ORIGINAL ARTICLE | Eur Ann Allergy Clin Immunol | Vol 50, N 5, 211-216, 2018

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Drug-induced anaphylaxis: seven-year single-center survey

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Keywords
allergological workup; anaphylaxis; antibiotics; drug hypersensitivity; nonsteroidal anti-inflammatory drugs

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Doi
10.23822/EurAnnACI.1764-1489.66

Summary
Background and objective. *Drug-induced anaphylaxis (DIA) is the most common cause of fatal anaphylaxis. We aimed to characterize patients with DIA and their allergological workup.* ***Methods***. *Systematic review of patients with history of DIA referred to our center over 7 years.* ***Results***. *125 patients were included (10% pediatric age), the median age of first episode being 36 years (ranging from 1 to 74 years). The main culprits were nonsteroidal anti-inflammatory drugs (NSAIDs) (43%), antibiotics (42%) and anesthetic agents (6%). In 24% of cases the reactions occurred in hospital setting and 14% were perioperative. The etiology was confirmed in 75% of cases through allergological workup.* ***Conclusions***. *NSAIDs and antibiotics were responsible for most of DIA. The heterogeneity of mechanisms, the severity of the reactions and the lack of standardized in vivo and/or in vitro tests for some drugs do not allow to confirm the diagnosis in all cases. Patients with DIA should be evaluated in specialized centers to perform accurate diagnosis, to prevent recurrence and to find safe alternatives.*

Introduction

Anaphylaxis is a rapid-onset, severe and potentially life-threatening systemic hypersensitivity reaction. It is usually characterized by airway, breathing, or circulatory manifestations and usually, although not always, associated with skin and mucosal symptoms (1). Anaphylaxis results from immunological (immunoglobulin E [IgE] or non-IgE mediated) or non-immunological mechanisms to certain antigens, with release of vasoactive mediators from tissue mast cells and peripheral basophils. Regarding drug anaphylaxis, the reactions are mostly mediated by antigen-specific IgE responses, but other mechanisms have been clarified (2). Most drugs are relatively too small to elicit an immune response, and are supposed to act as haptens or prohaptens in order to be immunogenic (IgE-dependent mechanism). IgE-independent drug anaphylaxis might result from direct mast cell degranulation, complement activation, kallikrein activation, histamine release or due to contaminants in drug formulation (3).

Drug-induced anaphylaxis (DIA) is the most common cause of fatal anaphylaxis (4,5). According to Jerschow et al., 58.8% of fatal anaphylaxis were drug-induced. Nevertheless, in 75% of the fatal cases the culprit drug was not specified (5).

Anaphylaxis related to nonsteroidal anti-inflammatory drugs (NSAIDs) is typically drug-specific or class-specific, as well as with beta-lactams antibiotics (BL). NSAIDs have been considered as the most common pharmacological cause of anaphylaxis (6). Some of these reactions occur with the whole class or appear to be drug-specific (3).

Although skin testing and drug provocation tests (DPT) can confirm the diagnosis, in severe cases the diagnosis is mostly based on clinical history. Furthermore, the main difficulty in confirming the diagnosis of DIA results from the lack of standardized tests to most drugs, and often the patients refuse to

undergo the challenge tests with the culprit drug, considering the severity of the reactions reported.

It is difficult to quantify the rate and mortality of DIA, due to the heterogeneity of methodology, different sample populations and definitions of anaphylaxis. Furthermore, the notification systems are not uniform (7). The estimated incidence of anaphylaxis in Western countries ranges from 8 to 50/100,000 person-years, with a lifetime prevalence of 0.05 to 2% (8). According to older studies, penicillin and anesthetic agents given during the perioperative period were the commonest causes of IgE-mediated allergic anaphylaxis, while NSAIDs and radiocontrast media were the most common causes of non-immunological anaphylaxis (6). Drugs are considered the main trigger of adult-age anaphylaxis, with the highest rate observed in the 55 to 84 year age group (3.8/100,000 individuals), and were the main cause of fatal anaphylaxis in the United Kingdom, New Zealand and Australia (7).

