

Insect sting–inflicted systemic reactions: Attitudes of patients with insect venom allergy regarding after-sting behavior and proper administration of epinephrine

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Background: Patients with insect venom allergy are at higher risk for development of a recurrent systemic reaction after re-sting. This risk significantly decreases with venom immunotherapy. Patients with insect venom allergy should be able to distinguish a life-threatening systemic reaction from all other various reactions after an insect sting. Accidental epinephrine injection by EpiPen has been reported in the past. Therefore patients with venom allergy should also be well trained in self-administration of their epinephrine when needed.

Objective: Our objective was to assess patients' attitudes regarding after-sting behavior and their capability to correctly self-administer the epinephrine autoinjector.

Methods: All patients with venom allergy attending our allergy unit either before commencement of or during venom immunotherapy answered a questionnaire addressing various aspects of their intended after-sting behavior. Using an EpiPen trainer device, patients' performance of EpiPen self-administration was evaluated.

Results: Ninety-six patients participated in the study. Seventy-six of them were equipped with an EpiPen device. Less than 30% of these patients carried it at all times. After re-sting, 50 (54%) patients planned to wait for the development of other symptoms before taking any further action. Twenty-two percent of the patients said that after re-sting they would immediately administer their EpiPen. Proper EpiPen administration technique was demonstrated by 44% of the patients. Having not reached the maintenance dose correlated with a better compliance with carrying of the EpiPen. EpiPen instruction provided by an allergist correlated with a better EpiPen administration technique by the patients.

Conclusion: Many patients with venom allergy hold wrong ideas about after-sting behavior. Compliance with carrying EpiPen at all times and the ability to correctly administer it are both poor in most patients. Thorough and probably repeated instruction, both written and oral, provided by knowledgeable physicians is mandatory. (*J Allergy Clin Immunol* 2000;106:1184-9.)

Key words: *Insect allergy, epinephrine, after-sting behavior*

Abbreviations used

MD: Maintenance dose
PIT: Proper injection technique
SR: Systemic reaction
VIT: Venom immunotherapy

A recurrent systemic allergic reaction is expected to occur in about 60% of the patients who have experienced a previous systemic reaction (SR).¹ Venom immunotherapy (VIT), which is the treatment of choice for such cases, has been shown to significantly decrease the risk for recurrent SR. Although VIT provides almost full protection against future stings, the frequency of recurrent SR with VIT varies between 1% and 10% and may be even greater in patients who have not yet reached the maintenance dose (MD).^{2,3} Because epinephrine is the most important single agent in treating anaphylaxis, every patient who has experienced SR inflicted by an insect sting is usually provided with a prescription for a self-administered epinephrine device.^{4,5} With VIT, most of the recurrent insect stings will not result in a recurrent SR. Therefore the patient should be able to diagnose the development of an emergency situation deserving epinephrine administration. He or she should also know how to properly administer the autoinjector when needed. Patients' after-sting behavior, including the proper administration of an epinephrine autoinjector, has never been studied. We therefore prepared to study the attitudes of patients with insect venom allergy regarding their intended response to a future sting, as well as their ability to properly administer the epinephrine autoinjector.

METHODS

All patients regularly receiving VIT and all patients first evaluated in the allergy unit after having been referred for allergic evaluation because of SR caused by an insect sting were asked to participate in the study. Ninety-six patients were enrolled. Twenty-two (23%) patients took part in the study on their initial evaluation at the allergy unit before the commencement of VIT. Eleven more patients were at the beginning stage of VIT but had not yet reached the MD of 100 µg. The patients answered a questionnaire composed of questions addressing the patients' attitudes regarding their expected behavior after a future insect sting. Children 12 years old or younger were assisted by a parent in answering the questionnaire, and the answers represent their parents' attitudes. After having

