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Anaphylaxis (M Sánchez Borges, Section Editor)

Drug-Induced Anaphylaxis

Natalia Blanca-López, MD, PhD[1]
María del Carmen Plaza-Serón, BSc[2]
José Antonio Cornejo-García, PhD[2,3]
James Richard Perkins, PhD[2]
Gabriela Canto, MD, PhD[1]
Miguel Blanca, MD, PhD[3,4,*]

Address
[1]Allergy Service, Infanta Leonor Hospital, Madrid, Spain
[2]Research Laboratory, IBIMA, Regional University Hospital of Malaga, UMA, Malaga, Spain
[3]Allergy Unit, IBIMA, Regional University Hospital of Malaga, UMA, Málaga, Spain
[*,4]Allergy Unit, Plaza del Hospital Civil s/n, Hospital Civil, Pabellón 6, 1° planta, 29009, Málaga, Spain
Email: mblancago@gmail.com

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Opinion statement

Drug-induced anaphylaxis can be a life-threatening condition occurring after drug intake by any route, including non-therapeutic exposure due to accidental contact. The most common culprit drugs are non-steroidal anti-inflammatory drugs and beta-lactam antibiotics. Other antibiotics, such as quinolones, are also becoming important elicitors. In the hospital setting, neuromuscular blocking agents and contrast media play an important role. In addition to specific immunological mechanisms (IgE-mediated), other non-immunological mechanisms may participate, including the generation of vasoactive mediators through the arachidonic acid metabolic pathway, direct stimulation of mast cells and the activation of other inflammatory cascades. Diagnosis of drug-induced anaphylaxis includes skin testing, in vitro testing in some instances, and very often requires drug provocation to search for alternatives or in some cases for diagnosis confirmation. Often, the diagnosis must be performed in the context of confounding agents. Factors contributing to the degree of severity include previous diseases (e.g. cardiovascular disease) and the intake of other drugs such as beta-blockers. In circumstances where the culprit drug must be administered, patients should be desensitised if possible. This may be carried out for drug-induced anaphylaxis caused by both immunological and non-immunological reactions, such as cross-intolerance to NSAIDs.

Introduction

Drug-induced anaphylaxis (DIA) consists of a systemic reaction occurring as the result of a quick release of histamine and other vasoactive mediators with multiple effects in different organs and can be life threatening [1]. In the past, several terminologies have been used to identify this clinical entity. The term DIA should be applied to all cases where acute symptoms indicative of a hypersensitivity episode appear after drug intake [2]. If the mechanism is IgE-mediated, we are dealing with allergic anaphylaxis. Non-allergic anaphylaxis was previously known as anaphylactoid; anaphylactic-like or pseudoallergic reactions and are now referred to as non-allergic hypersensitivity [3]. In adults the most common agents involved in anaphylaxis are drugs, whereas for children drugs are the second most common cause after food allergens, although in some studies, they both carry equal weight [1, 4, 5••].

Nowadays, there is great concern about the high prevalence of allergic diseases in general [6], including drug allergy and DIA [7••, 8]. Although the responsible agents for DIA can include vaccines [9] and biological agents [10] including humanised antibodies [11, 12], for didactic purposes and in order to reduce complexity, in this review, we will deal with anaphylactic reactions induced by drugs of small molecular weight (<1000 kDa). These are organic structures that require protein binding and multivalence to induce an immunological response [1]. We will also omit anti-neoplastic drugs and direct the readers to reviews in the literature dealing with this problem [13]. Given that over 80 % of anaphylactic drug reactions occur in ambulatory settings [14], we will therefore focus on the most relevant drugs involved: beta-lactam antibiotics (BLs) and non-steroidal anti-inflammatory drugs (NSAIDs).

From a mechanistic point of view, specific IgE-mediated DIA occurs very soon after contact has been made between the drug and the immunological system, through cross-linking of IgE antibodies at the surface of mast cells/basophils and the subsequent triggering of a mechanism that leads to the release of inflammatory mediators that induce the episode. The kinetics of this process is very well established [1]. In general, subjects react to therapeutic or very low concentrations of the drug that often occur after an inadvertent exposure [1, 15]. Some IgE-mediated DIA reactions can occur after a longer time period, for example, when the culprits are drug metabolites, where the drug must be metabolised before IgE recognition can occur [16]. In terms of administration, all routes can lead to DIA; however, reactions tend to be more severe when the agent is administered by parenteral route [1, 7••].

