CME

Sugammadex-Associated Anaphylaxis: Summary and Proposed Management

Pamela A. Chia, MD, MS and Michael W. Wolfe, MD

GLOSSARY

ACLS = advanced cardiovascular life support; **FDA** = Food and Drug Administration; **IgE** = immunoglobulin E; **IM** = intramuscular; **IV** = intravenous; **REVERSE** = R: recognize anaphylaxis, **E**: epinephrine, **V**: volume resuscitation, **E**: evaluate serial tryptases, **R**: record suspected allergy to chart, **S**: send to allergist and primary care, **E**: educate patient; **WAO** = World Allergy Organization

Sugammadex, a modified γ cyclodextrin, was approved by the US Food and Drug Administration (FDA) in 2015 for reversal of steroidal neuromuscular blockade.[1] Used in the perioperative setting for reversal of amino-steroid paralytics, such as rocuronium and vecuronium, sugammadex works effectively and rapidly by encapsulating the neuromuscular blocking agent and inactivating it. Studies have shown a faster recovery from neuromuscular blockade and fewer postoperative pulmonary and fewer cardiac complications with sugammadex compared to glycopyrrolate and neostigmine.[2] Although it has a relatively safe profile, adverse reactions such as nausea, vomiting, pain, hypotension, bradycardia, drug–drug interactions (eg, as a steroid binder, it may reduce the effectiveness of oral contraceptives), hypersensitivity, and anaphylaxis have been described.[2] An initial FDA safety study reported the incidence of sugammadex-related anaphylaxis to be 0.3%; in this randomized controlled trial of 299 patients, a single episode of anaphylaxis occurred after administration of sugammadex 16 mg/kg.[3] Multiple large observational and cohort studies with sample sizes of approximately 15,000 to 50,000 patients have since reported much lower rates of sugammadex-associated anaphylaxis, with the incidence ranging from 0.01% to 0.039%.[1,4,5] However, as the administration of sugammadex has become more widespread, it has been suggested that the rate of anaphylaxis may increase by one-third, from 1 in 10,000–20,000 to 1 in 6000–14,000.[6] Ultimately, timely diagnosis and early initiation of appropriate treatment is essential for the management of these cases.

Anaphylaxis is an uncommon but important cause of perioperative morbidity and mortality. Reported rates of perioperative anaphylaxis in the United States are approximately 1 in every 6500 procedures, leading to increased rates of perioperative mortality, hospital length of stay, and cost.[7] Female gender, younger age, history of drug allergies, and vascular, cardiac, and transplant procedures appear to be risk factors for anaphylaxis.[7] The major triggers for perioperative anaphylaxis include antibiotics, neuromuscular blockers, latex, chlorhexidine, and blue dye, which account for >90% of cases.[8] As these common allergens are typically encountered during induction or at the beginning phases of a procedure, most cases of anaphylaxis occur at the start of an anesthetic. Anaphylaxis to agents given typically at the end of a procedure (eg, ondansetron, opioid analgesics, amide-type local anesthetics) is uncommon. However, with increasing use of sugammadex both in the United States and worldwide, there is increasing potential to see anaphylaxis at emergence and recovery phases of an anesthetic.

Sugammadex-associated anaphylaxis is notable as cyclodextrin is a common molecule used as a food preservative, drug carrier, and in commercial products, so sensitization may occur even without previous sugammadex exposure.[9] Unfortunately, no common demographics or risk factors have been identified that may otherwise provoke a higher index of suspicion. Sugammadex-associated anaphylaxis has been reported in pediatric patients as young as 3 years and in elderly patients up to 89

From the Department of Anesthesiology & Perioperative Medicine, University of California, Los Angeles, Los Angeles, California.

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Address correspondence to Pamela A. Chia, MD, MS, Department of Anesthesiology & Perioperative Medicine, University of California, Los Angeles, 757 Westwood Plaza, Suite 3325, Los Angeles, CA 90095. Address e-mail to pchia@mednet.ucla.edu

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years, with no gender differences noted.[10] Common antigens have not been identified, and further, no link to individuals with atopy history has been identified. Recognition may be challenging without a clearly established risk profile and becomes more difficult during emergence where cardiorespiratory parameters are inherently and often rapidly changing. Advanced airways may already be removed, the level of monitoring may be lessened or monitors may be temporarily detached entirely, and the patient may be in a state of transfer to a postanesthesia care or intensive care unit during the time anaphylaxis presents. Given the unique challenges of identifying and treating sugammadex-associated anaphylaxis, an overview of the clinical and laboratory diagnostic steps is provided, followed by a summary of management considerations and a discussion of systemic issues.

