



Drug-induced anaphylaxis: is it an epidemic?

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Purpose of review

The present review addresses the epidemiology, analyzes the current data and promotes global awareness of drug-induced anaphylaxis.

Recent findings

Anaphylaxis is a medical emergency that may cause death! In the last decade, studies have shown an increasing incidence and prevalence of anaphylaxis.

Summary

Drug-induced anaphylaxis fatalities have increased, and this syndrome remains underdiagnosed and undertreated.

Keywords

anaphylaxis, drugs, epidemic, hypersensitivity reactions, mortality

DRUG-INDUCED ANAPHYLAXIS: IS IT AN EPIDEMIC?

Anaphylaxis is a medical emergency that may cause death! In the last decade, studies have shown an increasing incidence and prevalence of anaphylaxis, mainly due to drug-induced and food-induced reactions. Drug-induced anaphylaxis fatalities have also increased, and this syndrome remains underdiagnosed and undertreated [1[•],2,3^{••}]. In this scenario, guidelines and consensus have been developed to increase global awareness and to promote better diagnosis and management of anaphylaxis [1^{••}].

Anaphylaxis is a serious, life-threatening and immediate systemic hypersensitivity reaction (HSRs) induced by mast cells and basophils degranulation. The three main causes of anaphylaxis are drugs, food and hymenoptera venom [4]. HSRs induced by drugs are a subgroup of unexpected adverse drug reactions (ADRs) initiated by exposure to a drug at a dose tolerated by normal individuals and characterized by objectively reproducible symptoms or signs, which clinically resemble allergy [5,6]. As defined by the International Consensus on Drug Allergy, immediate HSRs, those that occur within 1–6 h after drug exposure, are characterized by urticaria, angioedema, rhinoconjunctivitis, bronchospasm and anaphylaxis [6].

In accordance with international guidelines, the diagnosis of anaphylaxis is based on clinical findings that constitute three criteria [4,7]. It relies on recognition of characteristic signs and symptoms, which occur minutes to a few hours after exposure

to a known or potential trigger, often presenting rapid progression. The principal aspects of anaphylaxis are summarized in Table 1.

Anaphylaxis can be classified as, first, allergic, in which there is a specific immune response, almost always mediated by IgE and, possibly, in few cases by IgG; second, nonallergic, with direct degranulation of mast cells/basophils (Fig. 1) [5]. Anaphylaxis can occur during the first or after several exposures to a specific drug. Reactions on the first or second exposure are generally nonallergic, as there is not enough time for sensitization and a specific immune response development, unless the patient is sensitized to another similar substance and a cross-reaction is involved [8]. For example, most anaphylaxis to taxanes, which usually occur at the first exposures, are probably not IgE-mediated [9[•],10^{••}]. A similar situation can be observed in reactions to iodinated-contrast agents [11^{••}]. In contrast, a patient can be sensitized to penicillin or a platinum-based agent after several exposures and then develop an allergic anaphylaxis [10^{••},12].

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KEY POINTS

- Anaphylaxis is a medical emergency that may cause death.
- In the last decade, studies have shown an increasing incidence, prevalence and mortality of anaphylaxis.
- Drug-induced anaphylaxis remains underdiagnosed and undertreated.

Antibiotics, mainly betalactams, iodinated contrast media (ICM), dextrans, allergen extracts and NSAIDs, have been described as the major causes of drug-induced anaphylaxis [13–16]. The group of drugs most frequently involved in anaphylaxis varies according to different populations, time, geographic regions, drug usage habits, genetic factors, anaphylaxis definitions, registries of cases and study designs [17–19].

Former studies in Europe and North America had shown betalactams as the main culprit drug involved in anaphylaxis [16,20]. More recent studies, particularly in Latin America and Europe, have highlighted NSAIDs as an important cause of these reactions [17,21,22]. In a research analyzing 117 outpatients with anaphylaxis induced by drugs, NSAIDs were implicated in most cases, and IgE-mediated reactions were less frequent but more severe [17,20]. Regarding hospitalized patients, we recently observed an overall incidence of ADRs of 16.2%. ICM and vancomycin were the main causes of these reactions. There were more ADRs in patients with chronic renal failure ($P=0.012$), prolonged hospital stay ($P<0.001$), higher number of diagnoses ($P<0.001$), and higher number of medications used during hospitalization ($P<0.001$). Increasing one medication during hospitalization caused a 14% increase in the chance of HSR ($P<0.001$). There was 57% less chance of new ADRs in patients with a previous history of ADRs ($P=0.017$) [23].

