

The incidence and nature of adverse reactions to injection immunotherapy in bee and wasp venom allergy

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Summary

The incidence, time course and nature of systemic reactions to injections of bee and wasp venom during immunotherapy have been estimated in an open, prospective, single centre study. One hundred and nine survivors of moderate to severe systemic reactions to stings from hymenoptera, received courses of bee or wasp venom by monthly subcutaneous injection for up to 3 years. Systemic reactions were recorded after 7.5% of 946 weekly venom injections during the initial phase of treatment, and after 2.1% of 1789 monthly maintenance injections. In both phases of treatment, reactions were more frequent after bee (17% of initial phase, 7.8% of maintenance treatment) than after wasp (3% of initial phase, 0.3% of maintenance treatment) venom injections. The percentage of patients experiencing at least one reaction was also higher for bee (46%) than for wasp (14%) sensitive patients. Over 80% of reactions began within 30 min of injection, over 90% within 1 h and only two (2%), between 1 and 2 h, the remaining six (5.5%) starting more than 2 h after injection. Only 0.47% of venom injections produced a systemic reaction which was severe enough to require adrenaline treatment. The female patients experienced more reactions (21% of the wasp, 60% of the bee, sensitive) than the males (5.5% wasp, 20% bee). Age and atopy did not appear to be significant risk factors for systemic reactions. We conclude that wasp and bee venom immunotherapy in a conventional dosage regimen was generally well tolerated. No safety advantage was apparent in keeping the patients under observation for more than 1 h after injections. Reactions are more likely to occur during the initial phase of treatment, in women and after bee, rather than wasp, venom injections.

Clinical and Experimental Allergy, Vol. 25, pp. 159–165. Submitted 24 June 1994; revised 25 July 1994; accepted 24 August 1994.

Introduction

The earliest report of immunotherapy for bee sting anaphylaxis was by Braun in 1925, who used an extract of the parts of the bodies of bees containing the venom sacs [1]. Many thousands of people were subsequently treated with extracts of whole bodies of insects. However, past claims about the effectiveness of treatment with whole body extracts for venom allergy did not consider the natural history of the disease. Forty per cent of patients who gave a history of anaphylaxis and

had a positive skin test to venom, did not react to a subsequent sting. It is now known that whole body extracts of bees and wasps are not significantly better than placebo for the treatment of venom allergy [2]. In 1978, it was demonstrated [2] that venom therapy could protect patients when whole body extracts of bees had failed. Venom immunotherapy has been established in placebo-controlled studies to be capable of preventing an anaphylactic reaction to subsequent stings, the evidence being more clear and unequivocal than for any other form of immunotherapy used in allergic disease.

Specific allergen injection immunotherapy has been used to treat allergic disorders ever since the beginning of this century, after Noon demonstrated the efficacy of treating hay fever with pollen extracts [3]. Between 1950

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and 1986, allergen injections were used widely in Britain, especially for treatment of seasonal allergic rhinitis. In 1986, the Committee on the Safety of Medicines (CSM) issued a report [4] on fatalities and adverse reactions associated with immunotherapy, which appeared to be increasing in frequency and especially dangerous in patients with bronchial asthma. The CSM acknowledged that immunotherapy in venom hypersensitivity was efficacious, but placed restrictions on the practice of all types of injection immunotherapy and suggested that treatment should only be performed where facilities for full cardiorespiratory resuscitation are immediately available. The CSM also advised that patients should be kept under medical observation for at least 2 h after treatment, rather than 30 min which had previously been thought adequate.

The result of the CSM report was to centralize the treatment of venom allergy to specialist units. This has allowed a detailed prospective analysis at Guy's Hospital of the nature and incidence of systemic adverse reactions to immunotherapy in bee and wasp venom allergy.

