Adverse drug reactions from adrenaline auto-injectors: Analysis of the French pharmacovigilance database.

Guillaume Pouessel, Nadine Petitpain, Luciana Kase Tanno, Sophie Gautier

Received: 12 June 2023 | Revised: 6 July 2023 | Accepted: 8 July 2023

DOI: 10.1111/cea.14375

RESEARCH LETTER

WILEY

Adverse drug reactions from adrenaline auto-injectors: Analysis of the French pharmacovigilance database

To the Editor,

In current guidelines, prompt intramuscular (IM) adrenaline injection is the first-line treatment for anaphylaxis.[1] The availability of adrenaline autoinjectors (AAI) facilitates the lay administration of adrenaline in community settings, at an appropriate dose ergonomically and safely. However, adverse drug reactions (ADRs) are reported with AAIs.[2] In the United States (US), a simulation based on data from the Food and Drug Administration evaluated the risk of accidental injection to be 4.3%, severe ADR to be 0.73%, and AAI-related mortality to be 0.07%.[2]

In France, the 30 regional pharmacovigilance centres are tasked with collecting the ADR declarations sent by healthcare professionals, patients, or patient organizations. The number of AAIs sold in France has steadily increased over the past 10 years (965,944 AAIs in 2022, with the following actual market-sharing: Anapen®, 60%; Epipen®, 25%; Jext®, 10%; Emerade®, <10%). Our aim was to analyse the AAI-related ADRs recorded in the national pharmacovigilance database (1984–2022).

Forty-two cases of AAI-related ADR were declared of which 28 (66%) occurred in the last 4 years. Thirty (72%) cases occurred in females and 11 (26%) in children (≤6 years, $n=4$; 7–11 years, $n=3$; 12–17 years, $n=4$). The mean age was 32.7 years (standard deviation: 19.4 years; range: 4–70 years). The characteristics of these ADRs are detailed in Table 1. Overall, 31 (74%) ADRs occurred at home and 11 (26%) in the workplace setting (during AAI training, $n=8$ including at school, $n=3$; during anaphylaxis, $n=3$). Twenty-five (60%) cases resulted from accidental exposure outside the context of an allergic reaction, whereas 17 (40%) cases occurred in the context of anaphylaxis. In cases of accidental exposure, the most common reason was the mishandling of the AAI by the patients themselves ($n=17$; 41%), when storing the device or checking its expiration date. Another person was involved in 21 (50%) cases, including healthcare professionals in 11 (26%) cases.

Among the 42 cases, the most frequent ADR was accidental injection ($n=33$, 79%) in the finger ($n=31$, of which 20 in the thumb), hand or thigh ($n=1$, respectively). The nine other cases were related to an activation failure of the AAI ($n=3$), and the occurrence of abnormal symptoms after single or multiple injections ($n=3$, respectively). With regard to the AAI device, 20 cases occurred with Epipen®, 13 with Jext®, 8 with Anapen®, and 1 with an unknown AAI.

Concerning the severity, only local ADRs (pain, induration) were observed in the 33 cases involving an accidental injection (including 31 cases in the finger). No local complications were identified, and no vasodilator was administered. In three cases, including one child, the anaphylaxis symptoms worsened in the context of a device malfunction, leading to hospitalization in two cases. In the third patient, a second adrenaline injection was performed at home with a favourable outcome.

In six cases, all adults, ADRs occurred after adequate AAI use in the context of anaphylaxis. In 3/6 cases, the ADRs occurred following a single adrenaline injection: chest tightness and paresthesia of the extremities ($n=1$), hypertension ($n=1$), and induration at the injection site ($n=1$). In the remaining 3/6 cases, the ADRs occurred following multiple adrenaline injections: lower limb vasospasm after three injections in the tight requiring hospitalization and ilomedin treatment; tachycardia and tremors after two injections ($n=2$). In total, 25 (60%) patients were admitted to the emergency department, 12 (29%) were treated at home, and 5 (12%) were finally hospitalized.

