

PERIOPERATIVE ALLERGY: CLINICAL MANIFESTATIONS

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Adverse drug reactions or side effects are usually expected, dose dependent, and occur at therapeutic doses. Anaphylactic and anaphylactoid reactions are unexpected and dose independent and can occur at the first exposure to drugs used during anesthesia. Perioperative anaphylaxis is a severe and rapid clinical condition that can be lethal even in previously healthy patients. The initial diagnosis of anaphylaxis is presumptive. A precise identification of the drug responsible for the adverse reaction is more difficult to establish in the case of anaphylactoid reaction because the adverse reaction could result from additive side effects of different drugs injected simultaneously. The timing of the reaction in relation to events, e.g. induction, start of surgery, administration of other drugs, i.v. fluids, is essential for the diagnosis. Generally, reactions are predominant in the induction and recovery phases, and manifested mainly as cutaneous symptoms. Reactions to drugs coincide with the phases when they are administered. Reactions to antibiotics are more frequent in the induction phase, to neuromuscular agents in the initiation and maintenance phases and to non-steroidal anti-inflammatory agents in the recovery phase. The differential diagnosis of any adverse reaction during or following anesthesia should include the possibility of anaphylaxis.

Anesthesiologists administer different drugs during the perioperative period, including blood products and drugs, or manage patients during exposure to multiple foreign substances, all of which have the potential to produce a spectrum of adverse reactions (1). Any drug administered during anesthesia can produce potentially life-threatening immune-mediated anaphylaxis.

Unfortunately, patients may not always know that they are sensitized to a drug or protein by previous exposure. Intraoperative anaphylaxis, especially after anesthesia induction, is often problematic because the patient is exposed to multiple drugs in an extremely short period, including induction drugs, opioids, antibiotics, neuromuscular blocking agents (NMBAs) and occult antigen such as latex or drug additives/preservatives. The drug responsible for the adverse reaction can be better identified in case of anaphylaxis. According to Mertes

and coworkers, NMBAs represent the most frequently involved substances, with a described range from 50 to 70% out of the reactions, followed by latex (12% to 16%) and by antibiotics (15%) (2). Hypnotics and opioids were involved in 3.0% and 1.3%, respectively (2).

Perioperative anaphylactic reactions are potential life-threatening immediate hypersensitivity reactions that are unrelated to the drug's pharmacologic characteristics and correspond to immune-mediated allergic and to non-immune-mediated, the so-called "pseudo-allergic or anaphylactoid" reactions (3).

MECHANISMS AND TIMING OF REACTION

Anaphylaxis is a life threatening reaction resulting primarily from the rapid antigen-induced, usually immunoglobulin (Ig) E dependent release of potent,

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pharmacologically active mediators from mast cells and basophils. Mediators are released after repeated antigenic exposure in a previously sensitized individual. The difference between IgE and non-IgE mediated anaphylactic reactions cannot be made on clinical grounds alone because clinical symptoms and signs can be very similar. All hypersensitivity reactions occurring during the perioperative period should be investigated to identify the mechanism(s) of the reaction as well as the responsible substance (4).

The main mechanism of hypersensitivity reactions to NMBAs, latex and antibiotics is the acute type I allergic reaction; reactions to penicillin may result from a variety of mechanisms, for example maculopapular rashes are usually not IgE-mediated, but severe, immediate reactions and particularly anaphylaxis are IgE mediated.

Vancomycin can elicit two types of immediate hypersensitivity reactions; the red man syndrome and anaphylaxis. The red man syndrome typically consists of pruritus, burning sensation, and erythematous eruption that spread over face, neck and upper torso. Less frequently angio-oedema, dyspnoea and hypotension can occur. Signs generally appear within 5-10 min after start of infusion and are often associated with too rapid (<1 hour) infusion of the first dose and result from non specific mediator release from mast cells and basophils. Teicoplanin can also cause the same red man syndrome (5).

Moreover, systemic reactions to latex rubber are IgE mediated; it is important to distinguish these systemic manifestations from contact dermatitis that causes slow-onset eczematous reactions and that is not life threatening and is caused by a type IV reaction, not involving IgE antibodies.

Reactions to colloid present with sudden loss of blood pressure, compatible with widespread vasodilatation; generation of bradykinin is a possible mechanism.