Epidemiology and Drugs Involved

DIA is responsible for over 230,000 hospital admissions in the USA annually and prevalence is increasing [1, 5••, 8]. In a study of 2458 anaphylaxis-related deaths in the USA between 1999 and 2010, medications were the most common cause, responsible for more than 50 % of the cases, followed by unspecified triggers, venoms and food. A significant increase over recent years was also noted [5••]. Very often, anaphylaxis occurs in ambulatory practice and figures are likely to be underreported [17].

For many years, antibiotics (in particular BLs) have been considered the most frequent culprit for DIA [14]; however, recent studies have questioned this view. In a nationwide study carried out by allergists in Portugal during a 4-year period, NSAIDs were shown to be the leading cause, followed by antibiotics. The mean age at which the reaction occurred ranged from 2 to 89 years, with a mean of 17.4, indicating that DIA may appear at any age [18•].

There is often disagreement between population-based surveys and studies carried out in specialised centres. The former generally find antibiotics as the most frequent cause of hypersensitivity drug reactions including anaphylaxis [14]; however, in specialised centres, NSAIDs predominate over BLs [7••]. In a

study carried out by Messaad et al., around 10 % of subjects evaluated for penicillin allergy were confirmed as such, compared to over 20 % for NSAIDs [19]. Similar data have been recently reported by Doña et al. [7••].

Concerning neuromuscular blocking agents, a study carried out by Reiter et al. consulting data from the French National Pharmacovigilance Database showed that from 2022 cases registered, 70 % developed anaphylaxis at grades 3 and 4 [20•].

Within NSAID hypersensitivity reactions, we must differentiate two main groups of patients, those who are cross-intolerant and those who are selective responders [21••]. Both groups can show anaphylaxis, although it is significantly more frequent amongst the latter [22, 23]. Out of all drug reactions attended to an emergency department, anaphylaxis to NSAIDs has been shown to be the most common entity [24•]; however, the most severe reactions are likely to be induced by BLs. Of these, amoxicillin is the most frequent culprit in many countries [25, 26], although clavulanic acid is becoming more prevalent in the induction of immediate hypersensitivity BL reactions including anaphylaxis [27, 28].

Case series, particularly hospital surveys, have shown muscle relaxants to be also relevant for an important number of drug reactions [14] as well as contrast media [4], which are potential inducers of anaphylaxis [4, 5••]. Other drugs that can elicit DIA include proton pump inhibitors [29, 30•], quinolones [31], heparins [32], codeine [33], amiodarone [34], *N*-acetyl cysteine [35], chlorhexidine [36], vitamins [37–39] and corticoids [40–42]. Many of these drugs are frequently prescribed and cannot be easily substituted, warranting further study of these reactions.

Underlying Mechanisms

Anaphylaxis involves the abrupt release of pro-inflammatory mediators with vasoactive properties that induce an often severe systemic response involving many organs. It has long been known that in addition to IgE-mediated responses, other mechanisms can be involved [1].

The most highly studied model of DIA mediated by specific immunological mechanisms is that of penicillin. The availability of diagnostic tests and determination of specific IgE antibodies has made it possible to study this model in great detail [1]. Clinical experience with such patients indicates that reactions can be induced by very low concentrations of drugs through the oral route, skin testing or inadvertent exposures [43–45]. If a subject takes amoxicillin or another BL derivative and develops an anaphylactic response after an interval of over 1 h, we are likely dealing with an accelerated reaction for which the proposed mechanism is a T cell response [46•]. In a study carried out by Torres et al., it was shown that for those patients who developed a positive response after amoxicillin challenge, the longer the interval between intake and reaction, the greater the dose required to elicit a positive response, usually consisting of urticaria with some systemic manifestations [44].

The situation is more complex for NSAIDs. According to the recent classification proposed by the ENDA, an anaphylactic reaction to dipyrone or diclofenac, two drugs frequently prescribed at all ages ranges, can be either a selective response or due to cross-intolerance (Table 1) [21••]. If these drugs are

Table 1. Classification of hypersensitivity reactions to NSAIDs

	Type of reaction	Clinical manifestations	Timing	Underlying disease	Mechanism
Cross-intolerance reactions (non-immunologic)	NSAID-exacerbated respiratory disease	Bronchial obstruction, dyspnoea and/or nasal congestion/ rhinorrhoea	Acute (immediate to several hours after exposure)	Asthma rhinosinusitis	COX-1 inhibition
	NSAID-exacerbated cutaneous disease	Wheals and/or angioedema		Chronic urticaria	COX-1 inhibition
	NSAID-induced urticaria/ angioedema	Wheals and/or angioedema			Unknown, probably COX-1 inhibition
Selective reactions (immunologic)	Single-NSAID-induced urticaria/anaphylaxis	Wheals/angioedema/anaphylaxis	Delayed onset (usually more than 24 h after exposure)		lgE-mediated
	Single-NSAID-induced delayed reactions	Maculopapular exathema			T cell-mediated
		Fixed drug eruption			
		Acute generalized exanthematous pustulosis			
		Drug reaction with eosinophilia and systemic symptoms			
		Stevens-Johnson syndrome/Toxic epidermal necrolysis			
		Organ-specific reactions			