Regarding the 11 paediatric cases, the ADRs concerned accidental injections in the finger ($n=7$, including three in the thumb) or thigh ($n=3$) and an activation failure of the device ($n=1$). Six out of seven cases of accidental injection occurred due to the mishandling of the AAI, including five cases of children "playing" with the AAI out of curiosity.

In our study, accidental digital injections were the main AAI-related ADRs in accordance with published data.[3–6] Strikingly, the number of ADRs seems low but probably underestimated compared to other studies because of under-reporting.[2–5] Notification of ADRs in France is compulsory but not enough implemented by health care professionals and covers mostly ADRs occurring in hospital settings. A US survey conducted with poison control centres (PCCs) (1994–2007) found 15,190 accidental injections related to AAIs, of which 0.2% were severe.[5] In our study, no side effects were observed related to accidental digital injections and no patient received

†Collaborators of the Anaphylaxis Working Group of the French Allergy Society are present in Appendix A.

TABLE 1 Overview of 42 cases of adverse drug reactions related to the use of adrenaline auto-injectors reported to the national pharmacovigilance database in France.

Context of exposure	Context	Number of cases	Age (year)	Adverse reactions	Person with ADR	Management and evolution
Anaphylaxis treatment	Mishandling	8	8, 12, 13, 20, 20, 24, 30, 53	Injection in thumb ($n=7$) Injection in finger ($n=1$)	Patient ($n=5$) Healthcare professional ($n=3$)	ED
	Activation failure of AAI	3	9, 69 (unknown)	Anaphylactic shock ($n=2$) Second injection necessary ($n=1$)	Another person ($n=2$) Patient ($n=1$)	Hospitalization ($n=2$) Home ($n=1$)
	ADR	3	6, 24, 33	Chest tightness, paresthesia ($n=1$) Arterial hypertension, excessive sweating ($n=1$) Induration at injection site ($n=1$)	Patient ($n=3$)	Home ($n=1$) ED ($n=1$)
	Multiple injections of adrenaline	3	40, 60, 70	Lower limb vasospasm ($n=1$) Tachycardia ($n=2$)	Patient ($n=2$) Another person ($n=1$)	Hospitalization ($n=2$) ED ($n=1$)
Outside context of allergic emergency	Treatment management	10	31, 31, 31, 32, 34, 35, 51, 56, 59, 60	Injection in thumb ($n=6$) Injection in finger ($n=4$)	Patient ($n=3$) Another person ($n=3$) Healthcare professional ($n=3$) 1 unknown ($n=1$)	ED ($n=1$) Home ($n=1$) Hospitalization ($n=2$)
	Curiosity, game	5	4, 6, 6, 10, 12	Injection in finger ($n=2$) Injection in thumb ($n=1$) Injection in thigh ($n=1$) Injection in hand ($n=1$)	Another person ($n=3$) Patient ($n=2$)	ED ($n=4$) Home ($n=1$)
	Training	6	25, 27, 36, 46, 49, 58	Injection in thumb ($n=4$) Injection in finger ($n=2$)	Healthcare professional ($n=5$) Patient ($n=1$) another person ($n=1$)	ED ($n=5$) Home ($n=1$)
	Unknown	4	17, 27, 53, 53	Injection in thumb ($n=3$) Injection in finger ($n=1$)	Unknown	Home ($n=1$)

Abbreviations: AAI, adrenaline auto-injector; ADR, adverse drug reaction; ED, emergency department.

vasodilators. This is in accordance with different studies reporting a favourable outcome in most cases.[4–6] In a US study conducted in PCCs (2013–2014), 6806 cases (41% in children <5 years) of accidental injections were reported; 42% of patients reported minor adverse effects and even 7% described no symptoms.[6] Different treatments may be administered after accidental digital injections, including heat, local injection of lidocaine or phentolamine, and nitroglycerine paste application.[2–7] However, there is a lack of consensus on the management of patients following such accidental digital adrenaline injections. Warm soaks and massaging of the injection site should be systematically applied as a first-line treatment and vasodilator treatment should be discussed case-by-case.[7]

Notably, in our survey, activation failures were reported in three patients, of whom two underwent worsening anaphylaxis symptoms. However, in these cases, the causal link between activation failure and poor outcome cannot be proven.