High-molecular weight dextrans are accompanied by significant side effects including dextran-induced allergic reactions (DIAR). Severe DIAR is characterized by bronchospasm, profound hypotension, cardio-respiratory arrest and fatalities (6).

Non steroidal anti-inflammatory drugs (NSAID), including aspirin, can cause reactions, by inhibition of cyclo-oxygenase, resulting in increased generation of leukotrienes. NSAID are increasingly recognized as a cause of non-IgE mediated anaphylactic reactions. All NSAID can cause bronchospasm, urticaria and angio-oedema.

Allergic reactions involving hypnotics (propofol, thiopental, midazolam, etomidate, ketamine) appear to be relatively rare. Most of generalized reactions are thought to be related to the ability to elicit direct leukocyte

histamine release; however, there is evidence for IgE mediated anaphylactic reactions based on skin tests and specific IgE assays.

Generalized reactions to opioids (morphine, codeine, etc) usually result from non specific mast cell activation, rather than from IgE-mediated degranulation. Most of these reactions are not life-threatening and include pruritus, urticaria and mild hypotension but are frequently misinterpreted as drug allergy (6).

Chlorexidine salts can trigger irritant dermatitis, allergic contact dermatitis, urticaria/anaphylaxis and combined urticaria/anaphylaxis and allergic contact dermatitis. Symptoms of chlorexidine anaphylaxis have been attributed to cutaneous, percutaneous, mucosal and parental application. Life threatening reactions with profound hypotension, ventricular fibrillation and cardiac ischemia are generally associated with mucosal or parenteral exposure as might occur during application of urethral gels implanted antimicrobial surgical mesh, and insertion of chlorexidine-coated central venous catheters, respectively. Severe, potentially life-threatening anaphylaxis from simple cutaneous application such as perioperative skin disinfection and wound cleansing remains anecdotal and probably underestimated.

Although generally considered as intrinsically safer than general anesthetics, local anesthetics can elicit a variety of side effects. Symptoms usually result from vasovagal episodes or anxiety reactions. Acute disorientation or seizures may occur after over dosage or inadvertent intravenous injection. In addition, many local anesthetics contain adrenaline as a vasoconstricting agent. Local anesthetics can also produce sympathetic effects that may include tremulousness, palpitations, tachycardia, diaphoresis, light-headedness, or near syncope, irrespective the presence or absence of vasoconstricting agents. Other excipients associated with local anesthetics such as anti-oxidants and preservatives (bisulphites, parabens, and para-aminobenzoic acid) can elicit adverse and even allergic reactions. Protamine, used for anticoagulant effect, can cause significant histamine release resulting in (fatal) hypotension and bronchospasm, and also causes pulmonary hypertension (6).

Factors, which influence allergic reaction symptom severity in the sensitized individual, include the distribution and reactivity of sensitized mast cells and basophils, individual organ susceptibility, released mediators and the endogenous response that they elicit (7).

Anaphylaxis is not a homogenous process: the pathways, mediators, time course and response to treatment depend on the trigger agent, its route and rate of administration, the nature of the patient's hypersensitivity

and the state of health of the patient, including incidental pathology such as respiratory or cardiovascular disease and the effect of concomitant medication (8). Anaphylaxis may occur at any time during anesthesia and may progress slowly or rapidly.

Finally, the onset and type of symptoms depend on the allergen concentration, whereas the length of symptoms (up to 36 h) may vary according to the mode of injection (e.g. when using dyes such as isosulfan blue or patent blue for lymphatic mapping and sentinel lymph node biopsy).

However, the main determining anaphylaxis factor during perioperative period is the route of administration. Anaphylaxis to the i.v. induction agents (e.g. antibiotics that are often given at induction) occurs within minutes of administration, as a large bolus of allergen is given intravascular. In contrast, in latex allergy, the allergen is absorbed more slowly, e.g. from surgeon's gloves through the peritoneum, mucosa or skin or from rubber equipment, although rubber anesthetic facemasks have been almost entirely replaced with non-rubber alternatives, and endotracheal tubes and laryngeal masks are latex-free. Onset is therefore slower and occurs intra-operatively, generally 30 minutes from the start of contact with latex but depends on the sensitivity of the patient and on the amount of allergen absorbed. Latex absorption is faster from the vaginal mucosa and peritoneum than through the skin. Therefore, a systemic reaction is unlikely to occur within a few minutes of latex exposure.