administered to patients with chronic spontaneous urticaria, this can also lead to an anaphylactic reaction or an accelerated reaction similar to those observed with amoxicillin [46•]. In summary, when dealing with an NSAID reaction indicative of DIA, there are four potential mechanisms to consider: selective and cross-intolerance in subjects without any underlying disease, and immediate and accelerated reactions in subjects with chronic spontaneous urticaria.

As stated above, the most highly studied model is that of BLs, where it has been shown that different penicillin structures can produce an epitope that induces selective or cross-reactive responses [47, 48]. When symptoms occur over an hour after drug intake, this may be due to a T cell response [46•, 49]. If anaphylaxis occurs following a long interval, as can occur with several drugs, the possibility of metabolite generation must be considered [15, 50]. This is thought to be relevant for several NSAIDs [50, 51].

Selective immediate reactions have been reported for all NSAIDs, with the most common being pyrazolones [23]. Since histamine and other mediators are released in NSAID reactions, an anaphylactic event may occur. It is now clear that when mediators are released, their metabolism and interactions with specific receptors contribute to the severity of the response [52, 53].

Serum sickness attributed to the formation of immune complexes has been proposed to be induced by penicillin [1], other antibiotics and other drugs [54]. However, protein-drug complexes with IgG or other antibodies have never been shown. Complement activation in the acute phase of these reactions has been reported, although the mechanism requires further clarification [55–57].

Monitoring the Acute Phase

Anaphylaxis involves the release of vasoactive mediators including histamine, tryptase and prostaglandin-leukotriene mediators [1]. Histamine appears very rapidly and can be detected between 5 and 10 min after the reaction initiation in peripheral blood [58]. It then becomes undetectable, but its metabolites can be measured in urine by taking samples at different time intervals after the episode [59]. Serum tryptase levels peak 60–90 min after the onset of anaphylaxis and can persist for up to 24 h [60, 61]. Both parameters can be used to monitor the anaphylactic response.

In addition, arachidonic acid derivatives can be monitored in peripheral blood or urine, although as with histamine, this is more feasible in sequential urine samples [1]. Levels of these mediators are indicative of mast cell activation but not the initial underlying mechanisms, since both IgE and other mechanisms can lead to their release [58]. Kinin generation, complement system activation and nitric oxide synthesis may also occur during anaphylaxis [1].

IgE-mediated reactions are caused by antigenic stimulation, leading to a boosting of the immunological response, which can be monitored. More specifically, the IgE response shows a Th2 pattern with an increase

of IL-4 and IL-13 and a downregulation of IFN-γ and IL-12 [62, 63]. Involvement of TNF-α in anaphylactic reactions has also been reported [62].

Clinical Manifestations

According to recently published work, the most common clinical manifestations appear in the skin, followed by respiratory, cardiovascular and gastrointestinal involvement [1, 4, 18•]. Histamine and the other vasoactive mediators are responsible for flushing, urticaria and angioedema in the skin, wheezing and upper airway involvement including laryngeal oedema, a decrease in blood pressure, cardiac arrhythmia in the cardiovascular system and abdominal cramps, nausea, vomiting and diarrhoea. DIA can be divided into several categories according to the extent of the reaction [64]. Isolated symptoms involving a single organ can also occur, such as cardiovascular collapse, syncope and seizure [1, 17]. Biphasic anaphylaxis can occur—this involves the aggravation of symptoms several hours after the initial episode. Sometimes, this may evolve into protracted shock [1, 65]. Although drug allergy may appear in subjects with mastocytosis, it is still unclear whether these patients are more prone to developing anaphylactic reactions after the intake of drugs, particularly for NSAIDs, codeine and muscle relaxants [66].

Risk Factors

Predictors of serious outcomes include a previous history of DIA, a history of allergic disease, multiorgan involvement, and old age [1, 4]. Diabetes, hypertension and other cardiovascular diseases can also be considered risk factors for developing anaphylaxis [1]. Patients with these conditions may develop complications during the treatment of anaphylaxis because some drugs (e.g. epinephrine or similar drugs) may induce adverse cardiovascular effects [2]. There is no consensus as to whether atopy is a risk factor for DIA [1]. Patients with penicillin allergy are more likely to develop allergy to other drugs [31].