DIAGNOSIS AND TESTING

The diagnosis of anaphylaxis is clinical and supported by a history of exposure to a known or suspected allergen. The criteria for anaphylaxis by the World Allergy Organization (WAO) are outlined in the Table.[11] On examination, generalized urticaria, bronchospasm or wheezing, angioedema, an increase in peak inspiratory pressure, hypotension, tachycardia, and hypoxemia are some of the signs and symptoms that can be observed during an anaphylactic reaction. One small case series showed hypotension as the most common presenting sign in sugammadex-associated anaphylaxis, occurring in 94% of cases; the next most common signs and symptoms were tachycardia (60%), cutaneous erythema (52%), oxygen desaturation (45%), and increased airway pressures (18%).[10] Notably, 18% of patients required reintubation in this case series. With small sample sizes in most studies reporting sugammadex-associated anaphylaxis, the true frequency of each organ system manifestation or dysfunction is currently poorly understood.

Table. Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when 1 of the following 2 criteria is met	
1	Acute onset[a] of an illness with involvement of the skin and/or mucosal tissue (eg, generalized urticaria, itching, or flushing) And any of the following • Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia) • Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia, syncope, incontinence) • Severe gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
	or
2	The presence of 1 of the following, after an exposure to a known potential allergen: • Acute onset of hypotension (eg, systolic blood pressure <90 mm Hg or >30% decrease from baseline) • Acute onset of bronchospasm • Laryngeal compromise (eg, voice changes, stridor)

Adapted From WAO Guidelines.[11]
Abbreviation: WAO, World Allergy Organization.
[a]Onset is defined as minutes to several hours.

Although laboratory biomarkers can neither confirm nor rule out anaphylaxis, skin testing, serum tryptase, and serum histamine are some of the tests available to support the diagnosis. Although consistent testing has not been performed in suspected cases of drug-induced anaphylaxis, tryptase has high specificity and known optimal timing of peak elevation after a reaction, making it a potentially useful adjunct in supporting the diagnosis of sugammadex-induced anaphylaxis.[12]

Tryptase is a protease released from activated mast cells and can be elevated in cases of anaphylaxis. Elevated levels are defined either by an absolute value (eg, >11.4 ng/mL; reference levels vary by laboratory) or in comparison to a baseline level (eg, >2 + [1.2 × baseline value]). Tryptase levels rise within minutes of the clinical development of anaphylaxis, peak in 30 to 90 minutes, and decline with a half-life of approximately 2 hours.[12] Accordingly, tryptase levels are optimally drawn within 2 hours of the suspected event. At least 1 level should be drawn 24 hours after the event, when levels have likely normalized, to establish the patient's baseline, as rarely patients may have chronically elevated tryptase (eg, patients with mast cell disorders).[12]

Serum tryptase levels have low sensitivity and high specificity; thus, tryptase should not be used to exclude the diagnosis of anaphylaxis but can be used retrospectively to support that an anaphylactic event occurred. One review detailing tryptase measurements, compared to standards of either skin testing or clinical WAO anaphylaxis criteria, found a sensitivity of only 41% to 78% for anaphylaxis during general anesthesia. However, specificity was high at 74% to 100%, with positive predictive value of 0.82 to 1.0.[12] Serial laboratories drawn within the optimal time interval further increase specificity, and may double the sensitivity when compared with a testing strategy that assesses a singular absolute value of tryptase elevation.[12,13] Of note, tryptase elevations correlate with the severity of anaphylaxis.[12] It is unknown whether mast cell stabilization from very early epinephrine administration affects tryptase sensitivity. Histamine levels can similarly be used to support the diagnosis of anaphylaxis; however, given its quick peak (5–10 minutes) and short half-life (1–2 minutes), it is often impractical to obtain these measurements while actively managing a patient with anaphylaxis.

Confirmatory testing, usually supervised by an allergist, should be considered; however, there is

no currently validated or well-accepted protocol for the testing of sugammadex-induced anaphylaxis.[14] In general, skin testing plays an important role in evaluating and confirming an immunoglobulin E (IgE)–mediated reaction to an allergen. Interestingly, sugammadex can trigger an anaphylactic response either by itself or when complexed with rocuronium despite no observed response to isolated sugammadex or rocuronium.[14,15] Accordingly, skin testing for a suspected anaphylactic response should include testing to the separate components of sugammadex, the sugammadex–rocuronium complex, and γ cyclodextrin. If any of these are positive, sugammadex should be avoided in future situations, even if other amino-steroid neuromuscular blockers are used.

