Narrative Review

Should We Use Sugammadex in Rocuronium-Induced Anaphylaxis?

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Abstract

Intraoperative anaphylaxis is a rare but potentially life-threatening complication of anaesthesia, with neuromuscular blocking drugs (NMBDs) being the most frequent cause. Published reports indicate that the incidence of anaphylaxis is higher for rocuronium compared to other non-depolarising NMBDs. Sugammadex is a novel reversal agent with a unique mechanism of action, specifically designed to encapsulate aminosteroid NMBDs and antagonise their pharmacological effects. Due to this mechanism, sugammadex has been suggested as a potential treatment option for rocuronium-induced anaphylaxis. Several case reports have described reversal or mitigation of rocuronium-induced anaphylaxis following sugammadex administration.

In contrast, both in vitro and in vivo immunological studies suggest that sugammadex is unable to modify a type I hypersensitivity reaction. The small number of available case reports and limited prospective non-clinical immunological studies do not fully explain the underlying pathophysiological mechanisms. The role of sugammadex in rocuronium-induced anaphylaxis therefore remains unclear. Despite the reported clinical benefits, there are currently no recommendations to include sugammadex in standard anaphylaxis management algorithms.

Keywords: anaphylaxis; sugammadex; rocuronium

Introduction

According to the European Academy of Allergy and Clinical Immunology (EAACI), anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction (1,2). Anaphylaxis during anaesthesia is a rare but potentially fatal complication with a wide spectrum of clinical presentations. It requires prompt recognition and the institution of life-saving therapy (1,3). The

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worldwide rate of allergic reactions during anaesthesia is difficult to estimate, and therefore the true incidence, morbidity, and mortality remain poorly defined. According to published data, the estimated incidence of perioperative anaphylaxis during anaesthesia is approximately 1 in 10,000–20,000 (3).

Intraoperative anaphylaxis may result from immunological (IgE-mediated or non-IgE-mediated) or non-immunological mechanisms. Approximately 60–70% of immediate hypersensitivity reactions occurring during anaesthesia are mediated by immunoglobulin E (IgE) (4). Mortality associated with these reactions varies between 3% and 9%, depending on the country (4,5). Neuromuscular blocking drugs (NMBDs) are the most common cause of intraoperative anaphylaxis, accounting for around 60% of anaesthesia-related cases (2). Anaphylaxis is approximately twice as likely to occur during surgery when a muscle relaxant is used (6). Rocuronium and suxamethonium are the NMBDs most frequently associated with anaphylaxis. IgE sensitisation towards quaternary ammonium groups in NMBDs is the main contributing factor in the development of these allergic reactions (7). Rocuronium and vecuronium are currently the most widely used steroidal, non-depolarising NMBDs (8).

The true incidence of anaphylaxis to individual NMBDs remains uncertain due to difficulties in determining accurate values for both the numerator (cases) and denominator (exposures). There is ongoing controversy as to whether the incidence of anaphylaxis is higher with rocuronium compared to other NMBDs, with reported rates ranging from approximately 1:3,500 to 1:445,000 (9). In a retrospective study conducted over a ten-year period in Western Australia, Sadleir et al. found that among eighty patients diagnosed with life-threatening NMBD-induced anaphylaxis, rocuronium was responsible for 56% of cases, succinylcholine for 21%, and vecuronium for 11%. Cross-reactivity with other non-depolarising NMBDs was highest with rocuronium and suxamethonium (10). The authors concluded that rocuronium has a higher rate of IgE-mediated anaphylaxis compared with vecuronium—a finding that is both statistically significant and clinically relevant—while cisatracurium demonstrated the lowest rate of cross-reactivity in patients who had previously experienced anaphylaxis to rocuronium or vecuronium (10).

Similarly, Reddy et al., in a seven-year retrospective observational cohort study of intraoperative anaphylaxis to NMBDs conducted at two hospitals in Auckland, reported an incidence of 1 in 22,451 new patient exposures for atracurium, 1 in 2,080 for succinylcholine, and 1 in 2,499 for rocuronium. The rates of anaphylaxis to succinylcholine and rocuronium were approximately ten times higher than those to atracurium (10,11). These studies highlight that clinicians should be aware of the increased risk of anaphylaxis associated with rocuronium when selecting an intermediate-duration NMBD (10,11).

Sugammadex is a unique, direct reversal agent for aminosteroid NMBDs with a novel mechanism of action based on encapsulation of the target drug. It is a modified γ-cyclodextrin composed of oligosaccharide units linked around a central cavity (12). The molecule is doughnut-shaped, featuring a hydrophilic exterior and a hydrophobic core, which enables it to encapsulate and inactivate aminosteroid NMBDs. Sugammadex exhibits the highest affinity for rocuronium, followed by vecuronium and pancuronium (12). The affinity for rocuronium is approximately 2.5

times greater than for vecuronium (13).

Encapsulation by sugammadex forms a 1:1 complex with free intravascular steroidal NMBD molecules. Shortly after administration, circulating aminosteroid NMBDs are captured within the cavity, leading to pharmacological inactivation. The subsequent decrease in plasma NMBD levels creates a concentration gradient between the neuromuscular junction and plasma, resulting in the displacement of NMBDs from the endplate back into the plasma, where they are further neutralised (14).

