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The clinical effect of percutaneous histamine on allergic contact dermatitis elicited to fragrance mix

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Histamine (2-(4-imidazol)ethylamine) has been shown to downregulate cell-mediated reactions in vitro. However, the rôle of such downregulation in vivo has not yet extensively been studied in humans. In an attempt to gain more insight into this, we studied in vivo the effect of percutaneous histamine on an allergic contact reaction elicited to fragrance mix in 28 human volunteers with previously-known sensitization (patch tests) to this allergen. Histamine (0.1 mg/ml) was administered either via subcutaneous injections or by scratching at the site of patch tests to one concentration (8% pet.) of fragrance mix at different times. Histamine and control solution were administered immediately before patch testing (0 hours) or 2× at 0 and 24 h (after application). No significant differences were observed in the grade of delayed-type hypersensitivity reaction (DTHR) to fragrance mix (8% pet.) by visual reading when histamine or control solution was administered. This study did not exclude the possibility that histamine could inhibit DTHR to lower concentrations of the allergen used, and therefore additional in vivo studies are required.

Key words: histamine; CAS 51-45-6; delayed-type hypersensitivity; fragrance mix; H2-receptor; histamine suppressor factor; immunological basis; allergic contact dermatitis. © Munksgaard, 1995.

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Histamine, an important mediator of Type I hypersensitivity, has been shown to downregulate cell-mediated reactions. In vitro, histamine inhibits the production and expression of interleukin-1 by monocytes (1). Histamine also suppresses the proliferation of T-helper cells and their production of interleukin-2 (2–7). Rocklin (8) had isolated a histamine suppressor factor (HSF) that downregulates T-helper cells. The stimulation of H2 receptors on suppressor/cytotoxic T-cells with histamine results in the release of HSF.

However, the results of in vivo studies are not consistent. Pepys (9) was the first to investigate the rôle of histamine in delayed-type hypersensitivity reactions (DTHR) in vivo, and described inhibition of Mantoux reactions in TBC patients after local injection of histamine. Schwartz & Gershan (10) and Rocklin (2) also observed inhibition of DTHR in animals after administration of histamine. In contrast, no clear inhibition of DTHR by local intracutaneous administration of histamine was observed in a human study in which only a limited number of patients were investigated. However, at that time, there was some doubt as to the inhibitory effects of histamine administered via local scratching (11).

The present study is the first study in which the effect of local administration of histamine on an elicited allergic contact reaction was evaluated in 28 patients. To elicit allergic contact reactions we used a patch test with fragrance mix in previously sensitized subjects.

Materials and Methods

All 28 subjects were volunteers. There were 20 women and 8 men aged between 20–78 years (mean age 48 years). All subjects were patch tested previously in the period from 1989 to 1993 and were found to be sensitive to fragrance mix (++ or +++), according to the international standard procedures: −=no reaction; +=erythema and papules; ++=erythema, papules and vesicles; +++=like ++ with confluent vesicles and/or bullae. Fragrance mix was selected as the allergen in this study because of the fact that in our series, it is one of the most frequently occurring allergens.

None of the subjects used oral or local medi-

Table 1. The 4 different protocols that were used (A, B, C and D); in all cases, 0.1 ml histamine (H) or control solution (C) were administered at the site of the fragrance mix patch test

	N	Histamine	Control
A scratch at 0 h	19	X	X
B scratch at 0 and 24 h	18	X	X
C subcutane at 0 h	19	X	X
D subcutane at 0 and 24 h	9	X	X

N: no. patients (out of the total group of 28) who were tested.

Table 2. Mean of reactions to histamine (mm^2) read 20 min after administration of histamine (H) and control solution (C)

	N	H	C
A scratch 0.1 ml at 0 h	19	1141	321
B scratch 0.1 ml at 0 h	18	1555	307
at 24 h[a)]	8	1926	355
C subcutane 0.1 ml at 0 h	19	1781	2
D subcutane 0.1 ml at 0 h	9	1714	9
at 24 h	8	2969	310

N: no. of patients (out of the total group of 28) who were tested.
[a)] Due to erythema induced by DTHR and/or by removing the plaster, not all the histamine-induced reactions to histamine could be evaluated at 24 h in 8 patients.

cation with immunomodulatory effects, antihistamines or had previous exposure to high doses of UV radiation (i.e., solarium, UVB or PUVA treatment or sun exposure) in the 4 weeks prior to testing.

This study was approved by the Medical Committee of the Academic Hospital Rotterdam-Dijkzigt.

We used van der Bend Square Chambers (van der Bend, Brielle, The Netherlands) and fragrance mix (8% pet. Trolab). The fragrance mix contained eugenol, isoeugenol, cinnamic aldehyde, cinnamic alcohol, hydroxycitronellal, oakmoss and α-amylcinnamic aldehyde. Histamine (0.1 mg/ml) was prepared in a solution containing phosphate buffer, 0.03% human serum albumin (HSA) and 0.5% phenol. The control solution contained identical substances except histamine.

Histamine and control solution (both 0.1 ml) were administered locally on the back using 2 different methods: subcutaneous (s.c.) injection and the scratch method. For s.c. injection, we used a 1.0 ml syringe and a 0.5 × 16 mm needle that is also used for routine insuline injection. In the scratch method, 4 superficial cross-scratches were made with a lancet and onto which 0.1 ml histamine or control solution was dropped.

