

Influence of the histamine control on skin reactivity in skin testing

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We investigated the effect of the histamine control (1 mg/ml) on the results of skin prick and intradermal testing with bee and wasp venom. Skin tests were done on the patients' forearms: on the right arm the histamine control and the bee venom dilutions, on the left arm the wasp venom dilutions only, at distances of 4–5 cm. In intradermal testing 11 (9%) of 122 patients showed a positive wheal and flare reaction to the bee venom solution positioned next to the histamine control. The subsequent solutions in higher concentrations did not produce any skin reactions. The results of intradermal testing with bee venom did not occur in intradermal testing with wasp venom or in skin prick testing with both allergens. Our results show clearly that in skin prick tests a distance of 4–5 cm is sufficient to avoid false positive skin reactions. However, using the same distance in intradermal testing showed that histamine affects the skin reactions produced by adjacent allergen solutions. Therefore false positive results may occur.

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Histamine hydrochloride is commonly used in a concentration of 1 or 10 mg/ml as positive control in skin prick and intradermal tests. The influence of histamine control in skin tests has been known for some time and has led to the suggestion of using variable distances between skin test solutions. Aas et al. (1) suggested a minimal distance of 2 cm, whereas Malling (3, 4) recommended a distance of 3 cm. When skin prick testing was done with a commercially available premarked tape with distances of 2 cm between the skin test solutions Terho et al. (5) observed positive results of allergen solutions more frequently when these were applied to the skin next to the histamine control. Thus, an assessment of the influence of histamine control in a concentration of 10 mg/ml on the diluent control (negative control) at various distances in prick test was made (6). A significant reduction of false positive wheal and flare reactions vis à vis the diluent control was observed when the latter was applied at a distance of 18 cm.

Similar results have not yet been reported for intradermal testing. Thus, the results of skin and intradermal testing for bee and wasp venom allergy were evaluated. Considering clinical observations during intradermal testing (occurrence of false positive skin test results) it would seem necessary to investigate the frequency of this phenomenon and to find solutions for avoiding false positive skin test results.

Material and methods

The results of skin prick and intradermal testing were documented – using an ink drawing pen – by copying the wheal size in 122 patients.

Histamine hydrochloride 1 mg/ml (Epipharm GesmbH; Austria) and sodium chloride 0.9% (negative control) as well as a solution of lyophilised aqueous and partially purified allergen extract (bee and wasp venom) with standardized content of major allergens (ALK Wässerig SQ®; Epipharm GesmbH, Austria) were used.

Skin prick and intradermal tests were done on the same day in the same patients.

Skin prick testing

The volar surface of the patient's right proximal forearm was used for testing histamine hydrochloride (1 mg/ml) and the bee venom concentrations (from proximal to distal: 0.01, 0.1, 1, 10, 100 µg/ml). The left arm was used for the negative control and wasp venom concentrations only. The distance between each test solution was 4–5 cm.

Intradermal testing

The right proximal forearm was used for the histamine control (1 mg/ml) and bee venom dilutions, 4–5 cm distally, were applied in steadily increasing

concentrations (0.01, 0.1, 1 µg/ml). The left forearm was used for the negative control and wasp venom dilutions (0.01, 0.1, 1 µg/ml) only.

False positive skin test results were obtained in those patients where a wheal and flare reaction occurred in the allergen dilution closest to the histamine control and where such reactions were not observed in the subsequent solutions.

Results

Of 122 patients tested for bee and wasp venom allergy 11 (9%) showed a positive wheal and flare formation in the test solution of bee venom close to the histamine control in intradermal testing (Table 1). This was also the dilution with the lowest concentration. Subsequent allergen solutions in higher concentrations did not elicit a wheal reaction.

Results obtained during intradermal testing with bee venom solutions did not occur during intradermal testing with wasp venom solutions and prick testing for both allergens, always at a distance of 4–5 cm from the histamine control.

Discussion

The present study demonstrates that allergen solutions positioned next to the histamine control will result in a positive intradermal test even at a distance of at least 4 cm. As this effect fails to appear both in intradermal testing with wasp venom only and in skin prick testing with bee and wasp venom, a new site distance for intradermal testing would be advisable.

It was assumed (6) that the mechanism of this phenomenon can be seen in "sensitization" of skin by histamine. Another explanation might be that the

histamine control leads to activation of unmyelinated C-fibres resulting in liberation of neuropeptides – substance P, vasoactive intestinal peptide (VIP) and somatostatin. As these nerve endings are topographically associated with the skin mast cells (2) an additional stimulus, such as observed during skin testing, may result in non-immunologic mast cell activation.

Based on these results intradermal testing should be done with as great a distance as possible between histamine control and the various allergens. For skin prick testing a distance of at least 4 cm is acceptable, but for intradermal testing this should be greater in order to exclude false positive results. The histamine control could also be done on the contralateral forearm if only one arm is needed for skin testing, or it could be applied on the upper arm.

It is possible that the critical distance is not related only to the influence of the histamine control on adjacent allergen solutions but also to an interrelationship between two allergens.

In conclusion we have shown that skin prick testing should be done with a distance of at least 4 cm between histamine and allergen solutions when histamine is used in a concentration of 1 mg/ml, in order to avoid false positive skin test results. For intradermal testing the distance should be greater, as with 4–5 cm false positive skin reactions were observed in 9%. We thus recommend applying the histamine control on the upper arm and a distance of at least 6 cm between each intradermally applied allergen solution.

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Table 1. Patients showing positive wheal and flare reaction only for allergen concentration 0.01 µg (next to the histamine control)

	Bee* n=122		Wasp n=122	
	n	(%)	n	(%)
Prick	0		0	
Intradermal	11	(9)	0	

* Histamine control (1 mg/ml) always on forearm used for testing of bee venom.

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