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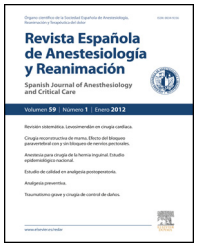

EDITORIAL

Sugammadex and anaphylaxis in the operating theater

Sugammadex y anafilaxia en la sala de operaciones

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Sugammadex, a chemically modified γ-cyclodextrin, has been developed specifically for the reversal of the action of the aminosteroid neuromuscular blocking drug (NMBD) rocuronium and to a lesser extent the structurally related vecuronium. It has a novel mechanism of action in that it encapsulates the target drug, forming an inclusion complex that reduces the plasma concentration of the blocking agent. This creates a concentration gradient between the plasma and neuromuscular junction and leads to rapid reversal of neuromuscular blockade.[1,2] Sugammadex is now available in over 60 countries, including the European Union and Japan where it was approved for clinical use in 2008 and 2010, respectively. However, in the USA some early concerns about the drug's involvement in allergic reactions were expressed by the US Food and Drug Administration (FDA) and currently sugammadex does not have approval for clinical use in the USA. Recently the FDA canceled a proposed discussion of sugammadex at the July 2013 Anesthetic and Analgesic Drug Products Advisory Committee raising issues concerned with ''operational aspects of a hypersensitivity study'' requested in 2008 (FDA News Washington Drug Letter Sept. 30, 2013).

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It has been claimed that sugammadex is well tolerated and is viewed as a relatively 'safe' drug[3,4] with only a documented hypersensitivity reaction being an absolute contraindication.[5] However, with more than 5 million vials of sugammadex said to be sold as of June 2013, two properties of this structurally and mechanistically unusual agent are proving of increasing interest to anesthetists. Firstly, reports of anaphylactic/anaphylactoid reactions to the drug are beginning to accumulate and, more intriguingly, reports of the beneficial effects of sugammadex in cases of rocuronium induced anaphylaxis are also being reported. These two apparent properties together with their implications for patients, physicians, and our understanding of underlying mechanisms of anaphylaxis, will be discussed.

Adverse drug reactions and the terms 'allergy', 'hypersensitivity', 'anaphylaxis' and 'anaphylactoid'

There is confusion in the appropriate use of the terms 'allergy', 'hypersensitivity', 'anaphylaxis' and 'anaphylactoid' reactions. Adverse drug reactions (ADRs) are classified on the basis of being dose-related and predictable (type A, approximately 80% of ADRs) or non-dose-related and unpredictable (type B, approximately 20% of ADRs). Type B reactions include the true allergic responses, that

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is, hypersensitivities or immune-mediated reactions, as well as three non-allergic (non-immune) categories of drug sensitivity, pseudoallergy, idiosyncratic reactions and intolerances.[6] The terms 'allergy' and 'hypersensitivity' are often misused even in the medical profession. True allergic, immune-mediated reactions comprise four different hypersensitivity states, type I, IgE antibody-mediated reactions; type II, cytotoxic reactions; type III, immune complex-mediated hypersensitivities; and type IV, delayed, cell-mediated responses.[7] Many adverse reactions are incorrectly described as hypersensitivities because there is no universally accepted definition of the term. 'Hypersensitivity' is often mistakenly applied to reactions that have no immune basis or to cases where the underlying mechanism has not been identified while other true hypersensitivities go unrecognized.[6,8] In relation to sugammadex, it is the type I, IgE antibody-mediated reactions that are of most interest here. For many years, the terms 'anaphylaxis' and 'anaphylactoid' have been used to label relatively rare but severe, immediate and often life-threatening reactions that show features of a true, type I IgE antibody-mediated hypersensitivity. Each reaction may occur within minutes or even seconds, involve the release of potent inflammatory mediators from mast cells and basophils and produce similar signs and symptoms such as hypotension, tachycardia, respiratory and gastrointestinal symptoms, and cutaneous manifestations such as erythema, urticaria, angioedema and pruritus. However, mechanistically, anaphylactic reactions are true type I hypersensitivities mediated by IgE antibodies while no immune mechanism can be demonstrated for anaphylactoid responses. Example of the latter reactions include drugs that directly provoke mast cell degranulation such as opioids, vancomycin and contrast media.[6]

Box 1: Summary of cases with a suspected hypersensitivity/anaphylactic/anaphylactoid reaction following administration of sugammadex