Regarding the frequency of cases reported in other studies and the number of AAIs sold annually in France, the number of ADRs observed is probably underestimated. A complementary study involving the French network of PCCs and the French National Agency for Drug and Health Product Safety could improve this assessment.

Due to the increasing sales of AAIs in countries where they are available, particular attention should be paid to the AAI-related ADRs. The majority of ADRs are accidental, mild to moderate and avoidable. The widespread use of an AAI trainer during training sessions may be the first step to address some of these issues. Barriers to carriage and adrenaline administration require novel technological solutions to optimize care. Products with improved shelf life and stability, optimized dosing, ease of use and carriage, and less invasive routes (nasal, sublingual, transcutaneous) of administration are needed by patients, caregivers and healthcare professionals as well. Innovative therapies and mechanisms of adrenaline administration are under investigation to help address well-recognized AAI limitations.[8]

KEYWORDS

accidental use, adrenaline, adverse effect, anaphylaxis, auto-injector, digital injection, side effect

AUTHOR CONTRIBUTIONS

SG and GP analysed and interpreted the data and wrote the draft. NP and LKT were major contributors in reviewing the draft and improving the paper with critical analysis. All authors and collaborators read, contributed to improving the paper and approved the final manuscript.

ACKNOWLEDGEMENTS

We thank all physicians working in the French regional pharmacovigilance centres who participated in this survey.

CONFLICT OF INTEREST STATEMENT

GP declares the following conflicts of interest: interventions and/or consultancy work for Mylan/Viatris, ALK-Abello, Bausch et Lomb, Stallergènes, Bioprojet, Novartis, AI Therapeutics/Nestlé, Theravia. The other authors declare no conflict of interest related to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Guillaume Pouessel[1,2]
Nadine Petitpain[3]
Luciana Kase Tanno[4,5,6]
Sophie Gautier[7]
Collaborators of the Anaphylaxis Working Group of the French Allergy Society†

[1]*F-59100, Department of Paediatrics, Children's Hospital, Roubaix, France*
[2]*F-59,000, Paediatric Pulmonology and Allergy Department, Hôpital Jeanne de Flandre, CHU Lille, Lille, France*
[3]*F-54,000, Regional Pharmacovigilance Center, CHRU Nancy, Nancy, France*
[4]*Division of Allergy, Department of Pulmonology, Allergy and Thoracic Oncology, University Hospital of Montpellier, Montpellier, France*
[5]*Desbrest Institute of Epidemiology and Public Health, UMR UA11, INSERM, University of Montpellier, Montpellier, France*
[6]*WHO Collaborating Centre on Scientific Classification Support, Montpellier, France*
[7]*F-59,000, Regional Pharmacovigilance Center, CHRU Lille, Lille, France*

Correspondence
Guillaume Pouessel, F-59100, Department of Paediatrics, Children''s Hospital, Roubaix, France.
Email: guillaume.pouessel@ch-roubaix.fr

ORCID

Luciana Kase Tanno https://orcid.org/0000-0003-3236-1225

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APPENDIX A

Collaborators of the Anaphylaxis Working Group of the French Allergy Society: J.C. Bonneau (Angers), E. Beaudouin (Metz), C. Chataing (Grenoble), F. Codreanu-Morel (Luxembourg), J. Corriger (Nancy), P. Demoly (Montpellier), A. Deschildre (Lille), M. Dona (Paris), J. Flabbée (Nancy), J.P. Jacquier (Chambéry), Y. Larroche (Brest), C. Neukirch (Paris), S. Leroy (Nice), D. Mariotte (Caen), B. le Mauff (Caen), P.M. Mertes (Strasbourg), L. Tazi-Daoudi (Casablanca), N. Pham Thi (Paris), C. Tacquard (Strasbourg), J. Vitte (Montpellier). [Correction added on 27 July 2023, after first online publication: The collaborator, N.P. Thi, has been corrected to N. Pham Thi.]