Method

Between November 1986 and October 1992, 109 patients (83 sensitive to wasp venom and 26 sensitive to bee venom) seen at the Guy's Hospital Allergy Clinic, who fulfilled our criteria for venom immunotherapy (a history of generalized reaction of greater severity than urticaria or flushing alone, i.e. Mueller grade III or IV [5], with a positive skin-prick test and/or evidence of venom-specific IgE) received their treatment at the hospital, in a weekly clinic. The regimen used was the standard one recommended by the makers of the standardized venom vaccines (Pharmalgen, ALK, Horsholm, Denmark) namely an initial course of weekly injections,

using doses of 1, 3, 5, 10, 20, 40, 70 and 100 µg subcutaneously, followed by 2 or 3 years (depending on response) of monthly maintenance injections with 100 µg of bee or wasp venom, or the maximum tolerated dose if less. Patients were kept under observation in the ward for 2 h after each injection, in line with the recommendations of the CSM in 1986.

Patients were informed that if any symptoms occurred during this period, they should immediately inform one of the medical or nursing staff in the clinic. A clinical evaluation would then take place, including recording of pulse rate, blood pressure and peak expiratory flow rate (PEFR), and appropriate treatment would be given. All the patients were given notebooks in which the physician recorded the site, time and dose of venom injected, and in which the patients themselves recorded any local or systemic symptoms or signs occurring either during the 2-h observation period in the ward or after leaving the ward. At the time of the next weekly or monthly injection, the books were inspected before the injection was given and the patients were questioned to elucidate any points which were not clear from the written record. On the cover of the books, guidelines were printed to help patients record the relevant data, with reminders to detail the timing of onset and resolution, the nature and severity of the adverse events and whether any treatment was required. The subsequent dose of venom was modified if appropriate. The data collected by these methods from November 1986 to October 1992 have been analysed and statistical significance was assessed by the chi-squared test (χ^2) with Yate's Correction.

Results

Incidence and timing of adverse reactions

Over the 6 years of the study, 109 patients (83 sensitive to

Table 1. The numbers and timing of development of systemic reactions in the induction (I) and maintenance (M) phase of the immunotherapy to wasp and bee venom. The data was collected from the Guy's Immunotherapy Clinic from November 1986 to October 1992 on 83 patients receiving wasp venom and 26 patients receiving bee venom immunotherapy. One reaction may consist of several symptoms

	Wasp			Bee		
	I	M	Total	I	M	Total
Number of injections	658	1365	2023	288	424	712
Systemic reactions 30 min	14	3	17	40	31	71
Systemic reactions 30 min–1 h	3	1	4	7	1	8
Systemic reactions 1–2 h	1	0	1	1	0	1
System reactions >2 h	3	3	3	2	1	3

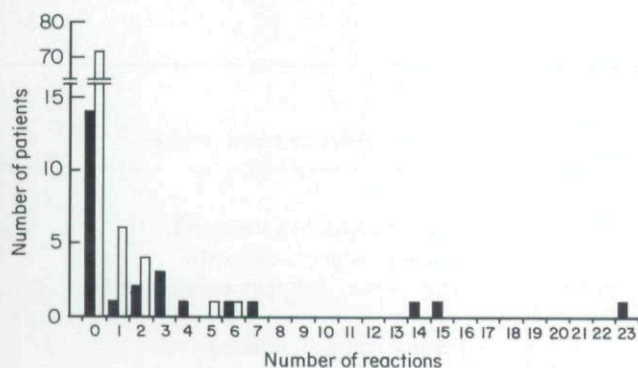


Fig. 1. The number of patients who experienced defined numbers of reactions during bee or wasp venom immunotherapy. ■. Bee. □. Wasp.

wasp, 26 to bee venom) received a total of 946 (658 wasp, 288 bee) initial weekly injections during an induction phase, using doses from 1 to 100 µg venom and 1789 (1365 wasp, 424 bee) monthly maintenance 100 µg venom in most instances (Table 1). During the induction phase, 71 systemic reactions (7.5%) were recorded (21 [3%] wasp, 50 [17%] bee) and during the maintenance phase of treatment, 37 systemic reactions (2.1%) were recorded of which only 0.3% followed wasp venom and 33 [7.8%] bee venom).