- 18 patients; age 7–89 years; 10 M, 8 F
- Dose of sugammadex administered 1.9–3.3 mg/kg
- Reactions developed within 1–7 min, most within 2–3 min
- Tests to confirm diagnosis carried out in 10 patients – skin test in 8; tryptase assay 6; histamine assay 2; lymphocyte stimulation test 2; no confirmatory test undertaken in 8 patients
- Positive skin tests to sugammadex in 8 patients but, as yet, *no conclusive* evidence of true type I IgE antibody-mediated (anaphylactic) reaction in any of the patients
- Investigators' diagnoses: hypersensitivity 6; anaphylaxis 7; anaphylactoid 2; allergy 1; hypotension 1; difficult to ventilate 1
- Investigations necessary to achieve reliable diagnoses:
  - validate sugammadex skin prick test and intradermal test
  - develop and employ specific assay to detect sugammadex-reactive IgE antibodies
  - employ tryptase assay (mature [preferred] or total) on preoperative and at least 1 or 2 peri-/postoperative blood samples
  - employ histamine assay if available
  - basophil activation test may be useful

Hypersensitivity to sugammadex

Early trials with sugammadex revealed an incidence of hypersensitivity reactions of less than 1%.[9] In two trials using doses of up to 32 mg/kg, a total of 6 subjects showed signs (including flushing, erythematous rash, nausea, difficulty breathing, tachycardia) of suspected short-lived and self-limiting ''hypersensitivity'' reactions.[3,9] In a higher dose study of 13 healthy adults, one male participant was judged to have experienced a ''hypersensitivity'' reaction following several adverse events after first exposure to the agent.[4] Skin testing with sugammadex appeared to confirm this.[9]

At the time of writing, there appears to be at least 16 published cases of sugammadex-induced reactions that have been given the different designations 'anaphylaxis', 'anaphylactoid', 'hypersensitivity' and/or 'allergy'.[4,10–19] In addition, one patient was reported to be difficult to ventilate[20] and another experienced hypotension[21] following the administration of sugammadex. This makes a total of 18 published cases where a suspicion of a hypersensitivity reaction existed. In addition, since 2011 the Japanese Society of Anesthesiologists has issued three warnings concerning sugammadex's involvement in (as of June 2013) 95 ''hypersensitivity'' reactions. It remains to be seen if this is simply a reflection of high usage in Japan. The main features of the observed reactions in the published reports, and the conclusions resulting from the clinical pictures and laboratory investigations aimed at obtaining information on the mechanisms of the reactions, are summarized in Box 1. While a positive skin test may reflect the immune basis of a reaction, that is, the presence of a sugammadex-reactive IgE serum antibody-mediated type I reaction, validation studies of the skin prick test (SPT) and the intradermal test (IDT) for sugammadex currently appear to be lacking. Prior to proceeding with skin test studies on any drug, testing for specificity and optimal test concentrations should be undertaken.[6,22] The latter is the highest concentration producing no skin test reactions in control subjects never before exposed to the drug, and in non-allergic previously exposed patients, but which will elicit a positive reaction in patients allergic to the drug. Test accuracy, that is sensitivity and specificity, of the sugammadex skin tests needs to be established[22] but this generally requires often risky and time-consuming provocation testing,[23] a procedure not always justified ethically.[6] Box 1 also summarizes the tests necessary to achieve a reliable diagnosis. Of course, these are in addition to a carefully gathered history and expert assessment of the clinical features, treatment and outcome of the patient's reaction.

Due, in the main, to the absence of clear and unequivocal evidence for an immune mechanism of the reported reactions, it is safe to say that some of the observed reactions to sugammadex are not IgE-mediated anaphylactic responses, that is, not true type I hypersensitivities. It is therefore also prudent to reserve final judgment on the

reactions where supporting evidence from appropriate validated tests is absent. A number of the reactions suggest that in some patients the drug may provoke a release of allergic/inflammatory mediators via a non-immune, direct effect on cells.

