Drug-induced shock

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Abstract:
Drug therapies grow more complex, thus a wide range of drug-related problems (DRPs) may arise. Adverse drug reactions (ADRs) are responsible for approximately 10% of all DRPs. The most severe form of ADR is an anaphylactic shock. It is estimated that severe anaphylaxis affects annually 1–3 per 10 000 people and causes death of 0.65–2% of those patients, i.e. 1–3 per 1 000 000 people. Fatal drug-induced anaphylactic shock is rare and its incidence can be estimated at 0.3 case per million inhabitants per year. The drug categories most frequently associated with life threats are: antimicrobials, dextrans, radiocontrast agents, and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). The unpredictability of anaphylaxis makes the prevention of drug-induced shock (DIS) difficult. However, there are several measures that ought to be undertaken to reduce a risk of its occurrence. Extremely important is the prompt introduction of thorough treatment, as soon as first symptoms of DIS are manifested.

Key words:
adverse drug reaction, anaphylaxis, drug, shock, epidemiology, pathomechanism


General aspects and definitions

Drug therapies grow more complex, thus a wide range of drug-related problems (DRPs) may arise. In a recent study, Blix et al. [3] found that even as much as four-fifths of the patients hospitalized in five general hospitals in Norway had DRPs. The number of DRPs per patient is usually linearly related to the number of drugs used on admission. However, polypharmacy as commonly defined (> 4 drugs) is an indicator of limited value in the assessment of this phenomenon [29].

The wide term DRPs encompasses several conditions. Among them Strand et al. [23] distinguished eight categories: need for additional drug therapy, wrong drug therapy, poor compliance, inappropriate or inadequate monitoring, unnecessary drug therapy, dosage too low, dosage too high, and adverse drug reaction (ADR). It should be pointed out that ADRs are responsible for approximately 10% of all DRPs. Its severest form is an anaphylactic shock.

According to the definition proposed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, an adverse drug reaction is: “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function”. Therefore, an adverse drug reaction is an adverse event with a causal link to a drug [6].
In general, drug reactions can be considered as being either predictable or unpredictable. A predictable reaction would be the result of the pharmacologic action of the medication, whereas an unpredictable reaction might be idiosyncratic, might result from drug intolerance, or might have an immunologic basis. Anaphylactic reactions to drugs are usually (except for situations that can be considered medication errors) unpredictable. World Allergy Organization defines anaphylaxis as “a severe, life-threatening generalized or systemic hypersensitivity reaction. The term allergic anaphylaxis should be used when the reaction is mediated by an immunologic mechanism, e.g. immunoglobulin E (IgE), immunoglobulin G (IgG), and immune complex complement-related. An anaphylactic reaction mediated by IgE antibodies, such as peanut-induced food anaphylaxis, may be referred to as IgE-mediated allergic anaphylaxis. Anaphylaxis from whatever nonimmunologic cause should be referred to as nonallergic anaphylaxis” [11]. Its severest form is an anaphylactic shock described as “a life-threatening condition in which blood pressure is too low to sustain life” [26].

An anaphylactic reaction usually manifests itself very quickly (within minutes), but sometimes it can be delayed by half an hour to several hours after ingestion of a trigger factor. The most frequent symptoms involve the skin and the respiratory system [5]. Anaphylactic shock cases after intravenous drug administrations are more frequent than anaphylactoid reactions or other ADRs, but more than one-third of these reactions are caused by an oral drug [15].

Epidemiology

There are many reports on the epidemiology of anaphylaxis utilizing very large electronic databases and ICD-9 codes or hospital retrospective data. Several of them are devoted to the assessment of drug-induced anaphylaxis (DIA) prevalence, but none exclusively to drug-induced shock (DIS).

In 2006 experts of the American College of Allergy performed a qualitative review of the major epidemiologic studies of anaphylaxis selected back to 1968. This review was restricted to articles in the English language. The roundtable discussion led to an estimation of lifetime anaphylaxis prevalence from 0.05% to 2.0%. The largest number of incident cases was observed among children and adolescents [16].

