Anaphylaxis during peri-anesthetic period - review of research

Dąbrowski S.¹, Mędrzycka-Dąbrowska W.²*, Wojtaszek M.³

1. Anesthesiology and Intensive Care Unit, District Health Center in Malbork, Malbork, Poland
2. Department of General Nursing, Medical University of Gdańsk, Gdańsk, Poland
3. The Institute of Emergency Medicine, Department of Medicine, University of Rzeszów, Poland

ABSTRACT

Peri-anesthetic anaphylaxis, mediated by immunologic, nonimmunologic, or undefined mechanisms is a severe and rapid clinical condition that can be lethal. Anesthesiologists use a myriad of drugs during the provision of an anesthetic. Muscle relaxants and latex account for most cases of anaphylaxis during the perioperative period. Symptoms may include all organ systems and present with bronchospasm and cardiovascular collapse in the most severe cases. Management of anaphylaxis includes discontinuation of the presumptive drug (or latex) and anesthetic, aggressive pulmonary and cardiovascular support, and epinephrine. The paper presents the pathophysiology, the most common causes and the management of anaphylaxis occurring during anesthesia, based on a review of available literature. Key words: anaphylaxis, anesthetics, intraoperative anaphylaxis

*Corresponding author:
Medical University of Gdańsk
Department of General Nursing
ul. Dębinki 7, 80-952 Gdańsk, Poland
Tel.: +48 583491247 e-mail: wioletta.medrzycka@gumed.edu.pl

Received: 01.04.2015
Accepted: 29.05.2015
Progress in Health Sciences
Vol. 5(2) 2015 pp 160-164
© Medical University of Białystok, Poland
INTRODUCTION

Anaphylaxis is an acute life-threatening immunologic or non-immunologic reaction that results from the sudden systematic release of chemical mediators from mast cells and basophils. Allergic anaphylaxis includes both IgE-mediated and IgG/IgM immunologic-mediated reactions [1,2]. Nonallergic anaphylaxis indicates the lack of a specific antibody or immune response, although the exact etiology for such reactions is unknown [3,4].

During the provision of modern anesthesia techniques, anesthesiologists use a myriad of drugs. Anaphylaxis can result from hypersensitivity to any of the agents administered in that time. Not surprisingly allergic reactions are among the major factors that contribute to morbidity and mortality during anesthesia and to changes in postoperative care. The incidence of anaphylaxis during provision of anesthesia is very difficult to estimate - criteria for inclusion vary in different studies and countries - and has been calculated to range from 1 in 3,500 to 1 in 25,000 cases, with mortality rate of up to 6% [4].

Among the agents most commonly causing anaphylaxis are: muscle relaxants (69.2% cases of perioperative anaphylaxis) latex (12.1%) and antibiotics (8%). Whereas latex anaphylaxis is decreasing because currently very few products being used in the operating theatre contain latex, there is a group of drugs increasingly seen to cause anaphylaxis - the medical blue dyes [5]. The identification of a causative agent may be challenging because of multiple drugs administered [3,6]. The paper presents the pathophysiology, the most common causes and the management of anaphylaxis occurring during anesthesia, based on a review of available literature.

MATERIALS AND METHODS

For the purposes of this study Medline database was used, provided by Ovid, Elsevier Ebsco. It was searched for the key words: "anaphylaxis", "anesthetics", "intraoperative anaphylaxis". The search returned 37 articles, of which 18 were selected for analysis of scientific articles published between 1994 and 2013.

Diagnosis

Both kinds of anaphylaxis present with similar clinical symptoms, though some distinguishing features exist:

- allergic anaphylaxis, particularly IgE-mediated, often is more severe with subsequent administration of the causal drug; in contrast - the severity of non-allergic anaphylaxis tends to be similar with repeat administration of the causal drug

- nonallergic anaphylaxis is more likely dose-dependent (i.e., lower doses or slower rates of administration may not result in reactions)

- a pretreatment regimen may be effective in nonallergic anaphylaxis, but pretreatment is generally of limited value with allergic anaphylaxis

One must bear in mind that some drugs (e.g. protamine or muscle relaxants) may result in both allergic and nonallergic anaphylaxis [1]. Diagnosis of peri-anesthesia anaphylaxis may be hampered by the limited ability of the affected subject to describe symptoms and skin manifestations may be masked by surgical drapes. Respiratory signs are often blunted by the bronchodilatory properties of inhalation anesthetics, and pharmacologically induced hypotension is common.

