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REVIEW ARTICLE

Treatments and therapies of honeybee venom induced allergy – A review

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Abstract

Honeybee sting is responsible for large number of casualties in tropical and sub-tropical countries. Honeybee venom is a mixture of biologically and immunologically distinct peptides. It generates serious patho-physiological effects in humans and human pet as well. Many of drugs and devises have been used to come out the allergic and toxic responses, but most of them could not fit the bill because of a variety of reasons. However, allergen immunotherapy is committed better, but this form of therapy has some risk of anaphylactic reactions. Hence, there should have to be more investigations to standardize the process of immunotherapy.

Introduction

Honeybee venom is a complex mixture of antigenic peptides, enzymes and biogenic amines, produced in modified venom gland and injected by the means of specialized mechanical device, called sting apparatus (Fitzgerald and Flood, 2006; Ciszowski and Mietka-Ciszowska, 2007). Because the composition of venom is generally same in all races of honeybees, the clinical manifestations are considered to be the same as mentioned in Table 1. Honeybee sting reactions are classified as local and systemic. Local symptoms include pain, pruritus, erythema, urticaria and angioedema (Riches et al., 2002). When these symptoms occur in remote locations, they are considered systemic reactions. Nausea, vomiting, diarrhea, and intestinal or uterine cramping are common systemic reactions (Upadhyay and Ahmad, 2010). More severe systemic reactions include bronchospasm with wheezing, laryngeal edema with inspiratory stridor, dyspnea and hypotension (Johansson et al., 1991). Hypotension may lead to loss of consciousness, bronchospasm obstruct breathing, and cardiac collapse can cause shock (Harvey et al., 1994). The onset of some systemic reactions can be delayed for 8 to 24 hours such as multi-organ dysfunction, hematological and neurological disorders (Ishay et al., 1975; Ahmad and Upadhyay, 2010; 2011a; Ahmad et al., 2013). Moreover, in about 2% of persons, hypersensitivity develops in which each additional sting produces a more severe reaction (Schmidt, 1995). Hypersensitivity may appear after a varying number of stings, usually each sting making the reaction progressively worse. Some develop sensitivity after one sting, whereas others after a series of normal reactions (Adamek-Guzik, 1994). Symptoms in an allergic person usually appear within a few minutes after the sting, but may not appear for 24 hours (Golden, 2007). Excessive swelling and hive like condition may break out over the body. There is a sensation of choking, difficult breathing, asthma, and the lips turn blue. Shock-like symptoms, vomiting, and loss of consciousness may follow in rapid succession (Hamilton, 2004).

Treatment and therapies

Person to person the sensitivity of the venom varies and they are treated to the extent of allergic symptoms accordingly (Fig 1).

First aid

By using swiping method, stinger can be scrap out of the skin (Gabriel et al., 2004). This method avoids risk of allergy and other skin reactions. The method of stinger removal is less relevant than the speed with which the stingers are removed (Winston, 1994). Further, apply a cold or ice pack, wrapped in cloth for a few minutes. Apply

a paste of baking soda and water and leave it on for 15 to 20 minutes, treat with a “sting swab” or dab on a bit of household ammonia. Take acetaminophen for pain relief (Perrott et al., 2004).

Table 1 Major constituent of honeybee venom and their activity

Constituents of honeybee venom		Activity
Peptides	Melittin	Hemolytic and cytolytic activity
	Apamin	Neurotoxic activity
	MCD peptide	Induce release of histamine and allergic reactions
Enzymes	Phospholipase A2	Block biological function of membrane, inhibit blood coagulation and decrease blood pressure
	Hyaluronidase	Cause spread of inflammation
	Acid phosphatase	Allergic activity
	Protease	Tissue necrosis
	Histamine	Allergic hypersensitivity and inflammation
	Dopamine	Increase pulse rate
	Norepinephrine	Increase pulse rate

