

# Original Article

## The role of sugammadex in the development and modification of an allergic response to rocuronium: evidence from a cutaneous model\*

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### Summary

The availability of sugammadex as a selective encapsulating agent for rocuronium has led to speculation that it may be useful in mitigating rocuronium-induced anaphylaxis. Off-label use of sugammadex for this indication has already been documented in case reports although there are theoretical objections to the likelihood of an allergen-binding agent's being able to attenuate the immunological cascade of anaphylaxis. Using a cutaneous model of anaphylaxis in rocuronium-sensitised patients, we were unable to demonstrate that sugammadex was effective in attenuating the type-1 hypersensitivity reaction after it has been triggered by rocuronium, but we were able to demonstrate that these patients are anergic to sugammadex-bound rocuronium. These findings demonstrate that a cyclodextrin can bind an allergen and exclude it from interacting with the immune system, and may potentially lead to novel applications in other allergic diseases. However, there is no evidence that sugammadex should be used for the treatment of rocuronium-induced anaphylaxis, and clinical management should follow established protocols.

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In many countries neuromuscular blocking drugs are the most common agents responsible for anaphylaxis during general anaesthesia, with rocuronium being one of the most frequently implicated [1, 2]. One of the basic principles in the management of anaphylaxis is the removal of the triggering agent [3]. However, although there is evidence that the removal of an allergen from its corresponding cell-bound-specific antibody will attenuate the process of mediator release from the mast cell in vitro [4], there is no evidence that it will alter the clinical course of anaphylaxis in vivo.

Sugammadex is a modified  $\gamma$ -cyclodextrin with a hydrophobic cavity designed to encapsulate rocuronium

and other steroid-based neuromuscular blocking drugs [5]. Intermolecular (van der Waals) forces result in a water-soluble complex with a high association rate. When used for the reversal of rocuronium-induced neuromuscular blockade, sugammadex is very effective [6]. Sugammadex is rapidly distributed to the effect compartment [7], its affinity for rocuronium is greater than that of the nicotinic acetylcholine receptor [8], and the influence of rocuronium at the nicotinic acetylcholine receptor is both reversible and relatively insensitive [9]. Consequently, sugammadex has been shown to reverse profound rocuronium-induced neuromuscular blockade within minutes [6].

The reported efficacy of sugammadex in reversing neuromuscular blockade has prompted speculation that sugammadex may also be effective in attenuating anaphylaxis caused by rocuronium [10]. Although this is an off-label use, there are both anecdotal and published case reports of its use for this particular clinical situation [11–13]. Harper et al. listed several criteria that needed to be fulfilled for sugammadex to be effective [14]. Most importantly, the allergenic epitope of rocuronium must be hidden from its corresponding paratope of IgE in the encapsulation process. Second, the affinity of rocuronium for sugammadex must exceed its affinity for IgE. Third, the removal of the bound allergen from its corresponding cell-bound specific antibody must attenuate the process of mediator release from the mast cell [4].

The immunological pathways of the cutaneous flare and wheal response, and systemic anaphylaxis, are similar. The former is the basis for diagnosing IgE-mediated allergy. Thus, we hypothesised that evaluation of the skin response in individuals known to be sensitised to rocuronium would enable us to assess the ability of sugammadex to bind rocuronium and prevent or attenuate a type-1 immediate hypersensitivity reaction.

Our first hypothesis was that incubation of rocuronium with sugammadex, and subsequent complex formation, would inhibit binding to specific IgE and prevent the skin response to intradermal injection. The second hypothesis was that the administration of an excess of sugammadex shortly after the intradermal injection of rocuronium, at the same site, would attenuate the skin response.

## Methods

The study was approved by the Sir Charles Gairdner Hospital Ethics Committee and all patients provided written informed consent.

Inclusion criteria were patients with known IgE-mediated hypersensitivity to rocuronium, who were identified from the database of the Anaesthetic Allergy Referral Centre of Western Australia. Nineteen patients were identified for the period from January 2006 to February 2011. Eleven out of 19 patients agreed to be involved in the study. One patient was anergic to rocuronium on a repeated intradermal skin test and so was not studied. The other 10 patients were enrolled in

the study. All had previously suffered a life-threatening episode of rocuronium-induced anaphylaxis under general anaesthesia.

