

Anaphylaxis in the operating room

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Purpose of review

The present article reviews the literature on anaphylactic reactions occurring in the operating room setting. The causes of anaphylaxis are discussed along with the clinical features, treatment and appropriate follow-up for patients who experience this reaction.

Recent findings

Anaphylaxis in the operating room can be caused by IgE-mediated reactions, non-IgE-mediated immunologic reactions as well as nonimmunologic reactions. The most common causes are neuromuscular blocking agents and latex, followed by antibiotics and other induction medications. Reactions may present with severe symptoms such as bronchospasm or cardiovascular collapse. Early recognition, followed by the administration of epinephrine, fluids, oxygen and airway control, is the key to a successful outcome. Follow-up testing, through in-vitro and in-vivo methods, is helpful in determining which agent caused the reaction.

Summary

The management of anaphylaxis in the operating room requires a collaborative effort between anesthesiologists, surgeons and allergists. Protocols for the management of suspected anaphylactic events and subsequent testing should be in place. To prevent future events, patients must receive adequate follow-up and high-risk patients should be identified before they enter the operating room.

Keywords

anaphylactoid, anaphylaxis, IgE, latex, mast cell tryptase, mast cells, neuromuscular blocking agent, operating room

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Introduction

Anaphylaxis is a progressive, potentially fatal, IgE-mediated reaction associated with the rapid release of histamine into the systemic circulation, producing hypotension, hypoxia and airway edema. Survival requires rapid diagnosis and the prompt initiation of medical treatment. A retrospective study [1] from the Mayo Clinic found that 20% of patients treated for anaphylaxis had no identifiable cause, while the known causes included food reactions (33%), insect stings (14%), drug reactions (13%) and exercise (7%).

The incidence of anaphylactic reactions in the operating room ranges from 1 in 4500 cases [2] to 1 in 25 000 cases [3] with an estimated mortality rate between 3 and 6% [4]. The management of these patients is more challenging because they receive multiple medications, present initially with more advanced symptoms and progress more rapidly than patients experiencing anaphylaxis in other settings. A coordinated effort by anesthesiologists, surgeons and allergists is important after the event to help identify the cause and establish a plan to prevent future events.

Causes of anaphylaxis

The degranulation of preformed histamine from mast cells produces fluid leakage from blood vessels, causing edema, bronchospasm and hypotension. Large, multicenter studies [5,6,7] have estimated the incidence of IgE-mediated reactions to be between 50 and 70% of all severe operating room reactions. Anaphylactoid reactions are clinically similar to IgE-mediated anaphylaxis, but are mediated by IgG, IgM, complement and kinins. Anaphylactoid reactions may also occur without the involvement of any specific immunologic mechanisms. Drugs such as morphine, codeine and neuromuscular blocking agents (NMBAs) may produce direct activation of mast cells. As immune sensitization is not occurring, previous contact with these substances is not necessary for a reaction to occur [8]. Anaphylactoid reactions tend to be less severe and more dose-dependent than anaphylaxis and, in the case of NMBAs, it is likely that both types of reactions are occurring [9•].

The most common cause of anaphylaxis in the operating room has been found to be NMBAs, with the incidence in the literature ranges between 50 and 70% [10–12]. IgE

has been detected against their two quarternary ammonium groups (NH_4^+), giving these drugs their anaphylactic potential [13]. Most people are exposed to quarternary ammonium groups through contact with foods, cosmetics, disinfectants and drugs, and this may explain why 55% of patients presenting with anaphylaxis to NMBA have never been exposed to them [14]. It has also been suggested that NMBA may trigger mast cell degranulation by activating the nicotinic acetylcholine receptors on the cell surface [15].

Allergy to latex has been reported to account for 16.9% of anaphylactic reactions in the operating room [16]. Fifty percent of latex reactions occur during obstetrics/gynecology procedures, 20% occur during abdominal surgery and 10% occur during orthopedic procedures [17]. Factors associated with high risk for latex reactions include early exposure to surgery, multiple surgeries, repeated insertion of latex catheters or chronic indwelling catheters and children with spina bifida [18,19]. In the pediatric population, it has been estimated that 80% of intraoperative anaphylaxis episodes are due to latex allergy [20].