NSAID may be given rectally towards the end of surgery, i.v., or sometimes with pre-medication, depending on the procedure. The onset of reaction is usually up to 10 min after i.v. administration and 30-60 min after oral administration. If the onset of reaction is at the end of surgery, this immediately excludes the induction agents, and the main differential diagnosis is a NSAID given late during the procedure, latex allergy or a reaction to colloid.

Reactions to gelatin often occur 15-20 min after the start of infusion. Similarly, reactions to chlorhexidine may be delayed, perhaps 10 min after mucosal contact, e.g. bladder instillation and longer after skin painting. However, entry of chlorhexidine directly into the circulation, for example during central venous catheter insertion, may result in immediate circulatory collapse.

Reactions to colloids are more difficult to diagnose clinically, partly because of the delayed and variable onset from the start of the i.v. infusion, although this happens usually within 30 min (9).

Ninety percent of reactions appear at anesthesia induction within minutes after the intravenous injection of the offending agent, such as in case of allergy to a NMBAs or antibiotics (10).

If the signs appear later during the maintenance of

anesthesia, some authors suggest to consider an allergy to latex, volume expanders, or dyes. Latex allergy should also be considered when gynecologic procedures are performed. Particles from obstetricians' gloves, which accumulate during obstetric maneuvers, could suddenly be released into the systemic blood flow following oxytocin injection (11).

CLINICAL FEATURES

Anaphylaxis is generally an unanticipated reaction. It is worthwhile mentioning that the signs of anaphylaxis occurring during anesthesia differ to some extent from signs and symptoms that occur during anaphylaxis not associated with anesthesia. All early symptoms usually observed in the awake patient such as malaise, pruritus, dizziness and dyspnoea are commonly absent in the anaesthetized patient.

In addition, cutaneous signs may be difficult to notice in a completely draped patient and also many signs such as an increase in heart rate, a decrease in blood pressure or an increase in airway resistance may be initially misinterpreted as the result of an interaction between the clinical status of the patient and the drugs administered during the procedure, dose-related side effect of the drugs, or excessively light anesthesia (11).

Manifestation can range from mild non-life threatening reactions to severe shock and death. The severity of the anesthetic reactions was based on the grading system for generalized hypersensitivity reactions by Brown (12) (Table 1). Grade I and II are usually not life-threatening conditions, whereas grades III and IV correspond to emergency situations necessitating prompt resuscitation.

Although, anaphylactic and anaphylactoid reactions cannot be distinguished on the basis of clinical symptoms alone, when a classification based on symptom severity was applied, clinical manifestations seemed to be more severe in patients with documented anaphylaxis than in patients presenting with an anaphylactoid reaction.

Anaphylaxis commonly involves the skin (pruritus, flushing, urticaria and angioedema), eyes (conjunctivitis), the upper (rhinitis and angioedema) and lower airway (bronchoconstriction with wheezing and dyspnoea and cyanosis), the intestinal tract (abdominal pain, nausea, vomiting and diarrhea), cardiovascular system (tachycardia, hypotension and shock) and can lead to cardiovascular collapse and death. In fact, virtually all systems, including the central nervous and genitourinary systems can be involved. Alternatively, reactions may be fatal without significant shock except as the terminal event following respiratory arrest (13).

The most commonly reported initial clinical features during severe reactions (grade III or IV) are pulseness,

desaturation and difficult lung inflation due to severe bronchospasm, for example a decreased end-tidal CO₂ could be also of diagnostic value (14). Respiratory signs can be of course enhanced in patients with underlying asthma and/or chronic obstructive pulmonary disease. Asthmatic patients experiencing perioperative anaphylaxis are therefore more likely to exhibit bronchospasm (15).

Asphyxia may be due to upper airway occlusion caused by angioedema, or bronchospasm with mucus plugging of the lower airways; the latter most commonly occurs in patients taking daily treatment for asthma. Anaphylaxis usually resolves in 2-8 hours but secondary pathology arising from the reaction or its treatment may prolong this phase.

