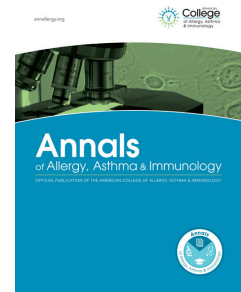


Journal Pre-proof

Are Drugs More Dangerous? Drug Induced Anaphylaxis Across the World

Anca Mirela Chiriac, MD, PhD, Professor of Immunology and Allergology, Pascal Demoly, MD, PhD, Professor of Pulmonology and Allergology



PII: S1081-1206(19)31455-3

DOI: <https://doi.org/10.1016/j.anai.2019.11.025>

Reference: ANAI 3085

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 19 November 2019

Accepted Date: 19 November 2019

Please cite this article as: Chiriac AM, Demoly P, Are Drugs More Dangerous? Drug Induced Anaphylaxis Across the World, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.11.025>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Are Drugs More Dangerous? Drug Induced Anaphylaxis Across the World

Anca Mirela CHIRIAC, MD, PhD, Professor of Immunology and Allergology; Pascal DEMOLY, MD, PhD, Professor of Pulmonology and Allergology

1 Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France;

2 Equipe EPAR - IPLESP, UMR-S 1136 INSERM - Sorbonne Université, Paris, France

Funding Source: none

Trial Registration: not applicable

Conflicts of interest: none

Word count : 1194

Drug-induced anaphylaxis (DIA) is a well recognized risk factor for virtually all classes of medications. The incidence and specific risk factors vary widely depending upon the class of drug and reported populations. This perspective addresses recent data reported on DIA and its impact on the understanding of the epidemiology, pathophysiology and management of anaphylaxis.

What is the epidemiological data supporting the knowledge about DIA?

Using electronic health record (EHR) data collected over two decades (roughly 2 million patients) from the allergy module of the Partners HealthCare System (Massachusetts, US), Dhopeswarkar et al (1) found that 1.1% of patients report DIA. Their study revealed a relatively stable prevalence of DIA over the year, well above that of the general population (2). Demographics like white race and female sex as well as comorbidities like mastocytosis were associated with a 2 and 4-fold increased odds of reporting DIA, respectively. Not surprisingly, penicillins were the 1st providers of DIA, but other culprits known to induce anaphylaxis (e.g., quinolones, cephalosporins) came in behind sulfonamides and non-steroidal anti-inflammatory drugs (NSAIDs). Two details of their study bear emphasis: less than 1% of these patients had a tryptase measurement performed within 1 week of anaphylaxis recorded date, and only 8% of patients were seen by an allergist.

In a pediatric (<15yrs) Korean population , 676 pediatric ED visits during the 5-year study period), Choi et al (3) identified 15.6% of all causes of anaphylaxis as DIA (29 patients, 0.03%), with beta-lactams and NSAIDs being the most frequent providers, followed by vaccines. A similar study conducted in the US (4) found that the number needed to harm (NNH) for ED visits that involved a moderate-to-severe allergic reaction (including DIA, but not only) was lowest not

for beta-lactams, but for the oral quinolones (1 in 2525 dispensed prescriptions), highlighting again that some drugs are more frequent inducers of DIA.

The European Anaphylaxis Registry (5) identified 101 cases of DIA in children and adolescents, accounting for 5% of all anaphylaxis reports in this population. There was a continuous evolution from food- to insect venom- and DIA up to age 10 years,. Drugs were the second main cause of anaphylaxis in adults (around 25%, after venom-induced anaphylaxis), being more prevalent in the elderly (> 65 years). Throughout all age groups, beta-lactams and NSAIDs (mainly diclofenac and metamizole in the adult population) were the main culprits. Quinolones accounted for 5% of events in adults. Mast cell disorders and physical exercise increased the severity of anaphylaxis. DIA will have a specific code in the International Classification of Diseases (ICD) version11 and although its implementation needs further work, the new classification should enable the collection of more accurate epidemiological data on DIA, together with the expansion and availability of more EHRs worldwide.