A challenge to the epidemiologic study of DIA is the lack of a precise standard case definition [12]. Although several studies use definitions that incorporate information about the number and type of signs and symptoms and the time interval between exposure and symptom onset, the specific elements of the definitions vary. In addition, commonly used classification of anaphylaxis is inconsistent with its definition, since several forms of stages I and II of four-stage anaphylaxis severity classification are not life-threatening events. Thus, shock is a component of many, but by no means every case of anaphylaxis.

To cope with this problem, Moneret-Vautrin et al. [20] introduced a term: “severe anaphylaxis” that can be considered as an equivalent of anaphylactic shock. In their worldwide review, they have estimated that severe anaphylaxis affects annually 1–3 per 10,000 people and causes death of 0.65–2% of those patients, i.e. 1–3 per 1,000,000 people.

There are no similar large epidemiologic data concerning the incidence of drug-induced shock. The only report comes from Denmark, where Lenler-Petersen et al. [14], basing on notifications to the Danish Committee on Adverse Drug Reactions and to the Central Death Register, identified 30 cases of fatal drug-induced anaphylactic shock during the period 1968–1990. It indicates that fatal drug-induced anaphylactic shock is rare and can be estimated at 0.3 case per million inhabitants per year. It should be stressed that four-fifths dying of drug anaphylaxis had no previous indication of their allergy [22].

Comparing Dutch results [14] with those presented by Moneret-Vautrin et al. [20], we can assume that DIA probably is responsible for around one-tenth of all cases of anaphylactic reactions.

Responsible agents

Data in this area vary depending on the country and a period of time analyzed.

Wang et al. [29] examined all cases of suspected drug-induced reactions classified as anaphylactic reactions or shock reported in Sweden between 1972 and 1995. There were 201 different drugs reported as “suspected”, most common of which were dextrans,
X-ray contrast media and antibiotics. For dextran, the rates of shock and fatal cases reported were 101 and 21 per million bottles respectively. This decreased to 9.8, and 0.4 per million bottles after the introduction of preventive treatment with Dextran 1 in 1983. The respective rates for ionic contrast media were 0.13 and 0.02/1000 cases, whilst non-ionic contrast media caused shock only in 0.02/1000 cases, and there was no report of a fatal case.

In the United States [18] the drug categories most frequently associated with life threats were antimicrobials and central-nervous-system agents, while in Italy [21] antimicrobials and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs).

There are also other drug categories that focus particular clinicians’ attention despite that they are not at the top of the anaphylactic shock frequency lists.

Anaphylaxis, which may occur during anesthesia, is a rare but important event. The largest review established on the basis of the more than 12,000 cases of peranesthetic anaphylactoid reactions published in the English and French literature during the consecutive 15 years was done by Laxennaire [13]. He found that (depending on the country) anaphylactoid reactions represented 9 to 19% of complications associated with anesthesia. In 1996, the incidence of anaphylactic reactions in France was estimated to be 1/13,000 for general and local or regional anesthetics. The mortality rate was about 5 to 7%. The most frequent trigger factors were: muscle relaxants in 62%, latex in 16.5%, and hypnotics in 7.4% of cases.

Many patients as well as physicians are afraid of potential anaphylaxis after vaccination. Data provided by Bohlke et al. [4] indicate that those fears are definitely exaggerated. These authors examined the cohort of 2,226,907 children and adolescents enrolled in their respective West Coast Health Maintenance Organizations (HMOs). There were identified only 5 cases of potentially vaccine-associated anaphylaxis after administration of 7,644,049 vaccine doses, for a risk of 0.65 cases/million doses. None of the DIA episodes resulted in death. Vaccines that were administered included: diphtheria-tetanus-pertussis, hepatitis B, measles-mumps-rubella, diphtheria-tetanus, *Haemophilus influenzae* type b, and oral polio vaccine.

Special situation is in the case of specific immunotherapy (SIT), where the patient is given an allergen to which he or she is sensitized. Between 1895 and 1965, over 70 deaths associated with SIT have been reported in the world literature [17]. However, the majority of them were caused by allergens, which are no longer in use. American Academy of Allergy, Asthma and Immunology surveyed severe reactions associated with SIT which occurred in North America between 1990 and 2001. There were 20 fatal immunotherapy reactions that were directly reported and 21 indirectly reported cases by local physicians. It was estimated that fatal reactions occurred every 1 per 2.5 million injections [2], while near-fatal reaction (anaphylactic shock) incidence was assessed at the rate 5.4 events per million injections [1].