The question of the effectiveness of sugammadex in mitigating rocuronium-induced anaphylaxis

Anaphylaxis to rocuronium is well documented and has been the subject of debate on claims that it is a higher risk for anaphylaxis than other NMBDs.[24] Following speculation that sugammadex in encapsulating rocuronium might offer a novel treatment to reverse anaphylaxis caused by the NMBD,[25] a number of case reports appearing to support this suggestion have been published over the last 3 years. In the 11 cases summarized in Table 1, 9 female and 2 male patients experienced what appeared to be an anaphylactic or, for cases 1, 4 and 7, possibly an anaphylactoid reaction, soon after the induction of anesthesia but, in each case, the administration of sugammadex appeared to dramatically reverse the ongoing and previously difficult to manage adverse effects. Central to the hypothesis that sugammadex may attenuate an allergic reaction is whether or not the allergenic ammonium groups of the NMBD are still able to interact with the complementary IgE antibodies once the NMBD is encapsulated[25,37] and, interestingly, molecular models indicate that the determinants may still be accessible to antibody binding.[37,38] The rapid alleviation of anaphylactic symptoms following administration of sugammadex described in the case reports is somewhat surprising. The cross-linked IgE-FcεRI receptor complexes necessary for allergen-induced mediator release from mast cells and basophils[39,40] are known to be long-lasting and to dissociate slowly[41] and it is difficult to see how sugammadex could rapidly sequester both the free and IgE-bound rocuronium which would, presumably, be necessary to switch off the allergic mediator cascade.[37] In considering this question, attention has been drawn to the relative affinities of the rocuronium–sugammadex and rocuronium–IgE antibody binding interactions.[37,42] The association constant K_a for the former interaction is $1.8 \times 10^7\ M^{-1}$ and while figures for IgE–allergen binding may be as high as 10^{10}–$10^{11}\ M^{-1}$,[43,44] there are no data available on the strength of binding and stability of NMBD–IgE complexes. However, the average affinities and avidities of these complexes may be lower than first expected since most, if not all, NMBD-reactive IgE antibodies were not formed to a NMBD in the first place,[45] presumably resulting in, for example, rocuronium–IgE complexes of poorer complementarity or 'fit' and interactions of lower affinity and avidity. If the affinity of the rocuronium–sugammadex complex were higher than for the rocuronium–IgE complex, mitigation of anaphylaxis may presumably follow; in the reverse situation anaphylaxis may proceed.[37,42]

Some other possible explanations for the observed sugammadex-induced improvement in a patient's hemodynamic state during anaphylaxis have been advanced. McDonnell et al.[27] suggested that encapsulation of rocuronium may prevent further mediator release and provide the opportunity for the previously administered epinephrine to work with ''increased efficacy''. Restoration of venous return and cardiac output assisted by the increase in muscle tone associated with the reversal of neuromuscular block was also offered as a possible explanation and these remain possibilities that are difficult to disprove. Although the possibility of coincidence needs to be considered, for example, the administration of sugammadex and alleviation of symptoms may have coincided with the beneficial effects of the already instituted epinephrine and fluid resuscitation,[27] some authors believe that the timing in relation to the drug's administration and the rapidity and extent of recovery makes this unlikely.[28] However, in a case similar to that described by McDonnell et al.,[27] Wordsworth et al.[46] reported that ''recovery... occurred in a dramatic way after 15–20 min with traditional anaphylaxis treatment'' but now, with an accumulating number of 11 cases from 7 different countries, ''coincidental decrudescence''[47] as an interpretation is looking more unlikely.

Outside the operating theater, some investigations designed to examine the relationship between sugammadex and rocuronium-induced anaphylaxis have been undertaken. Using blood samples from rocuronium-allergic patients, pre-incubation of rocuronium with sugammadex inhibited rocuronium-induced basophil activation as detected by lack of expression of CD63. In experiments when sugammadex was added *after* basophils were activated with the drug, CD63 expression could not be blocked.[48] However, the authors' conclusion that rocuronium-induced anaphylaxis can probably not be mitigated by sugammadex is not necessarily correct since it is not clear that termination of mediator release is accompanied by the removal or reversal of already expressed CD63.[38] Studies using a cutaneous model similarly concluded that sugammadex is unlikely to modify significantly the clinical course of an established allergic reaction[47] but it should be remembered that degranulation is a rapid process and, once initiated in the skin, the cascade of interactions between cells and liberated effector molecules begins with potent mediators rapidly initiating capillary permeability (wheal) and vasodilation (flare). Within 2 min of allergen challenge, histamine liberation and increased local blood flow begin and up to 50% of wheal size cannot be explained by histamine alone.[49–51] Already-liberated mediators, and events already so rapidly underway, would not be expected to be inhibited by sugammadex so prevention or perhaps even diminution of the cutaneous signs that ultimately develop may not eventuate. It is not known if this situation is reflected systemically but the apparent rapid mitigation of anaphylaxis observed in the patients suggests it is not, adding to the difficulty of explaining the action of sugammadex in the rocuronium-allergic patients.