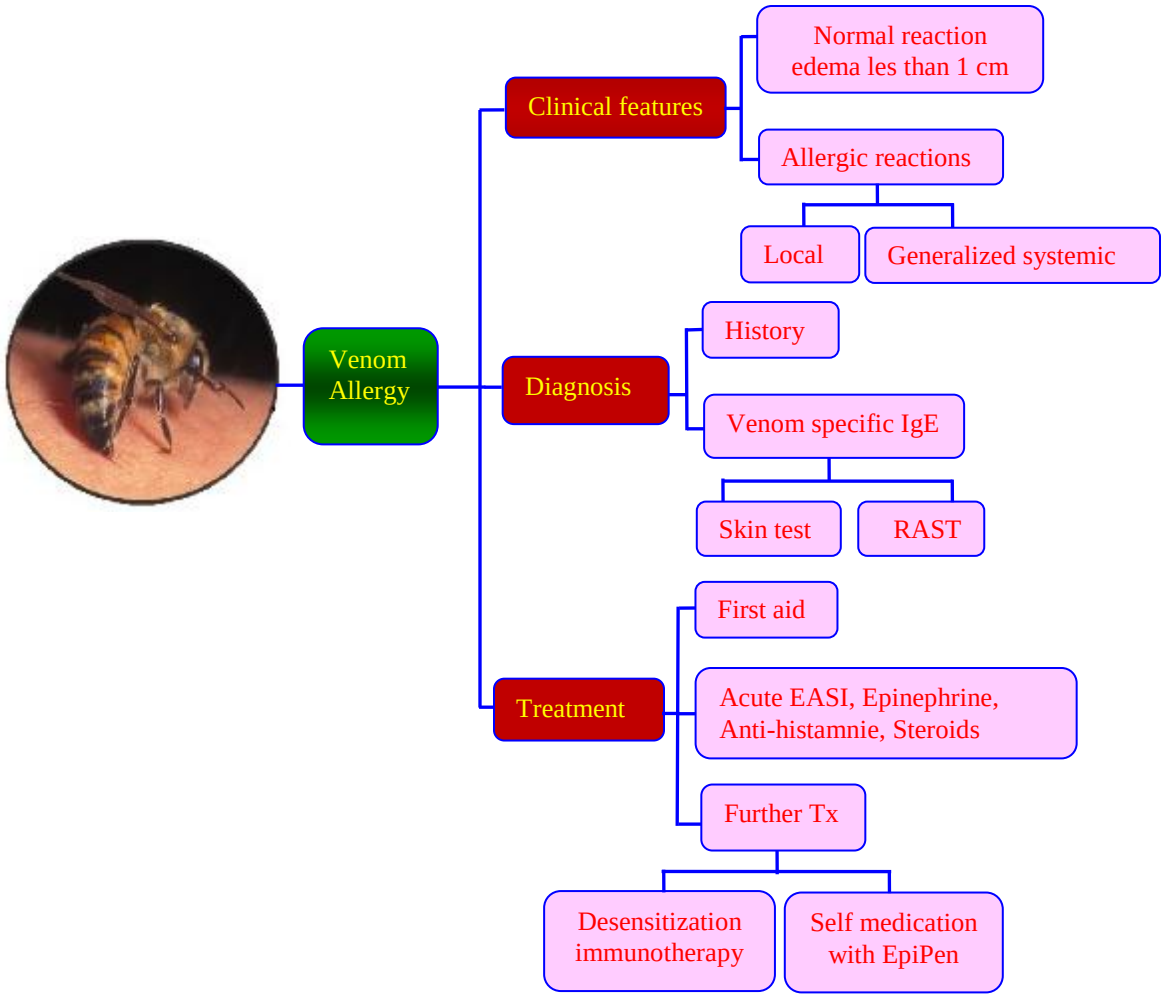

Fig 1. Flow diagram showing honeybee venom allergy, diagnosis and treatment types

Emergency treatment

It may not be clear whether a person stung by bees is having an allergic reaction or shows a toxic reaction. Initial treatment includes epinephrine, 1:1000, 0.3 to 0.5 ml given intramuscularly and diphenhydramine (50 mg) intravenously or orally can be given to the patients (Clark and Schneir, 2004). In heavy stinging oxygenation is highly required to maintain acid-base balance of the body. Aggressive fluid replacement also requires avoiding vomiting or the development of rhabdomyolysis. Histamine antagonists are given to treat the vascular effects of the venom (Schumacher and Egen, 1995). Steroids are also provided to prevent a delayed hypersensitivity, but there have a limited role in the management of acute toxic envenomation (Mitchel, 2006). Hospital admission is recommended for patients who have indications of cardio-respiratory obstructions (Sherman, 1995; Jones et al., 1999). The safety of the stinging victim requires appropriate treatment for maintaining stable physiological conditions (Kolecki, 1999). Therefore, this problem cannot be handled until the availability of specific and effective therapy to avoid the deadly symptoms of honeybee venom toxins. However, specific immunotherapy is thought to be only the curative treatment of honeybee venom.

Immunotherapy

Immunotherapy is the repeated administration of allergen to allergic individuals in order to provide long term relief and improvement in quality of life during subsequent allergen exposure (Ahmad and Upadhyay, 2011b). Immunotherapy is effective in patients who develop systemic anaphylactic reactions to the venom. In view of the risk of occasional systemic allergic reactions, immunotherapy should only be administered through sub-cutaneous route by trained nursing staff in specialist clinics (Bousquet et al., 1998).