Intradermal testing was conducted on the volar forearm of subjects with sites marked and tests conducted concurrently. The identity of the intradermal test at each site was varied, and not known to the blinded observer.

Single-injection intradermal tests were conducted with a 29-G, 12.7-mm hypodermic needle (0.5-ml BD Ultra-fine™ Needle; Becton, Dickinson & Co., Franklin Lake, NJ, USA). Multiple intradermal tests were conducted with a detachable 26-G, 13-mm hypodermic needle with a 0.02-ml dead space (Slip Tip with BD PrecisionGlide™ Needle; Becton, Dickinson & Co.).

Eight test sites were marked (Fig. 1). A histamine skin prick test (Histamine phosphate BP, 8 mg.ml<sup>-1</sup>; AUSPMAN, Subiaco, WA, Australia), and saline intradermal test (0.02 ml saline 0.9%) were conducted as positive and negative controls, respectively.

A high- and low-dose sugammadex (Bridion®, 200 mg in 2 ml; Schering-Plough Pty Ltd, North Ryde, NSW, Australia) intradermal test was conducted (0.02 ml of 0.13 mg.ml<sup>-1</sup> and 1.3 mg.ml<sup>-1</sup>, respectively) to exclude skin reactivity to sugammadex. The reference rocuronium intradermal test was conducted by intradermal injection of 0.02 ml of 0.01 mg.ml<sup>-1</sup> rocuronium (Rocuronium Sandoz®, 10 mg.ml<sup>-1</sup>; Sandoz Canada Inc, Boucherville, Quebec, Canada). Two separate intradermal tests were conducted by pre-mixing sugammadex and rocuronium to give final concentrations of rocuronium and sugammadex of 0.13 mg.ml<sup>-1</sup> (a 1:4 molecular ratio) or 0.65 mg.ml<sup>-1</sup> (1:20 molecular ratio), respectively.

A final intradermal test was conducted with a multiple-injection technique. Intradermal rocuronium, 0.02 ml of 0.01 mg.ml<sup>-1</sup>, was introduced via a fixed 26-G intradermal needle. Two minutes later, 0.05 ml of 0.13 mg.ml<sup>-1</sup> sugammadex was injected via the same fixed intradermal needle, which was then removed.

For the last three patients enrolled, a further two multiple-injection intradermal tests were conducted. At one site, 0.02 ml of 0.13 mg.ml<sup>-1</sup> sugammadex was injected via a fixed intradermal needle, followed at 2 min by 0.05 ml of 0.01 mg.ml<sup>-1</sup> rocuronium. At the other site, 0.02 ml of 0.01 mg.ml<sup>-1</sup> rocuronium was

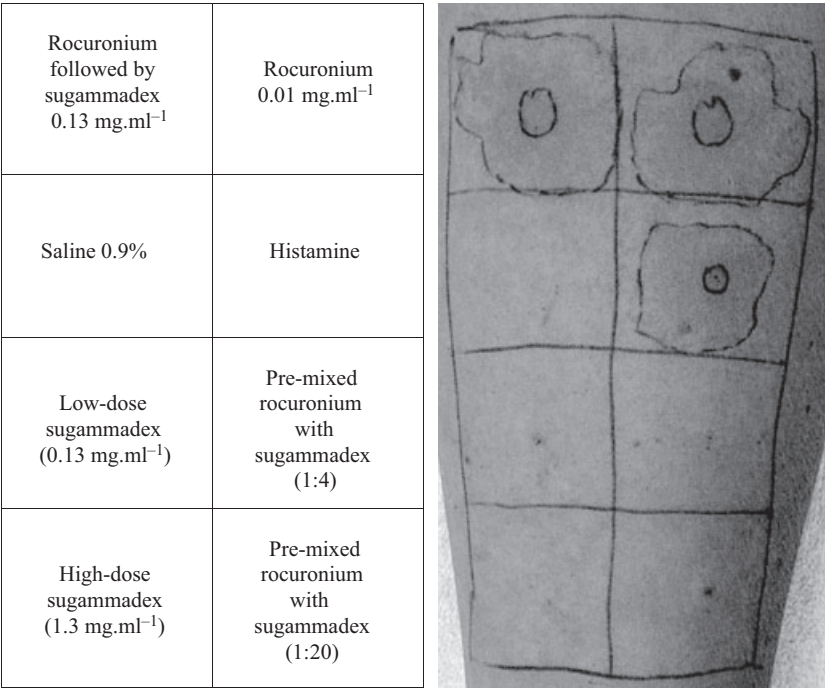


**Figure 1** Protocol for the cutaneous experiment (left) and the response in one subject at 20 min. The circumference of the flare (outer tracing) and wheal (inner tracing) has been marked.