Eighty-eight of the 108 (81%) systemic reactions occurred within the first 30 min after injection, with a

further 12 (11%) starting between 0.5 and 1 h thereafter (Table 1). Only two reactions, both of which occurred during the induction phase of treatment, began between 1 and 2 h after injection. The other six reactions, of which all but one occurred during the induction phase of treatment, began after 2 h, outside the period of observation in hospital. After systemic reactions, venom dosage was reduced until well tolerated before proceeding with the prescribed regimen, according to the manufacturers' recommendations.

Of the 83 patients receiving wasp venom treatment, 12 experienced systemic reactions, the number for each patient varying from 1 to 6. Of the 26 bee venom patients, 12 experienced systemic reactions, the number for each patient varying from 1 to 23 (Fig. 1). Despite the reactions, all patients receiving wasp venom immunotherapy eventually completed the induction phase and continued with maintenance treatment. In contrast, two bee venom allergic patients were withdrawn from treatment after seven and 14 severe reactions, respectively, during the induction phase.

Nature of adverse reactions and usage of adrenaline

The intensity of the reactions was generally mild and often only reassurance and observation was required. Itching or tingling and flushing were the most frequent symptoms reported (Table 2). Other frequent complaints

Table 2. The symptoms experienced during systemic reactions following wasp and bee immunotherapy in 12 patients. One individual may have more than one type of reaction

Grouping of reactions	Number of patients	
	Wasp	Bee
Flushing/feeling hot/erythema	2	9
Tingling/itching	5	10
Asthma/wheezing/cough/breathlessness/tight chest	4	5
Throat swelling/congestion/tightening/sore/hoarseness	2	3
Anaphylaxis	0	1
Hypotension/faint/light-headedness	1	5
Generalized itching	1	3
Tachycardia	1	0
Palpitations	0	1
Numbness (roof of mouth, tongue)	1	1
Angioedema	1	1
Urticaria	0	2
Abdominal cramps/nausea	2	1
Rhinitis/conjunctivitis	1	3
Chest pain	1	1
Pressure/throbbing in ears	0	1

Table 3. How side-effects relate to the initial reaction

Patient number	Initial reaction	Adverse reaction to IT
<i>Wasp</i>		
1	Loss of consciousness, vomited	Faint, flushed, hypotension
2	Itching, dyspnoea, loss of consciousness	Tingling palms, tachycardia
3	Nausea, stomach pains, itching, urticaria, drowsiness, dyspnoea, swelling eyes, nose and throat, diarrhoea and vomiting	Itchy palms, abdomen pains, nausea
4	Burning all over. Cardiac arrest	Feeling very hot, flushing
5	Generalized tingling, tightness in chest, light headed, semi-conscious	Generalized itch, abdomen pains
6	Tingling toes and fingers, drowsy loss of consciousness, hypotension	Tingling fingers and toes, itchy congested throat
7	Tachycardia, loss of consciousness	Chest tightness and hoarseness
8	Chest pains	Tingling lips
9	Angioneurotic oedema, loss of consciousness	Chest pain
10	Itching feet, dyspnoea, wheezing, loss of consciousness	Rhinitis, wheezing
11	Swollen face and neck, tightness in chest, wheezy, palpitations	Itchy mouth and nose, eyes swollen, wheezy
12	Burning sensation, rash, throat swelling, dyspnoea, loss of consciousness	Asthma
<i>Bee</i>		
1	Swelling of lips and tongue, itching, shiver	Tingling hands, feet, scalp, groin, throbbing in ears, flushed, palmar erythema
2	Giant urticaria, breathless	Flushing, faint, hot, dizzy
3	Generalized swelling, loss of consciousness, dyspnoea	Cough, breathless, erythema, face and neck, itchy palms, throat tightening, wheeze, light headed
4	Generalized itch, urticaria, swollen eyes and tongue, wheeze	Tingling palms, lips, mouth, head underarms, flushed, feeling very hot
5	Thumping heart, giddiness, dyspnoea, blurred vision, urticaria, facial swelling	Generalized itch, hot, flushed
6	Felt hot, abdomen and groin pain, loss of consciousness	Feeling hot and nauseated, light-headed
7	Rhinitis, dyspnoea, cough, hoarse voice, palms and soles tingling, faint	Rhinitis, breathless, throat, swelling, sore throat, itching mouth, palms and soles, wheezing, flushing hands and face
8	Dry mouth, swelling of lips and tongue, behind ears, face blotchy, ears stinging and blocked, felt sleepy	Tingling tongue, itching ears
9	Generalized itchy rash, throat swelling, dyspnoea	Itchy palms, thighs and neck, chest tightness, giant urticaria
10	Tingling in mouth, dry cough, difficulty swallowing, palpitations, vomited, overwhelming urge to defecate, loss of consciousness	Giant urticaria, angioedema, rhinitis, generalized itch, swollen mouth and lips, palpitations, itchy hands, nose and eyes
11	Shortness of breath, loss of consciousness, rash	Tingling lips and tongue, rash on neck, itchy red palms
12	Tingling hands, tunnel vision, felt hot, loss of consciousness, incontinent	Tingling palms, blocked nose, flushing face and palms