We aimed to characterize patients with DIA and their drug allergy workup, contributing to a better understanding about the main elicitors and the accuracy of a proper allergological investigation.

Materials and methods

A systematic evaluation of all patients with clinical history compatible with DIA reported to our drug allergy center over seven years (from January 2010 to December 2016) was performed. For each patient, the allergist filled in a questionnaire with all clinical information related with the episode and the investigation performed. The patients were investigated according to ENDA/EAACI (European Network of Drug Allergy/European Academy of Allergy and Clinical Immunology) recommendations, through skin testing (9) and specific IgE to drugs when they are standardized, and/or DPT when indicated (10,11). All patients signed an informed consent. Serum-specific IgE antibodies (ImmunoCAP®, Thermo Fisher Scientific) and skin testing were performed at least after a 4 weeks interval after the clinical reaction. For specific IgE a cut-off value of ≥ 0.35 kU/L was considered positive (12). Regarding drugs with standardized skin test concentrations, skin prick tests (SPT) were the first step of the in vivo investigation, and only if negative, intradermal tests (IDT) were carried out. For the BL workup we have used solutions of benzylpenicilloyl octa-L-lysine (PPL), sodium benzylpenilloate - minor determinant (MD), penicillin G, amoxicillin and clavulanic acid; other BL were tested if they were the culprit drug. PPL and MD were always performed with DAP® Penicillin extracts (Diater, Madrid, Spain). In the last two years, we also performed amoxicillin and clavulanic acid with DAP®-3 Amoxicillin and DAP® Clavulanic extracts (Diater, Madrid, Spain). IDT were carried out beginning with 10-100 times more diluted solutions, which were gradually increased until the appearance of a positive skin response, or until reaching the maximum concentration recommended for that drug (9). Histamine (10 mg/mL) was used as a positive control for SPT, and 0.9% saline solution as a negative control. In SPT, a mean wheal larger than 3 mm, accompanied by erythema, with a negative response to negative control, was considered positive. For IDT, 0.02 to 0.05 mL of solution is injected into the dermis to produce a small wheal, that is outlined; IDT was considered positive when the mean diameter of initial wheal increased more than 3 mm.

In case of negative results with in vitro and skin tests, and if needed to confirm diagnostic, the patients underwent DPT with the culprit drug. All in vivo tests were performed by allergists with experience in recognition and management of acute reactions. Epinephrine and other appropriate medication and resuscitation equipment were always available during the procedures.

Results

We report data from 125 patients, who were referred to our drug allergy center with a diagnosis of DIA performed by an allergist. We included patients from all ages, 10% aged under 18 years and 6% older than 65 years. Detailed demographic and clinical characterization is presented in **table I**.

The mean age at the first anaphylactic episode was 36.4 years, ranging from 1 to 74 years. Regarding the clinical manifestations, there was a predominance of mucocutaneous symptoms (96%), followed by respiratory (80%) and cardiovascular (45%) involvement, with loss of consciousness in 20% of cases and less frequently with gastrointestinal complaints (21%). In 68% of cases the reaction occurred within the first 30 minutes after drug administration.

Table I *- Demographic and clinical characterization.*

Baseline characteristics	
n (sex)	125 (66% female)
mean age at the first appointment (years) (± SD); (range)	41.1 (± 16.7); (1.5 - 75)
median age at the first anaphylactic episode (years); (range)	36.4 (1 - 74)
under 18 years	10%
atopic[1]	69%
asthma	25%
patients with recurrent episodes DIA	19%

[1]Atopy was defined as positive skin prick test to at least one common aeroallergen.

Abbreviations: DIA, drug-induced anaphylaxis; SD, standard deviation.