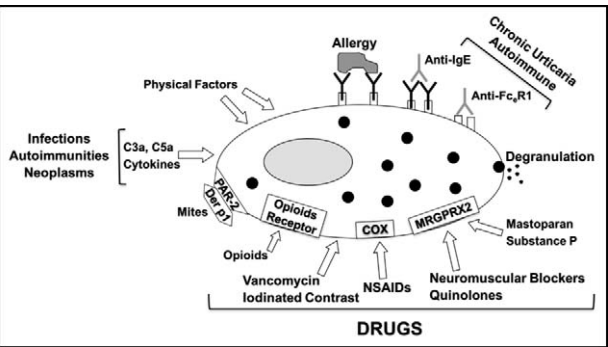


FIGURE 1. Mechanisms of mast cell degranulation.

Table 1. Key features of anaphylaxis

Medical emergence that may be fatal
Diagnosis based on clinical criteria
Systemic hypersensitivity reaction
Mast cells and basophils degranulation
Tryptase is a biomarker of mast cells degranulation
Must be treated with intramuscular epinephrine

In our case series, NSAIDs and beta-lactams are the main cause of drug-induced anaphylaxis in outpatients and inpatients, respectively [17]. Moreover, beta-lactams are the main cause of deaths due to anaphylaxis [24]. However, many new drugs, with special emphasis for chemotherapeutic agents and mAbs, are quickly being developed and approved, many of them through a fast track process to benefit patients who cannot wait. In parallel, adverse reactions to these drugs have increased dramatically worldwide [10²²]. In 2010, anticancer drugs were the third leading cause of fatal drug-induced anaphylaxis in the United States after antibiotics and diagnostic agents [24].

Perioperative anaphylaxis is a life-threatening condition with an estimated prevalence of 1:3500–1:20000 procedures and a mortality rate up to 9%. Several agents may cause these reactions, and neuromuscular blocking agents (NMBAs) and latex should be highlighted [25]. Perioperative anaphylaxis is a specific situation, and it is beyond the scope of this review.

Correct diagnosis and proper management of drug-induced anaphylaxis are fundamental to avoid unnecessary risks and to not deprive patients of the first-line treatment for their disease. Rapid drug desensitization is a ground-breaking procedure that enables selected patients to receive the drug that induced an immediate HSR in a safe way, minimizing the risks of anaphylaxis and treatment failure [26²²]. In this review, we update and discussed drug-induced anaphylaxis, assessing the most prevalent reactions to promote optimal management by allergist-immunologists (Table 2).

NSAIDs

NSAIDs are among the most widely prescribed and used medications in the world, and adverse reactions to this medication group constitute one of the most frequent reasons for allergy specialist's appointment. In Latin America, NSAIDs are the main cause of drug-induced anaphylaxis in outpatients. NSAIDs are overused in Brazil, and dipyrone

Table 2. Drugs most commonly associated with immediate hypersensitivity reactions

Drug class	Prevalence
NSAIDs	Up to 1.9% of the general adult population reports reactions to NSAIDs [27]
Antibiotics	
Beta-lactams	1–20%; Approximately 10–20% of the general population have been labeled as penicillin allergic, but over 90% of them are able to tolerate penicillins [28 [■]]
Quinolones	0.2 to 3%; As a result of their structural diversity, the frequency of adverse reactions with specific agents varies [29]
Contrast media	
Iodinated	Up to 8% for classical ionic high-osmolality iodinated contrast media [30] 0.7 to 3.1% for low-osmolality iodinated contrast media [31 [■]]
Gadolinium-derivatives	0.01% to 2%; Gadobenate has been associated with greater frequency and severity of HSRs [32]
Chemotherapeutic agents	
Platinum-compounds	8–27%; Peak incidence for carboplatin at the eighth or ninth dose [10 [■]]
Taxanes	5–15% in patients using premedication [9 [■]]
mAbs	0.1% to 10%, according to the mAb involved [33] 27% for patients living in the Southern USA and taking cetuximab [33]

(metamizole), which is available in our country, is the main cause of anaphylaxis among all NSAIDs [17]. HSRs to NSAIDs has been classified in five different types of reactions by the European Network for Drug Allergy (ENDA): NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease, NSAID-induced urticaria and/or angioedema (NIUA), single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) and single NSAID-induced delayed hypersensitivity reactions [34]. However, this classification does not allow a correct inclusion of all patients with HSRs to NSAIDs.

