

Evaluation of adherence and knowledge retention for adrenaline autoinjector use in hymenoptera venom-allergic patients with c-KIT p.D816V

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Abstract

Introduction: Severe anaphylaxis in patients with clonal mast cell disorders highlights the need for proper use of adrenaline autoinjectors. This study assessed knowledge retention and adherence to autoinjector use in c-KIT p.D816V-positive individuals with hymenoptera venom allergy undergoing venom immunotherapy (VIT) and prescribed two autoinjectors.

Methods: Seventy-one VIT patients received personalized autoinjector education, with knowledge assessed at 3, 4 to 12, 12 to 24, and > 24 months. Fifteen patients 5 years post-VIT underwent video-based retraining and were assessed 1 month later.

Results: Knowledge retention was 82.3% at 3 months, dropping to 40.0% at 12 to 24 months ($p = 0.0160$) and 22.2% after 24 months ($p = 0.0005$), indicating a clear decline over time. Common errors included ignoring the safety cap (16.7%), insufficient injection force, finger injection risk, and upper arm activation (totaling 19.0%). In addition, 19.8% failed to hold the autoinjector in the muscle for 3 seconds, 26.9% did not know to lie supine during anaphylaxis, and 14.3% did not seek emergency help. In the video-retrained group, 80.0% lacked proficiency 1 month later, 73.3% were unaware of the second dose, and 66.7% did not carry their devices.

Conclusions: Ongoing tailored education is essential to ensure effective autoinjector use, especially in c-KIT p.D816V-positive venom-allergic patients. Video instruction alone may be insufficient.

Keywords: anaphylaxis, hymenoptera, epinephrine, autoinjector, education

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Introduction

Anaphylaxis demands immediate action because it is a medical emergency. Less than 1% of all anaphylactic reactions result in fatalities (1). At least half of the deaths due to anaphylaxis occur within 60 minutes of contact with the allergen (2). According to a study conducted in 2021, there were 15 deaths in Slovenia between 2010 and 2020, almost all of which were the first appearance of an anaphylactic reaction, and nearly half were caused by hymenoptera stings (3).

The appropriate choice of treatment is crucial, with intramuscular administration of adrenaline taking precedence over all other measures. In addition to timely and correct adrenaline application, it is important for the patient to assume a lying position during anaphylaxis (2, 4–6). Despite adrenaline being the drug of choice for anaphylactic reactions, patients are often unsure of when and how to administer an adrenaline autoinjector (AAI) (7–10). It is estimated that a high percentage of individuals tested after 24 months no longer know how to correctly use an AAI. In addition, awareness regarding the importance of having an autoinjector at all times diminishes, along with a decrease in the recognition of signs of anaphylaxis (7, 10). Delayed recognition of anaphylaxis and late intervention can have serious consequences. Apart from being a financial burden due to hospitalization, it can lead to adverse outcomes, including death (1, 2, 11).

The capability to use an AAI is crucial for saving lives in individuals experiencing severe anaphylaxis. Patients with clonal mast cell diseases, particularly those harboring a gain-of-function mutation in the c-KIT gene, are at increased risk for life-threatening anaphylactic reactions (1, 3, 12), even during venom immuno-

therapy (VIT), and have a higher risk of relapse after its discontinuation. Therefore, they should be provided with two AAIs. This study's primary objective was to evaluate the retention of knowledge and adherence to correct use of AAIs among hymenoptera venom-allergic patients with the c-KIT p.D816V mutation.

Methods

Patient selection

Personalized education on AAI usage was provided to 71 individuals with the c-KIT p.D816V mutation undergoing VIT. Knowledge assessments were carried out at intervals of 3 months, 4 to 12 months, 12 to 24 months, and beyond 24 months. In addition, 15 participants that completed VIT 5 years earlier received retraining through video content, followed by knowledge evaluation 1 month post-retraining. This study was conducted at the Allergy Unit of the University Clinic of Respiratory and Allergic Diseases in Golnik, Slovenia. It was approved by the National Medical Ethics Committee of Slovenia (0120-40/2023/6). Informed consent was obtained from all subjects involved in the study.