injected via a fixed intradermal needle, followed by 0.05 ml of 1.3 mg.ml<sup>-1</sup> sugammadex (Fig. 2).

The individual conducting the intradermal tests measured the size of the intradermal bleb after initial injection and also, in the multiple-injection sites, following the removal of the fixed intradermal needle.

A blinded observer measured the size of the wheal and flare 5 min after the initial injection, and at 5-min intervals for 20 min. The size of the wheal or flare was

estimated by averaging the greatest diameter and the diameter at right angles to this.

The distribution of data was assessed by the Shapiro–Wilk test of normality. The means of normally distributed data were compared by a paired two-tailed t-test. For the primary variable of size of the wheal and flare at each site, the area under the curve (AUC) of the mean diameter over the 20 min was calculated. A p value less than 0.05 was considered significant.

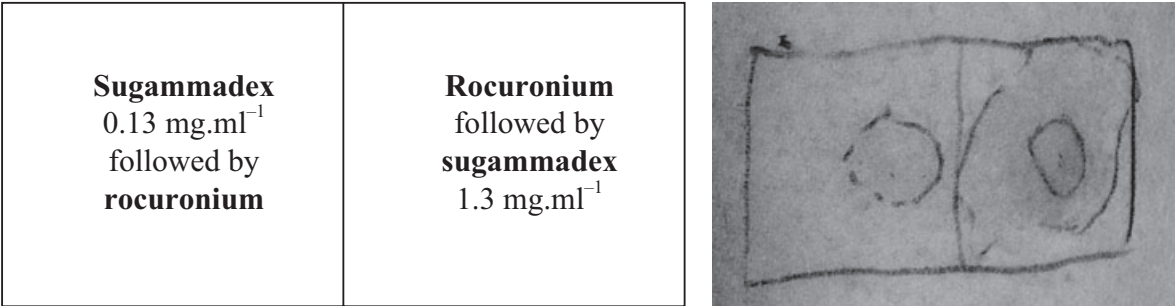


**Figure 2** Protocol for the additional cutaneous experiment (left) conducted in the final three patients enrolled. The response in one subject at 20 min is recorded on the right. The circumference of the flare (outer tracing) and wheal (inner tracing, present only on the right intradermal test site) has been marked.

## Results

All patients reacted normally to positive histamine and negative saline controls. No patient reacted to intradermal sugammadex at either 0.13 or 1.3 mg.ml<sup>-1</sup>.

Pre-mixed sugammadex and rocuronium at both a 4:1 (0.13 mg.ml<sup>-1</sup>: 0.01 mg.ml<sup>-1</sup>) or 20:1 (0.65 mg.ml<sup>-1</sup>: 0.01 mg.ml<sup>-1</sup>) molecular ratio almost completely attenuated the cutaneous response (Figs. 1 and 3).

The administration of either 0.13 or 1.3 mg.ml<sup>-1</sup> sugammadex through the fixed intradermal needle was ineffective in attenuating the reaction to rocuronium (Figs. 1-4).

The AUC for pre-mixed low-dose sugammadex and rocuronium was significantly reduced compared to rocuronium alone (mean (SD) wheal 22.7 (4.9) vs 6.3 (4.7) mm.min<sup>-1</sup> ( $p < 0.01$ ); mean (SD) flare 71.7 (32.8) vs 4.4 (10) mm.min ( $p < 0.01$ )), but not different from the saline control (mean (SD) wheal 6.3 (4.7) vs 3.4 (2.8) mm.min<sup>-1</sup> ( $p = 0.11$ ); mean (SD) flare 4.4 (10) vs 0 (0) mm.min<sup>-1</sup> ( $p = 0.20$ )).

