Anaphylaxis to Drugs

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KEYWORDS

• Anaphylaxis • Drug • Penicillin • NSAID • Radiocontrast • Vocal cord dysfunction • Proton pump inhibitor • Cephalosporin

KEY POINTS

- Drug-induced anaphylaxis is the most common cause of fatal anaphylaxis, with antibiotics and radiocontrast accounting for most fatalities.
- Vocal cord dysfunction can mimic anaphylaxis and is often overlooked as a cause leading to poor outcomes. Challenge with the culprit drug or drugs followed by laryngoscopy helps confirm the diagnosis.
- Nonsteroidal anti-inflammatory drug (NSAID) anaphylaxis is typically drug-specific, and other tolerated NSAIDs can be confirmed via graded challenge. Evidence for aspirin as a cause of anaphylaxis is lacking.
- Most patients with anaphylaxis from β-lactams can tolerate other classes of β-lactams. Skin testing and drug challenges can confirm tolerance to other β-lactam antibiotics.
- Immunoglobulin E (IgE)-mediated reactions may occur with nonionic radiocontrast media. Premedication regimens are not completely effective. The role of skin testing in the evaluation of patients with radiocontrast anaphylaxis is still evolving but should be considered.

INTRODUCTION

Anaphylaxis is a rapid-onset, multisystem hypersensitivity reaction with a potentially fatal outcome. It most often represents an immunologic (immunoglobulin E [IgE] or non-IgE-mediated) or nonimmunologic reaction to certain antigens, resulting in mast cell and basophil degranulation. In the context of medication allergies, it is mostly mediated by antigen-specific IgE responses, but other mechanisms have been well characterized, and the label of anaphylaxis encompasses all of these clinical syndromes.

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EPIDEMIOLOGY

The population prevalence, or incidence, of anaphylaxis has been difficult to quantify because of a lack of consensus on the definition of anaphylaxis, and analysis of different sample populations. Recent US studies have added important information on the epidemiology of drug-induced anaphylaxis.

Using a US nationwide cross-sectional telephone survey, the prevalence of anaphylaxis in the general adult population was 1.6% with medications being the most common trigger (35%).[1] Another US study using a pediatric emergency department (ED) database over a period of 5 years estimated that anaphylaxis is responsible for 0.18% of ED visits in the United States.[2] Excluding pediatric cohorts (wherein foods are the most common trigger), medications are the most frequent cause of fatal anaphylaxis in reports from the United States, as well as the United Kingdom, Australia, and New Zealand.[3]

In conjunction with an increasing worldwide incidence of anaphylaxis overall, drug-induced anaphylaxis admissions also increased by ~150% during the 8-year period studied in an Australian ED database.[4] In the same study, severe reactions (associated with hypotension) were more likely to be medication-induced ($P<.05$). This phenomenon is presumably in parallel with the increasing treatment of patients with multiple courses of sensitizing medications.

Medications are typically cited as among the most common triggers of fatal reactions. This finding was confirmed in a recent US study of fatal anaphylaxis (analyzed by coding of death certificates) by Jerschow and colleagues,[3] wherein 58.8% of fatal anaphylaxis were drug-induced. Unfortunately, the culprit drug was not specified in ~75% of these fatal drug-induced anaphylaxis cases. Among the ~25% of cases where a drug was identified, antibiotics accounted for 40% of the fatal episodes—most often penicillins, followed by cephalosporins, sulfa-containing drugs, and macrolides. Radiocontrast agents accounted for 27% of fatalities with antineoplastic drugs attributed to 12.5%. The remainder of culprit drugs was identified as serum, opiates, antihypertensives, nonsteroidal anti-inflammatory drugs (NSAIDs), and anesthetic agents.

RISK FACTORS

Clinical factors increasing the risk of drug-induced anaphylaxis are outlined in **Box 1**.

Demographic Factors

Of various demographic factors, older age has been associated with both higher rates of drug-induced anaphylaxis ($P<.001$)[3] and an increased risk of severe reactions.[5,6] African American race has also been associated with a higher prevalence of fatal drug-induced anaphylaxis.[3]

Banerji and colleagues[7] recently described the characteristics of 716 patients with drug-induced anaphylaxis in another ED database, most of whom were female (71%). In light of this conspicuous female predominance, it was postulated that female hormones may impact drug sensitization and the severity of associated allergic reactions. However, in the aforementioned study by Jerschow and colleagues,[3] there was no significant difference in rates of fatal drug-induced anaphylaxis between sexes.

Genetic Susceptibility

Decreased activity, or deficiency, of platelet-activating factor (PAF) acetylhydrolase, the enzyme that inactivates PAF, has been described as a risk factor for severe and