NIUA patients sometimes can present anaphylaxis, and not only urticaria or angioedema. Moreover, in clinical practice, it is not rare to see NERD patients who present cutaneous manifestations after exposure to NSAIDs. These patients are cross-intolerant reactors, presenting both respiratory and

cutaneous symptoms, and their HSRs have been named ‘mixed’ or ‘blended’ reactions [35–37]. However, this clinical presentation can be considered anaphylaxis according to the international guidelines [1[■]]. These cases are usually less severe than the SNIUAA and only rarely present cardiovascular compromise [17]. Our group proposed a new classification for HSRs to NSAIDs, considering blended reactions as anaphylaxis, as they compromise two different organs/systems simultaneously and can be life threatening, leading to ICU admission [38]. The current ENDA classification could lead to underdiagnose and undernotification of NSAIDs-induced anaphylaxis.

ANTIBIOTICS

Beta-lactams

The antibiotic class of beta-lactams includes aminopenicillins, cephalosporins, carbapenems, monobactams and clavams [12]. This group of antibiotics is recognized as one of the major causes of immediate and nonimmediate drug HSRs [39]. Regarding only allergic HSRs, beta-lactams are the drugs most frequently involved [12]. The real prevalence of penicillin hypersensitivity in the general population is unknown, although self-reported beta-lactam ‘allergy’ is common [40]. Up to 20% of hospitalized patients report penicillin allergy, but less than 10% are truly allergic when investigated with skin tests [41]. Beta-lactams-anaphylaxis are IgE-mediated reactions, which may be confirmed with the aid of skin tests, serum-specific IgE and basophil activation test [40].

Beta-lactams are classically cited as the major cause of drug-induced anaphylaxis, and penicillin induces about 0.7–10% of all cases of anaphylaxis [42]. In an interesting study with healthy military recruits from the United States of America, anaphylaxis after prophylaxis with a single dose of benzathine penicillin was 2.17/10 000 [43]. Furthermore, the risk of fatal anaphylaxis induced by penicillin is low, being estimated at 0.0015–0.002% of treated patients in former publications [44,45]. In recent years, reports of fatal anaphylaxis induced by beta-lactams have decreased and cephalosporins were involved in most of them [46]. There is a case report in the literature of a fatal anaphylaxis induced by intradermal test with ceftriaxone [47]. Although beta-lactams are a major cause of drug-induced anaphylaxis, those reactions are uncommon and these antibiotics should continue to be considered well tolerated.

The incidence of anaphylaxis to cephalosporin is not known but it was lower than to penicillin [40].

A recent study showed an incidence between 0.0003 and 0.002% of cephalosporin-induced anaphylaxis in a large case series [48[■]]. However, prescribing habits all over the world have changed, and penicillin prescriptions have been replaced by aminopenicillins and cephalosporins. Then, frequency of penicillin HSRs tends to decrease, whereas incidence of reactions induced by clavulanic acid and cephalosporins are probably increasing. In a recent case series of Portugal, amoxicillin and cephalosporins were more frequently reported as causes of HSRs to beta-lactams than penicillin, probably because of prescription habits in that country [49[■]]. Clinicians should be aware about these data, including aspects of cross-reactivity between beta-lactams.

Quinolones

Quinolones is another family of antibiotic most frequently associated with HSRs, probably due to its chemical structure and increased consumption. In Spain, quinolones are the third leading cause of confirmed HSRs to drugs, after NSAIDs and beta-lactams. Most HSRs induced by quinolones are immediate [50].

Almost a decade ago, a German study assessed the frequency of fluoroquinolones-induced anaphylaxis spontaneously reported in that country. The authors observed 166 cases of anaphylaxis possibly triggered by these drugs, and moxifloxacin was the major cause (54%), followed by levofloxacin (15%), ciprofloxacin (13%) and ofloxacin (10%) [51]. These findings were confirmed by two Spanish studies, showing moxifloxacin as the most frequently culprit fluoroquinolone involved in anaphylactic reactions, being also associated with the more severe cases [52,53].