IT. Immunotherapy.

were wheezing, coughing, breathlessness, light-headedness, throat swelling and hoarseness. Less frequent clinical features were anaphylaxis, tachycardia, numbness of the oropharynx and tongue, angioedema,

urticaria, abdominal cramps, rhinitis, chest pain and throbbing of the ears.

Clinical features which occurred during systemic reactions to stings but which did not occur during reactions to

venom injections, included loss of consciousness (12 patients) and vomiting and diarrhoea with or without incontinence (three patients) (Table 3). When the clinical features reported by the 24 patients were compared with those reported after their insect stings, in nine patients there were no clinical features in common between sting reactions and adverse reactions following venom injection.

In view of the CSM guidelines which extended the observation period from 30 min to 2 h, the nature of the reactions relative to time of onset was analysed (Table 4). The majority of reactions occurred within 30 min following venom injection. From 30 min to 1 h, the number of reactions was less, although there were still some

reactions such as wheezing, which necessitated treatment. In the case of reactions beginning later than 1 h following injection immunotherapy, the symptoms were mild and resolved spontaneously.

Adrenaline was administered to treat serious adverse systemic reactions on 13 separate occasions (0.47%) in 10 different individuals. Twelve of the 13 (92.3%) adrenaline injections were given during the initial 30 min and one injection was administered between 30 min and 1 h. Ten (76.9%) of the adrenaline injections were provided during the induction phase of therapy. Twelve of the adrenaline injections were given to patients who had received bee venom.

Table 4. The nature and timing of adverse reactions to venom immunotherapy

Time following venom injection	Clinical feature	Number of patients	
		Wasp	Bee
<30 min	Anaphylaxis	0	1
	Hypotension/faint/light-headed	1	4
	Flushing/feeling hot/erythema	2	8
	Tingling/itching	4	9
	Generalized itching	0	3
	Tachycardia	1	0
	Palpitations	0	1
	Throat swelling/congestion/tightening sore/hoarseness	1	2
	Numbness	0	1
	Angioedema	1	1
	Urticaria	0	2
	Asthma/wheezing/cough/tight chest breathlessness	2	5
	Abdominal cramps/nausea	1	1
	Rhinitis/conjunctivitis	0	2
	Pressure/throbbing in ears	0	1
30 min–1 h	Flushing/feeling hot/erythema	0	4
	Tingling/itching	1	3
	Throat swelling	0	1
	Wheezing/cough	1	1
	Abdominal cramps/nausea	1	0
	Rhinitis/conjunctivitis	1	2
1–2 h	Tingling	0	1
	Chest pain	1	0
>2 h	Light-headed	0	1
	Feeling hot	0	2
	Itching	0	1
	Generalized itching	1	0
	Hoarseness	1	0
	Tight chest	1	0
	Abdominal cramps and nausea	1	1
	Rhinitis	0	1

Each patient may have more than one type of reaction.