The AUC for rocuronium followed by sugammadex 0.13 mg.ml<sup>-1</sup> was not less than that of rocuronium alone (mean (SD) wheal 25.1 (5.1) vs 22.7 (4.9) mm.min<sup>-1</sup> ( $p = 0.03$ ), mean (SD) flare 67.2 (38.6) vs 71.8 (32.8) mm.min<sup>-1</sup> ( $p = 0.41$ )).

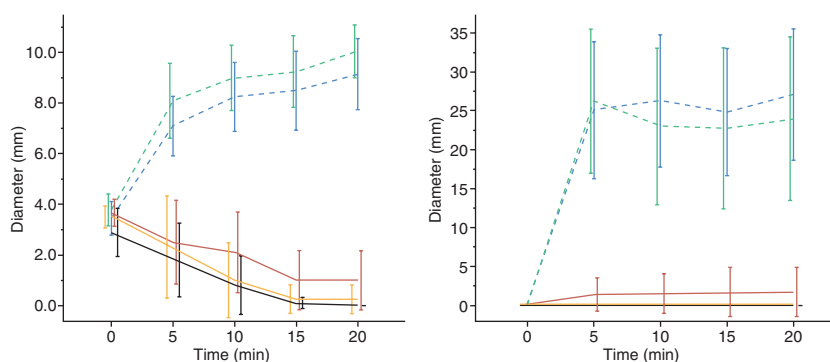


**Figure 3** Mean diameter of the wheal (left graph) and flare (right graph) at intradermal test sites over 20 min. The administration of sugammadex (0.13 mg.ml<sup>-1</sup>) at 2 min did not attenuate the cutaneous response to rocuronium (dashed green line) when compared to rocuronium alone (dashed blue line). Pre-mixing sugammadex at a 4:1 molecular ratio (red) or 20:1 (orange) prevented a cutaneous response, comparable with the saline negative control (grey). Error bars are SD.

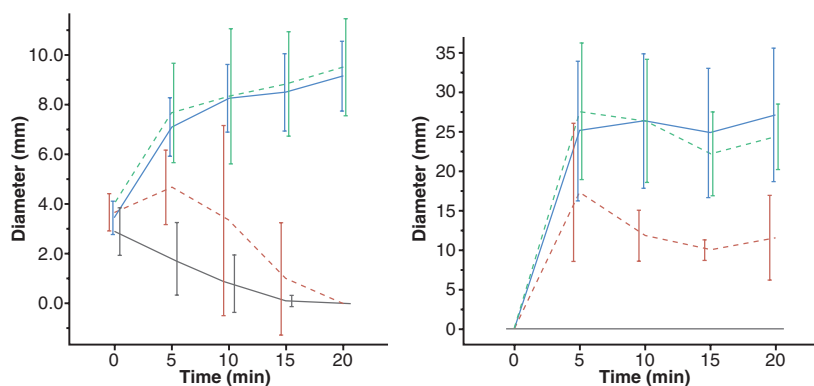


**Figure 4** Mean diameter of the wheal (left graph) and flare (right graph) at intradermal test sites over 20 min. Reversing the order of injection, administering sugammadex (0.13 mg.ml<sup>-1</sup>) followed by rocuronium (dashed red line) resulted in an attenuated cutaneous response compared to rocuronium alone (blue), but did not completely prevent a response (saline negative control, grey). Administration of a 10-fold concentration (1.3 mg.ml<sup>-1</sup>) of sugammadex at 2 min again did not attenuate the cutaneous response to rocuronium (dashed green line). Error bars are SD.

Reversal of the order of injection through the fixed intradermal needle resulted in inhibition of the wheal, and significant attenuation of the flare to rocuronium (Figs. 2 and 4)

## Discussion

Our experiment has confirmed our first hypothesis that, when bound by sugammadex, rocuronium is prevented from triggering a type-1 hypersensitivity reaction in sensitised individuals. However, in relation to the second hypothesis, sugammadex was ineffective in modifying the course of a reaction that has already been triggered by rocuronium.

The clinical correlate of this experimental model would be that sugammadex is unlikely to modify significantly the clinical course of an established allergic reaction caused by rocuronium. Although of no clinical benefit, pre-mixed rocuronium and sugammadex would be unlikely to cause a reaction in a sensitised individual.