NSAIDs, particularly aspirin, and food additives may exacerbate allergic symptoms in patients with chronic idiopathic urticaria and food-dependent exercise-induced anaphylaxis (FDEIA) [67–69]. In these cases, these drugs act as cofactors for triggering a response.

The worsening of symptoms in patients with chronic urticaria and FDEIA can be due to aspirin-enhanced histamine release from basophils via increased Syk kinase activation [70–72]. Confounding factors also exist leading to drugs being falsely identified as the culprit. For example, cold stimuli such as water, air or physical objects may sometimes induce anaphylaxis [73–75]. This can also occur following the infusion of fluids during surgery [74].

Cross-Reactivity Versus Cross-Intolerance

The term cross-reactivity refers to immunological reactions and implies that drugs with similar chemical structures will be recognised by the immunological

system and induce a response. It is known that in IgE-mediated reactions to penicillin, subjects can react to all penicillin determinants or to those with specific side chains [47, 49]. The production of monoclonal antibodies indicates that different parts of the amoxicillin molecule bound to a protein carrier can be recognised [48], and selective mediator release following drug administration has been shown using experimental sensitisation models [76]. It is very unlikely that a subject sensitised to the major benzyl penicillin determinant will also respond to BLs with very different chemical structures such as aztreonan [77]. This concept must be considered when desensitising BLs patients, as will be outlined below.

The concept of cross-intolerance applies only to NSAIDs and is not immunological in nature but rather related to the inhibition of the COX-1 and COX-2 enzymes [51]. Different drugs with similar inhibitory capacity may trigger the same response. Therefore, an anaphylactic reaction induced by cross-intolerance to ibuprofen can also be induced by diclofenac, aspirin or indomethacin [22]. Although subjects generally respond to strong COX-1 inhibitors, reactions have also been reported for weaker inhibitors like oxicams [78] or selective COX-2 inhibitors [78, 79]. In some cases, NSAID responses can also be immunologically mediated and therefore selective to specific drugs [23]. In these circumstances, subjects usually respond to a single drug/drug subgroup but tolerate other NSAIDs, including strong COX inhibitors [80–82].

Diagnosis

DIA diagnosis is performed using clinical history [1]. A precise description of symptoms is also essential to decide which in vivo and in vitro tests should be carried out, including a drug provocation test (DPT) [7••, 19, 49]. In allergic reactions to BLs, if the clinical history is indicative of an immediate reaction, i.e. anaphylaxis, a skin test is performed with penicillin determinants as recommended. The concept of major/minor determinants of benzyl penicillin (PPL and MDM) has now been surpassed since these drugs are not the most frequent elicitors of anaphylaxis [26], and it is now recommended to include amoxicillin determinants, and if the culprit drug is a cephalosporin, this must also be included. In those countries where clavulanic acid is becoming an important elicitor, the inclusion of this drug is also recommended (clavulanic for skin prick test) [27, 28]. For anaphylactic reactions to NSAIDs, if cross-intolerance is ruled out, skin testing is of very little value, except for pyrazolones [23, 81]. Skin test positivity to other NSAIDs is almost anecdotal, and only a few instances have been reported [23].

In vitro tests are considered useful alternatives in the case of penicillin determinants. Although they are generally less sensitive than skin testing [26], there are instances in which the in vitro test can be positive in the absence of an in vivo positive response [44]. Experimental prototypes have been developed for some drugs, such as pyrazolones and ASA; however, they are not yet available in routine clinical practice [80, 82]. Another in vitro option is the use of basophil activation tests. Although these have been proposed for subjects with NSAID hypersensitivity caused by cross-intolerance [83], they show a high number of false positives [84, 85]. However, the basophil activation has proved to be useful for beta-lactam [86], selective reactions to pyrazolones [81, 85], omeprazole [87], ranitidine [88], and other agents [89].

Other techniques, such as lymphocyte-stimulation-based tests, originally developed for T cell-mediated reactions [90, 91], have also been applied to IgE-dependent reactions [91, 92].

Muscle relaxants are particularly relevant for anaphylaxis occurring in hospital settings [93]. In these situations, skin testing, quantitation of specific IgE antibodies and basophil activation tests have been used to establish diagnosis [94, 95]. Cross-reactivity can occur for some of these drugs [93, 96].

In daily practice, a controlled challenge is often necessary to assess tolerance and confirm diagnosis, due to the low sensitivity and availability of many of the above-mentioned diagnostic tests [1, 7••, 19]. This is commonly used when the clinical history is unclear or when many drugs have been taken simultaneously [1]. The approach taken depends on the putative mechanism involved.

