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# Drug-induced anaphylaxis—elicitors, mechanisms and diagnosis

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**Abstract** Drugs are one of the major causes of anaphylaxis. For example 2346 cases of drug-induced anaphylaxis were reported to the anaphylaxis register as of March 2019. The most common triggers of drug-induced anaphylaxis were nonsteroidal anti-inflammatory drugs (NSAIDs; $n=902$) and antibiotics ($n=721$). Drug-induced anaphylaxis can be caused by IgE-dependent (e.g., penicillins) and IgE-independent mechanisms. Recently MRG-PX2 has been identified as a receptor for non-IgE-dependent mechanisms. Drug-induced anaphylaxis results more frequently in lethal reactions and is more commonly associated with cardiovascular symptoms. Also therapy refractory anaphylaxis is more frequently triggered by drugs. For the diagnosis of drug-induced anaphylaxis current national and international guidelines should be followed including provocation tests to avoid future reactions.

**Keywords** Allergy · Intolerance · β-lactams · Analgetics · Provocation tests

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## Abbreviations

| | |
|---|---|
| CARPA | Complement activation-related pseudoallergy |
| COX | Cyclooxygenase |
| Ig | Immunglobulin |
| MRG-PX | MAS-related G protein X |
| NSAID | Nonsteroidal anti-inflammatory drug |

## Common triggers of drug-induced anaphylaxis

After food and insect venom, drugs are the most common causes of anaphylaxis [1]. For example 2346 cases of drug-induced anaphylaxis have been reported to the anaphylaxis registry until March 2019. The average age of the registered patients was 50 years of them 65% were female and 35% male. The most common triggers of drug-induced anaphylaxis among the reported cases in the registry were nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics ($n=902$). Of these, 444 cases were caused by NSAIDs and 446 cases by other analgesics and antipyretics (Table 1). Leading NSAID triggers were the substances ibuprofen and diclofenac. The second most common trigger group of drug-induced anaphylaxis reported to the registry were antibiotics ($n=721$). Here, beta-lactam antibiotics with peni-

**Table 1** Reports of drug-induced anaphylaxis due to analgesics (data from the anaphylaxis registry as of March 2019, https://www.anaphylaxie.net/en/)

| 444 nonsteroidal anti-inflammatory drug (NSAID) | 446 other analgesics and antipyretics |
|---|---|
| 195 ibuprofen | 217 pyrazolones (e.g., metamizole) |
| 187 diclofenac | 130 salicylic acid and derivatives |
| 24 mefenamic acid | 43 anilides (e.g., paracetamol) |
| 17 COX-2 inhibitors | |

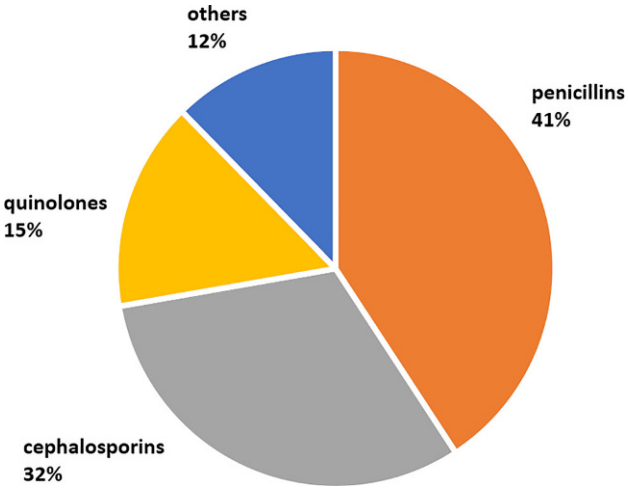


**Fig. 1** Anaphylaxis due to antibiotics, $n = 721$ (data from the anaphylaxis registry as of March 2019)

cillins and cephalosporins were the primary eliciting agents, but also quinolones and macrolides as well as sulfonamides were frequently reported (Fig. 1).

## Mechanisms

Drugs, which have been identified as triggers of drug-induced anaphylaxis, can elicit an immediate drug reaction through different mechanisms. IgE-dependent and IgE-independent pathomechanisms must be differentiated [2]. Penicillins are a classic example of drugs triggering IgE-mediated anaphylaxis, while fluoroquinolones, opioids, X-ray contrast agents and neuromuscular muscle relaxants probably mostly act via the recently identified G-protein signalling pathway (MRG-PX2) [3]. A third mechanism is the so-called CARPA—complement activation-related pseudoallergy [4]. Here an activation of the complement system occurs. Classic examples that can trigger such reactions are polyethylene glycol, paclitaxel and intravenous iron ([5]; Fig. 2).

Drug-induced anaphylaxis can also be triggered by a mast cell- and basophil-independent pathway. A classic example are the nonsteroidal anti-inflammatory drugs, which can trigger via the skin, the respiratory tract or just as real anaphylaxis reactions via the COX1 interference (COX [cyclooxygenase]) [6].

