Adverse drug reactions from adrenaline auto-injectors: Data from the French poison control centres.

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Received: 23 January 2024 | Revised: 1 March 2024 | Accepted: 5 March 2024

DOI: 10.1111/cea.14473

RESEARCH LETTER

WILEY

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To the Editor,

The current guidelines recommend adrenaline as first-line treatment for allergic emergencies.[1] In France, adrenaline auto-injectors (AAI) are widely available in the community.[2] In 2022, 965,944 AAI have been sold and four brands were commercialized with the following sharing market: Anapen®, 57%; Epipen®, 24%; Jext®, 11%; Emerade®, 8%.

We previously reported the AAI-related adverse drug reactions (ADR) declared to the French database of regional pharmacovigilance centres (RPVC) (1984–2022).[3] We hypothesized that the number of AAI-related ADRs was underestimated, compared to data from the United States.[4]

In France, a network comprising eight poison control centres (PCC) provides round-the-clock telephone expert treatment advice and assistance, by either physicians or nurses trained to handle these calls, in case of exposure to poisonous or hazardous substances. Both PCC and RPVC work independently to alert the French National Agency for Drug and Health Product Safety about any potential issue related to drugs or health products.

The aim of this retrospective study was to analyse cases of AAI-related ADR reported in the PCC database using a standardized questionnaire designed for this survey.

We identified 315 AAI-related ADRs from 2018 to 2022. The number of ADRs ranged from 51 to 83 per year and the ratio of AAI-related ADR to the total of AAIs sold ranged from 65 to 86 cases per million AAIs per year (Figure 1).

From overall 315 reports, 162 (51.4%) occurred in males (mean age: 21.7 years [standard deviation: 20.8]), with 184 (58.4%) cases reported in children (<7 years, $n=111$). The settings where the 315 ADR occurred were: home ($n=249$, 79%), working place ($n=12$, 3.4%), school setting ($n=12$, 3.4%), doctor's office ($n=9$, 2.7%), hospital ($n=9$, 2.7%), community pharmacy ($n=9$, 2.7%), kindergarten ($n=4$, 1.3%), and outdoor ($n=2$, 0.6%). Most cases ($n=293$, 93%) occurred due to an accidental use outside the context of an allergic reaction, whereas 22 (7%) cases followed the treatment of an allergic reaction.

The most common reason was the mishandling of the AAI by the patient or a third party when storing the device or checking its expiration date ($n=70$, 22.2%). Other reasons were: children "playing" with the device out of curiosity ($n=42$, 13.3%), or the mishandling of the AAI during a demonstration ($n=31$, 9.8%).

Summary box

- Most adrenaline auto-injector-related adverse drug reactions are of mild severity, avoidable, after accidental injections.
- Adrenaline injected by subcutaneous/intramuscular routes is well-tolerated, even out of the context of anaphylaxis.

The three most frequent accidental injection sites were the finger ($n=200$, 63.5%), the palm of the hand ($n=46$, 14.6%) and the thigh ($n=27$, 7.7%). One hundred and forty-one (44.8%) patients had auto-limited ADR, 89 (28.3%) required medical evaluation and 85 (27.0%) were admitted to an emergency department. Local symptoms/signs have been reported in 187 cases (59.4%): pain ($n=136$, 43.2%), pallor ($n=96$, 30.5%), coldness ($n=66$, 21.0%), hematoma ($n=51$, 16.2%), hypoesthesia-paraesthesia ($n=34$, 10.8%), ischemia ($n=5$ with necrosis in 2). Systemic symptoms have been reported in 22 (7.0%) cases: tachycardia ($n=20$, 6.3%), hypertension ($n=3$, 1.0%), dizziness ($n=2$, 0.6%), tremors ($n=2$, 0.6%), vomiting and chest pain ($n=1$, 0.3%, each). Six (1.9%) patients required the use of vasodilator (topical nitroglycerine, $n=4$; intravenous ilomedine, $n=2$; intravenous nicardipine, $n=1$).

ADR occurred mainly with Epipen® ($n=193$, 61.3%), but also Anapen® ($n=61$, 19.4%), Jext® ($n=49$, 15.6%) and Emerade® ($n=12$, 3.9%). The frequency of AAI-related ADR per million AAI sold was higher for Epipen® (187) and Jext® (108) than for Emerade® (40) or Anapen® (25) ($p<10^{-3}$).