Concerning the culprit drugs, the main causes were NSAIDs (54 patients) and antibiotics (52 patients). Other drug agents found were proton pump inhibitors (6 patients), neuromuscular blocking drugs (5 patients), carboplatin (3 patients), corticosteroids (2 patients), local anesthetics (2 patients), ranitidine, midazolam and patent blue (1 patient each). **Table II** describes all the drugs involved, according to age group. Two patients reacted subsequently with two drug classes (antibiotics and NSAIDs): one of them with penicillin and metamizole, and the other with minocycline and metamizole.

The circumstance in which the reaction occurred was documented. We found that 24% of reactions occurred in hospital setting, and 14% of patients had perioperative anaphylaxis. Despite the severity of the reactions, only 40% of patients were appropriately treated with epinephrine. However, 22% could not remember exactly which medications were administered.

We included 18 patients with perioperative anaphylaxis. The agents involved in these reactions were mainly antibiotics (eight patients) and neuromuscular blocking drugs (five patients), followed by NSAIDs (2 cases; metamizole and ketorolac), midazolam, local anesthetic (bupivacaine) and patent blue dye (1 patient each). Among antibiotics we had seven cases with cefazolin and one with ciprofloxacin. Among neuromuscular blocking drugs we had three cases with atracurium, one with rocuronium and one with succinylcholine.

Furthermore, 19% of patients had recurrent episodes of DIA, before the etiologic diagnosis was made. Most of the recurrent cases were due to NSAIDs, what supports the diagnosis of DIA.

Etiologic diagnosis of DIA was confirmed in 94 patients (75%), through skin tests in 72 patients (**table III**) - we highlight that two patients had a severe systemic reaction during IDT that resolved with intramuscular epinephrine - and the remaining 22 patients by in vitro tests (2 patients) or DPT (20 patients). Considering the severity of reactions and the lack of standardized tests for some drugs, the remaining patients whose DIA was based on clinical history were successfully challenged with alternative drugs. In most of these cases, the culprit drugs were NSAIDs, COX-1 preferential inhibitors, and the patients had previous history of allergic reaction with these drugs.

In two patients, the diagnosis was accomplished by in vitro tests, namely after positive results in specific IgE to bela-lactams (one patient with specific IgE to amoxicillin, ampicillin and penicillin G and V > 100 kU/L, and the other patient with specific IgE to amoxicillin 11.4 kU/L).

Twenty patients were diagnosed through DPT with the culprit drug. We highlight six patients with positive BL oral challenge (four with amoxicillin, one with clavulanic acid [with negative DPT to amoxicillin] and another with cefuroxime) and one patient who had positive ropivacaine subcutaneous challenge. In the remaining cases the culprit drugs were NSAIDs.

Table II *- Culprit drugs by age group.*

Drug class / Drug	Total (n = 125)	< 18 years (n = 13)	≥ 65 years (n = 8)
NSAIDs	54 (43.2%)	6	3
acetylsalicylic acid	15	1	
ibuprofen	13	3	
metamizole	14	1	2
diclofenac	9		1
paracetamol	3	2	
etodolac	1		
ketorolac	1		
clonixin	1		
Antibiotics	52 (41.6%)	7	5
beta-lactams	43	7	3
amoxicillin	27	6	2
cefazoline	7		
cefuroxime	1		
clavulanic acid	2		
flucloxacillin	2	1	
penicillin	4		1
quinolones ciprofloxacin	4		2
macrolides clarithromycin	3		
fosfomycin	1		
minocycline	1		
Others	21 (16.8%)		
Proton pump inhibitors	6		
omeprazole	3		
pantoprazole	2		
esomeprazole	1		
Neuromuscular blocking drugs	5		
atracurium	3		
rocuronium	1		
succinylcholine	1		
carboplatin	3		
Corticosteroids	2*		
hydrocortisone	2		
budesonide	1		
Local anesthetics	2		
bupivacaine	1		
lidocaine	1		
ranitidine	1		
midazolam	1		
patent blue	1		

* One patient had anaphylaxis to both hydrocortisone and budesonide.

