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Allergic reactions to North African scorpion venom evaluated by skin test and specific IgE

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In Algeria, hundreds of deaths per year are caused by scorpion stings (Benguedda, oral communication, 1995), mainly because of the presence in the venom of a variety of toxic proteins,^{1,2} which are immunogenic in animal models.³ Acute allergic reactions caused by scorpion venom have been reported recently in Texas⁴ but have never been documented for the North African *Androctonus australis Hector* (AaH) (Buthidae family) scorpion venom. The aim of this study was to determine whether an IgE-mediated mechanism could be responsible for the clinical symptoms in subjects stung by AaH.

Abbreviations used

AaH: *Androctonus australis Hector*
RU: RAST units
SPT: skin prick test

METHODS

Thirty-nine Algerians (37 male and 2 female subjects aged 5 to 63 years), living in the Sahara area of El Oued, were studied 3 to 24 months after the last sting: 16 had been stung only once, 14 had been stung between two and five times, and nine had been stung more than eight times. During the last sting, 32 patients had only a local reaction, and seven had a local reaction plus mild or severe systemic symptoms. According to the classification of Goyffon et al.,¹ the clinical effects of scorpion stings are classified in four stages of increasing severity: stage I, local burning pain with or without edema; stage II, stage I plus general symptoms (sweating, shivering, nausea, tachycardia); stage III, stage II plus hyperthermia, cardiovascular disturbances, and disturbances of consciousness; stage IV, neurotoxic stage leading to cardiovascular collapse. The local reactions observed were of the immediate type, and no delayed

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TABLE I. Clinical data, SPT responses, and RAST results in 10 subjects allergic to scorpion venom

Subject	Age (yr)	Sex	Months since last sting	Clinical stage*	Wheal diameter (mm)			RAST (class)†
					0.01	0.1	1 mg/ml†	
TS	10	M	24	I	0	0	4	1
MS	21	M	12	I	0	0	5	1
AN	7	M	13	I	0	4	7	2
BA	14	M	11	I	0	0	5	1
BB	35	M	24	II	0	0	4	1
NM	61	M	3	I	0	0	5	2
DS	15	M	4	I	0	5	8	2
CA	24	M	5	I	0	4	7	1
TS	63	M	3	I	0	0	5	3
RM	43	F	2	I	0	5	7	3

*Level of clinical reactions after the last scorpion sting: stage I = local burning pain with or without edema; stage II = local + mild systemic reaction (sweating, shivering, nausea, tachycardia).

†Scorpion venom extract concentrations (mg/ml protein).

‡RAST values. A class ≥ 2 was considered positive.

local reactions were reported. Twenty healthy adults, who had never been stung by a scorpion, were included as negative control subjects. All subjects gave their consent to participate in this study. Skin prick tests (SPTs) were performed in duplicate by using Stallerpoint needles (Stallergenes, Fresnes, France) with AaH scorpion venom extract at three concentrations (0.01, 0.1, and 1 mg protein/ml). Histamine (1 mg/ml) and glycerosaline solution were used as positive and negative controls, respectively. The size of the wheal-and-flare reactions was measured after 15 minutes. A skin test response was considered positive when the mean diameter of the wheal (largest diameter + orthogonal diameter $\div$ 2) was 4 mm greater than that of the negative control.

Venom of AaH scorpions was collected by electric stimulation and freeze-dried (Institut Pasteur d'Algerie). A venom protein extract (12.6 mg/ml) in Coca's solution was prepared and sterilized by filtration through a 0.22 μ m Millipore filter. For SPTs, the extract was concentrated to half volume and mixed with phenolated glycerine.

Patients' sera were tested for specific IgE antibodies by RAST as previously reported.⁵ RAST disks were prepared by coupling CNBr-activated cellulose disks with 10 μ g of the venom protein extract per disk.

RESULTS AND DISCUSSION

All assays for IgE antibodies were quantitated on the basis of a calibration curve with five dilutions (from 0.35 to 52.5 RAST units [RU]) of serum IgE standard.⁵ Results were expressed as RAST class: class 0, less than 0.35 RU; class 1, 0.35 to 0.7 RU; class 2, 0.7 to 3.5 RU; class 3, 3.5 to 17.5 RU; and class 4, greater than 17.5 RU. Only 10 of 39 patients who were skin tested had a positive wheal-and-flare response (Table I). Among these patients, four had a significant response to the 0.1 mg/ml concentration and a larger reaction to 1 mg/ml. Three of them (DS, CA, and RM) had been stung between 2 and 5 months before the SPT, and one (AN) had been stung 1 year before. No late cutaneous reactions were observed in patients with a positive SPT response. All of the patients had had a local reaction (stage I) after the last sting, and only one (BB) had experienced systemic symptoms (stage II). Only slight

erythema was observed in two control subjects, one of whom was atopic. There were no local or systemic symptoms of envenomation as a result of the ST. The presence of IgE at significant levels (RAST classes 2 and 3) against AaH venom was found in five of 10 patients with positive SPT responses (Table I). A good concordance between SPT and RAST results was observed in the five patients with positive RAST results, except for patient CA who had significantly positive SPT results and RAST class 1. Among the 29 patients with negative SPT responses, 15 had RAST class 1, which was not considered to be significant. However, we did not observe a good correlation between SPT results and specific IgE or between the severity of clinical symptoms and the specific IgE levels. Although the same extract was used, differences in potency between the extract used for SPTs and those used for in vitro tests may account for these discrepancies.