Antibiotic reactions, considered to be the third most common cause of anaphylaxis in the operating room, generally present in the perianesthetic period [4]. The most common agents implicated are the β -lactam antibiotics and vancomycin [21]. Anaphylaxis from parenteral penicillin occurs in approximately 0.001% of subjects [22]. Although skin and blood testing is available for penicillin allergy, the major determinant product is still not commercially available. Vancomycin reactions are most commonly caused by direct mast cell activation rather than IgE-mediated. Quinolones produce IgE-mediated reactions 50% of the time, but there are no validated skin reagents or IgE assays currently available [23].

Approximately 300 cases of anaphylaxis to barbiturates, particularly thiopental, have been reported. These reactions are believed to be primarily IgE-mediated, and women are affected three times more than men [24]. Nonbarbiturate hypnotics, such as propofol, may be useful in patients with previous reactions to barbiturates. Anaphylactic reactions have also been reported for opioids, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, protamine, aprotinin, benzodiazepines, local anesthetics, chlorhexidine, hyaluronidase, oxytocin and patent blue dye [25].

Clinical features

In a study from Norway, bronchospasm was found to be the most common presenting sign of operating room anaphylaxis (78.3%), followed by hypotension with a systolic blood pressure less than 60 mmHg (63.9%), rash

(54.2%), hypoxemia with an O_2 saturation less than 90% (49.4%), angioedema (16.9%) and cardiac arrest (6.0%). In three of the 83 cases, bronchospasm was the sole feature [6]. In a 2-year study in France [10], comparing the signs of anaphylaxis and anaphylactoid reactions, cardiovascular symptoms were seen in 74.7 versus 33.9%, whereas bronchospasm was noted in 39.8 versus 19.2% and cutaneous symptoms were seen in 71.9 versus 93.7%.

Anaphylactic reactions occurring within minutes of induction are likely due to intravenous agents [26]. Reactions occurring more than 15 min after induction are more likely due to agents that have contacted the skin or mucosa, such as latex or chlorhexidine [27]. Rapid infusion of vancomycin may produce pruritis, a burning sensation and erythema across the face, neck and upper torso. Bronchospasm, which is a common symptom of anaphylaxis, rarely occurs with direct histamine release or after experimental histamine infusion and this suggests that other mediators besides histamine are required for anaphylaxis to occur [9,28].

The diagnosis of anaphylaxis is difficult because patients under anesthesia cannot verbalize complaints and skin findings may be hidden under surgical drapes. Jacobsen *et al.* [29] studied this by placing 21 pairs of anesthesiologists in a full-scale anesthesia simulator. None of the teams could correctly identify the diagnosis of anaphylaxis within 10 min. After 15 min and hints from the instructor, only six of 21 teams considered the correct diagnosis. The differential diagnosis of anaphylaxis in the operating room includes asthma exacerbation, arrhythmia, hemorrhage, angioedema, mastocytosis, acute myocardial infarction, drug overdose, pericardial tamponade, pulmonary edema, pulmonary embolus, sepsis, tension pneumothorax, vasovagal reaction, venous air embolus, laryngospasm, blood transfusion reaction and malignant hyperthermia [9].

Treatment

The intraoperative treatment plan is guided by the most life-threatening effects of anaphylactic reactions: cardiovascular collapse, bronchospasm and edema of the airway, particularly the larynx. Treatment consists of the instant interruption of medications or procedures that might be causing it along with epinephrine, 100% oxygen, volume support and intubation.

The α -agonist properties of epinephrine reverse vasodilatation, whereas its β -agonist properties relax the smooth muscle of the airway, increase myocardial contractility and suppress the release of inflammatory mediators such as histamine and leukotrienes [30]. Epinephrine, with a half-life of 15 min, is metabolized rapidly in the liver and may need to be readministered. Continuous epinephrine infusion should be considered if repeat doses are required

[31]. Larger doses of epinephrine may be required for patients who are on β -blockade, but caution must be taken to avoid a subsequent hypertensive crisis from unopposed α activation. The successful use of isoproterenol in a patient with refractory anaphylaxis in the operating room because of β -blocker therapy has been reported [32^{*}].