Literature Review

One of the fundamental principles in the management of anaphylaxis is the immediate removal of the triggering agent. Jones and Turkstra were the first to speculate that sugammadex might represent a novel therapeutic strategy for rocuronium-induced anaphylaxis. Theoretically, the removal of free rocuronium molecules from circulation could mitigate or even halt an ongoing anaphylactic reaction (15,16,17,18). The hypothesis suggests that sugammadex, as a selective encapsulating agent for rocuronium, may prevent propagation of the anaphylactic response by binding circulating rocuronium molecules already present in the patient's blood. It has been further proposed that the rapid removal of rocuronium from the circulation could lead to prompt cardiovascular recovery, occurring as quickly as the reversal of neuromuscular blockade (15,16,17,18). McDonnell et al. (17) published the first case report describing the successful use of sugammadex in the management of rocuronium-induced anaphylaxis. Since then, several case reports from different countries have demonstrated clinical improvement in confirmed rocuronium-induced anaphylaxis, with haemodynamic and respiratory recovery occurring within minutes of sugammadex administration (16,18,19,20). In the majority of published cases, the administration of sugammadex resulted not only in the expected reversal of neuromuscular blockade but also in improvement of the patient's adverse haemodynamic status (17,18,19,20,21,22).

Baldo and McDonnell summarised eleven cases from seven different countries in their review published in 2014, demonstrating recovery from anaphylaxis following sugammadex administration (23). The exact mechanisms underlying these clinical improvements remain unclear and may or may not be immunologically mediated (17–22). Because the sugammadex molecule does not completely encapsulate the rocuronium molecule, it remains uncertain whether the allergenic quaternary ammonium groups of NMBDs are still capable of cross-linking with IgE antibodies when bound to sugammadex (15,24). Another important question is whether the encapsulation of rocuronium by sugammadex can prevent further mediator release from mast cells and basophils (15,24).

Many authors have suggested that the clinical improvement observed after sugammadex administration may be partly attributed to an increase in muscle tone following the reversal of neuromuscular blockade, which in turn enhances venous return and cardiac preload (17,18,23). The importance of venous return in anaphylactic shock has been demonstrated in various experimental and clinical settings (23).

Several case reports have also described a lack of efficacy of sugammadex in reversing rocuronium-induced anaphylaxis, both at low and high doses (25,26). Platt et al. published the first case–control study that did not support the effectiveness of sugammadex in this context (27). Their findings did not support the hypothesis that sugammadex modifies the immunological cascade of anaphylaxis (27). They also noted that anesthesiologists' perceptions of the clinical benefit of sugammadex appeared to be subjective (27). Finally, Platt et al. concluded that sugammadex does not interfere with the correction of the immune dysfunction caused by rocuronium, but may improve cardiac preload by increasing muscle tone following the reversal of neuromuscular blockade (27). There is a limited number of immunological studies (both in vitro and in vivo) that have examined the immune-modifying potential of sugammadex. Clarke et al. conducted a study using a cutaneous model of anaphylaxis in rocuronium-sensitised patients and were unable to demonstrate that sugammadex was effective in attenuating the type I hypersensitivity reaction once it had been triggered by rocuronium. They also concluded that sugammadex is unlikely to significantly modify the clinical course of an established allergic reaction caused by rocuronium (28). Similar to the findings of Platt et al., Clarke et al. considered that the mechanism responsible for the haemodynamic improvements was the restoration of muscle tone, which may complicate the management of a patient with a potentially compromised airway due to angio-oedema (28). Leysen et al. performed an in vitro experiment using basophils isolated from rocuronium sensitive subjects. Their results were consistent with those of Clarke et al., showing that while sugammadex pre-mixed with rocuronium prevented basophil activation, it could not inhibit ongoing activation once triggered by rocuronium, even at very high concentrations of sugammadex (29). They concluded that encapsulation of rocuronium by sugammadex can prevent, but not terminate, in vitro basophil activation induced by the neuromuscular blocking agent (29). Therefore, based on immunological studies, it appears unlikely that the administration of sugammadex would attenuate rocuronium-induced anaphylaxis.

Several hypotheses have been proposed to explain the discrepancy between findings from clinical and laboratory settings. The main contributing factors may include the effects of concurrently instituted anaphylaxis management measures (such as epinephrine administration and intravenous fluids), as well as the reversal of neuromuscular paralysis, which could enhance venous return and cardiac preload by increasing muscle tone in the lower extremities (16,17).

According to the most recent systematic review published in 2025, which analyzed data from 11 reports encompassing a total of 11 patients, the evidence regarding sugammadex use in rocuronium-induced anaphylaxis remains limited (30). Although some studies have described the administration of high "rescue doses," the median dose reported in the review was 450 mg, which is lower than typical rescue regimens. This finding suggests that the therapeutic effect of sugammadex may not be strictly dose-dependent, but rather influenced by factors such as timing of administration, severity of the reaction, and interindividual variability. Given the small sample size and the predominance of cases with favorable outcomes, identifying predictors of treatment success remains challenging, highlighting the need for further reports, including those with less favorable responses.

According to some authors, sugammadex may be considered a useful adjunct to the standard management of perioperative anaphylaxis secondary to rocuronium (31,32). However, its use is not without risk: reversal of neuromuscular blockade may complicate airway management and ventilation, and sugammadex itself has been reported to induce anaphylaxis (17,23,28).

Conclusion

Despite the reported efficacy of sugammadex in several case reports, clinicians should recognise that its use for rocuronium-induced anaphylaxis remains an unlicensed or off-label indication. Maybe the greatest concern, as noted by Clarke et al., is that reliance on sugammadex may distract clinicians from the prompt implementation of established anaphylaxis management protocols. Given ethical and practical limitations, controlled clinical trials in humans are unlikely, and current knowledge will continue to rely on case reports and non-clinical studies. Until stronger evidence becomes available, there are no expert recommendations to include sugammadex in anaphylaxis management algorithms. Clinicians should therefore continue to follow established guidelines for the management of anaphylaxis during anaesthesia.

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Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

Author Contributions

E.G. conceived the review topic, collected and analysed the literature, and wrote the original draft of the manuscript. Other authors contributed to data interpretation, critical revision, and editing of the final version. All authors read and approved the final manuscript.

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