The results of this study demonstrate that IgE-mediated hypersensitivity to AaH scorpion venom can occur in some patients. This was confirmed by positive specific IgE and positive SPT responses to scorpion venom extract, producing immediate wheal-and-flare reactions in some venom-exposed patients but not in control subjects. Demain et al.⁴ reported positive venom SPT responses in patients stung by *Centruroides vittatus* scorpion without performing the serologic determination of specific IgE. Demain et al.⁴ observed delayed reactions after intradermal tests, which were not observed in our study. The IgE-mediated response to scorpion venom might be more frequent than suspected, because in many cases the clinical picture—with edema, nausea, cardiovascular reaction with hypotension and shock—could be due to either a toxic or an immunologic mechanism. Some cases of fatal scorpion envenomation may be due to anaphylaxis. The characterization of the allergenic venom proteins involved in these allergic reactions is under investigation.

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A comparison of drug delivery from a metered-dose inhaler plus an inspiratory flow control device with a metered-dose inhaler plus a spacer device

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Metered-dose inhalers (MDIs) deliver medication directly to the airways and thus reduce systemic effects without compromising the desired response. Problems with patient compliance exist, and there is concern about whether a therapeutic dose reaches the airways.¹ Slower inspiratory flow rates (400 to 500 ml/sec) for delivering aerosol medication may be better than rapid (1300 ml/sec) flow rates.² A device that controls inspiratory flow rate at 500 or 700 ml/min has been introduced. This study evaluates pulmonary albuterol delivery by this device and compares it with a standard spacer device that is known to enhance MDI efficacy.³

METHODS

Five volunteers without lung disease used both devices. They were trained to use an MDI with an inspiratory flow control device (IFCD), which can be set to maintain inspiratory flow at about 500 or 700 ml/min (MistAssist; Ballard Medical Products, Draper, Utah) and with a commonly used spacer device (Aero-chamber; Monaghan Medical Corp., Plattsburgh, N.Y.). On different days, 30 minutes after drinking 500 ml of water, subjects used either the IFCD or the spacer device with an albuterol MDI and inspired four inhalations of 100 µg of albuterol. After a normal expiratory maneuver to approximately the functional residual capacity level, the mouthpiece of the IFCD or the spacer device was placed between the lips. With the spacer device the MDI was actuated, and the subject inspired the mist in the

Abbreviations used

IFCD: Inspiratory flow control device
MDI: Metered-dose inhaler

chamber until total lung capacity was reached. With the IFCD the subject set inspiratory flow at 700 ml/min and inhaled. When the indicator ball reached the top of the device, the MDI was actuated while the subject continued to inspire until total lung capacity was reached. The end of the mouthpiece of the IFCD is 9 cm from the point of delivery of the MDI. Subjects held their breath at total lung capacity for 10 seconds with both devices and then exhaled slowly. This was repeated for all inhalations with each device. Inhalations were performed at 30-second intervals. Instructions provided with the two devices were followed. Thirty minutes later, urine was collected; the volume was measured and then frozen and stored at -20° C.

Unmetabolized urine albuterol was measured by high-pressure liquid chromatography with the method of Hindle and Chrystyn.⁴ This was performed by National Medical Services, Inc. (Willow Grove, Pa.). This is representative of pulmonary albuterol delivery.^{4,5} A previous study has shown that there is very little absorption of albuterol in the oral cavity.⁶ Comparisons were made by using a paired *t* test.

RESULTS

There were five participants, all healthy lifelong non-smokers: four male subjects ages 13, 15, 45, and 46 years and one 43-year-old woman. Table I presents the results. In each participant the IFCD set at 700 ml/min resulted in more unmetabolized urinary albuterol (*p* = 0.011). The increases with the IFCD when compared with the spacer device ranged from 6.26% to 63.55% more urinary albuterol in these five participants.

DISCUSSION

This study demonstrates that an IFCD set at 700 ml/min during albuterol delivery from an MDI increases

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Mr. Dwork, the developer of MistAssist, has transferred all rights to Ballard Medical Products, Draper, Utah 84020 and thus, still has a financial interest in the product. Neither Dr. Kanner nor Dr. Kanter has any financial interest whatsoever in MistAssist.

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