Abstract

Objectives Honeybee stings often lead to anaphylactic shock. We surveyed Japanese beekeepers to examine whether adrenaline auto-injectors are properly used after honeybee stings.

Methods. We contacted representatives of the Japanese Beekeeping Association in all 47 prefectures for assistance distributing allergist-developed questionnaires. Representatives in 33 prefectures distributed questionnaires to their members and we received valid responses from 826 beekeepers.

Results Adrenaline auto-injectors had been prescribed to only 46 of the 826 participants (5.6%) to prevent systemic reaction (SR) to honeybee stings. Of the 33 beekeepers who experienced a honeybee sting after adrenaline auto-injector prescription, 16 (48.5%) developed SRs; 9 of these 16 (56.3%) were treated with an adrenaline auto-injector.

Conclusions Japanese beekeeping organizations should consider encouraging medical institutions to prescribe adrenaline auto-injectors. Furthermore, physicians and other health care workers should better educate beekeepers and others who have been

prescribed an adrenaline auto-injector in order to improve compliance and raise awareness of the risk posed by SRs.

Key words;

Beekeepers, Japanese, anaphylaxis, adrenaline auto-injector

Abbreviations

outdoor workers, OWs

systemic reaction, SR

specific immunoglobulin E, sIgE

Introduction

Stings from the Hymenoptera family of insects, which includes bees, vespids, and ants, can result in anaphylactic shock and death.[1] Because the main work of beekeepers is to collect honey and maintain breeding colonies, they are at high risk of honeybee stings and develop occupation-related allergies after being stung. Therefore, the prevention and treatment of honeybee stings is extremely important. Nonetheless, evidence from Germany suggests that, although sensitized beekeepers are more likely to wear protective clothing than beekeepers who have not developed a systemic reaction (SR), less than 50% of sensitized beekeepers wear full-body protective clothing.[2] In another study, despite a large number of forestry workers having experienced stings, nearly 75% of them were not concerned about being stung or having a reaction to stings.[3] These findings suggest that there is a lack of awareness of anaphylaxis due to Hymenoptera stings.

Adrenaline administration is vital for the prevention of anaphylactic shock after Hymenoptera stings.[4] Epidemiological investigations of occupational allergies have

recently been conducted, and awareness is growing of the use of adrenaline auto-injector preparations for preventing anaphylaxis.[5] In Japan, adrenaline auto-injectors have been covered by national health insurance since 2011 to prevent anaphylaxis to not only food and drugs but also Hymenoptera stings, and can only be prescribed by a physician. However, there have been no reports on their subsequent use and re-prescription to beekeepers who have previously been prescribed an adrenaline auto-injector.

Accordingly, here we surveyed Japanese beekeepers to examine whether adrenaline auto-injectors were properly used after a honeybee sting and the re-prescription of the adrenaline auto-injector.

Methods

Representatives of the Japan Beekeeping Association, which is the largest beekeeping organization in Japan, with 2900 members in all 47 prefectures were contacted by both e-mail and telephone. Representatives in 33 prefectures agreed to distribute

allergist-developed questionnaires to the members in their prefecture. Valid responses were received from 826 of approximately 2000 beekeepers. In one prefecture, there are dozens of groups of individual private enterprises, each comprising a few to a few dozen beekeepers. All questionnaires were completed between June 2017 and May 2018. The study was approved by the Research Ethics Committee of Dokkyo Saitama Medical Center (authorization number 1817).

The questionnaire included the following items: sex, adrenaline auto-injector prescription (yes, no, or don't know), honeybee sting experienced after adrenaline auto-injector prescription (yes, no, or don't know), SR (e.g., limb tremor, cold sensation, palpitation, vertigo, urticaria, flare, abdominal pain, vomiting, dyspnea) experienced after a honeybee sting (yes, no, or don't know), adrenaline auto-injector use after a honeybee sting (yes, no, or don't know), hospital visit immediately after adrenaline auto-injector use (yes, no, or don't know), and adrenaline auto-injector re-prescription (yes, no, first prescription, or don't know).

Results

Adrenaline auto-injectors had been prescribed to only 46 (41 men and 5 women) of the 826 participants (5.6%) to prevent anaphylactic reactions to honeybee stings. As shown in Figure 1, of the 826 participants, only 46 (5.6%) had received a prescription for an adrenaline auto-injector; 6 (0.7%) did not know whether they had received a prescription for an adrenaline auto-injector. Of the 46 who had received an adrenaline auto-injector prescription, 33 (71.7%) had experienced a honeybee sting after the prescription and 10 (21.7%) had not; 3 (6.6%) did not know whether they had been stung by a honeybee since receiving their prescription. Of the 33 beekeepers who experienced a honeybee sting after receiving their adrenaline auto-injector prescription, 16 (48.5%) developed an SR; 9 of these 16 (56.3%) were treated with an adrenaline auto-injector. The remaining 17 who did not develop an SR following a honeybee sting were not treated with an adrenaline auto-injector.