Increasing our knowledge about fatal drug-induced anaphylaxis

DIA can induce fatal reactions from drugs used in therapeutic or exploratory settings. With regards to the latter, beta-lactams are responsible for deaths occurring during allergy work-up, such as skin testing (6) and controlled provocation (7). Drugs are the first or second cause of fatal anaphylaxis across publications. In some databases (8), fatal anaphylaxis due to unknown causes accounted for a significant percentage of cases with previous episodes of alleged drug hypersensitivity reactions (DHR) indicating that a relevant percentage of cases of unknown causes could be due to DIA. Globally, prior episodes of DHR in patients with fatal DIA have been reported within a range of 6 to 100%.

The main culprit drugs are consistent across studies, namely antibiotics (mainly beta-lactams) and NSAIDs, whether the analysis is performed on inpatient (8) or outpatient deaths (9). The later encompass a wider range of culprits including contrast media, anaesthetic agents, antineoplastic agents (8). In Spanish hospitals, eight drugs accounted for over 75% of deaths from DIA.

Cardio-respiratory arrest in DIA ensued in most cases due to cardio-circulatory failure as primary pathophysiological mechanism of death. This observation is enhanced by the frequent presence of ischemic heart disease in the subgroup of patients dying of DIA (9). Arrest could occur within 5 minutes (median; range =1-80 min) when drugs were given intravenously and patients dying of DIA were older than those suffering food allergy fatal anaphylaxis (8,9).

Insights into the pathophysiology of drug-induced anaphylaxis

DIA in drug-naïve patients can be often explained by IgE cross-sensitization or the action of non-IgE-dependent mechanisms.

IgG-dependent drug-induced anaphylaxis in humans

Specific IgG antibodies to drugs have been proposed to trigger human IgE-independent anaphylaxis induced by some protein antigens (therapeutic antibodies) or high molecular weight drugs, including dextran or protamine. In mice, anaphylactic reactions may occur in the absence of IgE, FcεR1s, or mast cells, through an IgG antibody–neutrophil-platelet activating factor (PAF) pathway. The multicentric Neutrophil Activation in Systemic Anaphylaxis (NASA) study (10) has recently analyzed patients with perioperative anaphylaxis (PA) and documented FcγRs

engagement by immunocomplexes of [anti- NMBA IgG-NMBA], supporting the hypothesis that the IgG-mediated pathway for small molecules is clinically relevant, either enhancing the IgE-dependent pathway or autonomously.

The role of MRGPRX2 in drug-induced anaphylaxis

An antibody-independent, pathway of anaphylaxis has been reported after cationic drug administration, involving an interaction with Mas-related G-protein coupled receptor member X2 on mast cells (11) which may explain reactions to quinolones, opioids and other direct mast cell activating drugs.

However, drug-induced mast-cell activation is not a uniform event. Mast cells differentially exteriorize secretory granules in response to different stimuli and spatiotemporally distinct degranulation patterns have been documented, such as with substance P, complement anaphylatoxins C3a and C5a and endothelin 1.

Is it drug-induced anaphylaxis?

Antineoplastic and new biological drugs, small molecules and monoclonal antibodies can induce infusion related reactions (IRR) or more severely, cytokine release syndromes (CRS). IRR are generally managed by slowing the infusion rate and/or use of antihistamines or antipyretics, whereas desensitization protocols have been used in CRS management (12). DIA and CRS have some overlapping features. In a large series of drug allergy work-up and desensitizations to biologicals (12), one third of either CRS or mixed (suggesting Type I allergy and CRS) phenotypes were initially identified as DHR. Elevated serum IL-6, as opposed to tryptase, was used as a biomarker for CRS. Interestingly, the authors noted a shift from the Type I allergy

pattern to the CRS (52% of all reactions), following desensitization, but could not explain this conversion.

Conclusion

Generally, medications available today around the world are both safe and effective. As new drugs with allergenic potential such as monoclonal antibodies and small molecules enter the market, DIA is becoming better diagnosed and managed which can mitigate increased risk. According to current guidelines, epinephrine is the medication of choice for immediate treatment of anaphylaxis regardless of its mechanism or trigger. Alternatives to the classical IgE/FcεRI crosslinking model as the main cause of DIA are emerging, providing evidence of a shift in paradigm and paving the way for the development of novel diagnostic and therapeutic strategies..

