

EDITORIAL

Anaphylaxis to sugammadex: should we be concerned by the Japanese experience?

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Sugammadex, a modified γ -cyclodextrin, is effective at reversing the effects of aminosteroid neuromuscular blocking agents (NMBAs), even in patients with profound neuromuscular blockade.^{1,2} This capability led the rocuronium/sugammadex combination to be promoted as an alternative to succinylcholine for rapid onset and short duration of effect, with adverse drug reactions to succinylcholine considered a prominent reason for the need of a replacement. A multicentre observational study of the incidence of anaphylaxis to sugammadex in Japan published in this edition of *British Journal of Anaesthesia*,³ however, raises the possibility that the incidence of anaphylaxis to sugammadex is so high that it renders the rocuronium/sugammadex combination the most risky NMBA/reversal agent combination in terms of adverse drug reactions. The potential clinical impact of the data generated by Orihara and colleagues³ is such that we should consider how they compare with previous estimates of sugammadex anaphylaxis, their rigour, and their generalisability.

The US Food and Drug Administration (FDA) did not approve the initial application for a licence for sugammadex in 2008 because of concerns about adverse effects, including hypersensitivity reactions.⁴ Before reconsideration for approval, the FDA required further information on the incidence of hypersensitivity reactions after repeat exposure to sugammadex. Subsequent studies on awake volunteers undertaken by Merck Sharpe and Dohme^{5,6} suggested a high propensity for sugammadex to cause hypersensitivity reactions. These studies concluded that the incidence of mild/moderate hypersensitivity was 1:20, with an incidence of anaphylaxis of 1:150 with sugammadex 16 mg kg⁻¹. We commented that this high apparent rate of sensitivity to sugammadex could present a major problem for anaesthetists if it

were to be translated into clinical practice.⁷ However, despite these data, approval for sugammadex in the USA was granted in 2015. This was presumably on the weight of post-marketing surveillance data from countries that had licensed sugammadex, in which 273 cases of anaphylaxis were reported from approximately 11.5 million exposures (an incidence of 0.0024%).⁴

In the UK, the 6th National Audit Project (NAP6) study found only one confirmed case of sugammadex anaphylaxis in an estimated 64 121 administrations (an incidence of 0.0016%).⁸ A recent review of the comparative epidemiology of perioperative hypersensitivity reactions concurred that the incidence was low in Europe but suggested that the picture in Japan, where sugammadex is much more frequently used, may be different,⁹ with a single-centre study reporting an incidence of anaphylaxis of 1:2500 (0.039%).¹⁰ However, that study determined sugammadex as the culprit agent based on the timing of events with no confirmatory testing, risking over-reporting of the incidence.¹⁰ The true number of drug administrations was also unknown, introducing another source of error.

Aside from seeking to avoid over-reporting of anaphylaxis to sugammadex through mis-diagnosis, the study by Orihara and colleagues³ sought to avoid underestimating the incidence of anaphylaxis, which is associated with self-reporting of events as used in post-marketing surveillance and audits. They conducted a 5 yr retrospective study of four large tertiary hospitals in Japan. All general anaesthesia cases were included, and the drugs used were confirmed by examining the anaesthesia records. Cases of sugammadex anaphylaxis were included only when strict diagnostic criteria were applied (a high likelihood based on a clinical scoring algorithm¹¹ and concordant confirmatory skin and blood test

results). The study identified six cases of anaphylaxis to sugammadex from 29 962 patients who received the drug, an incidence of 1:5000 (0.02%). It is worth noting that teicoplanin, established by NAP6 to be the most allergenic drug in the anaesthetic cupboard in the UK, has a risk of anaphylaxis of 1:6500 doses.⁸

Although the diagnostic criteria used by Orihara and colleagues³ would be widely accepted for making the diagnosis of sugammadex hypersensitivity, only four of the six cases were considered to be life-threatening, thereby meeting the strict criteria for anaphylaxis used elsewhere, including NAP6.¹² Even so, we need to try and account for an almost 10-fold difference in apparent incidence between these data and UK data presented in NAP6.⁸ The first consideration is to appreciate the problem of drawing inference about rare events, even with relatively large samples. For example, there would only need to be one missed case from NAP6 (there was indeed one suspected but unconfirmed case of sugammadex anaphylaxis⁸) for the two estimates to be statistically indistinguishable. Next is the possibility that higher doses of sugammadex were used more frequently in the Japanese cohort; previous work, albeit on relatively small numbers of healthy volunteers, has indicated that anaphylaxis is dose-dependent.^{5,6} The third consideration is that the high usage of sugammadex in Japan may have immunologically sensitised the population, thus predisposing them to immunoglobulin E (IgE)-mediated sugammadex hypersensitivity on subsequent exposure (it should be noted that the diagnostic tests used by Orihara and colleagues³ do not distinguish between IgE-mediated and non-IgE-mediated mechanisms). A further possibility, again assuming an IgE-mediated mechanism, is that sensitising environmental exposure to cyclodextrins, for example in the diet, is more prevalent in the Japanese population, and this predisposes to sugammadex hypersensitivity. Lastly, genetic factors can affect the degree to which an individual is likely to suffer adverse drug reactions. Examples include human leucocyte antigen (HLA) variant-dependent clozapine-induced agranulocytosis¹³ and severe cutaneous adverse reactions to abacavir, an antiretroviral drug.¹⁴ Although there are no known examples of genetic predisposition to drug-induced immediate hypersensitivity reactions, it is an area of active research interest.¹⁵