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answered the questionnaire, patients were asked to demonstrate epinephrine administration by using a placebo EpiPen injector. (EpiPen is the only self-administered epinephrine device available in Israel.) Proper injection technique (PIT), according to the manufacturer's recommendations, is composed of several steps: (1) pulling out the gray safety tip; (2) holding the device in the palm; (3) placing the black tip on the outer thigh; (4) pushing in hard until the trainer function is heard; and (5) holding it in place for 10 seconds. Ranking of the patients' performance was carried out on a scale of 1 to 4 as follows: (1) not pulling out the safety tip or placing the safety tip on the thigh; (2) performing steps 1 to 3 correctly and then either waiting for the injector to be spontaneously activated or useless manipulation of one or both tips of the injector; (3) correctly performing steps 1 to 4 but not holding the injector in place for 10 seconds; and (4) correctly performing steps 1 to 5. Performance was assessed by one of the authors. Ranking was compared between the 2 authors, and discrepancies were reconciled until reaching minimal interobserver variability. Data are presented by frequencies and percentages. Differences between participants' work type and education, for example, were compared by using χ^2 analysis, and differences were considered statistically significant at *P* values of less than .05.

RESULTS

Patients

Ninety-six patients (74 male and 22 female patients) regularly attending our allergy unit were asked to participate in the study, and none of them refused. Their mean age was 29.8 years (range, 3-74 years). Severity grading of the SRs (Mueller's criteria)⁶ resulted in the following: 11 patients, grade 1; 62 patients, grade 2; 15 patients, grade 3; and 8 patients, grade 4.

Patient medication

Although all patients were evaluated after having experienced an SR, there were still 7 (7%) patients who stated that they had never been prescribed the EpiPen. The severity of their SR was as follows: 4 patients, grade 2; 2 patients, grade 3; and one patient, grade 4. Nineteen (20%) patients had been prescribed oral antihistamines, but only 10 patients were actually carrying these medications with them. Seventy-six (79%) patients were equipped with the EpiPen. Of these, 45 (59%) patients had their EpiPen with them on the day the questionnaire was answered. Of the 45 patients who carried their EpiPen with them on that day, the syringe was expired for 5 (11%) patients, and a valid syringe was found for 40 (89%) patients. All 31 patients who did not have their EpiPen when filling out the questionnaire could not provide a reliable answer regarding the expiration date of their syringe. Less than 30% of the patients who were equipped with an EpiPen actually carried it wherever they went (Fig 1).

EpiPen instruction

Primary instruction for proper use of the EpiPen was given by various persons. An allergist belonging to our allergy unit in most cases instructed 46% of the patients, a nurse instructed 11.5% of the patients, a primary physician instructed 10.3% of the patients, a pharmacist

instructed 10.3% of the patients, and an emergency department physician instructed 1.1% of the patients. All medical professionals other than the allergists were not part of the allergy unit. Nine percent of the patients were instructed by a nonprofessional person (usually another person equipped with EpiPen). Eleven percent of the patients stated that they had not been given any instruction at all. Only 10.7% of the patients were given a second instruction regarding proper use of the EpiPen device.

The mean time interval that had elapsed since the last instruction was 2.6 years (range, 1 month-16 years). In 64% of the patients, the last instruction was given more than 6 months before answering the questionnaire. Other than frontal explanation or demonstration of the use of the autoinjector, only 18% of the patients had the opportunity for self-training with the placebo device.

Compliance with carrying the EpiPen

Carrying the EpiPen at all times was not more common among patients with higher education or among high-risk patients (ie, patients with a more severe initial SR or patients who had not started VIT or had not reached the MD) or patients with higher professional exposure to insect stings (field vs office work). It was not more common among either patients instructed by an allergist or by another medical professional or in patients who had received their last instruction for EpiPen administration in the previous 6 months. However, when the above-mentioned variables were compared with the prevalence of carrying the EpiPen at all times or carrying it at all times other than short excursions out of the home (data refer only to patients who were equipped with EpiPen), more patients who had not yet started VIT (19/19 [100%]) complied with these recommendations compared with both patients who had already reached the MD (28/48 [58%], *P* = .001) and patients who had started VIT but had not reached the MD (5/9 [56%], *P* = .002). Patients who had not yet started VIT complied better with carrying the EpiPen compared with all patients who had already started VIT (19/19 [100%] vs 33/57 [58%], *P* = .001; Fig 1).