Process description

The initial focus of this study was to meticulously track and assess the accurate application of an AAI through a detailed step-by-step process: 1) Open the yellow lid of the protective box and remove the AAI from the protective casing. 2) Grasp the AAI firmly with the dominant hand, turn the needle end downward, and remove the blue safety cap. 3) Select the upper lateral thigh for

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administration and trigger the autoinjector into the muscle until it clicks. 4) Post-injection, hold the autoinjector in the muscle for at least 3 seconds. After removing the AAI, gently massage the area. 5) Assume a lying position. 6) Promptly call emergency medical services.

Participants demonstrated their skills using a training device with the same mechanism as a real AAI. Activation of the AAI was considered successful if the patient correctly demonstrated the training device's activation in less than 1 minute. The first four steps are crucial for the patient to correctly activate an AAI and receive the medication.

In addition to these steps, the patients were assessed on whether they had their device with them, whether they could recognize signs of a systemic reaction, whether they knew when to administer the first dose of an AAI and when to administer the second dose, and whether they were aware of the expiration date of their AAI.

Statistical analysis

The statistical analysis was performed using MATLAB R2024a (The MathWorks, Natick, MA, USA). A Kruskal–Wallis test was used to compare groups based on the percentage of knowledge, followed by post-hoc Dunn's tests for pairwise comparisons between multiple groups (with Bonferroni correction) and Mann–Whitney *U* tests for independent groups. The correlation between time and percentage of knowledge was assessed using Spearman's rank correlation to evaluate monotonic association across time groups. The Mann–Whitney *U* test was employed to compare two specific groups regarding the number of errors in using an AAI. A *p*-value < 0.05 was considered statistically significant.

Results

The cohort consisted of 86 participants with sensitivity to hymenoptera venom with a c-KIT p.D816V mutation, all equipped with two AAIs, whose data were analyzed in this study. The average age

Table 1 | Demographic and clinical characteristics of participants.

Category	Variable	Value	n
Age (years)	Mean age	54.5	86
Sex (%)	Male	58.1	50
	Female	41.9	36
Venom sensitivity (%)	Wasp venom	66.0	57
	Honeybee venom	22.1	19
	Both venoms	11.6	10
Treatment (%)	Currently undergoing VIT	82.6	71
	Completed VIT > 5 years ago	17.4	15

VIT = venom immunotherapy.

Table 2 | Participant errors in adrenaline autoinjector administration and awareness of appropriate use.

Error	n	%
Use of AAI: stepwise errors		
1. Opening yellow lid and removing AAI from protective casing	4	3.2
2. Turning AAI needle end down and removing blue safety cap	21	16.7
3. Selecting upper lateral thigh and triggering autoinjector	24	19.0
4. Holding in place for ≥ 3 seconds and massaging area	25	19.8
5. Assuming lying position	34	26.9
6. Calling emergency medical services	18	14.3
Knowledge and behavior gaps		
Not carrying AAI	27	38.0
Unable to recognize signs of systemic allergic reaction	5	7.0
Uncertain when to administer first AAI	7	9.9
Uncertain when to use second AAI	31	43.7
Unaware of AAI expiration date	20	28.2

AAI = adrenaline autoinjector.

of participants was 54.5 ± 13.3 years (mean $\pm SD$, range 25 to 80), with 58.1% male. Out of the total, 66.3% ($n = 57$) were sensitive to wasp venom, 22.1% ($n = 19$) were sensitive to bee venom, and 11.6% ($n = 10$) were sensitive to both types of venom. Out of these, 71 participants were undergoing VIT, and 15 had concluded their treatment over 5 years earlier (Table 1).

In the sample of those undergoing VIT ($n = 71$), significant differences were observed among groups assessed for their knowledge of AAI use at 3 months, 4 to 12 months, 12 to 24 months, and 24 months or more post-training. The "after 3 months" group ($n = 17$) exhibited a knowledge rate of 82.3%, notably higher than the "after 12 to 24 months" group ($n = 15$) at 40.0% ($p = 0.0160$) and the "after 24 months" group ($n = 18$) at 22.2% ($p = 0.0005$). No significant differences were found among other time intervals. The correlation between time and the decline in knowledge was assessed using Spearman's rank correlation, confirming a perfectly decreasing monotonic trend ($p = -1$) that supports the observed decline. Due to the small number of groups and aggregated data, the associated *p*-value should be interpreted with caution and is not considered a formal test of statistical significance (Fig. 1).