Examination of the results for patients 2, 3 5, 6, 8, 9, 10 and 11 summarized in Table 1 leaves the impression that their appears to be an association between the administration of sugammadex to patients experiencing a rocuronium-induced anaphylactic reaction and recovery in the patients' hemodynamic state. This also appears to be true for patients 1, 4 and 7 where, in each case, the absence of supporting test results prevents a confident diagnosis of anaphylaxis. In some cases the recovery after sugammadex was sudden and dramatic. In most of the cases, the first signs

Table 1 Summary of case studies of rocuronium-induced 'anaphylaxis' treated with sugammadex including clinical outcomes and conclusions.[a]

Patient number sex, age and [ref]	Initial treatment for anaphylaxis	Sugammadex dose and temporal relationship to rocuronium admin/symptoms/start of resuscitation	Response to sugammadex	Diagnostic tests employed	Retrospective assessment and comments
1 F, 27 [26]	Phenylephrine; epinephrine; clemastine; methyl prednisolone	200 mg 45 min after rocuronium	Within 5–10 min patient hemodynamically stable[1]	None	No confirmatory tests to confirm anaphylaxis; rapid recovery after sugammadex
2 F, 33 [27]	Epinephrine; chest compression; iv fluids	500 mg (6.5 mg/kg) 19 min after start of resuscitation	45 sec later signs of recovery; SPO_2 from non-recordable to 97%	Tryptase 62.9 μg/l[2] 7.5 h after event; IDT +ve to rocuronium 10 μg/ml	Anaphylactic reaction; rapid recovery after sugammadex
3 F, 47 [28]	Epinephrine; crystalloid; hydrocortisone; chlorpheniramine	400 mg (5.1 mg/kg) 1 h after reaction onset	2.5 min later awake and spontaneous respiration; HR from 150 to 84 bpm	Tryptase 182 μg/l 3 h after cardiac collapse; type I hypersensitivity ''confirmed by SPT''[3]	Anaphylactic reaction; rapid recovery after sugammadex
4 F, 62 [29]	Epinephrine; Ringer's acetate; Trendelenburg positioning[4]	200 mg (4.4 mg/kg) ~30 min after rocuronium	Cutaneous symptoms and hypotension resolved ''shortly after''[5]	None	Absence of profound hypotension and confirmatory tests; recovery time vague; anaphylactoid reaction?
5 F, 51 [30]	O_2; epinephrine; Ringer's lactate; HES	2000 mg (18 mg/kg) 20 min after rocuronium	2 min later skin recoloration; at 5 min AP and SPO_2 from non-measurable to 186/104 mmHg and 87%	At 90 min: histamine 923 nmol/l[6]; tryptase 126 μg/l[7]; roc-spec IgE[8], BAT[9] and SPT[10] all +ve	Anaphylactic reaction; rapid recovery after sugammadex
6 F, 61 [31]	Epinephrine	180 mg (4 mg/kg) 14 min after intubation	3 min later pulse rate, airway pressure and $EtCO_2$ improved[11]	Tryptase at 10 min > 36.5 μg/l; histamine >100 nmol/l; rocuronium-specific IgE detected	Anaphylactic reaction; rapid recovery after sugammadex
7 F, 62 [32]	O_2; epinephrine; crystalloid	700 mg (9.7 mg/kg) 5 min after rocuronium	Improvement over 2 min in HR, BP, SaO_2; gradual disappearance of erythematous plaques	None	Possibly anaphylaxis but lack of confirmatory tests; rapid recovery after sugammadex
8 F, 52 [33]	O_2; HES; Ringer lactate; epinephrine	1000 mg (13 mg/kg) 20 min after start of resuscitation	Carotid pulse returned and hemodynamic restoration after 5 min	Tryptase 102 μg/l; histamine >100 nmol/l; IgE and SPT positive to rocuronium	Anaphylactic reaction; hemodynamic restoration within 5 min

Table 1 (*Continued*)