An additional finding lacking statistical significance revealed that when a similar correlation was made regarding the duration elapsed since the last EpiPen instruction, patients who had been instructed more than 6 months before complied better with carrying the EpiPen than those who had been instructed less than 6 months before (15/17 [88%] vs 24/38 [63%], *P* = .06).

Intended after-sting behavior

Considering the fact that the majority of our patients were receiving VIT (77%), most of them at an MD (66%), the potential risk for severe anaphylaxis after resting in these patients was rather small. Nevertheless, only 50 (52%) patients said that after being re-stung they would wait for the development of clinical symptoms before taking any further action. The rest of the patients would rather administer the EpiPen immediately (22%), rush to the nearest emergency department (17%), take

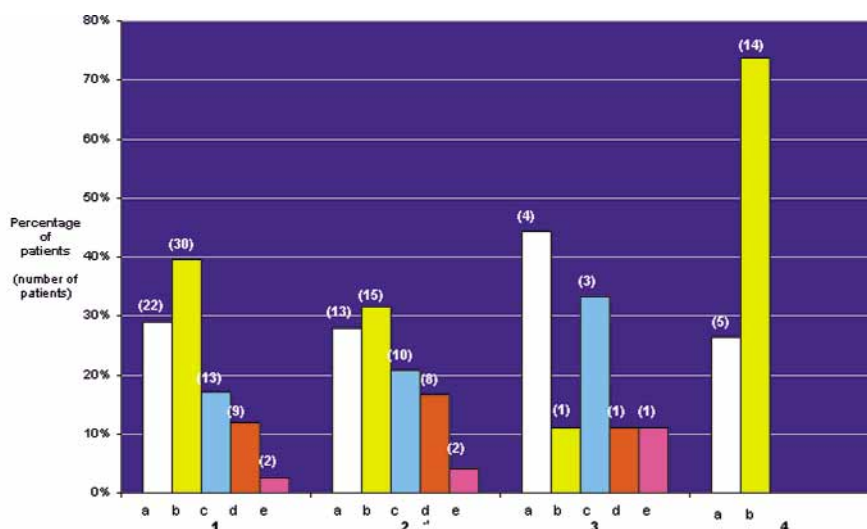


FIG 1. EpiPen carrying by different patient groups. Numbers relate to 76 patients actually equipped with EpiPen. *Group 1*, All patients; *group 2*, patients on MD immunotherapy; *group 3*, patients on immunotherapy before having reached the MD; *group 4*, patients who have not yet begun immunotherapy. **A**, Carrying EpiPen at all times; **B**, carrying EpiPen at all times other than short periods out of the home; **C**, carrying the EpiPen only for nature excursions; **D**, carrying the EpiPen only for extended stays in nature; **E**, carrying the EpiPen only for tours abroad.

antihistamines and wait (6%), or take antihistamines and administer the EpiPen immediately (1%). Responses of patients actually possessing an EpiPen were very similar (data not shown). Furthermore, the severity of the initial SR did not affect the patients' expected immediate behavior after re-sting (Fig 2). A "wait-and-see" behavior is considered the correct strategy after re-sting in patients with venom allergy. However, correct or incorrect expected behavior was not associated with higher education or with belonging to a high-risk group or with the specific type of medical professional who had instructed the patient in use of the EpiPen. Thus among patients instructed by allergists, 47% would wait and see, whereas 45% would immediately administer the EpiPen or rush to the nearest emergency department.

The patients who said that they would wait for the appearance of clinical symptoms after re-sting were also asked what kind of symptoms would make them administer the EpiPen. Thirteen percent said that a large local swelling would make them respond in such a manner, 7% cited a mild nondiffuse rash, 24% cited a severe diffuse rash, and 56% cited shortness of breath, weakness, or dizziness.