Anaphylaxis always should be considered if immediate, unexpected hypotension develops, with or without bronchospasm, following parenteral administration of a therapeutic agent or the induction of anesthesia [2]. Typically there is a profound drop in arterial blood pressure, often requiring active treatment, e.g. use of vasoconstrictive agent [7]. Although the hemodynamic changes occurring during anaphylaxis and anaphylactoid reactions may vary, the major factors causing cardiovascular abnormalities are universal and result from an initial loss of intravascular fluid and vasodilation, which may be followed shortly by vasoconstriction and then myocardial depression. Fluid shifts to the extravascular space, due to increased vascular permeability, can result in a loss of 50% of vascular volume within 10 minutes [8,9]. This loss of blood volume leads to compensatory mechanisms that involve the secretion of catecholamines, such as norepinephrine and epinephrine; activation of the angiotensin system, with conversion of angiotensin I to angiotensin II and increased production of these agents; and the production of endothelin-1, a potent vasoconstrictor peptide that was previously found to be elevated in patients with heart failure, stroke, or hypotension. Increased levels of endothelin-1 indicate that the endothelium responds to hypotension with increased production of this agent. Because anaphylactic episodes are dynamic, the cardiovascular status can change during different stages of the event. For example, during the initial phase, systemic vascular resistance can be reduced, whereas during the later phases of progressing shock, systemic vascular resistance can rise, presumably through the compensatory vasoconstrictor response or the administration of endogenous vasoconstrictive agents, or both. Cardiac output, which can initially be increased, characteristically declines as the event progresses. Central venous pressure may be normal during the early phases of the event and then should
consistently fall with progression of the reaction. The same occurs with pulmonary capillary wedge pressure.

Other manifestations of anaphylaxis during anesthesia include:
- pruritus, flushing, swollen lips-tongue-uvula, periorbital oedema, conjunctival swelling (skin/mucosa)
- increased peak inspiratory pressure, increased end-tidal CO₂, decreased oxygen saturation, bronchospasm (respiratory system)
- tachycardia, bradycardia, arrhythmias, cardiac arrest (cardiovascular system)
- decreased urine output secondary to ATN (renal system)
- DIC (hematologic system)

Differential diagnosis of peri-anesthetic anaphylaxis should, among others, include: asthma, arrhythmia, hemorrhage, myocardial infarction, overdose of vasoactive drug, pulmonary embolus or sepsis [9]. The clinical diagnosis of anaphylaxis can sometimes be supported by the elevated concentrations of serum mast cell tryptase. Blood samples should be ideally collected as soon as the patient has been resuscitated and stabilized. To assess a baseline concentration of tryptase, one sample should be obtained 24 h after reaction. The normal range is 1-11.4 ng/ml. Patients with suspected anaphylaxis should be referred to a specialist clinic for further investigation alongside with copies of perioperative records and investigations [10].

Causal agents

**Muscle relaxants** are used to facilitate endotracheal intubation and to optimize surgical exposure. Anaphylaxis is caused both by IgE antibodies and, more commonly, by direct mast cell degranulation. Because many over-the-counter drugs, cosmetic and food products contain ammonium ions, which are also a part of molecules of many muscle relaxants, anaphylaxis may develop on the first exposure to a muscle relaxant in a sensitized patient. Benzylisoquinolinium compounds, such as d-tubocurarine, metocurine, doxacurium, atracurium, and mivacurium, are more likely to cause direct mast cell degranulation than aminosteroid compounds such as pancuronium, vecuronium, rocuronium, and pipecuronium. Cisatracurium, a benzylisoquinolinium compound and an isomer of atracurium, and succinylcholine have the lowest potency of direct mast cell activation [11].