Table III *- Positive results of skin testing (72 patients).*

Positive skin tests	Patients
SPT (n)	16
BL (AX-7, Pen-1)	8
metamizole	4
quinolone (levofloxacin)	1
carboplatine	1
PPI (esomeprazole and omeprazole)	1[1]
local anesthetics (lidocaine, mepivacaine)	1[1]
IDT (n)	59
BL (AX-12, PPL-3, MD-1, cefazoline-7, flucloxacillin-2, clavulanic acid-1)	24[2]
NSAIDs (metamizole-5, diclofenac-4, paracetamol-1)	10
NMBD (atracurium-3, cisatracurium, rocuronium, succinilcoline)	5[3]
PPI (omeprazole-3, pantoprazole-2)	5
macrolides (clarithromycin-3, erythromycin-1)	3[4]
quinolones (ciprofloxacin, levofloxacin)	2
carboplatine	2
hydrocortisone	1
midazolam	1
local anesthetics (bupivacaine, ropivacaine and procaine)	1[1]
ranitidine	1

Abbreviations: AX, amoxicillin; BL, beta-lactams; IDT, intradermal test; MD, sodium benzylpenilloate - minor determinant; NMBD, neuromuscular blocking drugs; Pen, penicillin; PPL, benzylpenicilloyl octa-L-lysine; PPI, proton pump inhibitors; SPT, skin prick test.
Three patients had positive results to both SPT and IDT (different extracts within the same class, quinolones and local anesthetics; and one patient with drugs of different classes, metamizole and penicillin).
[1]Positive skin tests in the same patient; [2]Two patients have IDT positive with both amoxicillin and PPL; [3]One patient had IDT positive with both atracurium and cisatracurium; [4]One patient had IDT positive with both clarithromycin and erythromycin.

In case of anaphylaxis to local anesthetics, both patients were found to be allergic to all drugs within this pharmacological group. It was not possible to find an alternative drug (neither amides nor esters), therefore these two patients were advised to keep strict avoidance of all local anesthetics.
We found seven patients with immediate severe reactions in perioperative setting to cefazolin. One of these patients developed Kounis syndrome after cefazolin infusion. Exploring the cross-reactivity between cefazolin and other BL we confirmed that all these patients with IgE-mediated hypersensitivity reactions to cefazolin can tolerate other beta-lactams, which explains a selective pattern of reactivity.

Discussion

We found that NSAIDs and antibiotics were the most common causes of DIA. However, there is only a slight predominance of NSAIDs (43.2%) as culprit drugs comparing to antibiotics, which were responsible for 41.6% of the anaphylactic reactions. In our sample the anesthetics agents, namely the neuromuscular blocking drugs, were less often reported as culprit of DIA. Anaphylaxis related to local anesthetics are very rare, considering how often they are used, but we had two patients with severe reactions. It is also important to notice the emergence of proton pump inhibitors (six patients), previously considered as unsuspected elicitors of anaphylaxis (13). We did not find any case of severe reaction due to radiocontrast agents. In our sample, we did not register any fatal case of DIA.
Considering an American survey from 1999 to 2010, the antibiotics accounted for 40% of the fatal episodes, mainly penicillins, followed by cephalosporins, sulfonamides and macrolides; radiocontrast agents were implicated in 27% of fatalities and antineoplastic drugs in 12.5%. The remaining culprit drugs

were NSAIDs, serum, opiates, antihypertensive agents, and anesthetic agents (5).

According to a Portuguese drug anaphylaxis survey over a 4-year period (2007-2010), NSAIDs were responsible for 48% of all cases (acetylsalicylic acid, diclofenac, and ibuprofen as main culprits) (6). Similar results were found in a 6-year observation study performed in a Spanish tertiary university hospital, in which NSAIDs were responsible for 49% of the anaphylactic reactions (dipyrone, aspirin and diclofenac as main culprits) (14). Comparing to a previous study reporting a decade review of reactions to a Portuguese Pharmacovigilance Authority, NSAIDs are the culprit drugs in 13% of cases (after antibiotics) (15). In the same study, a subgroup analysis in pediatric population showed that NSAIDs account for 7% of the reported cases (15). According to Online Latin American Survey on Anaphylaxis (OLASA), NSAIDs were the culprit agents in 73% of the DIA (16).