In addition, analysis of AAI usage errors highlighted prevalent issues. Common errors encompassed several steps: failure to remove the blue safety cap at 16.7% ($n = 21$), failure of AAI activation in 15 participants, and potential finger injection in eight individuals, with one inadvertently activating the AAI into the upper arm muscle (totaling 19.0% of participants). Furthermore, 19.8% ($n = 25$) failed to hold the AAI in the muscle for at least 3 seconds. In scenarios requiring a supine position during anaphylaxis, 26.9% ($n = 34$) were unable to assume the position, and 14.3% ($n = 18$) did

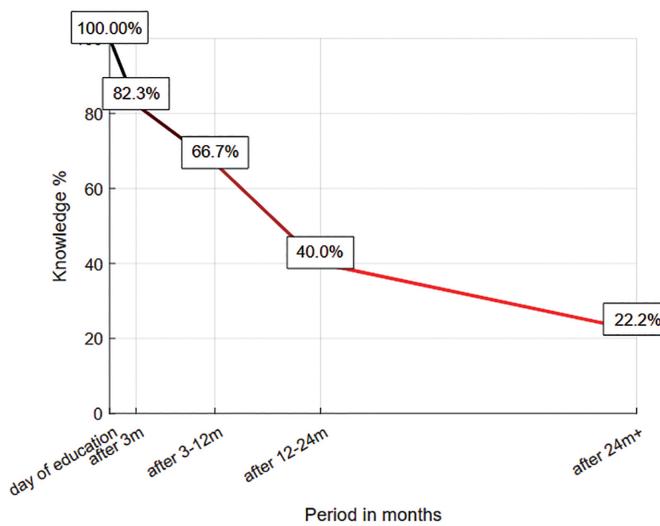


Figure 1 | Variation in knowledge of adrenaline autoinjector use over time.

not contact emergency medical services (Table 2).

The results indicated that 38.0% do not carry their AAI, 7% would not recognize signs of a systemic allergic reaction, 9.9% are unsure when to administer the first AAI, and 43.7% are uncertain about when to use the second. In addition, 28.2% of participants are unaware of the expiration date of their AAI (Table 2).

To illustrate the average errors in using an AAI concerning critical steps, participants were divided into two large groups: before 12 months and after 12 months. The average error count in the “after 12 months” group was 3.97, significantly higher compared to the “before 12 months” group, which averaged 2.24 ($p = 0.0244$). These findings highlight a noticeable increase in errors over time.

Patients that had completed specific immunotherapy 5 years earlier were also invited to participate in the study, and 15 of them responded to do so. They were invited for a follow-up visit at the allergy clinic, where a film demonstrating the correct use of an AAI was shown to refresh their knowledge. Their knowledge was assessed at the allergy unit after 1 month. The findings revealed that 80.0% of the patients did not know how to correctly use an AAI, 73.3% were unaware of when to administer a second AAI, and 66.7% did not have their AAI with them (Table 3). Based on these results, it can be concluded that refreshing knowledge with an emphasis on video content might not be suitable for achieving an adequate level of proficiency.

In all groups, among those that did not have two AAIs with them, the reasons cited were as follows: 12.1% did not understand the necessity for two devices, 9.1% because it was not the season for hymenoptera, 9.1% did not have two prescribed AAIs, and one patient used an AAI without being prescribed a new one. Moreover, 45.0% did not provide a specific reason for not carrying an AAI.

Table 3 | Reevaluation of patient knowledge and adrenaline autoinjector possession after instructional video.

Patient knowledge after watching video	%	n
Did not correctly know how to use AAI	80.0	12
Unaware when to administer second AAI	73.3	11
Did not have AAI device with them	66.7	10

AAI = adrenaline autoinjector.

Discussion

The study's assessment of AAI usage among individuals with hymenoptera venom sensitivity and the c-KIT p.D816V mutation revealed several critical insights into the challenges associated with knowledge retention and proficiency over time.

One of the most prominent observations was the noticeable decline in knowledge retention among participants as time elapsed post-training. The study found a perfectly decreasing monotonic association between time post-training and retained knowledge of correct AAI usage. This decline highlights a concerning trend, indicating the limitations of one-time training sessions in maintaining essential skills necessary during anaphylactic emergencies. In line with findings from a study in Turkey (10), the proper use of AAIs by caregivers shows a strong connection with training frequency, particularly every 6 months. Regular training improves AAI utilization during anaphylaxis, emphasizing the necessity of having access to an AAI at all times for its appropriate use in emergency situations. A similar topic was investigated in another study, the results of which indicate a decline in AAI usage skills after 6 months. This highlights the importance of regular training to maintain proficiency (7). As evidenced in a study by Warren et al., patients express a desire for improved education on anaphylaxis and request more dedicated time for education (13).

