

NSAIDs-Induced Anaphylaxis

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Opinion Statement

Drugs are between the main triggers of anaphylaxis. They have been described as major cause of fatal anaphylaxis. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed drugs around the world because of their analgesic, anti-inflammatory, antipyretic, and antithrombotic effects. This class of drug is the first or the second after antibiotics as the cause of drug hypersensitivity reactions, including anaphylaxis. However, frequency of NSAIDs as the drug implicated in anaphylactic reactions is too variable among different countries. We believe there are discrepancies between genetics, frequency of exposure and mainly between classification of hypersensitivity reactions to NSAIDs and definition of anaphylaxis. Actual classification of NSAIDs hypersensitivity considers as anaphylaxis only those severe reactions presented by selective responders, probably IgE-mediated. Blended reactions, when respiratory *plus* mucocutaneous symptoms are presented after intaking NSAIDs from different groups (cross-intolerant), are not included in this classification. It can lead to underdiagnosis of non-immunological anaphylaxis. International groups of researchers must try to better define phenotypes of hypersensitivity reactions to NSAIDs, in order to include those blended reactions and better manage these cases.

Introduction

Drugs are between the main triggers of anaphylaxis, particularly in adults. They are a serious public health problem in both inpatient and outpatient facilities because of high morbidity and socioeconomic costs and are also potentially fatal [1].

Anaphylaxis diagnosis is based on clinical features (Table 1). It depends on recognition of characteristic

symptoms and signs that occur minutes to few hours after exposure to a potential causative agent, often followed by rapid progression. Target organ involvement is highly variable, but typically affects two different organs or body systems. The most commonly affected system is the skin, but upper and lower airways, gastrointestinal tract, and cardiovascular system are also

Table 1. Clinical criteria for diagnosing anaphylaxis (adapted from Simon FE et al. [4•])**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:**

1. Acute onset of an illness with skin-mucosal involvement
And at least one of the following:
 - A) Upper or lower airways compromise
 - B) Reduced blood pressure, syncope, or collapse OR
2. Two or more of the following that occur rapidly after exposure to a *likely* allergen for that patient
 - A) Mucocutaneous compromise
 - B) Upper or lower airways compromise
 - C) Reduced blood pressure, syncope, or collapse
 - D) Gastrointestinal symptoms OR
3. Reduced blood pressure after exposure to a *known* allergen for that patient

impaired. Central nervous system is frequently affected due to shock or hypoxia. In few conditions, anaphylaxis can be diagnosed when only cardiovascular system is involved; for example, in a patient allergic to bee venom, after an insect sting, sudden onset of signs of shock might be the only manifestations. Mucocutaneous compromise is present in 80–90% of all patients, making anaphylaxis harder to recognize when they are absent.

There is no standard pattern of clinical presentation and it differs from one patient to another. Even in the same patient who presents two anaphylactic reactions, they are frequently different in terms of clinical symptoms and signs. Moreover, when a new episode is initiating, the rate of progression or the ultimate severity are frequently difficult to predict [2, 3]. Misdiagnosis or overdiagnosis of anaphylaxis can occur, as described in

patients with acute multisystem symptoms after ingestion of caustic substances, foreign body inhalation, acute urticaria, and angioedema [4•].

In emergency departments, drugs are the causative trigger in 40 to 60% of anaphylactic reactions. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed drugs around the world because of their analgesic, anti-inflammatory, antipyretic, and antithrombotic effects. They are implicated in 20–25% of all adverse drug reactions and hypersensitivity reactions (HSR). It is estimated that 0.3–2.5% of individuals in the general population are hypersensitive to NSAIDs. This class of drug is the first or the second after antibiotics as the cause of drug HSRs, including anaphylaxis (depending on the population studied) [5, 6, 7••, 8••].

Epidemiology

The prevalence of anaphylaxis is not well known, with an estimated overall incidence that ranges from 3 to 50 per 100,000 person years, with a lifetime prevalence of 0.05 to 2% [9]. Major causes of anaphylaxis in epidemiologic studies are food, hymenoptera venom, and drugs [4•]. Frequency of anaphylaxis seems to be increasing, probably due to enhancement of food allergy. However, an increase in anaphylaxis fatalities has been reported to be caused by drug HSRs [10, 11]. Furthermore, excluding pediatric cohorts (wherein foods are the most common trigger), medications are the most frequent cause of fatal anaphylaxis in reports from the USA, the UK, Australia, and New Zealand [12]. However, the rate of anaphylaxis induced by different classes of drugs is widely

variable around the world.