NSAIDs were the main cause of DIA in our sample. It is consensual that COX-1 inhibitors are the main class within the group involved in anaphylaxis. In our study, acetylsalicylic acid, ibuprofen, metamizole and diclofenac account for 87% of all cases related to NSAIDs. We stress three cases with anaphylaxis to paracetamol, two of them at pediatric age, confirmed by DPT. Despite the small number of children and adolescents (13 patients), in this age group antibiotic-induced anaphylaxis (7 patients) is slightly higher than NSAIDs-induced anaphylaxis (6 patients).

Pyrazolones (metamizole) are a common cause of NSAIDs-induced anaphylaxis. Anaphylaxis was reported in 18-30% of patients hypersensitive to pyrazolones (17). In our sample, metamizole accounts for 26% of NSAIDs-induced anaphylaxis.

Regarding antibiotic-induced anaphylaxis, our results agree with previous reports, showing a higher rate of episodes related to beta-lactams (83%) comparing to other groups of non-beta-lactam antibiotics. In a UK database of anaphylaxis, amoxicillin was the most prevalent cause of antibiotic-related anaphylaxis (18). Benzylpenicillin, the initial inducer of allergic reactions, has been replaced by amoxicillin and recently, although in a lesser extent, by cephalosporins. These molecules often show extent cross-reactivity among similar chemical compounds. However, selective responses have been observed, restricted to one group or one single compound, as occurs in the group of cephalosporins (19). In our sample we found 7 patients allergic to cefazolin (16% of beta-lactam-induced anaphylaxis). We speculate this higher incidence might be due to the frequent use of this first-generation cephalosporin, by parenteral route in prophylactic surgical protocols.

The incidence of perioperative anaphylaxis varies between studies from different countries, ranging from 1/1250 to 1/18 600 (20). There is a substantial geographical variability of drugs or substances involved. Studies in different countries have shown that neuromuscular blocking drugs are a leading cause of perioperative anaphylaxis (20-22). Reactions involving antibiotics, dyes, or chlorhexidine become more frequent in most series. Reactions to latex are decreasing, due to effective avoidance measures (20). In our study, neuromuscular blocking drugs were the second most common cause of perioperative anaphylaxis (29.4%) after antibiotics (41.2%). Reactions involving local anesthetics are very uncommon in series from all countries (20). Our series includes one case of anaphylaxis to bupivacaine, whose allergological workup revealed hypersensitivity to all local anesthetics (amides and esters).

Analyzing host related factors, females appear to be more likely to develop drug allergies than males (7). We found similar results, with predominance of cases in females (66%).

Regarding age groups, it is not clearly demonstrated if the incidence of drug allergy is lower in children. We documented only 13 patients aged under 18 years (10%). We can speculate the lower rate of anaphylactic reactions in children and adolescents can be explained by lower exposure and time necessary for sensitization to occur (7).

In our sample, skin tests were useful to confirm IgE-mediated reactions to the suspected drugs and to assess potential cross-reactivity. Etiologic diagnosis of DIA was supported by skin testing in 58% of the patients. Diagnostic accuracy and standard concentrations of most of the skin tests used are widely proven, allowing to avoid a DPT in case of positive result.

Conclusions

NSAIDs and antibiotics were responsible for most cases of DIA. Anaphylactic reactions can be reported at any age. The heterogeneity of mechanisms involved, the severity of clinical reactions and the lack of standardized in vivo and/or in vitro tests do not allow to confirm the diagnosis in all cases. Patients with DIA should be evaluated in specialized centers, to perform accurate diagnosis, to prevent recurrence, and to find safe alternatives.

Conflict of interest

The authors declare that they have no conflict of interest.

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