Anaphylaxis induced by quinolones can be both allergic and nonallergic, but an IgE-mediated mechanism is hardly demonstrated [52,54–57]. A novel mechanism was recently described to explain some nonallergic (pseudoallergic) reactions induced by these drugs [58[■]]. Drugs acting as basic secretagogues activate mouse mast cells *in vitro* and *in vivo* through a single receptor, the Mrgprb2, which is ortholog of the human G-protein-coupled receptor MRGPRX2. Quinolones, as well as NMBA and icatibant, may activate mast cells through Mrgprb2 [59,60].

Taking into consideration that both IgE-mediated and nonallergic mast cell degranulation induced by quinolones occur, it is expected that immediate HSRs to these drugs become more frequent due to increased consumption. These reactions include anaphylaxis, which can be life-threatening, and attention should be paid by clinicians who prescribe quinolones in daily basis.

CONTRAST MEDIA: IODINATED AND GADOLINIUM

Iodinated contrast media

ICM have been used in clinical practice for more than 70 years. ICM are one of the main causes of immediate HSRs, but they are underreported [11[■]]. ICM used to trigger immediate HSRs in up to 8% of patients, but the rate decreased to less than 1% nowadays, mainly due to the substitution of classical ionic high-osmolality ICMs to nonionic low-osmolality ICMs [30,31[■],61]. The incidence of anaphylaxis is 0.01–0.04%, depending on the contrast used. On the other hand, incidence of non-immediate reactions has increased during the last years [31[■]].

Most immediate HSRs to former contrast media (ionic and high-osmolality) were induced by nonallergic mechanisms, including direct membrane effect, possibly related to the osmolality of the ICM solution, activation of the complement system and synthesis of bradykinin. With the progressive introduction of nonionic low-osmolality ICMs, the incidence of immediate HSRs, including anaphylaxis, dramatically decreased [11[■]]. Furthermore, many premedication protocols have been suggested to prevent immediate HSR to ICMs, and they help to prevent recurrence of reactions, particularly when the initial reaction was induced by an ionic high-osmolality ICM [62,63]. In our experience, the classic premedication protocol suggested by Greenberger *et al.* [62] (prednisone and difenidramine), combined with administration of nonionic low-osmolality ICMs, turn novel iodinated contrast procedures in patients with previous HSRs dramatically safer.

Although ICM-induced anaphylaxis has been mostly attributed to nonallergic mechanisms, there is growing evidence that some reactions can occur through an IgE-mediated mechanism [64–66]. Studies have shown positive skin and basophil activation tests in patients with HSRs to ICM. In these cases, premedication and the use of nonionic ICM may be less effective and do not completely prevent anaphylaxis, requesting a careful assessment by the allergist [63].

Gadolinium-derivatives

Most paramagnetic contrast media used in MRI are gadolinium chelates or complexes. Gadolinium-based contrast agents (GBCAs) are classified depending on their net charge as ionic or nonionic and on their structure as linear or macrocyclic. GBCA-induced HSRs are considered rare and, therefore, these contrast agents are considered safer than ICMs

[67]. Immediate HSRs are responsible for almost all the data available in the literature and both immunologic (IgE-mediated) and nonimmunologic mechanisms can be involved [11[■],67].

An incidence of immediate HSRs to GBCAs ranging between 0.08 and 0.1% has been reported, but there is underreporting [68,69]. Regarding gadolinium-induced anaphylaxis, an incidence between 0.0004 and 0.0008% has been described, and some data suggest an increasing prevalence as more exams have been requested lately [68,70,71]. Gadobenate has been associated with greater frequency and severity of HSRs [68,71]. A recent case of fatal anaphylaxis induced by gadobenate has been reported [72]. Therefore, physicians, particularly radiologists, should be aware of GBCA-induced HSRs to promptly diagnosis and treat their patients.

CHEMOTHERAPEUTIC AGENTS

Immediate HSRs to chemotherapeutic agents are unpredictable ADRs with potentially lethal consequences. These reactions have become more frequent with the growing incidence of cancer and increased administration of chemotherapy [3[■],10[■]].