Intradermal injection is a well-established model of IgE-mediated type-1 hypersensitivity, validated by the widespread use of intradermal testing for the investigation of anaphylaxis. It has been established that a dilution of 1:1000 of 10 mg.ml<sup>-1</sup> rocuronium, injected intradermally, is non-irritant and unlikely to cause non-IgE-mediated histamine release [2]. The concentration chosen was also a clinically relevant concentration of rocuronium (0.01 mg.ml<sup>-1</sup>), comparable with the plasma rocuronium levels measured in patients in the first 10 min after bolus administration of rocuronium 0.6 mg.kg<sup>-1</sup> during general anaesthesia [6]. A positive reaction after intradermal injection of this concentration indicates an IgE-mediated, type-1 hypersensitivity reaction. All of the subjects had a history of severe systemic anaphylaxis after exposure to rocuronium, and maintained a positive skin reaction to repeat intradermal injection on enrolment to this study.

By pre-mixing sugammadex with rocuronium before intradermal injection, we were able to assess the ability of sugammadex to bind rocuronium and prevent it from interacting with cell-bound IgE and activating mast cells. The lower concentration of sugammadex studied, 0.13 mg.ml<sup>-1</sup>, resulted in an excess of sugammadex molecules (4:1 ratio with rocuronium) that is comparable with the maximum manufacturer's recommended dose of 16 mg.kg<sup>-1</sup> of sugammadex to reverse

an intubating dose of rocuronium (1.2 mg.kg<sup>-1</sup>). The higher concentration resulted in a 20:1 molecular ratio. Both convincingly prevented a skin reaction to rocuronium in sensitised patients, suggesting that sugammadex binds rocuronium and excludes the allergenic epitope from the immune system.

However, when sugammadex was administered to a developing rocuronium-induced IgE-mediated hypersensitivity reaction, it was ineffective in attenuating the response. Sugammadex was again administered at a concentration of 0.13 mg.ml<sup>-1</sup>, and at a greater volume to compensate for needle dead space. While the triggering dose of rocuronium (0.02 ml of 0.01 mg.ml<sup>-1</sup>) was identical to the reference rocuronium test site, the injection at 2 min included 0.02 ml of rocuronium in the needle dead space, and 0.01 ml of sugammadex (leaving a volume of 0.02 ml of sugammadex in the needle dead space). Although this still results in an excess of sugammadex molecules given in total, to ensure that the negative result was unlikely to be due to underdosing, the experiment was repeated with 0.05 ml of a 10-fold increase in concentration of sugammadex (1.3 mg.ml<sup>-1</sup>) in the final three patients enrolled. This resulted in a delivered molecular ratio of sugammadex to rocuronium of 60:1. The clinical correlate would be administering 240 mg.kg<sup>-1</sup> of sugammadex to a patient suffering from systemic anaphylaxis, which is both expensive and impractical in its current formulation.

The reliability by which the fixed intradermal needle delivered the second (delayed) drug to the intradermal bleb was validated by reversing the order of agents in an additional experiment in the final three enrolled patients. The inhibition of the cutaneous response to the delayed rocuronium by an initial intradermal injection of sugammadex confirms that the fixed intradermal needle was effective in delivering the initial and delayed drug to the same intradermal site. This is certainly more precise than would be expected in a patient with severe distributive-hypovolaemic shock, who is given sugammadex intravenously, while receiving cardiopulmonary resuscitation and multiple doses of adrenaline [11].

Another consideration is the timing of administration of sugammadex to the developing cutaneous reaction. Given that perivascular tissues are rich in mast cells, and that the concentrations of rocuronium

administered in the intradermal bleb are comparable with intravenous concentrations immediately after intravenous bolus dosing, it would seem reasonable that the time course of mast cell activation would be comparable. The next question is the minimum delay between initiation of anaphylaxis and sugammadex administration in the clinical situation. The first signs of anaphylaxis may become apparent within a minute of intravenous allergen administration, but recognition of the likely trigger, institution of conventional management, as well as sourcing and administering sugammadex is likely to take considerably more time. In published case reports, sugammadex was administered at either 19 min, 45 min or 1 h after onset of anaphylaxis [11–13]. We felt that 2 min was the absolute minimum possible reaction time, and represented a period when the cutaneous reaction was in its early stages; it was still ineffective.