Patients were then asked whether they would actually be willing to self-administer the EpiPen. Twenty-three percent of the patients admitted that in such a situation they would probably not be brave enough to self-administer the autoinjector. This percentage was doubled in patients 12 years of age or younger. Half of the patients admitting that they would not be able to self-administer the EpiPen said they would rather rush to the nearest emergency department. The other half of the patients said that they would seek another person to administer the EpiPen. A family member who could hopefully adminis-

ter the EpiPen was available in 47% of all patients and in 91% of patients 12 years old or younger. Patients were also asked about their expected action after having used the EpiPen. Most patients (84%) said they would rush immediately to the nearest emergency department, whereas 16% would still wait for further clinical symptoms before seeking medical help.

Thirty-seven patients had been re-stung after the primary SR. Only 5 (13.5%) patients used their EpiPen. One patient administered his EpiPen injector immediately after being stung, whereas the other 4 patients waited for the development of systemic symptoms before administering the EpiPen. Self-administration of EpiPen was reported by 2 patients. Three other patients (ages 9, 40, and 46 years) required another person to administer the EpiPen.

Self EpiPen administration technique

Full and proper administration of the EpiPen (rank 4) could be demonstrated by 36.1% of the patients older than 12 years and by 41.7% of the parents of the patients 12 years old or younger (Fig 3). The manufacturer recommends that the EpiPen be held in place on the thigh for 10 seconds after its activation. On the basis of our previous clinical impression that the duration of time needed for complete injection of the whole content of the EpiPen was significantly shorter than 10 seconds, we decided to measure this time interval. We examined brand new, as well as almost expired, injectors from 5 different lots by pushing the EpiPen tip hard against a tight piece of material and measuring the time elapsed between activation of the syringe and termination of epinephrine injection. Ten autoinjectors were examined. The mean duration for injection of all of the epinephrine content was 0.6 seconds, with duration not longer than 1.0 seconds in any of

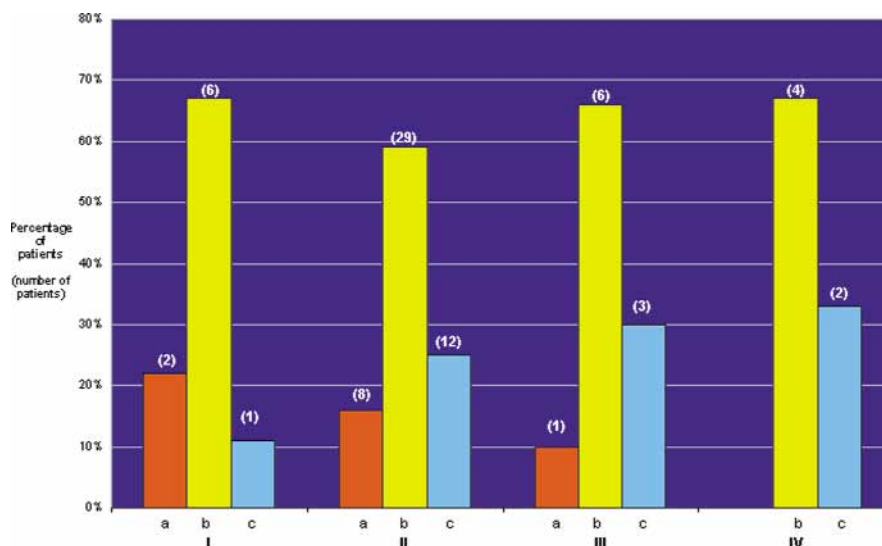


FIG 2. Patients' intended immediate behavior after re-stinging according to the severity of the initial SR (Mueller's criteria I-IV). **A**, Rush to nearest emergency department; **B**, wait for development of clinical symptoms; **C**, immediate administration of EpiPen.

the syringes. Therefore, considering the short duration actually needed for the epinephrine to be injected, we assumed that in assessing EpiPen administration technique, it might be appropriate to consider both ranks 3 and 4 as a clinically proper technique. Dividing the patients into those with proper (rank 3 and 4) and improper (rank 1 and 2) administration techniques revealed that an improper technique was demonstrated by 41.7% of the patients older than 12 years and by 50% of parents of the patients less than 12 years old. PIT was not more common among high-risk patients, patients with higher education, or patients who received their last EpiPen instruction during the past 6 months. PIT was more common among patients older than 18 years who were instructed by an allergist compared with all other instruction providers (13/23 [56%] vs 9/31 [29%], respectively; $P < .05$).