### Mechanisms

Drug induced shock can develop due to either immunologic or nonimmunologic reactions. In both cases symptoms result from excessive mediator release from effector cells. Immunologic anaphylaxis occurs upon subsequent contact with an antigen (allergen) in a sensitized individual, whilst the nonimmunologic one may manifest itself after the first administration of a given agent.

IgE-dependent mechanism is observed in allergy to antibiotics, muscle relaxants or latex [13, 29]. In these cases cross-reaction (for example between β-lactam antibiotics and muscle relaxants) might be very important. In turn, blood-derived therapeutics induce shock through IgE-independent mechanism involving immune complexes with IgG antibodies [7].

Nonimmunologic anaphylactic reaction is responsible for shock caused by radiocontrast agents. Its essence relies on the pharmacologic action of a drug on mast cells and basophils that induces the release of histamine from these cells [9]. Aspirin and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase 1 (COX-1), which results in decreases in prostaglandin E2 production. This prostaglandin has inhibiting effects on 5-lipoxygenase-activating protein and 5-lipoxygenase, which participate in the generation of leukotrienes pathway [8, 24]. In a part of apparent DIS cases even thorough examination does not allow to confirm any drug allergy or intolerance or to find out any other responsible factor. Then, idiopathic anaphylaxis should be suspected whose prevalence is estimated between 15–23% of all anaphylactic reactions [10, 27].
It should be underlined that some drugs may induce anaphylaxis in different patients through different mechanisms. The route of drug administration plays an important role [15].

**Prevention and treatment**

The unpredictability of anaphylaxis makes the prevention of DIS difficult. However, there are several measures that ought to be undertaken to reduce a risk of its occurrence. There is primary, secondary and tertiary prevention.

The U.S. Preventative Services Task Forces’ Guide to Clinical Preventive Services [26] defines primary prevention measures as “those provided to individuals to prevent the onset of a targeted condition”. They include general activities that help avoid a given problem such as health protecting education.

Secondary prevention measures are described as those that “identify and treat asymptomatic persons who have already developed risk factors or preclinical disease but in whom the condition is not clinically apparent”. Thus, patients who have previously shown any clinical signs and symptoms suggesting an allergic reaction to drugs should be thoroughly examined to confirm or exclude his or her sensitization to agents which are likely to be used [19]. There is actually no way to prevent primary sensitization to radiocontrast agents, NSAIDs or muscle relaxants. Anaphylactic reactions to these agents can occur in the absence of their prior administration. In patients at high risk of DIA, a relevant premedication with glucocorticosteroids and antihistamine agents ought to be established before diagnostic imaging with the use of contrast media, anesthesia or surgery. On the other hand, drugs that may augment anaphylactic reaction, such as angiotensin converting enzyme inhibitors or β-blockers should be avoided.

Tertiary prevention activities involve the care for established disease, with attempts made to restore function, minimize the negative effects of disease, and prevent disease-related complications.

Since anaphylactic shock usually manifests itself within minutes and can further develop very quickly, the prompt introduction of relevant treatment is extremely important. First of all, epinephrine should be administered (as soon as possible) intravenously by bolus in titrated doses, depending on the patient’s hemodynamic status. Alternatively, the intramuscular route can also be used (0.3 to 0.5 mg), with injections repeated after 5 to 10 minutes, if necessary. It must be remembered that the delayed administration of epinephrine may result in patient’s death [20]. The next step is to restore the vascular volume with isotonic crystalloid. Colloids should replace salt solutions when the volume of salt solution exceeds 30 mL/kg. Then glucocorticosteroids (at high doses) and antihistamines are to be given, as well as 100-vol% oxygen. Any additional treatment depends on the specific concomitant symptoms, like bronchospasm or cardiac arrhythmia [13].

**References:**