**Opioids**

Narcotics used in anesthesia are common causes of flushing and urticaria following intravenous administration. Morphine causes nonimmunological histamine release, and meperidine causes nonimmunological histamine release more often than any other opioid. There are reported cases of IgE-mediated reactions to these opioids. Fentanyl belongs to the phenylpiperidine group and does not cause nonimmunological histamine release, but there are a few reported cases of IgE-mediated anaphylaxis to fentanyl. There is cross-reactivity between different opioids of the same family, but not between phenylpiperidine derivatives [1].

**Induction drugs**

**Barbiturates**

The incidence of anaphylaxis to thiopental is estimated to be 1 in 30,000 administrations. Though IgE-mediated hypersensitivity reactions to thiopental, a thiobarbiturate, have been described, no reports of IgE-mediated hypersensitivity reactions to methohexitol, an oxybarbiturate, have been described [11].

**Propofol**

Propofol (2,6-disopropylphenol) is currently formulated in a lipid vehicle containing soybean oil, egg lecithin, and glycerol. The incidence of anaphylactic reactions with this formulation is 1 in 60,000. Propofol is formulated in a lipid emulsion containing 10% soybean oil, 2.25% glycerol, and 1.2% egg lecithin. The egg lecithin component of propofol’s lipid vehicle is a highly purified egg yolk component. Ovalbumin, the principal protein of eggs, is present in the egg white. Skin prick and intradermal testing with propofol and with its lipid vehicle (Intralipid) were negative in 25 patients with documented egg allergy. The measles-mumps-rubella vaccine does contain small amounts of egg-related antigens (ovalbumin), which are grown in cultures of chick-embryo fibroblasts. However, the measles-mumps-rubella vaccine has been given to egg-allergic children without any episodes of anaphylaxis. Therefore, current evidence suggests that egg-allergic patients are not more likely to develop anaphylaxis when exposed to propofol [1,12,13].

**Etomidate and Ketamine**

Etomidate is perhaps one of the most immunologically safe anesthetics. There are reports of IgE-mediated reactions to ketamine, and an intradermal skin test has been used in one patient [13].

**Benzodiazepines**

The Cremophor EL solvent was responsible for most reactions to benzodiazepines. Diazepam is more likely than midazolam to cause an anaphylactic reaction because of the propylene glycol solvent that replaced Cremophor EL. The active metabolite desmethyldiazepam may be responsible for the cross-reactivity with other
Benzodiazepines. Midazolam is a safe drug, because it does not have any active metabolites. Although anaphylactoid reactions to midazolam have been reported, no serologic or cutaneous testing was performed. In addition, midazolam has been used safely for the induction of anesthesia in patients with drug allergy [8,13].

**Inhaled Anesthetics**

There are no reports of anaphylaxis related to volatile anesthetics. However, these drugs have been associated with hepatic injury due to an immune-mediated toxicity [4].

**Antibiotics**

Antibiotics frequently are administered before, during, or immediately after anesthesia and surgery. The most commonly implicated antibiotics resulting in reactions are b-lactam antibiotics and vancomycin [2,13]. There is a rise in severe allergic reactions to teicoplanin – an antibiotic of choice in the UK for orthopedic surgery [10].

**Nonsteroidal anti-inflammatory drugs**

Aspirin and NSAIDs are the second most common cause of drug-induced anaphylaxis (after antibiotics). Anaphylactic reactions to NSAIDs are unrelated to other reactions caused by these drugs, such as respiratory reactions and exacerbations of chronic idiopathic urticaria. True anaphylactic reactions to NSAIDs appear to be medication specific in that some patients who have had an anaphylactic reaction to one NSAID [2,4,14]. The onset of reaction is usually up to 10 min after i.v. administration, 15-30 min from rectal administration and 30-60 min after oral administration [15].