Platinum-based agents

Platinum-based chemotherapeutic agents are commonly used in the treatment of solid tumors, including ovarian, breast, endometrial, lung, gastrointestinal, pancreatic and prostate cancers. In many treatment protocols, these medications are the first-line agents, and immediate HSRs limit their use, often resulting in the selection of an alternate, and at times, less optimal treatment protocol. Immediate HSRs are primarily IgE-mediated and affect about 8–27% of adult and pediatric patients treated with carboplatin [10[■]]. Regarding carboplatin, the incidence of HSR increases from 1% after the first dose of carboplatin to 27% after seven doses, with the peak incidence of HSR at the eighth or ninth dose, which often corresponds with restarting treatment for malignancy recurrence [73,74]. The onset of HSR to oxaliplatin also occurs on average during the eighth course [10[■],75]. Scientific data suggest that atopy and BRCA 1/2 mutations are independent risk factors for immediate HSR to carboplatin [76[■],77], and patients with these mutations develop the initial immediate HSR with lower cumulative doses of carboplatin and are more prone to present reaction during rapid drug desensitization.

Taxanes

Taxanes are chemotherapeutic agents that are mainly used in the treatment of ovarian, endometrial, breast, nonsmall cell lung, head and neck,

pancreatic, gastric and prostate cancer. The two main taxane molecules are paclitaxel and docetaxel. Given their low solubility, they are formulated with solvents (cremophor for paclitaxel and polysorbate 80 for docetaxel) to allow intravenous administration. The mechanism of HSRs to taxanes remains uncertain and can be more than one. Solvents used to solubilize the taxane molecules can cause complement activation leading to anaphylatoxins production and mast cell activation. A solvent-free paclitaxel formulation (nanoparticles albumin-bound paclitaxel) was developed. It can be infused faster, without premedication and presents a lower rate of immediate HSRs. More recently, IgE-mediated HSR to the taxane molecule itself has been reported, generating interest in providing skin test evaluation for patients with HSR to taxanes [9[■],10[■]].

In the initial studies with taxanes, HSRs were very frequent and led to the use of premedication with corticosteroids and antihistamine. Even with the use of premedication and with lower infusion rates, HSRs occur in about 5–15% of patients, and in 1% are severe. Most of these reactions occur during the patient first or second lifetime drug infusion, after few minutes have elapsed, which suggests a nonallergic mechanism. A recent study showed that risk stratification based on skin testing and the severity of the initial HSR can safely guide patients' management. In patients that react to taxanes, rapid drug desensitization has been shown to be a safe and effective mean of reintroducing the drug [9[■],10[■]].

mAbs

mAbs are drugs with a wide range of indications, including treatment of cancer and chronic inflammatory and autoimmune diseases. Recently, we proposed a classification of acute ADRs to anticancer agents, such as chemotherapeutic agents and mAbs, in three categories: toxic, systemic inflammatory response syndrome (SIRS) and immediate HSRs. The systemic inflammatory response syndrome is composed by a group of acute reactions characterized by nonspecific inflammatory and immune reactions induced by anticancer agents [10[■]]. Actually, SIRS has been previously described in the literature as an inflammatory and immune response to injury and traumatic insults such as infection, pancreatitis, ischemia, multiple trauma, cytokine administration, immune-mediated organ injury, among others. SIRS needs to be further studied and characterized, but it would include different hypersensitivity and non-HSRs such as the cytokine-release, the tumor-lysis, and the vascular-leak syndromes. Some acute reactions may be even mixed reactions

(e.g. rituximab), with components of SIRS and immediate HSR. There is an urgent need to standardize nomenclature that will promote better health assistance and allow researchers to compare their findings.

HSRs to mAbs are a growing problem, as new antibodies are constantly being developed and their use has increased. Even fully human mAbs, which don't contain mouse peptides and are considered less immunogenic than humanized or chimeric mAbs, may elicit HSRs [78[■]]. According to the mAb involved, HSR may range from 0.1 to 10% of patients, as has been observed with rituximab, or even 27% of patients living in the Southern USA who are taking cetuximab [33].

CONCLUSION

Drug-induced anaphylaxis are frequent, potentially serious and should be better monitored through pharmacovigilance interventions, which increase the number of notifications, as many events are not reported spontaneously. These reactions have become more frequent with the growing utilization of new drugs to treat chronic diseases and cancers. The present review assessed the epidemiology of drug-induced anaphylaxis, contributing to warn health professionals about the rational use of medications and to support the prevention of ADRs.

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- of special interest
- of outstanding interest

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