Because cardiovascular disturbances are the hallmark of severe anaphylaxis, cardiovascular collapse as the sole feature or cardiac arrest may be the inaugural event (16). Acute coronary events associated with hypersensitivity reactions were recently referred to as Kounis syndrome, which is also called allergic angina or allergic myocardial infarction (17). Two variants were described as the consequences of mast cell mediator release: type I includes patients without predisposing factors for coronary artery disease, whereas type II includes patients with predisposing factors. The allergic reaction may induce coronary artery spasm with normal cardiac-specific enzymes in variant I, whereas acute infarction may be seen in both groups (type I and type II). A threshold level of mast cell content has been suggested to be involved in the occurrence of such events.

Tachycardia is not variable; bradycardia is seen approximately in 10% patients with allergic anaphylaxis during anesthesia. Hypotension is the sole clinical feature in approximately 10% patients and is likely to be exaggerated in patients undergoing anesthesia with neuraxial blockage.

Angioedema and urticaria may be features of anaphylaxis but commonly result from mechanisms other than anaphylaxis. Although widespread flushing or urticaria is seen in the majority of patients, the absence of cutaneous signs does not exclude anaphylaxis. Cutaneous symptoms were more frequent in anaphylactoid reaction, whereas cardiovascular collapse and bronchospasm were more frequent in cases of anaphylaxis.

The incidence of symptoms and the severity of the clinical manifestations are reported with wide variations. Some authors identified that most anaphylactic reactions were grade 2 (23%) or grade 3 (58.9%), whereas anaphylactoid reactions were mainly grade 1 (55.3%) (11).

In another report, anaphylactic reactions were severe (88.1% of cases, grade II or more) and often life-threatening (65.1% grade III and IV). This is in contrast

with reactions of a non immune type, which were grade 1 (55.3%). Nevertheless, some cases corresponding to true IgE mediated anaphylactic reactions were classified as grade I or II (2). In fact, cutaneous symptoms were observed in only 66 to 70% of patients in case of IgE-mediated reactions, whereas they were present in more than 90% in non-IgE mediated reactions (2).

On the contrary, cardiovascular collapse and bronchospasm were present in more than 50% and 39% of IgE-mediated reactions but only in 11% and 19% of non IgE-mediated reactions, respectively (11). Similarly, anaphylaxis due to NMBAs or antibiotics seemed to be more severe than anaphylactic reactions to latex (18).

According to Karila and coworkers, 48% of children during perioperative period had a history of atopic manifestations (asthma, atopic dermatitis, rhinitis, food allergy); 13% of children presented hypersensitivity to a single drug (antibiotic, aspirin). Of the 51 patients presenting an IgE mediated anaphylactic reaction, 23 were atopic (45%), seven presented hypersensitivity to a drug (13.7%) and 21 were not atopic (41%). Nine of the 17 patients in whom the adverse reaction was not IgE mediated were atopic (53%), one have a hypersensitivity to a drug (5%) and seven were not atopic (41%). The distributions of atopy and drug hypersensitivity were not significantly different in these two groups of patients. Twenty of the 68 children studied, were referred for grade 1 reactions, 27 for grade 2 reactions and 21 for grade 3 reactions. None of children had a grade 4 reaction. No significant relationship was found between the type of drug, and the character of IgE mediated or non-IgE mediated reaction and the severity. No significant relationship was found between the occurrence of an anaphylactic reaction during anesthesia and the number of previous anesthetic procedures (19).

Even though bradycardia can occur more often with perianaesthetic anaphylaxis as compared with other causes of anaphylaxis (20), according to Harboe and coworkers, the most frequently reported clinical sign was bronchospasm in 78.3%, whereas hypoxemia (oxygen saturation measured by pulse oximetry < 90%) was reported in 49.4% of the reactions. Severity grading allocated 6.0% to grade IV (patients received cardiopulmonary resuscitation), 62.7% to grade III, 30.1% to grade II, and 1.2% to grade I (21).

Lobera and coworkers found that as for clinical symptoms, skin eruption was recorded in 83% of cases, cardiovascular involvement (hypotension, tachycardia), in 27% and respiratory symptoms (bronchospasm, increased airway resistance, breathlessness) in 23%. Although cutaneous manifestations were predominant in all phases of anesthesia, as usually occurs in drug allergy, respiratory and cardiovascular manifestations show equal

ratios in the maintenance phase. During the induction and/or premedication phase, the most frequent type of reaction was cutaneous (generalized erythema, rash or urticaria/angioedema). During recovery phase, cutaneous symptoms were once again predominant (22).