Risk factors for adverse reactions

One striking feature was the higher systemic reaction rate following venom injections in females than in males, for both wasp- and bee-allergic patients (χ^2 6.94, $P = 0.0084$). Ten of the 47 wasp-sensitive women (21%), but only two of 36 men (5.5%), reported systemic reactions. Six of the 16 females with bee venom allergy (60%) and two of the 10 males (20%) suffered systemic reactions.

Atopic status did not appear to be a significant factor in determining the number of reactions experienced by the patients, since 68% of those experiencing systemic adverse reactions and 59% of those who did not experience systemic symptoms after treatment were atopic.

Age did not alter the likelihood of experiencing systemic side-effects after immunotherapy since the age of individuals who did and did not experience systemic side-effects from venom immunotherapy were 49 years (range 29–70) and 45 years (range 17–75) respectively.

Bee venom immunotherapy was more likely to produce systemic reactions than wasp venom desensitization (χ^2 9.81, $P = 0.0017$). Of individuals receiving bee and

wasp venom injections 46.1% and 14.4%, respectively, developed systemic side-effects.

The systemic reactions to venom injections were approximately twice as likely to occur during the induction than the maintenance phase of treatment. From a total of 108 documented systemic reactions, 71 reactions (65.7%) were experienced during the induction phase and 37 reactions (34.3%) occurred during the maintenance phase of immunotherapy. The incidence of reactions was spread fairly evenly across all the doses used during the induction phase of treatment (Fig. 2).

Discussion

In a population of survivors of moderate to severe anaphylactic reactions to stings from hymenoptera, a minority experienced systemic adverse reactions during venom immunotherapy. The conventional dosage regimen used in the initial phase of weekly injections appears to give a satisfactorily low rate of systemic reactions, most of them being quite trivial and requiring no treatment other than modification of the venom dosage regimen. These results are similar to those reported by Müller *et al.* who observed systemic side-effects to venom immunotherapy in 41% and 25% of patients receiving honey bee and yellow jacket venom injections, respectively [6]. Nelson reports that 6% of patients experience only a systemic reaction following immunotherapy with pollen and 11% of patients experience both a local and a systemic reaction [7]. Rieckenburg *et al.* reported that approximately 6.7% of patients developed an adverse systemic reaction to immunotherapy with mixed allergens [8]. Lockey *et al.* studied the incidence of systemic reactions to six different insect venoms and reported that 12% of patients experienced systemic side-effects [9]. Tamir *et al.* reported that 10% of patients had systemic reactions during a course of immunotherapy to honey bee and wasp venom [10].

The timing of onset of these reactions is of particular interest in relation to the 1986 recommendation of the CSM, in the case of immunotherapy with pollen, mite and other inhalant allergens, that patients should remain under observation for 2 h after each injection, rather than the 20 or 30 min that had previously been thought adequate. The findings in this study suggest that most reactions had begun by 1 h, with only two minor reactions starting between 1 and 2 h. Reactions could start after 2 h following immunotherapy but these resolved spontaneously and required no treatment.

Few of the reactions even in asthmatic patients involved frank bronchoconstriction and those that did were generally mild. This is in contrast to the findings in adverse reactions to respiratory allergen immunotherapy,