Orihara and colleagues³ also shed light on the impact on anaesthetic practice of the introduction of sugammadex where the cost of the drug is not a limiting factor in its use.³ In Japan there was a dramatic uptake of the use of sugammadex within 1 yr of its introduction in 2010. Not only is sugammadex the NMBA reversal agent of choice in Japan (90% of reversed cases compared with 8% in the UK¹⁶), but almost 95% of general anaesthetic cases use an NMBA (47% in the UK¹⁶), almost exclusively rocuronium, whereas in the UK anaesthetists use atracurium the most (45%), followed by rocuronium (38%), with succinylcholine occupying a much smaller share (10%).¹⁶

Irrespective of the generalisability of these new data from Japan, the incidence of anaphylaxis to sugammadex reported by Orihara and colleagues³ should, at least, lead to a re-evaluation of the NMBA/reversal strategy in that country. If we combine the NAP6 data for NMBAs⁸ (there are no published comparable data for Japan) with the data for sugammadex provided by Orihara and colleagues³ (grade III or IV cases only, i.e. true anaphylaxis), we find that the NMBA/relaxant combination with the highest incidence of anaphylaxis is

rocuronium/sugammadex (19.23 cases per 100 000 patients), compared with atracurium/neostigmine (4.15 cases per 100 000 patients) or succinylcholine/atracurium/neostigmine (15.25 cases per 100 000 patients). Even if we factor in the 1.59 cases of malignant hyperthermia per 100 000 patients given succinylcholine in the UK during 2016 (PM Hopkins, unpublished data), rocuronium/sugammadex has the highest incidence of life-threatening adverse reactions. We should not forget that succinylcholine produces superior intubating conditions to rocuronium for early intubation,¹⁷ whereas neither recovery from succinylcholine nor reversal of the action of rocuronium by sugammadex can be relied upon in a critical 'can't intubate, can't ventilate' situation.¹⁸ In other situations where reversal from profound block is not required, and providing that standards for neuromuscular monitoring are applied, sugammadex is advantageous over neostigmine only if rocuronium has been used, but here rocuronium has no advantages over atracurium or vecuronium.

The possibility that the incidence of anaphylaxis to sugammadex may increase because of immunological sensitisation must be considered in other countries when the cost pressures associated with sugammadex use reduce, for example when it comes off patent in 2023. The combination of rocuronium and sugammadex will remain invaluable when succinylcholine is contraindicated (patients with hyperkalaemia, myopathies, functional neuromuscular denervation, butyrylcholinesterase deficiency, malignant hyperthermia, or succinylcholine allergy) and in other niche clinical scenarios where rapid and complete reversal from profound neuromuscular block is required. It would be regrettable if the safety of sugammadex was compromised by its use in situations where it has not been shown to improve clinical outcomes, as has occurred in Japan.

An alternative to limiting the use of sugammadex might be to find approaches to mitigate the frequency or severity of the hypersensitivity reactions. The mechanism for these hypersensitivity reactions remains unclear and is not elucidated by Orihara and colleagues.³ de Kam and colleagues⁵ did not identify specific IgE to sugammadex in volunteers who developed hypersensitivity reactions, but the sensitivity of their assay is unknown. It remains unclear whether sugammadex anaphylaxis is a true allergic phenomenon mediated by IgE antibodies or by other immune mechanisms, or if it involves a non-allergic mechanism such as direct mast cell activation. In this sense, sugammadex resembles teicoplanin, another drug that we now understand to be highly allergenic, but for which the underlying mechanisms responsible for severe adverse reactions remain poorly understood.¹⁹ In any case, more extensive studies into the mechanism of sugammadex hypersensitivity reactions are warranted.

The paper by Orihara and colleagues³ provides firm evidence that sugammadex has the propensity to cause anaphylaxis. Although the scale of this problem may be limited in countries where the pricing of sugammadex precludes widespread use,⁹ this may not remain so in the future as the drug comes off patent and is more readily available. We should be alert to this possibility and perhaps consider restricting the use of sugammadex to specific patient groups where reversal from deep neuromuscular block provided by an aminosteroid NMBA is required, even when cost is no longer the main concern.

Authors' contributions

Conception and design of the article: all authors.

Drafting of manuscript: LS, PMH.

All authors reviewed and revised drafts of the manuscript and approved the final version.

Declarations of interest

PMH is an editorial board member of the *British Journal of Anaesthesia*.

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