As of the fluid that has leaked out of the circulatory system, replacement with crystalloid or colloid is necessary to support blood pressure. Other medications, such as antihistamines and steroids, are useful to diminish immediate symptoms as well as late-phase reactions that may occur up to 24 h after the initial reaction [33]. Recent work has been done examining the role of nitric oxide in the refractory hypotension that may occur during anaphylaxis. Takano and colleagues [34^{**}] determined that L-NAME (*N*-nitro-L-arginine methyl ester), a nitric oxide synthase inhibitor, was able to attenuate this hypotension in mice. The use of terlipressin for refractory hypotension after anaphylaxis to neuromuscular blockade has also been reported [35^{*}].

Follow-up

Reactions are classified into three groups according to Ring and Messmer in 1977 [36], modified by Galletly and Treuren in 1985 [14]:

Class I	Mild reactions resolving spontaneously, usually involving only one organ system (e.g. urticaria, angioedema, rash)
Class II	More severe reactions requiring treatment but resolving within 10–20 min, usually involving one or more organ systems (e.g. hypotension, bronchospasm and urticaria)
Class III	Very severe reactions requiring prolonged treatment (e.g. anaphylactic shock, usually involving more than one organ system)

Controversy exists whether or not patients in class I should be tested, but proponents of this state that detection of the offending agent may be useful in preventing a future, possibly more severe, event. Generally, class I reactions do not require specific follow-up. One exception to this is localized or generalized urticaria occurring after chlorhexidine exposure, in which mild reactions may precede a more severe reaction [37].

Any reaction beyond class I should undergo immediate blood testing to help determine the nature of the reaction. Histamine, with a half-life of only a few minutes, peaks at approximately 5 min and returns to baseline by 15–30 min [38]. Mast cell tryptase (MCT), with an elimination half-life of 2.5 h, makes it a more useful marker for anaphylaxis provided that levels are obtained within 1–2 h of the event [39]. The cutoff for positive MCT levels ranges in the literature from 10 to 24 $\mu\text{g/l}$ and a

decline in levels should be demonstrated 24 h after symptoms have improved to rule out mastocytosis [5^{*},6,38,40].

It has been found that in cases of fatal and near-fatal anaphylaxis, the MCT is not elevated, possibly because the reactions were not mast cell dependent [41]. Basophils, which produce 1/500 the tryptase of mast cells, may be the effector cells along with other mediators such as complement or kinins. False negatives are seen in testing for tryptase, so a negative MCT does not remove the need for continued testing to find the cause of the reaction [42].

In a retrospective review of 67 cases of operating room anaphylaxis, the suspected cause did not match the results of subsequent investigation 73% of the time, and this underscores the importance of developing an evidence-based testing protocol [27^{**}]. One possibility for investigation is the determination of serum IgE levels for relevant agents such as latex, NMBA, morphine and antibiotics. Unfortunately, specialized laboratories, which are able to test for anesthetic agents, are not available in every country. For many years, the only widely available NMBA-specific IgE assay was for suxamethonium, but Ebo *et al.* [43^{**}] recently reported a reliable IgE assay for rocuronium using the ImmunoCAP technique. In-vitro testing is recommended for latex because of the widespread availability of a standardized assay and the dangers of skin testing with nonstandardized latex reagents [9^{**}].

It is commonly believed that IgE testing should not be done for at least 2–3 weeks after an anaphylactic reaction because of the presumed consumption of IgE during the reaction [44]. Nevertheless, IgE levels taken up to 6 h after the reaction have been found to be similar to levels taken days or weeks after the event [45^{**}]. IgE testing should be done within 6 months of the reaction, because of the slow decline in levels over time, or even sooner if chlorhexidine is a suspect [46].