Epidemiologic publications about drug-induced anaphylaxis (DIA) have increased in numbers in the last 5 years. Until 2005, few studies evaluated drugs as triggers of systemic HSRs. Classes of drugs most commonly cited as triggers of anaphylaxis were antibiotics, mainly betalactams, dextrans, radiodinated contrast media, allergen extracts, and analgesics, particularly diclofenac [13–15].

Since 2013, a few studies have been published with different results about the classes of medications associated with anaphylaxis [7••, 8••, 16, 17, 18•, 19•, 20••]. Two of them, performed in France and Portugal, respectively, showed that antibiotics are still the main cause of DIA, followed by anesthetic agents, NSAIDs, radiocontrast media, vaccines, immunotherapy, chemotherapeutic and biologic agents [16, 17]. On the other hand, all the other series reported NSAIDs as the major cause of DIA, particularly in Latin American populations [7••, 8••, 18•, 19•]. There is some hypothesis to explain such discrepancies between different populations.

First, genetic basis is different and can be associated with higher risks to develop reactions to some drugs, despite this is still not well established for NSAIDs. Second, NSAIDs are used indiscriminately in Latin America, particularly in Brazil. Moreover, in many Latin American countries, dipyrone (metamizole) is available and it has been reported to be the main cause of HSRs between all NSAIDs [7••, 8••]. Lastly, there must be disagreement in terms of definition and registry of cases. In the first Portuguese report, based on the national Pharmacovigilance System, NSAIDs were not included between the main causes of anaphylaxis [17]. On the other hand, a second Portuguese case series was published by allergologists from that country 1 year later based on spontaneous notification in Allergology units [20••]. In that study, NSAIDs were between the main causes of DIA, in accordance with Latin American publications [7••, 8••, 18•, 20••]. As it will be explained below, to confirm the diagnosis of anaphylaxis due to NSAIDs can be difficult based on ENDA classification of NSAIDs HSRs [21]. Then, many cases, particularly less severe ones, may have been lost in the French and Portuguese pharmacovigilance studies published in 2013 [16, 17].

Classification and pathophysiology of hypersensitivity reactions to NSAIDs

In terms of clinical features and based of pathophysiology, HSR to NSAIDs have been classified in five different patterns of reactions. Four main groups of acute HSRs associated with NSAIDs were described: NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), NSAID-induced urticaria and/or angioedema (NIUA), and as single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) [21, 22]. The last group is represented by delayed-type reactions, mainly T cell dependent reactions, as eczematoid or fixed-drug eruptions, severe bullous reactions, etc. [21].

These five different patterns of HSRs associated with NSAIDs intake can also be classified into two categories based on mechanisms involved: non-allergic (non-immunological) or allergic (immunological) reactions. Non-allergic

HSRs do not involve specific immunological mechanisms and represent the most common type of reported reactions, as NERD, NECD, and NIUA [21]. It has been shown that NERD and NECD occur via inhibition of cyclooxygenase (COX)-1 and subsequent alteration in eicosanoid biosynthesis, most prominently cysteinyl leukotriene overproduction. It has also been postulated that NIUA is also induced by a similar mechanism, but it is still under investigation [21]. These patients are clinically cross-intolerant (CRI) responders, as they usually reproduce symptoms after re-exposure to different COX-1 inhibitors.

On the other hand, allergic HSRs involve specific immunological mechanisms, as type-I IgE-mediated (SNIUAA) and T cell dependent (delayed reactions). Both these patients are considered selective responders (SR), as they tend to tolerate NSAIDs not chemically related to the one imputed in the first reaction [21, 23–25, 26•].

Definition of anaphylaxis induced by NSAIDs

It seems this classification in five patterns of reactions does not allow a correct inclusion of all patients with HSRs to NSAIDs. First of all, NIUA patients sometimes can present anaphylaxis, and not just urticaria or angioedema. Moreover, in clinical practice, it is not unusual to see NERD patients who present cutaneous manifestations after exposure to a NSAID [26•]. These patients present cutaneous *plus* respiratory symptoms in an acute manner. Although this clinical presentation can be considered anaphylaxis according to guidelines (Table 1) [4•], this subgroup is not included in ENDA classification [21], as they are CRI patients presenting both respiratory and cutaneous symptoms. Moreover, CRI anaphylaxis patients rarely present cardiovascular compromise [7••], what could lead physicians to underdiagnose anaphylaxis. Finally, ENDA classification only names “anaphylaxis” those reactions presented by SR, possibly IgE-mediated and more commonly caused by pyrazolones [21].

Nevertheless, a few manuscripts have described those non-allergic systemic reactions, when patients present cutaneous *plus* respiratory symptoms, mediated by non-allergic mechanisms. Those reactions have been named “blended reactions” [27, 28, 29•].

