

BRIEF COMMUNICATION

Simultaneous intradermal testing with hymenoptera venoms is safe and more efficient than sequential testing

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Abstract

Background: According to current guidelines, skin testing for hymenoptera venom allergy should be performed in a stepwise manner, maintaining 15- to 20-min intervals between the injections of venom. Given the long-winded procedure of sequential skin testing, we retrospectively explored the safety of simultaneous intradermal testing.

Methods: Four hundred and seventy-eight consecutive patients with a convincing history of an anaphylactic reaction after a hymenoptera sting were tested. All venom concentrations (0.02 ml of 0.001, 0.01, 0.1, and 1.0 µg/ml of honey bee and wasp venom) were administered simultaneously to the skin.

Results: Four hundred and seventy-two (98.7%) patients tolerated the simultaneous intradermal test without any side-effects. Only three subjects (0.6%) had a presumed allergic reaction during the test; another three reactions were considered vasovagal.

Conclusion: Our skin test protocol with four simultaneously injected concentrations of two hymenoptera venoms is safe and permits the investigator to draw rapid conclusions about the individual's sensitization pattern.

According to current guidelines, skin testing with hymenoptera venom should be performed in a stepwise manner, maintaining 15- to 20-min intervals between the injections of venom (1, 2). This recommended approach is based on the results of early studies (3, 4) and has remained undisputed for decades. The procedure of sequential skin testing is laborious and time-consuming for patients as well as medical staff (5). Other tests such as the determination of sIgE and the basophil activation test are also reliable (6, 7), but skin testing has the advantages of being cost effective, providing rapid results, and being a reliable and safe *in vivo* test. A partly simultaneous skin test was mentioned by Mueller in 1990. However, no detailed data concerning safety were provided (8). Another fast skin test protocol was described in 1996 (5), but the procedure left much to be desired by the way of efficiency. We established simultaneous intradermal testing with bee as well as vespid venom at our department in 2005. Here, we report our experience with the rapid skin test protocol for the diagnosis of hymenoptera venom allergy in a retrospective study.

We tested 478 consecutive patients (239 men and 239 women) between 2005 and 2011. The patients' mean age at the time of testing was 41.2 (±16.3) years. All subjects had a

convincing history of an anaphylactic reaction after a hymenoptera sting. According to Ring and Messmer's modified classification, generalized skin symptoms such as flush, urticaria, and angioedema were classified as grade I reaction; mild to moderate pulmonary, cardiovascular or gastrointestinal symptoms as grade II reaction; bronchoconstriction, emesis, anaphylactic shock, and loss of consciousness as grade III reaction; and cardiac arrest and/or apnea as grade IV reaction.

Intradermal tests (IDT) were performed using purified venom extracts (ALK-Abelló, Horsholm, Denmark). IDTs were considered to be positive in the presence of a wheal diameter ≥ 5 mm and erythema. All venom concentrations (0.02 ml of 0.001, 0.01, 0.1, and 1.0 µg/ml of honey bee and vespid venom) as well as negative and positive controls were administered simultaneously in the skin.

Thirty patients (6.3%) had a history of grade I reactions, 283 (59.2%) grade II reactions, 158 (33.1%) grade III reactions, and 7 (1.5%) grade IV reactions. On the intradermal test, 69 were positive for bee venom, 180 for vespid venom, 178 were double positive and 51 double negative for bee and vespid venom. Of 247 bee venom-sensitized patients, 227 (91.9%) only reacted to high venom

Table 1 Comparison of skin testing methods

	Standard method (10) 1989	Modified method (5) 1996	Proposed method
Prick test	Controls and one venom concentration	Controls and one venom concentration	Not done
Intradermal test	Controls and up to 4 venom concentrations	Controls and 2 venom concentrations	Controls and 4 venom concentrations
Administration	Sequentially; 20 min per concentration	Partly simultaneously; 20-min prick test, 20-min intradermal tests	Simultaneously
Volume per concentration	0.05 ml	0.03 ml	0.02 ml
Patients	3236	446	478
Total adverse reactions <i>n</i> (%)	64 (2.0)	9 (2.0)	6 (1.3)
Presumed allergic reactions <i>n</i> (%)	45 (1.4)	5 (1.1)	3 (0.6)
Total time (min)	100	40	20