DISCUSSION

Anaphylaxis is a life-threatening event demanding emergency treatment. Patients with previous insect sting-induced SR are at increased risk for an anaphylactic reaction on being re-stung. Concomitantly, because of the natural history of insect allergy, according to which more than 40% of the patients spontaneously lose their sensitivity, and because of a success rate greater than 95% with VIT, the risk for recurrent anaphylaxis may be reduced significantly. Therefore these patients should be familiar with the symptoms of anaphylaxis, as well as being trained in its treatment on the one hand, but should not become panicky and overreactive about any insect sting on the other hand. The number of such panic reactions has resulted in an accidental digital injection of epinephrine from an autoinjector device.⁷

Neither the attitudes of patients with venom allergy regarding after-sting behavior nor their capability to use

their emergency self-treatment have been studied. A study partially addressing this issue showed that in patients with various causes of anaphylaxis who responded to a follow-up survey, 47% failed to carry epinephrine.⁸ A recently published study demonstrated medical professionals' significant lack of knowledge regarding the administration of an EpiPen injector.⁹ We preferred to study the unique population of patients with venom allergy and examined not only their EpiPen administration skills but rather their entire attitudes to after-sting behavior.

Almost half of our patients (46%) said that instead of waiting for the development of clinical symptoms after re-sting, they would rather take different action. In some of these patients, actions such as rushing to the nearest emergency department or taking oral antihistamines would not necessarily be associated with adverse reactions. However, in 23% of the patients planning to immediately administer their EpiPen syringe, such actions may well be associated with completely unnecessary adverse reactions. Even in patients who would rather wait for the development of clinical symptoms before using an EpiPen, 13% said that they would do so in the case of development of a large local reaction. On the other hand, 16% of the patients said that after administering the EpiPen, they would still wait for further symptoms to develop before seeking medical help. From the above data, it may be concluded that the rule of *primum non nocere*, which in this case refers to the patients taking care of themselves, was not properly implemented in a significant number of the patients.

In addition to the lack of knowledge regarding when to use the EpiPen, about one fifth of the patients said that even in a situation regarded by them as deserving epinephrine administration, they would still not be able to do so. Instead, they would rather rush to the nearest emergency department or ask another person to administer the EpiPen.

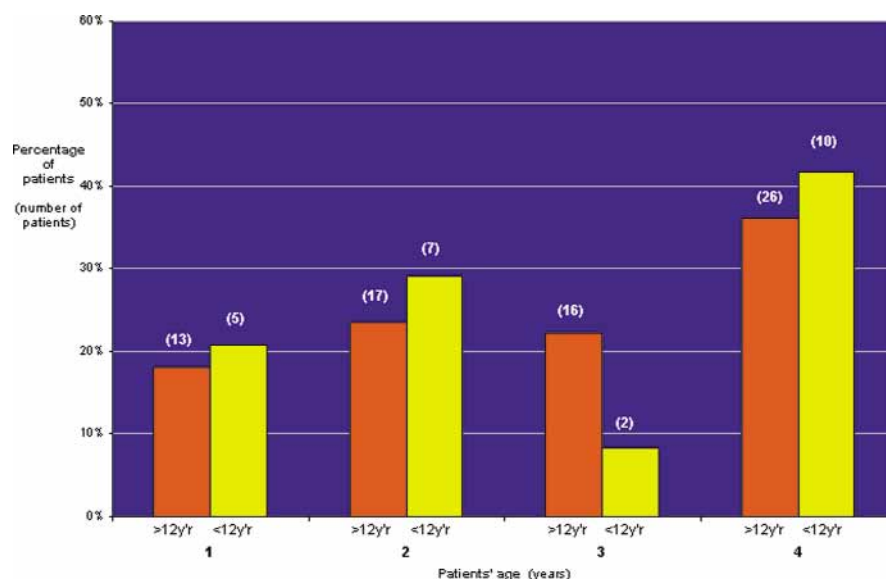


FIG 3. Technique of EpiPen self-administration, as demonstrated by a placebo device. 1, Not pulling out the safety tip or placing the safety tip side of the injector on the thigh; 2, waiting for the injector to be spontaneously activated or not pushing it hard enough after having placed it correctly on the thigh and pulling out the safety tip; 3, holding the injector on the thigh after its activation for less than 10 seconds; 4, performing all steps correctly.