Our study focused on AAI-related ADR reported to the French national database of the PCC. Compared to our analysis of the French RPVC database, more cases have been captured (42 cases between 1984 and 2022), even if the real number of ADRs may remain underestimated.[3,4] For comparison, two US surveys conducted with PCC found 15,190 AAI-related ADRs from 1994 to 2007, and

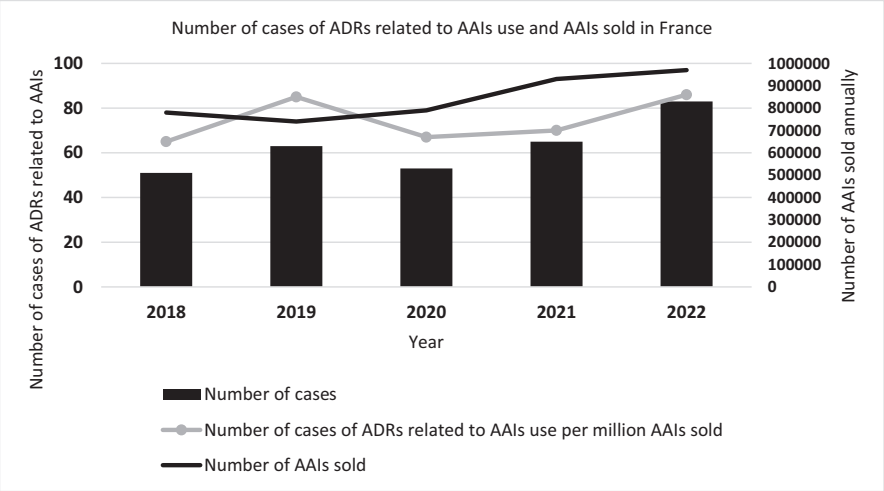

FIGURE 1 Number of cases of adverse drug reactions (ADR) related to the use of adrenaline auto-injectors (AAI) reported to the poison control centres (in bars, left scale) and number of AAI sold annually (in line, right scale) in France, between 2018 and 2022.

6806 cases from 2013 to 2014.[5,6] There is no similar data reported in Europe.

In our study, most of the ADRs were avoidable and of mild severity, mainly related to accidental injections out of the context of an allergic reaction. By contrast, in the United States, 40% of the 15,190 unintentional injections from AAI occurred during attempts to treat allergic reactions.[5] Strikingly, we found that most AAI-related ADR occurred in children (58%) as reported in the United States.[5] This should underline the need to improve AAI design along with increased vigilance in training children and families. AAI device design is known as a major determinant of successful adrenaline administration.[6] In addition, our data highlight that adrenaline injected by subcutaneous and intramuscular routes is well-tolerated even out of the context of anaphylaxis.

We found that most of the AAI-related ADR resolved spontaneously or using warm soaks and massaging, similar to a US survey.[7] Only 2% of the ADR resulted in digital ischemia treated with topical or intravenous vasodilators. However, in a systematic review, of 58 accidental digital adrenaline injections with detailed information 52% were treated with phentolamine and 24% with topical nitroglycerine.[8] In case of an accidental digital injection, warm soaks and massaging of the injection site are recommended as first-line management whereas patients with more severe ADR should be addressed in a healthcare setting to discuss the use of vasodilators on an individual basis.[8]

Prevention of AAI-related ADR requires better training of patients, caregivers and healthcare professionals using toolkits and AAI trainers as well as technological innovations from manufacturers to improve the ergonomics and safety of devices. There remains a large unmet need in the anaphylaxis treatment with new administration routes for adrenaline (nasal and sublingual) being under investigation as alternatives to adrenaline injection.

AUTHOR CONTRIBUTIONS

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

KEYWORDS

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

ACKNOWLEDGEMENTS

We thank the collaborators of the French poison control centers and the Anaphylaxis Working Group of the French Allergy Society. Collaborators of the French Poison Control Centers (PCC) Research group not listed as main authors: M. Deguigne, G. Le Roux, A. Descatha (Grand Ouest/Angers PCC); R. Azzouz (North/Lille PCC); A.M. Patat, N. Paret (Lyon PCC); M. Labadie, I. Blanc-Brisset, A. Nardon, C. Paradis (Bordeaux PCC); L. de Haro, N. Simon (Marseille PCC); N. Delcourt, F. Pelissier (Toulouse PCC); E. Puskarczyk (East PCC), J. Langrand, H. Laborde-Casterot, W. Care, D. Vodovar (Paris PCC). Collaborators of the Anaphylaxis Working Group of the French Allergy Society: J.C. Bonneau (Angers), E. Beaudouin (Metz), C. Chatain (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), D. Sabouraud-Leclerc (Reims). We thank Yasmin Karaca (Department of Paediatrics, Children's Hospital, Roubaix, France) for the statistical analysis.

CONFLICT OF INTEREST STATEMENT

GP declares the following conflicts of interest: interventions and/or consultancy work for 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.

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