Controlled challenge is made with increasing drug concentrations until a therapeutic dose is achieved. In DIA the initial concentration should be very low and increased at intervals of 30 min [26]. This approach is different for cross-intolerant NSAID-induced DIA. In these circumstances, the incremental steps can be performed using higher doses [22].

Differential Diagnosis

Anaphylaxis may occur in the context of a clear-cut episode induced by a single drug; however, in many cases, a patient will have taken several drugs simultaneously alongside other potential triggers such as foods [67]. To make matters even more complex, anaphylaxis can occur following the intake of drugs and foods and undertaking exercise [67, 69, 72]. Therefore, a detailed clinical history with a precise description of the timing of drug intake, other potential factors, and appearance of symptoms is essential. As previously stated, cold stimuli can also lead to anaphylaxis, and these must also be considered in the diagnosis of DIA [73–75]. Other complications that may mimic DIA include scombroidoisis due to histamine poisoning in spoiled fish. If this occurs alongside drug intake, it can be incorrectly diagnosed as drug allergy [97].

Treatment and Desensitisation

For this section, we refer the reader to different position statements that provide protocols for the treatment and management of DIA. Once anaphylaxis has been recognised, the sooner the treatment is administered, the more effective it will be. Intramuscular injection in adults of 0.3–0.5 ml (1 mg/ml), or 0.01 mg/kg of body weight for children, epinephrine to the mid outer thigh has been recommended [1, 2]. This can be repeated every 5–15 min if necessary. Protocols used for treating DIA are the same as those recommended for anaphylaxis in general. In addition to epinephrine, these include antihistamines and corticosteroids plus administration of parenteral fluids and other supporting measures. We refer the reader to references [1, 2] for a full description of treatment options. DIA can occur in allergy units where drug allergy diagnosis is performed, even with very low concentrations (e.g. through skin prick or intradermal testing). For BLs, it is recommended, according to severity, to begin with doses of less than one thousandth of the initial concentration and in some cases not testing all

determinants simultaneously [19, 26, 45]. The use of this measure has led to an important reduction in the number of reactions induced in such units [26]. Often, symptoms mainly affect the lung or upper airways, for example, laryngeal oedema, with mild skin involvement and no systemic cardiovascular effects. In these cases, particularly for older patients, administration of epinephrine is particularly risky, and a careful balance between drug administration and blood pressure control must be achieved.

The aim of desensitisation is to achieve the situation where basophils and mast cells become unresponsive to the drug [1, 98, 99]. Desensitisation in DIA is indicated when the drug is crucial to the patient and no alternatives are available. In the past, this was almost exclusively performed for BLs and NSAIDs [1] but is now used for chemotherapeutic agents, contrast media and many other drugs [100].

Desensitisation to BLs is antigen specific. It consists of administering progressive doses of the drug every 30-60 min until the therapeutic dose is achieved. If minor symptoms occur, they should be treated adequately [98, 99]. A reduction in skin test sensitivity during desensitisation has been observed in some patients [100, 101], although the mechanism has not been fully elucidated [102].

Whenever possible, rapid oral desensitisation is preferable to intravenous desensitisation since the cost is much lower and the procedure has similar efficacy [17]. However, the oral route is less feasible due to difficulties in obtaining the precise dose due to absorption and other factors related to drug distribution.

If adverse effects occur during desensitisation, the time interval and number of doses should be extended and treated when necessary [1]. Once desensitisation is completed, patients should be able to tolerate the full dose of the drug with minimal side effects [100–102].

Desensitisation can also be performed for DIA due to NSAIDs [103, 104]. Although most studies of NSAID desensitisation have been performed for patients with respiratory airway involvement, it can also be used for DIA. It is critical to establish whether we are dealing DIA due to cross-intolerance or to a selective response in order to choose the correct dosage regime and to see if alternative NSAIDs are available.

An increasing concentration of the drug is given during a period of 2–3 days until the required dose has been acquired. This is then maintained. Subjects with cross-intolerance generally respond to relatively high doses, and doses below 300 mg may be tolerated without the need for desensitisation [105, 106].

For selective reactions, desensitisation is not indicated unless there is a very specific need for a particular NSAID, for example, aspirin for the treatment of stroke [23].

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Compliance with Ethics Guidelines

Conflict of Interest

Natalia Blanca-López, María del Carmen Plaza-Serón, José Antonio Cornejo-García, James Richard Perkins, Gabriela Canto, and Miguel Blanca declare no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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