One may argue that all the above data relate only to patients' intentions. However, when asked about steps taken by patients who had actually administered epinephrine after having been re-stung, the results of their real action correlated with that of the intended one. Thus one of the 5 patients who used their EpiPen injector did it immediately after the sting, without waiting for any clinical symptom to develop. Three patients, only one of them below the age of 12 years, were not able to self-administer their EpiPen and required someone else to do so for them.

Checking the availability of the EpiPen, we found that one third of the patients who were not equipped with an EpiPen denied having been prescribed such a device. Our results thus correlate with those of a previous study.¹⁰ Finding an expired EpiPen autoinjector was not uncommon among our patients. However, this may not be very problematic because both epinephrine content and bioavailability in outdated EpiPen devices were found to be satisfactory to a certain degree.¹¹

Carrying the EpiPen at all times, as recommended by the American Academy of Allergy, Asthma and Immunology Board of Directors,³ was implemented by the minority of the patients. Only less strict recommendations, such as carrying the EpiPen at all times or carrying it at all times other than short excursions out of the home, were significantly more common in patients who had not reached the MD. Although the instruction for EpiPen administration was provided to 20% of the patients by a nonmedical professional, a better compliance with carrying the EpiPen was not associated with the profession of the instruction provider. This poor compliance might be related either to the low quality of ini-

tial instruction or to the lack of repeated periodic instructions. The fact that compliance with carrying the EpiPen was not higher in patients instructed within the past 6 months before answering the questionnaire suggests that the quality of the instruction is mostly responsible for the poor compliance.

By demonstrating that less than 1 second was enough for injecting all of the EpiPen epinephrine content, we could consider the technique proper if only steps 1 to 4 were carried out correctly, leaving out step 5, as opposed to Grouhi et al.⁹ Defining PIT this way revealed that 40% to 50% of the patients used an improper technique. By using this technique in real time, under the expected emotional stress after having been re-stung would have probably resulted in complete failure to administer epinephrine, in a significant delay in its administration, or as already pointed out,⁷ in accidental injections of epinephrine into different body sites other than the thigh, where its beneficial effect might be overruled by untoward adverse reactions.

When constructing the study design, we anticipated several variables that might favor a correct after-sting behavior, a better compliance with EpiPen carrying, and a better EpiPen administration technique. These parameters included higher education; EpiPen instruction provided not long (<6 months) before evaluating its administration technique; instruction provided by an allergist or by another medical professional; patients with increased risk for a recurrent SR upon re-sting, like those who had not reached the MD; patients with a greater professional exposure to insect stings; and patients with a more severe initial SR, in whom this experience might be more frightening and, as a result, more strenuous.

To our surprise, only patients who had not reached the MD complied better with carrying of the EpiPen, and only EpiPen instruction provided by an allergist had any effect on PIT. The absence of any effect by all other variables on PIT seems to be strictly related to the physicians in their function as being responsible for proper patient education. Patient failure to properly administer the EpiPen might result from a combination of several factors: lack of elementary knowledge by the instructing physician⁹; poor and negligible instruction provided by a knowledgeable physician; and lack of continuous repetitive periodic instructions.

Our study sheds light, for the first time, on the intended behavior of patients with venom allergy. It especially addresses the questions of when and how to use the EpiPen autoinjector. Our study demonstrates the high prevalence of lack of patient understanding regarding after-sting behavior and of poor EpiPen administration technique executed by many patients. It suggests that spending more time with the patient and providing detailed written instruction about after-sting behavior, together with having the patient experience the EpiPen trainer device and frequent repetitions of this instruction, may increase the benefit and decrease the hazard of the EpiPen autoinjector.

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