The mechanism of mast cell activation in systemic anaphylaxis and cutaneous anaphylaxis is similar, and the response to mast cell activation is stereotypical. Although released mediators will have different effects in different tissues (e.g. prostaglandin D<sub>2</sub> causes increased capillary permeability in the skin but bronchoconstriction in the airways), we felt it reasonable to extrapolate observation of local mediator effects at the skin to likely systemic mediator effects in a systemic anaphylactic reaction. It is difficult to argue that sugammadex is effective in attenuating systemic anaphylaxis if we cannot demonstrate a diminution in tissue effects in the skin.

The off-label and unproven use of sugammadex in the management of rocuronium anaphylaxis is based on the assumption that removal of the triggering allergen may modify the subsequent immune reaction. This seems reasonable in a situation where the allergen dose results in submaximal activation of the immune response (for example, in clinical provocation testing), or if there is continued absorption of the allergen. However, it is yet to be scientifically validated. It is less clear that removal of the allergen would be advantageous in anaphylaxis due to rocuronium. Although the minimum dose of intravenous rocuronium that may lead to anaphylaxis is unknown, it is likely that 1.2 mg.kg<sup>-1</sup> is far in excess, and will result in saturation of mast cell activation. Furthermore, no further doses are likely to be given once the reaction is recognised. Efficacy relies on

the assumption that the mast cell-leucocyte-cytokine cascade is allergen-dependent. However, there is ample evidence that once mast cells are activated by an allergen, allergen-independent mechanisms are, at least in part, responsible for the propagation and amplification of the type-1 hypersensitivity reaction (e.g. tryptase, neuropeptides, sphingosine-1-phosphate, platelet activating factor, anaphylatoxins and the mast cell-leucocyte-cytokine cascade have all been shown to activate mast cells) [15–19].

Clinicians are likely to have been impressed by the spectacular efficacy of sugammadex in reversing rocuronium-induced neuromuscular blockade, or by the binding of sugammadex to rocuronium. Sugammadex is effective in reversing rocuronium-induced neuromuscular blockade because it is rapidly distributed to the effect compartment [7], its affinity for rocuronium is an order of magnitude greater than that of the nicotinic acetylcholine receptor (association constants  $\sim 1 \times 10^7 \text{ M}^{-1}$  vs  $\sim 1 \times 10^6 \text{ M}^{-1}$ , respectively) [8], and rocuronium's influence at the nicotinic acetylcholine receptor is both reversible and relatively insensitive (clinically relevant neuromuscular blockade requires more than 75% receptor occupancy by rocuronium) [9]. As such, sugammadex has been shown to reverse profound rocuronium-induced neuromuscular blockade within minutes [6].

The process of IgE-mediated, type-1 hypersensitivity has many important differences to that of neuromuscular blockade. The IgE-mediated hypersensitivity is an exquisitely sensitive process; histamine release occurs with the cross-linking of as few as 100–200 IgE receptors on the surface of a basophil, which may contain up to 200 000 receptors [20]. Furthermore, the affinity of rocuronium for sugammadex is likely to be several orders of magnitude less than that for rocuronium-specific IgE, based on the known association constants of specific IgE for common allergens (for example, ragweed, Amb a 1, or dustmite, Der p 1, where the allergen-IgE association constant may be as high as  $1 \times 10^{11} \text{ M}^{-1}$ ) [3]. Mast cell activation is also followed by the irreversible process of mediator release, with exocytosis of preformed and immediately synthesised mediators. These propagate and amplify the hypersensitivity reaction, at least in part by non-allergen-dependent mechanisms. These differences are problematic for the

suggestion that sugammadex would attenuate rocuronium-induced anaphylaxis.