MANAGEMENT AND FOLLOW-UP

The management of sugammadex-associated anaphylaxis is similar to other sources of perioperative anaphylaxis but does have some unique considerations. Sugammadex is often given immediately before emergence, a time that can already be accompanied by changes in cardiorespiratory parameters, making recognition and diagnosis of anaphylaxis challenging.[6] Delay in diagnosis may lead to further cardiopulmonary insult. Polypharmacy at this stage can also make it difficult to identify which medication is the offending agent even when anaphylaxis is suspected. A sugammadex-induced anaphylactic reaction at the end of a surgical procedure can potentially be catastrophic.

Anaphylaxis after sugammadex administration generally occurs within 5 minutes of exposure, during which time a patient may experience tracheal extubation, transfer from the procedural table, and potentially even reduction or removal of monitoring and exit from the procedural theater.[10] If an endotracheal tube has been removed, edema may rapidly compromise the patency of the airway. Thus, it is important to recognize the signs of anaphylaxis, because complete obstruction of the airway from angioedema can make tracheal reintubation extremely challenging or impossible. According to the most recent anesthesia advanced cardiovascular life support (ACLS) guidelines, immediate tracheal intubation or reintubation is recommended in cases of severe anaphylaxis.[16] If muscle relaxation is required for tracheal reintubation, succinylcholine administration should be considered if not otherwise contraindicated. Further doses of an amino-steroid nondepolarizing neuromuscular blocker may both be ineffective in the presence of sugammadex and worsen anaphylaxis if the complex is the inciting allergen, and a benzylisoquinoline nondepolarizing neuromuscular blocker may be too slow if airway edema is rapidly progressing. Assistance from other providers should be sought, including providers who can establish a surgical airway, and any monitoring that has been discontinued should be promptly reestablished. Consideration should be given to establishing invasive monitoring and access for continuous blood pressure measurement and administration of indicated medications. Clinical vigilance is paramount after sugammadex administration, and prompt management and supportive treatment are required whether or not the offending agent is known.

The management of anaphylaxis has been well-documented, with epinephrine as the first-line treatment. The adrenergic properties of epinephrine treat most of the clinical manifestations of anaphylaxis. α-1 Receptor agonism leads to vasoconstriction, improvement of blood pressure, and reduction of mucosal edema. β-1 Receptor agonism leads to increased cardiac inotropy and chronotropy, which improves blood pressure, and β-2 agonism causes bronchodilation and stabilizes mast cells and basophils, leading to a reduction of vasoactive mediator (eg, histamine) release. In the perioperative arena, where intravenous (IV) access is usually already established, IV epinephrine can be considered by providers familiar with its use, titration, and side-effect profile. The recommended dosing of epinephrine varies depending on the severity of the reaction but applies to most general cases of anaphylaxis. Suggested initial epinephrine dosing for moderate hypotension is 20 μg IV, followed by a recommended dose of 50 μg IV after 2 minutes if there is an insufficient response.[17] For severe hypotension, the suggested initial dose is 50 to 100 μg depending on whether other vasopressors are given, followed by a recommended dose of 200 μg for severe hypotension at 2 minutes if there is no clinical improvement.[17] For cardiovascular collapse, 1 mg IV as an initial and follow-up dose is recommended as outlined in the ACLS[17] and anesthesia ACLS guidelines.[16] An infusion of 0.05 to 0.1 μg/kg/min is suggested for refractory hypotension.[17] In cases where IV access is lost or if the provider is unfamiliar with dosing and titration of IV epinephrine, intramuscular (IM) epinephrine and transtracheal epinephrine can be considered. The IM route has been associated with fewer side effects and similar efficacy to the IV route, though there is a paucity of literature on route of administration in the perioperative arena.[18] Recommended dosing of IM epinephrine varies, with suggested dosing of 0.01 mg/kg up to 0.5 mg total.[11,18] Although transtracheal epinephrine via the endotracheal route has not been described in the treatment of anaphylaxis, for ACLS, transtracheal epinephrine is typically given at a dose of 2 to 2.5 times the indicated IV dose.