In response to the venom toxins, B- lymphocytes release a group of high-affinity circulating specific IgG, which encounters the venom toxins (Jeanning et al., 1998; Muller et al., 1992). Early evidence supported the role of IgG antibodies in clinical protection shown by the passive transfer of immunity by infusion of IgG derived from beekeepers (Muller et al., 1986). Comparatively, higher level of venom specific IgG antibody was found associated with protection, but was not reliably able to predict the outcome of a sting in each individual patient (Golden et al., 1992). Moreover, after a long time of immunotherapy, even patients with low IgG levels did not react to stings, suggesting a different mechanism for tolerance induced by long-term immunotherapy. More studies demonstrate a TH2 to TH1 shift in cytokine responses during initial immunotherapy, with a prominent role for IL-10 (McHugh et al., 1995; Jutel et al., 1995; Akdis et al., 1998). The mechanism of long-term immune tolerance remains uncertain but might involve other regulatory cells, cytokines, and pathways (Konno et al., 2006). There is renewed interest in the role of IgG-blocking antibodies on the basis of observations of altered specificity and affinity during immunotherapy and effects on memory B cells and antigen-presenting cells (Wachholz and Durham, 2004). However, the efficacy of sub-cutaneous venom immunotherapy has been confirmed by both sting challenge and in-field sting in prospective controlled and uncontrolled studies (Ross et al., 2000; Watanabe et al., 2010).

Safety of immunotherapy

Patients with venom immunotherapy may have anaphylaxis that represents the biggest risk. Presently there is no reliable test able to predict the extent of the risk. Further, increased basophil sensitivity to allergen-specific stimulation is significantly associated with major side effects to venom immunotherapy even in children (Incorvaia et al., 2011). Therefore, venom immunotherapy should only be carried out by allergists with experience and knowledge in this field (Krishna et al., 2011). Hence, optimal time for its administration, the appropriate dosage, the long-term effects, and the best incremental protocol of venom immunotherapy to be used still remain unknown (Bilo and Bonifazi, 2011).

Future Strategies

At present production of recombinant venom allergens is in lime light hopping that it will enhance the accuracy of the diagnosis and help to make the way towards novel therapeutic techniques in future. As for diagnosis, majority of relevant honeybee venom allergens are available in recombinant form. Further, the recombinant allergen-based concept of component-resolved diagnostics and immunotherapy (CRD and CRIT) will enable physicians to discriminate between genuine double sensitization and cross-reactivity in patients with double-positive IgE results to conventional venom extracts, allowing optimization of patient selection for venom immunotherapy (Valenta et al., 1999). Concerning treatment, a number of new strategies using sequences of one or more honeybee venom allergens, mostly based on genetic engineering, have been studied though only in animal models (Muller, 2003). The only trial performed in humans in whom the efficacy of the treatment was verified by a sting challenge, used a

mixture of three dominant T-cell peptides of phospholipase. Out of five patients, complete protection was observed in three and partial protection in the remaining two, confirming that treatment with only one major allergen, even in recombinant or point mutated form, may be insufficient (Karamloo et al., 2005). Finally, the therapeutic potential of phospholipase bee venom intralymphatic immunization was analyzed in sensitized mice using an anaphylaxis model, showing an enhanced allergen-specific IgG and T-cell responses and a Th1-dependent subclass IgG2a production when compared with subcutaneous injections (Senti et al., 2008; 2009). Similar studies in humans, including clinical parameters and sting challenges, are needed to assess the effectiveness of this route of allergen administration.

Therefore, there is a great requirement for more researches regarding venom immunotherapy, because till now no appropriate protocol has been approved. Though recombinant allergen immunotherapy has shown some positive response, but there should have to some more novel explorations to evaluate the role of recombinant allergen in improving sensitivity and specificity of diagnostic testing in honeybee venom allergy.

Conclusion

During the literature survey it has been found that there is scarcity of appropriate treatment of honeybee venom allergic reactions to the extent of its severity. Primarily, patients are given first aid and then emergency treatment if required, but in case of massive envenoming the patient can't be relieved even by hospital admission. Therefore, venom specific immunotherapy is seems to be effective for the treatment of anaphylactic reactions. Although it is still unclear exactly how this form of therapy works and is not extremely safe. This form of therapy, however, does carry the risk of anaphylactic reactions and, therefore, should only be prescribed by physicians who are adequately trained in the treatment of allergy. Furthermore, immunotherapy should be administered only by physicians who are equipped to manage life-threatening anaphylaxis.

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