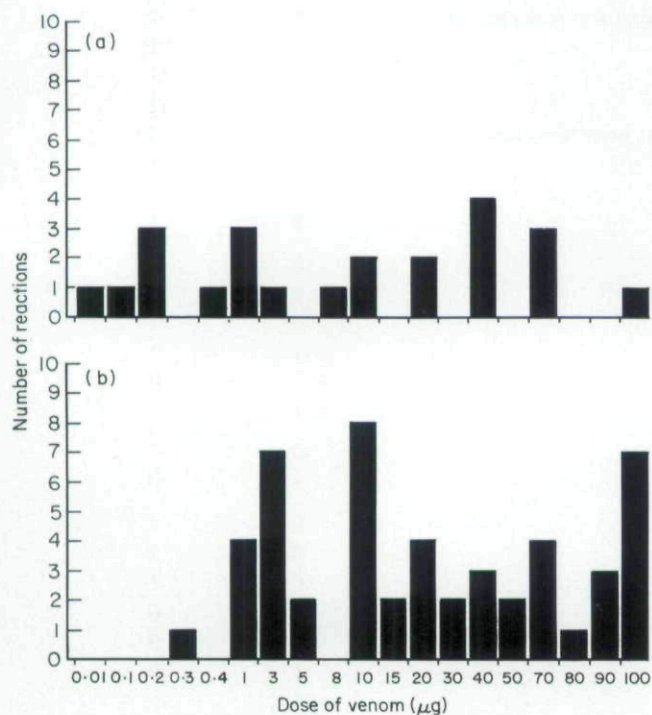


Fig. 2. The effects of dose of (a) wasp venom or (b) bee venom on the number of reactions experienced during injection immunotherapy.

where the most severe reactions, including those with a fatal outcome, were related to exacerbations of asthma [4]. In the venom-allergic patients, we paid particular attention to those patients with asthma, and they were not given injections during exacerbations as judged by a decrease in peak flows, increased symptoms or reduced lung function at the clinic. In these circumstances, patients were advised to increase their inhaled steroid dose, or have a course of oral steroids, and the next injection was deferred until the asthma exacerbation had resolved.

The finding of a higher reaction rate among female patients confirms previous data in adverse reactions to honey bee and yellow jacket [6] allergen immunotherapy injections, pollen immunotherapy [7] and treatment with mixed allergens, including ragweed, other weeds, tree pollens, grasses and moulds [8]. There are two other anaphylactic or anaphylactoid phenomena where a similar large preponderance of females is found, namely aspirin-sensitive asthma [11] and muscle-relaxant anaphylaxis during general anaesthesia [12].

The higher reaction rates among bee venom-, rather than wasp venom-allergic, patients may reflect the greater potency of bee venom, but may also be due to the fact that most bee-sensitive patients have received a larger number of stings than those who are wasp-sensitive, because they are mainly bee-keepers, their families or neighbours. Bee venom is obtained by electro-stimulation and wasp venom is obtained by dissection of the venom sac. The latter contains large amounts of body proteins and thus, its allergenic potency may be reduced [6].

The clinical features of systemic adverse events following venom injections are frequently, but not always, similar to those experienced by the respective patients during the sting reaction, which led to their referral to the clinic. While some features, such as tingling of the extremities and feeling faint, might be ascribed to non-anaphylactic causes, the great majority of reactions observed appeared to be consistent with minor anaphylactic reactions. The reduced incidence of such reactions during the monthly maintenance phase of treatment, compared with the weekly initial, lower dose injections supports evidence of the efficacy of venom immunotherapy in increasing the tolerance to venom in survivors of sting anaphylaxis.

In conclusion, our results show that venom immunotherapy in wasp and bee venom allergy is safe. Bee venom immunotherapy is more likely to produce adverse reactions than wasp venom desensitization. Reactions will occur more commonly during the induction than maintenance phase of treatment. Adverse reactions to venom injections are more common in

female patients for reasons which are unclear. The majority of reactions occur during the first 60 min after injection and reactions which appear after 1 h are minor.

The results support the recommendations by the British Society for Allergy and Clinical Immunology [13] that patients should be kept under supervision for 60 min after each injection. This period only needs to be extended if the patient has symptoms at the end of the observation period. Patients should be advised to bring their adrenaline syringes with them on the days of injections so that effective treatment is available in the unlikely event of a severe reaction starting after they have left the clinic.

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