It has been postulated that those blended reactions are mixed reactions when patients with NERD present cutaneous urticarial or angioedema, or patients with NECD present bronchospasm after NSAIDs intake [29•]. We also believe some CRI patients with NIUA can present respiratory symptoms after exposure to high doses of NSAIDs, as we have published before [7••].

We have recently proposed a new classification of HSRs to NSAIDs in a review paper, where NIUA would be turned to MNIA (multiple NSAID-induced anaphylaxis type reactions, as anaphylaxis, urticaria, angioedema and blended reactions) [26•]. Nevertheless, our proposal is not complete, as it separates blended reactions from NERD and NECD, but those patients can also present mixed symptoms. Thus, as cited above, blended reactions are characterized by symptoms in two different organs/systems (skin and respiratory tract), presented rapidly. Then, it should also be classified as anaphylaxis according to guidelines [4•].

In conclusion, HSRs to NSAIDs are heterogeneous and complex and no actual classification is complete. We should extend research in this area,

probably including more studies in the topic of genetics, so that we could better classify and treat our patients.

Diagnosis

Detailed analysis of patient history is the primary tool available for diagnosis and management of NSAID HSRs. This is critical to assessing if the patient's HSR is CRI (NERD, NECD, or NIUA) or SR (SNIUAA or NIDHR). A diagnostic algorithm based on the current classification that helps to determine the next steps of investigation has already been proposed by ENDA group for NSAID HSRs [22].

A history of similar signs or symptoms induced in the past by another NSAID is suggestive of CRI. NERD should be suspected if upper or lower airways symptoms occur and NECD or NIUA if skin signs and symptoms are reported. On the other hand, a history of good tolerance to potent COX-1 inhibitors (e.g., aspirin) after a previous HSR to another NSAID suggests SR, an immunologically mediated type of reaction. Nevertheless, those patients may evoke reactions to another NSAID belonging to the same chemical group, which shares a common epitope/hapten. For example, a patient with SNIUAA and history of anaphylactic reaction to dipyrone will tolerate ibuprofen but may react to phenylbutazone, that is also a pyrazolone, the chemical group of dipyrone. It has been proposed that history of three or more episodes of reactions induced by two different NSAIDs is predictive of CRI, while two or more reactions triggered by the same NSAID with concomitant history of good tolerance to another NSAID with high potency suggests SR [23, 30•].

Although a detailed analysis of the clinical history might be sufficient to establish the diagnosis of one of the NSAID HSR phenotypes, it is associated with relatively low specificity. Definition of tolerance to other NSAIDs has tremendous implications for patient's management. Then correct phenotype should be confirmed, even by oral provocation tests. If a patient has previously reacted to a NSAID other than aspirin, oral challenge with aspirin is the gold standard. A positive provocation test with aspirin determines that patient is CRI. Drug provocation tests with aspirin confirm the diagnosis of MNIUA in up to 92% of cases with an unequivocal clinical history, when reactions occur within 1 h and more than two different NSAIDs are involved [31].

If aspirin is the culprit drug, the patient should be challenged with an alternative potent COX-1 inhibitor, and the conclusions are the same as the above mentioned in case of a positive challenge result. If the provocation test with aspirin or other potent COX-1 inhibitors is negative, the immunologically selective mediated type of acute NSAID HSR (SNIUAA) should be suspected.

If CRI is diagnosed, the patient is prompted to avoid all NSAIDs with strong COX-1 inhibitory activity. However, selective COX-2 inhibitors can be recommended if anti-inflammatory treatment is indicated, but those drugs should also be prescribed after a negative provocation test.

In the case of SR, NSAIDs with structural similarity may result in immunological cross-reactivity (e.g., IgE-mediated HSRs to pyrazolones). In this case, the entire class should be avoided [22].

In some circumstances, skin tests with the culprit drug may be applied, particularly in case of a possible immunologic HSR (SNIUAA). Since the

immunological mechanism of SNIUAA involves IgE, skin tests (prick and intradermal) with the culprit drug or determination of serum specific IgE is justified. Positive skin test results have been reported in SR patients with a history of HSR to pyrazolones, although sensitivity is not optimal, and the risk of systemic responses after intradermal tests exists [32, 33]. On the other hand, reliability of routine skin tests to other NSAIDs (including propionic acid derivatives) has not been well documented in systematic studies, and there are no standardized protocols for non-pyrazolone NSAIDs [34].

If the cross-intolerance HSR is suspected, skin tests are not indicated, as these reactions are non-immunological. The utility of drug-specific IgE detection in serum has not been demonstrated. Although several *in vitro* cell activation tests have been used to confirm a diagnosis of the acute type of NSAID HSR, they have not been validated. Then, they are not recommended for clinical practice to date [35].