Because anaphylaxis leads to increased vascular permeability as well as increased venous capacitance, patients may experience a dramatic

reduction in cardiac preload. Accordingly, fluids are indicated in the majority of patients with anaphylaxis, usually starting with a bolus of 500 mL of a crystalloid solution for moderate hypotension and 1 L for severe hypotension, with repeated dosing until there is an appropriate clinical response.[17] Bronchodilators such as albuterol can be used as needed for respiratory symptoms such as bronchospasm.[17,18] Medical evidence supporting the role of corticosteroids and antihistamines in the acute treatment of anaphylaxis is weak, and although administration may be considered, it should not delay first-line medications.[17,18] The suggested dose for steroid administration is 1 to 2 mg/kg of methylprednisolone or the equivalent of a different corticosteroid,[18] and for diphenhydramine (H1 blocker), it is 25 to 50 mg IV.[18]

SUMMARY AND PROPOSED RECOMMENDATIONS

Although anaphylactic events from sugammadex are infrequent overall, with its growing use, the potential for an anaphylactic event during emergence could increase. Thus, we propose a general framework after a suspected sugammadex-induced anaphylactic episode (Figure) to help guide medical providers to provide consistent and appropriate follow-up, which can be easily remembered with the mnemonic "REVERSE."

- "R" represents the need for early recognition of the clinical signs of anaphylaxis. During this step, it is also important to quickly assess and rule out other causes for instability as the clinical picture evolves.
- "E" is for epinephrine, the first-line treatment for anaphylaxis. This is preferably administered through the IV or IM route. Suggested initial epinephrine dosing is dependent on the severity of the reaction, with doses ranging from 20 µg to 1 mg. In cases of refractory hypotension, an infusion of 0.05 to 0.1 µg/kg/min can be started. If IV access is not available, IM epinephrine can be administered as 0.01 mg/kg up to 0.5 mg total.
- "V" represents volume resuscitation, which usually starts with a bolus 500 mL of a crystalloid solution for moderate hypotension and 1 L for severe hypotension, with repeated administration until there is an appropriate clinical response.
- "E" highlights the evaluation of serial tryptase levels within 2 hours and again at 24 hours after a suspected event. We believe this is a reasonable and easily obtained laboratory test that can be quickly drawn once clinical stability is achieved. A tryptase level should be drawn within 2 hours to coincide with peak levels, and at 24 hours when acutely elevated levels will have normalized in this time frame, to establish a patient's baseline. Although the results from these tests are not immediate, this objective data would be helpful during a case review and help guide future management.
- "R" is for recording the suspected allergy to the chart as documentation of suspected events is vital in these situations.
- "S" represents sending the patient to see an allergist and primary care physician after a suspected anaphylactic event to ensure confirmatory testing for an accurate diagnosis. Testing should be performed at least 6 weeks after an anaphylactic event.[19] Additionally, with confirmatory testing and appropriate follow-up, we hope to avoid inaccurate medication allergy reporting. It is important to acknowledge that 25% of Americans do not have access to a primary care provider, and there is an overall shortage of physicians, including primary care providers and allergists.[20,21] Systemic barriers to health care access may also make follow-up difficult or impossible. For those facing obstacles to health care access, allergy consultations can be considered before discharge from the hospital to arrange for appropriate testing, precautions, and aid with care coordination. Telehealth and video visits with health care providers offer follow-up that may be more convenient to schedule and attend. Additionally, if hospitals have a perioperative clinic, this may be an opportunity for coordinated care among the surgical, primary, allergy, and anesthesiology providers to ensure optimal communication and minimize loss to follow-up.
- "E" stands for educate, as it is important the patient is knowledgeable of their potential allergy so they may play a role in the active avoidance of potential allergens, especially before future surgeries that may use sugammadex as a reversal agent.

R	Recognize anaphylaxis
E	Epinephrine
V	Volume resuscitation
E	Evaluate serial tryptases
R	Record suspected allergy to chart
S	Send to allergist & primary care
E	Educate patient

Figure. REVERSE mnemonic can be used to summarize suspected sugammadex-associated anaphylactic events.

In summary, sugammadex is a medication that is widely and increasingly used for reversal of the action

of nondepolarizing amino-steroid muscle relaxant medications; we present the above framework as a tool to help physicians not only manage and treat a sugammadex-induced anaphylactic event but also assist in aligning appropriate follow-up for the patient. Diagnosis, appropriate treatment, and follow-up can be challenging for clinicians and can create an inconsistent and confusing experience for patients. We seek to help providers improve the management of sugammadex-associated anaphylaxis through the use of this straightforward framework.

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