It is also possible that patients who have not previously received the drug (drug naive patients) develop reactions. As pathomechanisms, cross-reactivity (e.g. cephalosporin in penicillin allergy), a non-IgE-mediated mechanism via MRG-PX2 (e.g. muscle relaxant antigen) or other nonspecific induced histamine release must be mechanistically considered.

## Symptoms and risk factors of drug-induced anaphylaxis

Drug-induced anaphylaxis can be fatal. A recent analysis from France showed the highest proportion of deaths from anaphylaxis in the group of drug-induced anaphylaxis ($n = 55$) compared to anaphylaxis induced by food ($n = 26$) and insect venom ($n = 19$) [7]. While food-induced anaphylaxis is more commonly associated with respiratory symptoms, cardiovascular symptoms are more common observed in drug-induced anaphylaxis [1]. This is probably related to the higher age of the affected patient, the more frequent intravenous delivery and possibly the more frequent simultaneous presence of cardiovascular comorbidities. In a recent analysis cases of therapy-refractory anaphylaxis were evaluated, a form of anaphylaxis with reactions that has been treated with at least two applications of therapeutic adrenaline is particularly frequently triggered by medications [8].

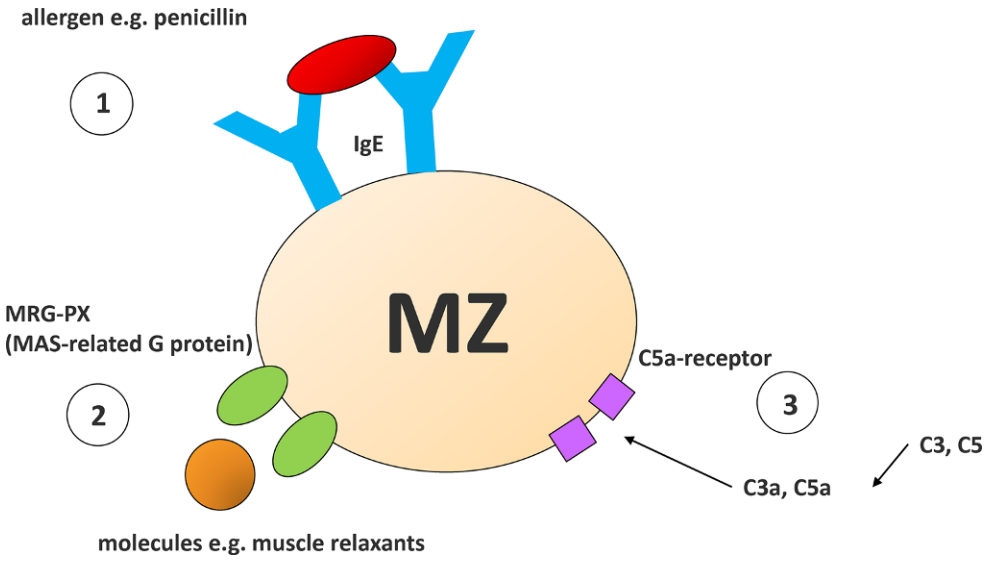


**Fig. 2** Mechanisms of drug-induced anaphylaxis (according to Spoerl et al. [2])

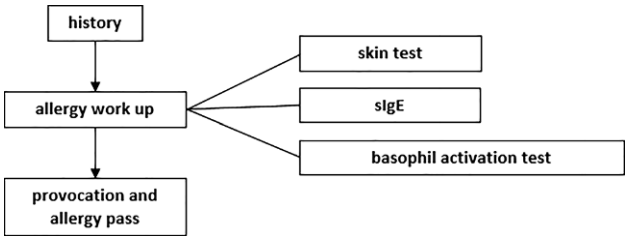


**Fig. 3** Flow chart for diagnostic workup in drug-induced anaphylaxis (according to Brockow et al. [9])

## Diagnosis of drug-induced anaphylaxis

The diagnostic approach in drug-induced anaphylaxis using skin and sIgE testing depends on the suspected elicitor and ultimately makes only sense if IgE-mediated reactions are suspected. All other forms of drug-induced anaphylaxis should, if necessary, be proven by oral provocation testing. For the extended diagnostic workup of IgE-mediated reactions, the basophil activation test can be performed if available. The potential use and limitations of allergy testing in drug-induced anaphylaxis have recently been specified in a European guideline ([9]; Fig. 3).

In case of skin tests, it should be taken into account that some drugs are irritative and can therefore result in false-positive reactions (e.g. ciprofloxacine). Patients with a drug-induced anaphylaxis should undergo an allergological workup and should be given a document where the time, the reaction pattern and the ultimate trigger are documented. If provocation tests have been performed, it is important to document the appropriate alternative medications including the maximum single and cumulative total dose. Underlying mastocytosis should always be considered and basal serum tryptase measurement is recommended as a first diagnostic step. To avoid the repeated occurrence of such reactions and consecutive deaths in the long term, appropriate allergological workup is necessary. Nonetheless, data from the anaphylaxis registry show that up to 10% of patients with drug-induced anaphylaxis have repetitive reactions [1]. These findings point to the need for sound allergological care and education for patients with drug-induced anaphylaxis.

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