Discussion

Adrenaline auto-injectors had been prescribed to approximately 6% of the present study population to prevent anaphylactic reactions to honeybee stings, even though honeybee venom sIgE had previously been found in more than 70% of Japan Beekeeping Association members in three Japanese prefectures.[6] In addition, despite experiencing anaphylaxis due to a honeybee sting, 71% of the respondents (25 of the 35 participants) did not receive an adrenaline auto-injector prescription.[6] The only report on the adrenaline auto-injector prescription rate in UK beekeepers who had experienced an SR to honeybee stings found that 23% of UK beekeepers had been prescribed an adrenaline auto-injector.[7] Thus, the rate of prescription to Japanese beekeepers in the present study was about a quarter of that of UK beekeepers. In contrast, 40% of Japanese public sector outdoor workers (OWs) in Japan had been prescribed adrenaline auto-injectors to prevent anaphylactic shock to Hymenoptera.[8] In a previous study, we found that 9.2% of private sector OWs in Japan had received adrenaline auto-injectors. These distinct findings are thought to indicate differences in awareness of Hymenoptera sting anaphylaxis among employers and their workers. Although not investigated in the present study, it is expected that many workers in family-owned and operated

beekeeping businesses have experience with sensitization to honeybee venom and anaphylaxis. There may also be differences in awareness of the risk posed by honeybee stings among families. We also found that 24 of the 34 beekeepers (70.6%) who needed to be re-prescribed an adrenaline auto-injector were given re-prescriptions. Of the 46 beekeepers who had received an adrenaline auto-injector prescription, 8 (17.4%) had received their first prescription and that prescription had not yet expired. These results are similar to those found in OWs in Japan[8] and suggest that beekeepers should be given re-prescriptions for as long as they continue their work.

In this study, we found that 56.3% of Japanese beekeepers who developed an SR were treated with an adrenaline auto-injector. In addition, no beekeepers who did not develop an SR to a honeybee sting were treated with an adrenaline auto-injector. In contrast, only 36.9% of OWs in Japan who developed an SR were treated with an adrenaline auto-injector whereas 4.2% who did not develop an SR were treated with an adrenaline auto-injector.[4] The difference between these reports may suggest that, as a result of frequent honeybee stings and experiences with anaphylaxis, beekeepers who are

123 prescribed an adrenaline auto-injector are more aware of the high risk of anaphylaxis
124 than both OWs and other beekeepers who are not prescribed an adrenaline auto-injector.
125 Thus, beekeepers might generally be aware of the potential need for an adrenaline
126 auto-injector during working hours.
127
128 One study found that the mortality rate increased when adrenaline was injected 30 min
129 or more after a sting,[4] demonstrating the importance of prompt and appropriate
130 adrenaline auto-injector use when an SR develops. We found that all beekeepers in this
131 study who used an adrenaline auto-injector visited the hospital immediately thereafter,
132 whereas only 44% of beekeepers who reported SRs after a honeybee sting sought
133 emergency treatment in the UK.[7] These results indicate possible differences in
134 awareness of the potential risk of allergic reaction. All people with symptoms of an SR
135 should visit the hospital promptly, regardless of whether an adrenaline auto-injector is
136 used.
137

138 The clinical features and management of insect stings have been reviewed in guidelines
139 from Germany and other European countries.[9] However, no systematic decision-making
140 process has yet been established to manage honeybee stings in beekeepers in Japan.
141 Measurement of specific sIgE is important for examining sensitization to Hymenoptera
142 venom.[10] The sensitivity and specificity of serum sIgE in Hymenoptera venom allergy
143 has been reported to be 76%–91.2% and 85%–100%, respectively.[10] Several investigators
144 have found that patients with a positive venom skin test, which is a cost-effective method
145 to demonstrate sIgE to Hymenoptera venom,[11] have a 10%–17% chance of an SR to their
146 next sting.[12,13] These findings suggest that people with positive results of sIgE to
147 honeybee venom, with or without SRs, should be prescribed an adrenaline auto-injector.
148 It should be noted, however, that sIgE levels decline over several years if a person does
149 not experience a subsequent Hymenoptera sting, and sIgE levels are thought to decrease
150 immediately after stings.[13] Thus, people who have experienced an SR due to a honeybee
151 sting but had a negative sIgE result to the honey bee venom should also be prescribed an
152 adrenaline auto-injector. Furthermore, patients with recent severe reactions and positive
153 venom skin test results might have a 40%–70% chance of experiencing an SR to their