**Latex**

Natural rubber latex sensitivity is the second most common cause of perioperative anaphylaxis. The absence of a history of reactions or prior anesthesia should not eliminate the suspicion of latex causality, because latex allergy may develop from multiple medical and nonmedical sources. The prevalence of latex allergy increased in the later part of the 20th century. Individuals at high risk for latex allergy include health care workers and patients who have spina bifida, urogenital abnormalities, and multiple prior surgeries. Anaphylaxis caused by latex is more likely to be delayed or to occur later during the procedure compared with muscle relaxants or induction agents. Latex gloves and catheters are the most common medical sources of significant exposure [11]. Latex reactions may occur immediately with latex contact or may be delayed from 30 to 60 min [2,14]. Intraoperative latex anaphylaxis may be related to the administration of drug through a latex port prior to surgery, or during the surgical procedure itself. Latex reactions have also been reported to occur during dental procedures from latex gloves or dams, during obstetrical or gynecologic examinations and during latex condom use. Spina bifida patients are potentially at risk during each surgical procedure because of the numbers of procedures they undergo [4].

**Other Drugs**

Protamine, antiseptics (chlorhexidine, povidone iodine), diagnostic dyes and iodinated contrast agents may also induce anaphylaxis.

**Management of perioperative anaphylaxis**

Management must be immediate, because anaphylaxis is life threatening and may produce cardiovascular collapse. It consists of withdrawing the offending drug, interrupting the effects of the preformed mediators that were released in response to the antigen, and preventing more mediator release. Immediate discontinuation of the anesthetic, administration of intravenous epinephrine and an expansion of intravascular volume are the key points of perioperative management of anaphylaxis [7]. Epinephrine is the drug of choice in the treatment of anaphylaxis, because its [alpha]1 effects help to support the blood pressure while its [beta]2 effects provide bronchial smooth-muscle relaxation. The early administration should be the rule. Epinephrine is used at 5- to 10-μg IV bolus (0.2 μg/kg) doses for hypotension and at 0.1- to 0.5-mg IV doses in the presence of cardiovascular collapse. Even if given promptly, epinephrine alone may not be sufficient for the treatment of severe anaphylactic shock. The cardiovascular effects of a continuous infusion of epinephrine are more pronounced than with an intravenous bolus injection. However, boluses can rapidly achieve high epinephrine concentrations and stop mast cell mediator release. Studies support the use of pure alpha -adrenergic agents such as methoxamine10 and metaraminol6 for the treatment of anaphylaxis refractory to epinephrine [9]. Airway support with 100% oxygen will compensate for the increased oxygen consumption. IV crystalloid (2-4 L) replacement will compensate for the peripheral vasodilation that often accompanies anaphylaxis. Histamine 1 blockers (e.g., diphenhydramine 0.5-1 mg/kg), histamine 2 blockers (e.g., ranitidine 150 mg or cimetidine 400- mg IV bolus), bronchodilators (e.g., albuterol and ipratropium bromide nebulizers), and corticosteroids (e.g., hydrocortisone 1–5 mg/kg) should be given. Histamine 1 blockers are used in the early phases of anaphylaxis, but once cardiovascular collapse occurs, their role is controversial. Corticosteroids can decrease the airway swelling and prevent recurrence of symptoms, as seen in biphasic or protracted
anaphylaxis. Hydrocortisone is the preferred steroid because it has a fast onset. One must remember though that their effects have never been evaluated in placebo-controlled trials [7]. Extubation should be delayed, because airway swelling and inflammation may continue for 24 h. Bronchodilators should be continued during bronchospasm. Histamine 1 receptor antagonists should be continued in the presence of urticaria and angioedema, and a histamine 2 receptor antagonist should be added to a histamine 1 receptor antagonist in the setting of hypotension [1,3,15,16].

**CONCLUSION**

Peri-anesthetic anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. Recognition and immediate treatment are particularly important, because anesthetized subjects are at greater risk for adverse outcomes caused by the physiologic effects of anesthesia. The complexity and severity of anaphylaxis is such that no single algorithm can adequately treat all cases. Immediate discontinuation of the anesthetic, administration of intravenous epinephrine and an expansion of intravascular volume are the key points of perioperative management of anaphylaxis. Vigilance for the signs of anaphylaxis and consideration of risk factors, with possible modification of the agents used, likely will reduce the morbidity and mortality associated with these reactions [1,11,15,17]. Thus, the need for systematic screening before surgery and the awareness and expert advice to anesthesiologists seems to be critical [18].

**Conflicts of interest**
The authors declare no conflicts of interest in this work.

**REFERENCES**