The study design was as follows: histamine (= H) and control solution (=C) were administered locally using both methods, either only immediately before application of the allergen (0 hours), or both at 0 h and again at 24 h. Thus, 4 different test procedures were used (Table 1). Subsequently, (0 h), the fragrance mix test allergen was applied on the back. In all tests, the time of application was 24 h. 20 min after administration of histamine and control solution, the reactions to histamine (flare-reaction) were measured in each case. The DTHR were recorded after 24, 48 and 72 h as mentioned above.

In each of the 4 different designs, the DTHRs were compared at 2 patch test sites: one treated with histamine (DTHR-H) and the other treated with control solution (DTHR-C). When the DTHRs did not differ by more than 1/2 a grade (for example + and +/++) they were scored as being equal: DTHR-H=DTHR-C. When the DTHR caused by histamine was weaker than that caused by the control, it was scored as: DTHR-H<DTHR-C. If the opposite was true, it was scored as: DTHR-H>DTHR-C. Except for the above-mentioned procedures, a simultaneous patch test with fragrance mix was also done without administration of histamine or control solution.

Results

In Table 2, the mean (mm^2) reactions to histamine after 20 min due to histamine and control solution are summarized. As expected, the mean values after administration of histamine were significantly higher than those after administration of control solution. The results of DTHR to fragrance mix obtained after the scratch method and after S.C. injection are summarized in Tables 3, 4, respectively. When histamine was administered via scratching, a weaker DTHR-H than DTHR-C was observed in only 2 cases (total number tested = 37).

Table 3. Comparison of DTHR reaction after administration of histamine (H) and control solution (C) using the scratch model

	h	DTHR-H=DTHR-C	DTHR-H<DTHR-C	DTHR-H>DTHR-C
A administration of H and C at 0 h	24	19	0	0
(*N*=19)	48	18	1	0
	72	18	1	0
B administration of H and C at 0 and 24 h	24	18	0	0
(*N*=18)	48	17	1	0
	72	16	1	1

Table 4. Comparison of DTHR after subcutane injection of histamine (H) and control solution (H)

		h	DTHR-H = DTHR-C	DTHR-H < DTHR-C	DTHR-H > DTHR-C
C	administration of H and C at 0 h ($N=19$)	24	19	0	0
		48	18	1	0
		72	16	2	0
D	administration of H and C at 0 and 24 h ($N=9$)	24	9	0	0
		48	9	0	0
		72	8	1	0

The DTHR-H was stronger than the DTHR-C in only 1 case (Table 3). When histamine was injected S.C., the DTHR-H was weaker than the DTHR-C in only 3 cases (total number of tests = 28). In all the remaining cases, the DTHR-H and DTHR-C were equal (Table 4). A significant inhibitory effect of histamine (visual grading with difference more than one +) on the DTHR was observed in none of the cases. In all cases in which DTHR-H was weaker than DTHR-C ($n=8$, Table 3 and 4), the DTHR-H remained positive ($\geq +$).

Patch tests with fragrance mix (without histamine or control) were all positive after 48 and 72 h, but were all negative at 20 min.

Discussion

Several authors consider that histamine (2-(4-imidazol)ethylamine) has not only a vasoactive function, but also an immunomodulatory function such as stimulation of H2 receptors on T cells (2–7, 12). The results of patch testing with persulphates, which are well-known histamine-liberating agents, indicate that inhibition, probably due to the in situ liberation of histamine caused by persulfates at the patch test site, can occur in the early phases of clinical DTHR in humans who have been sensitized to these agents (13). It is of interest that in humans, the H2-anogonist cimetidine was able to enhance a DTHR (14, 15), but this observation could not be confirmed by others (16). A definite inhibitory rôle of histamine of DTHR in vivo has not been established in humans (11).

In the present study, we tested the rôle of histamine in vivo after it had been administered S.C. or by scratching. The patch test procedure was performed using only a single patch test concentration, and therefore this study did not answer the question of whether histamine could inhibit DTHR at low concentrations of the allergen or not. A dilution series of fragrance mix in the context of percutaneous histamine at each patch test site was, however, refused by the vast majority of volunteers in this study. Considering that visual reading has limited sensitivity, we were unable to detect any difference in the grades of DTHR to fragrance mix after administration of histamine and control solutions. In addition, no inhibitory effect on DTHR was observed after administration of histamine on 2 subsequent occasions at 0 and at 24 h.

Since the reactions to fragrance mix (without histamine and/or control) were negative in all patients at 20 min, it is unlikely that the allergen itself was actively involved in the liberation of histamine. With regard to the short half-life of histamine (17), it can be hypothesized that only 1 or 2 different doses of histamine would result in a slightly raised level of local histamine in the skin. Another possibility might be that the influence of histamine on the DTHR was not strong enough to be reflected in the morphologic measurements we used, but only expressed itself in meticulous measurements as used by Rocklin (2).

More in vitro and in vivo studies are required to elucidate the influences of histamine on T-cell-mediated contact dermatitis.

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