The three test methods did not differ in terms of total adverse reactions ($P = 0.548$) and presumed allergic reactions ($P = 0.348$).

concentrations of 0.1 and/or 1.0 $\mu\text{g/ml}$, while 110 (44.5%) tested positive only at 1.0 $\mu\text{g/ml}$. The 358 vespid venom-sensitized patients differed slightly: 306 (85.5%) had positive reactions at 0.1 and/or 1.0 $\mu\text{g/ml}$, and 114 (31.8%) tested positive only at 1.0 $\mu\text{g/ml}$. 472 (98.7%) patients tolerated the simultaneous intradermal test without any side-effects. Six (1.3%) subjects had a systemic reaction during simultaneous intradermal testing. Three of these six reactions were vasovagal: two patients had obvious panic reactions after routine insertion of the intravenous catheter before testing while one patient collapsed after injection of the first venom concentration. Importantly, all subsequent tests for bee and vespid venom were negative in these three patients. The remaining three (0.6%) patients might have had allergic reactions: one 72-year-old woman experienced mild dizziness during testing. The skin test was negative for bee venom, but positive at 0.1 and 1 $\mu\text{g/ml}$ for vespid venom. One man suffered from dyspnea, heat sensation, and dizziness during injection of the venom concentrations. He tested positive for bee and vespid venom at 1 $\mu\text{g/ml}$. Neither patient required emergency treatment. Only one putative anaphylactic reaction was observed among 478 simultaneous intradermal tests: a 29-year-old woman experienced erythema at the site of the skin test, nausea and shivering but neither tachycardia nor hypotension. After intravenous administration of antihistamines and glucocorticoids she recovered fully. The skin test was positive at the 1 $\mu\text{g/ml}$ concentration of vespid venom and negative for bee venom. Therefore, also in a stepwise manner, the maximum concentration of bee and vespid venom would have been administered in this patient. In accordance with current guidelines, which recommend a stepwise approach, the maximum concentration of vespid venom would not have been injected in one patient, who might have benefited from a stepwise intradermal test.

This rapid skin testing protocol is practical as well as efficient in terms of time and costs. However, the most important issue is the patient's safety. Theoretically, it should make no difference if all venom concentrations were to be

injected simultaneously in the skin: simultaneous testing involves injection of 0.02 ml of each concentration (0.001, 0.01, 0.1, and 1.0 $\mu\text{g/ml}$) of the respective venom. If the test is performed with bee and vespid venom, a total quantity of 0.02222 μg per venom is administered, which is 1/2655 of the delivery from natural bee stings and 1/765 of that from wasp stings (9). Furthermore, the large majority of patients tested positive only at higher venom concentrations of 0.1 or 1.0 $\mu\text{g/ml}$; up to 44.5% tested positive only at 1.0 $\mu\text{g/ml}$. Thus, nearly one-half of patients must be tested with the highest concentration anyway. It appears quite implausible that patients have side-effects to 0.02222 μg venom, but not to 0.02 μg administered in a stepwise manner. This hypothesis is supported by our data, which indicate an even lower frequency of side-effects compared with those observed using published methods (Table 1). The small quantity of 0.02 ml per venom concentration, and further reduction to three instead of four test concentrations (0.01–1.0 $\mu\text{g/ml}$), would permit testing of additional wasp venoms such as *Polistes* venom if necessary.

To summarize, the rapid skin test protocol with four simultaneously injected concentrations of two hymenoptera venoms is safe and provides a quick overview of the individual's sensitization pattern. The benefits are obvious: the approach requires a half of the testing time taken by the modified method and just 1/5th of time taken by the standard method. Therefore, at least twice as many patients could be tested. The saving in time obviously reduces the cost of performing the skin test as well. Refraining from the use of prick test solutions and injecting minimal quantities of venom also reduce costs without increasing the risk of side-effects.

The dogma of sequential hymenoptera venom skin testing has remained undisputed for decades, although it is not based on hard facts. This study is not intended to alter current guidelines, but to serve as a basis for further discussion and possibly encourage a multicenter study under the auspices of the Interest Group on Insect Venom Hypersensitivity of the EAACI.

Author contributions

BS wrote the manuscript, WA revised the manuscript, DB and PK collected data, GJS designed the study and revised the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

All authors have no conflicts of interest to declare.

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