154 next sting.[12] Several reports have been published on the usefulness and safety of allergen
155 immunotherapy, which is a fundamental treatment.[14] Therefore, beekeepers who have
156 actually experienced an SR to a honeybee sting with sIgE should receive venom
157 immunotherapy. However, there is no insurance indication for allergen immunotherapy
158 using venom extracts in Japan and most beekeepers cannot simply abandon their
159 livelihood. For these reasons, consistent use of protective clothing among not only
160 sensitized beekeepers but also healthy workers as well as education on the proper
161 prescription and use of adrenaline auto-injectors is vital. Furthermore, when a healthy
162 beekeeper who has either never been stung by a honeybee or who has been stung but had
163 a negative sIgE result to the honeybee venom is stung by a honeybee without developing
164 an SR, their sIgE response to the honeybee venom should be measured immediately.
165 Based on the proposed considerations and results of both our present and previous
166 studies,[6,8] emphasis should be placed on resolving organizational issues related to the
167 occupational setting of beekeepers and OWs with respect to Hymenoptera stings and
168 insurance coverage for allergen immunotherapy in Japan.
169

In conclusion, this study found that most Japanese beekeepers might not be properly prescribed an adrenaline auto-injector for a honeybee sting. Furthermore, the proper use of adrenaline auto-injectors and their re-prescription may not be widespread. The employers of Japanese beekeepers should provide better education to their employees and advise them to consider obtaining adrenaline auto-injectors. Employers should work with local medical providers to encourage compliance with best practice management after honeybee stings with severe SRs. Any pre-placement medical examinations would provide an opportunity for medical providers to consider individual risks for new employees and make recommendations.

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References

1. Golden DB. Anaphylaxis to insect stings. *Immunol Allergy Clin North Am* 2015;**35**:287-302.
2. Münstedt K, Hellner M, Winter D, *et al.* Allergy to Bee Venom in Beekeepers in Germany. *J Investig Allergol Clin Immunol* 2008;**18**:100-5.
3. Dillae D, Richards SL, Balanay JAG, Langley R. Risk Assessment and Recommendations for Forester Exposure to Hymenoptera. *J Agromedicine* 2019;**24:**146-56.
4. Barnard JH. Nonfatal results in third-degree anaphylaxis from hymenoptera stings. *J Allergy*1970;**45:**92-6
5. Ricciardi L, Papia F, Cataldo G, *et al.* Hymenoptera sting reactions in southern Italy forestry workers: our experience compared to reported data. *Clin Mol Allergy* 2018;**16:**8. doi: 10.1186/s12948-018-0087-6. eCollection 2018.
6. Hirata H, Tatewaki M, Shiromori S, *et al.* Specific IgE sensitization to honey bee venom and auto-injector adrenaline prescriptions for Japanese beekeepers. *Allergol Int* 2017;**66:**149-51.
7. Richter AG, Nightingale P, Huissoon AP, *et al*. Risk factors for systemic reactions to bee venom in British beekeepers. *Ann Allergy Asthma Immunol* 2011;**106:**159-63.
8. Hirata H, Yoshida N, Tatewaki M, *et al.* Survey on the proper use of an adrenaline auto-injector in 551 Japanese outdoor workers after Hymenoptera stings. *Allergol Int* 2018;**65:**153-5.

9. Przybilla B, Ruëff F. Insect stings: clinical features and management. *Dtsch Arztebl Int* 2012;**109:**238-48.

10. Yoshida N, Hirata H, Watanabe M, *et al*. Improved sensitivity to venom specific-immunoglobulin E by spiking with the allergen component in Japanese patients suspected of Hymenoptera venom allergy. *Allergol Int* 2015;**64:**248-52.

11. Krishna MT, Ewan PW, Diwakar L, *et al.* Diagnosis and management of hymenoptera venom allergy. *Clin Exp Allergy* 2011;**41:**1201-20.

12. Golden DB, Marsh DG, Freidhoff LR, *et al.* Natural history of Hymenoptera venom sensitivity in adults. *J Allergy Clin Immunol* 1997;**100:**760-6.

13. Golden DB, Tracy JM, Freeman TM, *et al.* Insect Committee of the American Academy of Allergy, Asthma and Immunology, Negative venom skin test results in patients with histories of systemic reaction to a sting. *J Allergy Clin Immunol* 2003;**112:**495-8.

14. Krishna MT, Ewan PW, Diwakar L, *et al.* Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and ClinicalImmunology (BSACI) guidelines. *Clin Exp Allergy* 2011;**41:**1201-20.

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Figure legend

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Figure 1. Number of prescriptions and usage of adrenaline auto-injectors in Japanese

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beekeepers after a honeybee sting.