Patient number sex, age and [ref]	Initial treatment for anaphylaxis	Sugammadex dose and temporal relationship to rocuronium admin/symptoms/start of resuscitation	Response to sugammadex	Diagnostic tests employed	Retrospective assessment and comments
9 F, 44 [34]	O_2; epinephrine[12]; crystalloid	(a) 1200 mg (12 mg/kg); (b) 2nd dose 400 mg (4 mg/kg)[13]. Total sugammadex admin 1600 mg (16 mg/kg)	(a) ''immediately'' BP↑ HR ↓ and rash appeared before return of hypotension, tachycardia, bronchospasm; (b) again BP↑ HR↓bronchospasm relaxed[14]	Histamine, tryptase and spec IgE results ''supported diagnosis of anaphylaxis''[15] and identified rocuronium as source – miv and vec also positive[16]	Anaphylactic reaction; authors suggest recovery dose-dependent with at least 16 mg/kg sugammadex required; relative contributions of epinephrine and sugammadex not clear
10[17] M, 11 [35]	Dexchlorpheniramine; epinephrine	200 mg (3.3 mg/kg)[13]	Easier to ventilate after 2 min; after 9 and 13 min tidal vols were >200 and 250 ml, respectively	Tryptase 104 μg/l	Probably anaphylaxis; symptoms improved 2–13 min after sugammadex
11 M, 19 [36]	Epinephrine	200 mg (3.2 mg/kg)[13]	BP became stable without epinephrine[18]; exanthema disappeared ''gradually''[18]	Tryptase 46 μg/l; blood Hb 21.3 g/dl; marked increase in vascular permeability	Anaphylaxis improved by sugammadex

[1]Systolic pressure increased to 95–105 from 50 to 55 mmHg. Heart rate (HR) declined from 90 to 63 bpm. [2]'Normal' (total) tryptase level <14 μg/l. [3]No details provided. [4]Patient did not develop profound hypotension and epinephrine was not administered. [5]Time not stated. [6]Histamine 38.4 nmol/l at 3 h ('normal' value <10 nmol/l). [7]73.7 μg/l at 3 h. [8]'Quaternary ammonium ion'–specific IgE 98.8 kU/l. [9]Basophil activation test (BAT) positive for rocuronium, negative for atracurium, cisatracurium and succinylcholine. [10]Skin prick test (SPT)-positive to rocuronium (10 mg/ml) and vecuronium (4 mg/ml). [11]Sugammadex given with the sole intention of reversing paralysis. Authors surprised by result. [12]0.1 mg given iv, [13]Time administered relative to relevant events not stated. [14]As well as second dose of sugammadex, six additional doses of epinephrine 0.1 mg and an iv infusion of 2 mg/h also given. Time before improvement not stated. [15]No quantitative results provided. [16]No test details given. [17]Allergic patient – used Epipen® on several occasions. Premedicated with hydrocortisone 100 mg iv. [18]Time for this to occur not stated.

[a] Cases listed in order of publication.

of recovery appeared 2–5 min after administration but in one report (case 9) an initial dose of sugammadex 12 mg/kg had to be supplemented with a second dose of 4 mg/kg together with more epinephrine before the recovery was sustained. This led the authors to recommend a dose of 16 mg/kg for rocuronium anaphylaxis,[34] which is considerably higher than the doses administered in some of the other cases.

Conclusions

From the accumulating number of cases it appears that sugammadex has the capacity to induce allergic type reactions in susceptible patients but it is not yet clear whether sugammadex is more allergenic than other commonly used agents in anesthesia. It also remains unclear how many of the reported cases of 'hypersensitivity' are true immune-mediated type I responses and how many are non-immune-mediated anaphylactoid reactions. To establish the mechanism(s) of these reactions to sugammadex there is a need to validate the sugammadex skin tests (SPT and IDT), to apply mediator assays such as the tests for released tryptase and perhaps histamine and to develop an immunoassay for the detection of sugammadex-reactive IgE antibodies. The basophil activation test might also prove useful.

With our current understanding of mechanisms underlying allergic mediator release in anaphylaxis, it is difficult to explain how sugammadex might attenuate severe reactions in a relatively short period of time but we must emphasize that there is still much to learn about anaphylaxis.[6] Suggested explanations such as restoration of muscle tone and/or increased venous return need to be considered and investigations devised (in laboratory animals if necessary) to test their possible contribution. Previously, it has not been possible to completely remove a systemic antigen

rapidly and easily from the circulation once administered and, in this regard, sugammadex may open up a number of potentially novel therapeutic options for the future of anaphylaxis management. In the meantime, it would seem reasonable that in cases of suspected rocuronium- or vecuronium-induced anaphylaxis, when other conventional measures have not been successful then the administration of sugammadex may be considered.

Conflict of interest

No financial contribution or any other assistance was received by BAB in relation to the preparation and presentation of this work. NJM has received honoraria from MSD for talks on neuromuscular blockade and the role of sugammadex.

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