homann et al. 2010; Schlueter and Johnston 2011). As to the underlying mechanisms involved in the drop in blood histamine level by ascorbic acid, previous investigations suggested both a nonenzymatic degradation of histamine (Chatterjee et al. 1975; Uchida et al. 1989) and an inhibition of the histamine forming enzyme histidine decarboxylase (Oh and Nakano 1988; Dwivedi et al. 1993). Diamine oxidase (histaminase) activity and histamine release appeared not to be affected by ascorbic acid administration (Chatterjee et al. 1975).

To the best of our knowledge, the present study is the first systematic investigation of the influence of ascorbic acid infusion on systemic histamine concentration in man. In our patients, histamine concentrations were found to be elevated both in allergic patients and in patients with mild to moderate upper respiratory tract and systemic infections or common cold, respectively. Although an increased level of serum histamine was to be expected in allergic individuals, it is of note that also the patients in the infectious disease group in whom a type 1 helper T cell immune response is generally supposed had elevated basal serum histamine concentrations above the normal range of 0.56 ng histamine/ml×m^2 BSA. This might explain the occurrence of infection-triggered bronchial asthma, tachycardia or sneezing during respiratory tract infections (Mohsenin 1987; Bucca et al. 1989; Cirillo et al. 2007; Jarisch 2009).

The intravenous administration of 7.5 g ascorbic acid induced a significant decrease of serum histamine in our patients by 31.3 %. The decreasing effect was observed in all patients, irrespective whether the underlying disease was of infectious or allergic nature. But in allergic individuals the decline in serum histamine level was more pronounced than in non-allergic patients with infections (Figs. 1 and 2a, b).

The results of the present study are in agreement with previous data from guinea pigs and from reports on patients with seasickness, hyperemesis gravidarum or scurvy describing a histamine decreasing effect of ascorbic acid (Wilson and Loh 1973; Bucca et al. 1989; Johnston et al. 1992a; Jarisch 2009). The present results also fit well to the previous clinical findings that orally taken 2 g ascorbic acid significantly inhibited the histamine-induced bronchial responsiveness in persons with airway infection and significantly improved force expiratory volume 1 h after vitamin C infusion (Bucca et al. 1989).

The conclusions from the present data are limited by open questions for the best application form of ascorbic acid to induce a maximum and sustained histamine-lowering effect, the pharmacokinetics of orally and intravenously administered ascorbic acid and for the optimum doses which have to be addressed in detail in future studies. Nevertheless, the present data demonstrate that intravenous supplementation of ascorbic acid leads to a decrease in blood histamine concentration. The decreasing effect increased with increasing histamine levels. Although we did not determine the clinical benefit of the ascorbic acid-induced decrease in systemic histamine level in terms of e.g. symptom score values, it seems justified to assume that the clinical benefit of ascorbic acid supplementation observed

in diseases with pathologically increased systemic histamine levels such as systemic mast cell diseases (Homann et al. 2010) is at least in part related to its histamine-lowering effect.

Conflict of interest The authors declare that they have no conflict of interest.

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