After negative in-vitro testing, or if in-vitro testing is unavailable, skin testing may be performed 6 weeks after the reaction using skin prick testing and/or intradermal testing. In general, skin testing is thought to be more sensitive than in-vitro testing, but the true sensitivity is currently unclear because of the lack of standardization of guidelines and the inherent difficulties in determining the false negative rates with this infrequent event. Skin prick testing in healthy volunteers to undiluted rocuronium and vecuronium resulted in 50 and 40% positive reactions, respectively [47]. Intradermal testing for NMBA, however, has also been criticized for causing nonspecific skin reactivity, and it has been speculated that this leads to an overestimation of the incidence of true anaphylactic reactions to these agents [48,49]. In an attempt to improve the specificity of this testing, Mertes

et al. [50**] have determined the maximal nonreactive concentrations for common NMBAs in healthy, NMBA-naïve volunteers.

A previous severe reaction to anesthesia or documented anaphylaxis whereas under anesthesia represents a significant risk factor for a subsequent event [12]. Patients must have the results of their prior testing so that surgeons and anesthesiologists can decide whether or not elective procedures should be performed, whether other forms of anesthesia (such as local or region) should be used or which alternate agents should be used. Selecting alternate agents for NMBAs may not be straightforward, given the 60% cross-reactivity rate for skin testing and 80% for in-vitro testing [51]. Cross-reactivity patterns may also vary from patient to patient. If multiple NMBAs test positive, one of the ones that tested negative should be used subsequently if neuromuscular blockade is necessary. Cases have, however, been reported in which anaphylaxis occurred with an agent that tested negative [52].

Although routine screening for all patients entering the operating room cannot be justified, who should be considered at high risk? It has been found that 40% of patients experiencing anaphylaxis under anesthesia have a history of atopy or allergies, five times higher than patients who had no anaphylaxis while in the operating room [53]. Nevertheless, extraprecautions or preoperative screening is not routinely recommended for every patient with inhalant allergies who enters the operating room.

Females experience reactions at a rate of 4:1, but this may reflect the fact that they undergo more high-risk procedures than men. In addition, females have been found to be approximately 10 times as sensitive to NMBAs as males [54]. Although this has been thought to be due to the cosmetic use in females, no evidence supports a higher incidence of NMBAs allergy in patients with allergies to cosmetics [55].

Patients who have a known history of latex allergy should have latex precautions in place, and these steps should also be considered for any patient with a history of a severe anesthesia reaction who tested negative or was never worked-up. There has also been found to be an association between fruit and vegetable sensitivity among patients with latex allergy, particularly bananas, avocados, kiwi, mango, papaya, tomatoes and potatoes [56,57]. Many hospitals create special 'latex-free' suites, but if regular operating rooms are used, equipment should be wiped down by personnel wearing synthetic gloves. Latex-free anesthesia and procedure carts should also be available and high-risk cases should be first of the day so latex in the air is the lowest.

Pretreatment with antihistamines and steroids has been found to be useful in diminishing or preventing adverse effects associated with direct histamine release, but has not been found to be beneficial in preventing severe, IgE-mediated reactions [58,59]. Therefore, the current data only supports the usefulness of pretreatment in the prevention of anaphylactoid reactions, but not for anaphylaxis [9**]. Other management strategies for patients who have reacted to agents and require subsequent procedures are currently under investigation, such as desensitization and the administration of small test doses of the drug. Drugs that are known to release histamine should be avoided or injected slowly, one by one.

Conclusion

Anaphylaxis in the operating room is an infrequent, but potentially fatal event. Uniform standards need to be adopted worldwide for the screening of high-risk patients, the workup that occurs after a reaction and the reporting of the event. Currently, there are specialized Anesthesia Allergy Centers in Denmark, France, New Zealand, Australia and the United Kingdom, but centers need to be available worldwide. In-vitro testing needs to be more widely available and continued research is needed to better define the role of skin testing as part of the subsequent investigation. Anesthesiologists should receive regular training on the recognition and management of anaphylaxis and the threshold for initiating latex precautions should remain low.

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