An oral provocation test with the causative drug remains the gold standard for diagnosis of HSR to NSAIDs. They can be performed mainly in patients with unclear clinical history or when a definite diagnosis is required. Nevertheless, physicians must take into consideration that, although sensitivity and specificity of oral provocation tests with NSAIDs are higher than 90%, severe reactions can occur. To avoid them, careful analysis of risk-benefit ratio should be taken before the procedure. Moreover, they must be performed in facilities equipped to treat anaphylaxis, under supervision by experienced medical and nursing staff [30•].

Management

Anaphylaxis is a life-threatening medical emergency in which prompt intervention is critical. During the acute attack, the patient should be placed on the back with their lower extremities elevated. Epinephrine (adrenaline) is the drug of first choice to treat anaphylaxis because it is the only medication that seems to reduce hospitalization and death. It should be injected by the intramuscular route in a dose of 0.01 mg/kg of a 1:1000 (1 mg/mL) solution, up to a maximum of 0.5 mg in adults (0.3 mg in children). The dose can be repeated every 5–15 min, as needed [3, 4•].

Large volumes of fluids should be recommenced as soon as hypotension and shock are recognized. Second-line medications such as antihistamines, beta-2 adrenergic agonists, and glucocorticoids must not delay adrenaline administration. Glucocorticoids are typically administered to prevent biphasic episodes of anaphylaxis and have little or no effect on initial symptoms and signs [3, 4•].

After the first attack, prevention of new episodes is crucial. Once the diagnosis of NSAID HSR has been established, the mainstay of treatment is avoidance of NSAIDs. However, recommendations for management and alternative NSAIDs should be tailored based on the particular phenotype of NSAID HSR [22]. If the patient is CRI, it is recommended to avoid NSAIDs altogether and use alternative analgesics (e.g., opioids) or to consider further challenge with a COX-2 inhibitor. Avoiding all COX-1 inhibitors in patients with a reaction to one NSAID without first defining their status as SR or CRI significantly limits the NSAID repertoire. Certain features of the history or presentation are associated

with challenge positivity and with selective reactions or cross-intolerant status; however, we advise against any assumptions on the basis of history alone in the absence of challenge confirmation. Once the final diagnosis has been defined, a warning device such a bracelet might be considered to guard against inadvertent NSAID administration, such as during emergency surgery in injectable or suppository form [36, 37].

Avoidance of the culprit drug and potentially cross-intolerant compounds (COX-1 inhibitors) is meant to prevent recurrence of attacks. However, if chronic intake of acetyl salicylic acid (e.g., for cardiovascular disease) is necessary, desensitization can be performed [30•]. Several protocols of aspirin desensitization have been published, but no comparison between them is available [30•, 38, 39]. They are better defined in cases of NIUA and NERD, but they have not been well evaluated in anaphylactic patients. This can be considered a relative contraindication, due to the risk of severe and potentially fatal reactions occurring during this procedure [40].

On the other hand, in patients with NERD who present a blended reaction, aspirin desensitization is still an alternative approach. Nevertheless, it has been postulated that these patients can be more difficultly desensitized because of cutaneous reactions.

Despite the fact that most patients with HSR to COX-1 inhibitors can tolerate highly selective COX-2 inhibitors, such as celecoxib or etoricoxib, it is recommended that provocation tests should be performed to confirm their tolerability [41, 42]. On the other hand, in a patient with HSR to a single NSAID (SR) and when the culprit drug has been identified, it can be safely replaced by another NSAID with an unrelated chemical structure but similar anti-inflammatory potency. In those cases, desensitization is not indicated [37].

Conclusion

NSAIDs are between the major causes of HSR to drugs, including anaphylaxis. However, actual classification of HSR to NSAIDs considers as anaphylaxis only those severe reactions presented by selective responders, probably IgE-mediated. Blended reactions, when respiratory *plus* mucocutaneous symptoms are presented after intaking different NSAIDs, are not included in this classification. It can lead to underdiagnosis of non-immunological anaphylaxis. International groups of researchers must try to better define phenotypes of HSR to NSAIDs, in order to include blended reactions and better manage these cases.

Compliance with Ethical Standards

Conflict of Interest

Dr. Marcelo Vivolo Aun declares that he has no conflict of interest. Dr. Marisa Rosimeire Ribeiro declares that she has no conflict of interest. Dr. Jorge Kalil declares that he has no conflict of interest. Dr. Pedro Giavina-Bianchi declares that he has no conflict 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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