No case report has explained how sugammadex was able to antagonise, by either pharmacodynamic or pharmacokinetic mechanism, the vasoactive mediators that had been released and were at that time causing severe physiological derangement. It is interesting to note that in two of the case reports [11, 13], each patient had markedly raised serum tryptase levels. This is what would be expected in IgE-mediated anaphylaxis. One had a serum tryptase concentration of  $62.9 \mu\text{g.l}^{-1}$  (normal  $< 14 \mu\text{g.l}^{-1}$ ) 7.5 h after the event, the other had  $182 \mu\text{g.l}^{-1}$  (normal  $< 15 \mu\text{g.l}^{-1}$ ) at 3 h. Tryptase is one of the many mediators present in mast cell granules and released in anaphylaxis, and has been shown to cause mast cell degranulation, histamine release and increased microvascular permeability [17, 21]. It would have been much more impressive if these patients had recorded a surprisingly low serum tryptase level due to altered mast cell release caused by sugammadex. As neither tryptase nor the other mediators released are antagonised by sugammadex, one would assume that if the effects of sugammadex were immunological, the clinical improvement would only occur after resolution of the physiological effects of the mediators.

It seems much more plausible that a non-immune mechanism was responsible for the improvement of cardiovascular status, such as resumption of muscle tone and increased venous return, or coincidental decrudescence of the reaction. It is unclear from the case reports about the presence and time course of other more prolonged features associated with anaphylaxis, such as angio-oedema and gastrointestinal disturbance.

It may be argued that the mechanism of improvement may or may not have been immunologically mediated but this is irrelevant, as there was still a dramatic clinical improvement in the referenced case reports. However, it is important to appreciate the potential deleterious effects of the administration of sugammadex in such a situation. The mechanism that we feel is responsible for the haemodynamic improvements observed is restoration of muscle tone, and this may make the management of a patient with a potentially compromised airway due to angio-oedema, very difficult. An alternative neuromuscular blocking drug, even from a different drug class, is contra-

indicated because of the unpredictable nature of neuromuscular blocking drug cross-reactivity [22]. Additional hypnotic agents may also be contra-indicated because of their undesirable effects on the patient's already compromised cardiovascular system. Finally, the life-threatening event may not be anaphylaxis precipitated by rocuronium. Another agent may have been the allergen or there may be an alternative, non-allergic cause for the distributive shock.

Despite the above, our main concern is that the use of sugammadex in anaphylaxis may distract the clinician from instituting well-established management protocols for anaphylaxis [23].

Such is the nature of anaphylaxis that a clinical trial involving such a rare event is impractical, and it would be unethical to conduct a provocation experiment to assess the effectiveness of sugammadex. Experiments using animal models of human anaphylaxis may unfortunately be limited by the species-specific nature of the immunological response. In vitro models can only mimic individual steps of this complex neurohumoral and endocrine response. Nonetheless, Leysen et al. [24] used flow-cytometric analysis of CD63 expression on human basophils (a marker of degranulation) to examine the ability of sugammadex to modify basophil activation by rocuronium. Using basophils from three rocuronium-sensitised subjects, they were able to demonstrate that pre-mixing sugammadex with rocuronium did prevent basophil activation, but that delayed administration of sugammadex (after 3 min) did not alter rocuronium-induced CD63 expression. This in vitro experiment parallels our in vivo experiment, and agrees with our conclusions that sugammadex is able to conceal the allergenic epitope of the rocuronium molecule from its specific antibody, but is ineffective in modifying cell degranulation once it has been activated. The kinetics of the association between rocuronium, its specific IgE and sugammadex could be further investigated by in vitro techniques, such as surface plasmon resonance. However, propagation and amplification of the immunological signal after rocuronium-IgE binding, mast cell activation or degranulation may limit the relevance of any future encouraging in vitro findings in rocuronium anaphylaxis. There may be wider implications for the potential use of cyclodextrins in the management of allergic disease. Our demonstration that

a cyclodextrin can bind an allergen and exclude it from interacting with the immune system in vivo may lead to novel applications in other allergic diseases, especially where the allergen is administered in a dose that results in submaximal immune activation, and where it is not possible to prevent continued absorption or exposure to the allergen.

Our conclusion is that sugammadex is unlikely to modify significantly the clinical course of an established allergic reaction caused by rocuronium. Clinicians should continue to follow established protocols for the management of rocuronium anaphylaxis.

## Competing interests

No external funding and no competing interests declared.

## Supplementary material

Slides and audio from presentation of this work are available at [www.tinyurl.com/6rwyajh](http://www.tinyurl.com/6rwyajh) and [www.tinyurl.com/cvs96qw](http://www.tinyurl.com/cvs96qw), respectively.

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