Moreover, the analysis underscored common errors in AAI usage, ranging from basic oversights such as failure to remove the safety cap to more critical mistakes such as incorrect injection sites or inadequate duration of AAI placement in the muscle. Notably, the prevalence of these errors increased significantly in participants assessed after 12 months compared to those evaluated within the initial year post-training. This escalation in errors emphasizes the necessity for recurrent education and skill reinforcement to sustain optimal proficiency in handling AAIs effectively. Furthermore, the attempt to refresh knowledge through video content for individuals that completed immunotherapy 5 years ago yielded concerning results. The majority of these patients demonstrated a lack of retained knowledge regarding AAI usage. These findings indicate that passive video-based refresher content may not be sufficient to maintain proficiency in AAI use over extended periods. In contrast, other studies have demonstrated that interactive digital education tools can effectively support knowledge retention. For instance, a mobile web-based educational program designed for parents of school-aged children with food allergies led to improvements in knowledge and practical skills for managing food allergies and anaphylaxis (14). Likewise, the AllergyAware online course in Canada was effective in enhancing participant satisfaction, improving post-course evaluations, and increasing confidence in managing anaphylaxis (15). Based on our findings, it would be advisable to develop educational programs that combine interactive digital content, practical simulations, and regular knowledge refreshers because active engagement of participants is essential for maintaining long-term proficiency in using AAIs. Furthermore, future research could explore how different forms of real-time digital interaction influence learning and knowledge retention across various age groups or target populations, which would help optimize programs to meet participants' specific needs.

However, enhancing knowledge alone may not guarantee optimal AAI use because practical challenges in real-life situations can still limit proper device handling. Importantly, our findings also revealed practical barriers to optimal AAI use because participants frequently did not carry two AAIs due to misunderstanding their necessity, seasonal considerations, or insufficient prescribed quantity. These results underscore that, in addition to effective educational interventions, addressing practical obstacles and reinforcing the importance of having two AAIs readily available is essential to minimize risks in emergency situations. A study in the US revealed that patients do not always have an AAI with them; approximately 44% carry only one, and a mere 24% carry multiple devices (13). In Slovenia, Kadivec and Košnik (2021) also demonstrated that only 61% of patients examined carried an AAI upon visiting an allergy unit, and only 54% of these patients could effectively use an AAI within 1 minute (16). This highlights the challenges among patients related to carrying AAIs and properly using them, potentially impacting appropriate management in cases of anaphylaxis. The studies have shown that a single educational session is insufficient for patients to acquire sufficient knowledge in using an AAI. Instead, continuous refreshment of knowledge and educating patients through structured programs delivered by healthcare professionals is crucial (7, 10, 17–19). Overall, these findings highlight the importance of combining effective educational strategies with practical guidance and ongoing support to ensure that patients not only retain knowledge but are also able to apply it correctly in real-life anaphylaxis situations.

Limitations

There are several limitations to this study. First, the sample was specific, including only patients allergic to hymenoptera venom with the c-KIT p.D816V mutation, which limits the generalizability of the findings to the broader population of allergy patients. Second, data were collected from a single teaching clinic, and so the study was not multicentric, further limiting the wider applicability of the results. Third, the study did not include a control group, making it impossible to reliably determine the optimal interval for repeating education on use of AAIs. Despite these limitations, the study provides valuable baseline data and highlights key areas for future research.

Conclusions

Recognition of signs of a systemic hypersensitivity reaction,

knowledge of proper action during anaphylaxis, and knowledge of how to use an AAI tend to decline over time. Ongoing education and knowledge reinforcement programs are designed to enhance skills and proficiency in using an AAI, thus necessitating regular implementation. The timeframe for conducting recurrent healthcare educational activities is not precisely defined, opening paths for further research. The delivery of healthcare information can be tailored individually; however, consistently carrying out refresher programs and assessment procedures is crucial to ensure high-quality care for patients prescribed an AAI.

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