References

1. Dhopeswarkar N, Sheikh A, Doan R, Topaz M, Bates DW, Blumenthal KG, Zhou L. Drug-Induced Anaphylaxis Documented in Electronic Health Records. *J Allergy Clin Immunol Pract.* 2019;7:103-111.
2. Tanno LK, Bierrenbach AL, Simons FER, Cardona V, Thong BY, Molinari N, Calderon MA, Worm M, Chang YS, Papadopoulos NG, Casale T, Demoly P; on behalf the Joint Allergy Academies. Critical view of anaphylaxis epidemiology: open questions and new perspectives. *Allergy Asthma Clin Immunol.* 2018;14:12.
3. Choi B, Kim SH, Lee H. Missed Registration of Disease Codes for Pediatric Anaphylaxis at the Emergency Department. *Emerg Med Int.* 2019;2019:4198630.
4. Lovegrove MC, Geller AI, Fleming-Dutra KE, Shehab N, Sapiiano MRP, Budnitz DS. US Emergency Department Visits for Adverse Drug Events From Antibiotics in Children, 2011-2015. *J Pediatric Infect Dis Soc.* 2018 Aug 23. doi: 10.1093/jpids/piy066. [Epub ahead of print]
5. Grabenhenrich LB, Dölle S, Moneret-Vautrin A, Köhli A, Lange L, Spindler T, Ruëff F, Nemat K, Maris I, Roumpedaki E, Scherer K, Ott H, Reese T, Mustakov T, Lang R, Fernandez-Rivas M, Kowalski ML, Bilò MB, Hourihane JO, Papadopoulos NG, Beyer K, Muraro A, Worm M. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol.* 2016;137(4):1128-1137.
6. Chiriac AM, Vasconcelos MJ, Izquierdo L, Ferrando L, Nahas O, Demoly P. To challenge or not to challenge: literature data on the positive predictive value of skin tests to beta-lactams. *J Allergy Clin Immunol Pract.* 2019 Mar 4. pii: S2213-2198(19)30199-0. doi: 10.1016/j.jaip.2019.01.060. [Epub ahead of print] PubMed PMID: 30844483.
7. Sompornrattanaphan M, Wongsas C, Kreetapirom P, Taweechue AJ, Theankeaw O, Thongngarm T. Fatal anaphylaxis from a second amoxicillin/clavulanic acid provocation after a prior negative provocation. *J Allergy Clin Immunol Pract.* 2019 Jul 31. pii: S2213-2198(19)30640-3.
8. Tejedor-Alonso MA, Vallejo-de-Torres G, Escayola EN, Martínez-Fernandez P, Moro-Moro M, Masgrau NA. Postmortem tryptase cutoff points and main causes of fatal anaphylaxis. *J Allergy Clin Immunol Pract.* 2019 Jul 24. pii: S2213-2198(19)30632-4.
9. Martínez-Fernandez P, Vallejo-de-Torres G, Sánchez-de-León-Robles MS, Navarro-Escayola E, Moro-Moro M, Alberti-Masgrau N, Tejedor-Alonso MA. Medical and pathologic characteristics of fatal anaphylaxis: a Spanish nationwide 17-year series. *Forensic Sci Med Pathol.* 2019 Sep;15(3):369-381.

10. Jönsson F, de Chaisemartin L, Granger V, Gouel-Chéron A, Gillis CM, Zhu Q, Dib F, Nicaise-Roland P, Ganneau C, Hurtado-Nedelec M, Paugam-Burtz C, Necib S, Keita-Meyer H, Le Dorze M, Cholley B, Langeron O, Jacob L, Plaud B, Fischler M, Sauvan C, Guinnepain MT, Montravers P, Aubier M, Bay S, Neukirch C, Tubach F, Longrois D, Chollet-Martin S, Bruhns P. An IgG-induced neutrophil activation pathway contributes to human drug-induced anaphylaxis. *Sci Transl Med*. 2019;11(500). pii: eaat1479. doi: 10.1126/scitranslmed.aat1479.
11. McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature*. 2015;519:237-241.
12. Isabwe GAC, Garcia Neuer M, de Las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. *J Allergy Clin Immunol*. 2018;142(1):159-170.