Three predictive criteria of the severity of an ongoing anaphylactic reaction, which may or may not be associated, include the following:

1. The more rapidly anaphylaxis occurs after allergen exposure, the more likely the reaction is to be severe and potentially life-threatening (23).

2. Cutaneous signs may be absent in rapidly progressive anaphylaxis. (24) Accordingly, the subcutaneous vascular bed is susceptible to vasoconstrictive influences during anaphylaxis (being the first vascular bed compromised when circulatory homeostasis is threatened). Cutaneous signs may therefore only appear after the normalization of blood pressure. Consequently, the absence of initial cutaneous vasodilatation should not preclude the diagnosis of anaphylaxis.

3. Another potentially confounding sign might be bradycardia, which can be seen in massive hypovolemia, probably as the result of the Bezold-Jarish reflex, a cardioinhibitory reflex that has its origin in sensory receptors on the left ventricle transmitted by unmyelinated vagal C fibers (16). This paradoxical bradycardia occurring during extreme hypovolemia that has been reported to occur in approximately 10% of patients with anaphylaxis during anesthesia (8). In this case, bradycardia may be considered as a life-protecting adaptive mechanism that allows the ventricles to fill before they start contracting again despite a massive hypovolemia.

An anaphylactic reaction restricted to a single clinical symptom (e.g. bronchospasm, tachycardia with hypotension) can easily be misdiagnosed because many other pathological conditions may have an identical clinical presentation. In mild cases restricted to a single symptom, spontaneous recovery may be observed even in the absence of any specific treatment should be kept in mind, however, that, under such circumstances, the lack of a proper diagnosis and appropriate allergy assessment can lead to fatal re-exposure. In most cases, after adequate treatment, clinical signs regress within one hour without sequelae. However, in some cases, bronchospasm can be particularly severe and resistant to treatment, with a risk of cerebral anoxia or death (18).

The clinical diagnosis of intraoperative anaphylaxis is problematic because most anesthetics, including propofol, cause vasodilatation, hypotension and potentially cardiopulmonary dysfunction for their direct and indirect effects on sympathetic-adrenergic responses on the heart and the vasculature. Furthermore, the patient with preexisting cardiovascular disease and hypovolemia may

even be more acutely affected by the changes that occur after anesthetic induction (25).

The difficulty in recognizing anaphylactic symptoms in anesthetized subjects may also be explained by the need to exclude various other clinical conditions. The differential diagnosis of peri-anaesthetic anaphylaxis includes conditions, which are not specific to allergic reactions, such as overdose of vasoactive substance, asthma, arrhythmia, myocardial infarction, pericardial tamponade, pulmonary oedema, pulmonary embolism, tension pneumothorax, venous embolism, sepsis, hereditary angioedema, mastocytosis, malignant hyperthermia, myotonias and masseter spasm and hyperkalaemia (26) (Table 2).

CONCLUSION

Adverse drug reactions or side effects are usually expected, are dose dependent, and occur at therapeutic doses. Anaphylactic and anaphylactoid reactions are unexpected and dose independent and can occur at the first exposure to drugs used during anesthesia.

Perioperative anaphylaxis is a severe and rapid clinical condition that can be lethal even in previously healthy patients. The initial diagnosis of anaphylaxis is presumptive, although essential, because anaphylaxis may progress within minutes to become life-threatening. The first line of evidence for the diagnosis of anaphylaxis includes the features and severity of clinical signs and the timing between the introduction of a suspected allergen and the onset of symptoms.

The presentation of anaphylactic and anaphylactoid reactions are clinically indistinguishable (27).

A precise identification of the drug responsible for the adverse reaction is more difficult to establish in the case of anaphylactoid reaction because the adverse reaction could result from additive side effects of different drugs injected simultaneously.

The timing of the reaction in relation to events, e.g. induction, start of surgery, administration of other drugs, i.v. fluids, etc, is essential for the diagnosis.

Generally, reactions were predominant in the induction and recovery phases, and manifested mainly as cutaneous symptoms. Reactions to drugs coincide with the phases when they were administered. Reactions to antibiotics were more frequent in the induction phase, NMBAs in the initiation and maintenance phases and NSAID (dipyrone) in the recovery phase (22).

Therefore, vigilance is essential, as reactions may be well established before they are noticed (18).

The differential diagnosis of any adverse reaction during or following anesthesia should include the possibility of anaphylaxis (28).

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