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Sugammadex – the sting in the tail?

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Sugammadex, a modified cyclodextrin molecule, encapsulates rocuronium and other aminosteroid neuromuscular blocking agents (NMBAs), to provide rapid and reliable reversal of neuromuscular block. In comparison to the standard reversal agent neostigmine, the quality and speed of reversal is impressive, reversing moderate block around 17 times faster[1] and with fewer episodes of partial reversal in recovery[2,3]. In addition, it can provide reversal from deep blockade[3,4], a feature not possible with neostigmine. Arguably, sugammadex is the ideal reversal agent whenever an aminosteroid NMBA is used, as it can potentially speed recovery and improve turnaround time in surgical lists[5]. Sugammadex has also been proposed as an agent to treat rocuronium-induced anaphylaxis, with isolated case reports in the literature suggesting an almost immediate reversal of the anaphylaxis cascade when sugammadex was administered[6,7].

The main barrier to use of sugammadex, in the majority of countries, is cost. It is up to 20 times more expensive than neostigmine at a dose of 2-4 mg kg^{-1} (for reversal of moderate block), and clearly even more expensive with the 16 mg kg^{-1} dose (for reversal of profound block). In Japan, however, the national healthcare insurance system subsidises patient care, and the cost of drugs seems only a minor consideration for anaesthetists. Here, sugammadex is used routinely, and an estimated 10% of the population received sugammadex during an 8 year period from 2010 to 2018[8].

Another concern around the use of sugammadex is the risk of hypersensitivity. Indeed, sugammadex was only approved for use un the United States in 2015 (compared with 2008 in Europe and Australia) because of concerns about hypersensitivity. It is ironic that since sugammadex was approved by the US Food and Drug Administration (FDA) the body of evidence of hypersensitivity to the drug in clinical settings seems to be strengthening: in Japan, sugammadex is now the leading cause of peri-operative anaphylaxis[8].

Two articles in this edition of *British Journal of Anaesthesia* report investigations of sugammadex hypersensitivity[9,10]. These clinical trials undertaken prior to FDA approval and funded by the manufacturer of sugammadex were presumably done with a view to allaying concerns about the incidence of hypersensitivity, whereas they may have had the opposite effect. Both trials involved giving sugammadex at doses of either

4 or 16 mg kg^{-1}, or placebo, repeated twice at weekly intervals, to healthy non-anaesthetized subjects. The aim was to establish the rate of hypersensitivity, and to determine whether hypersensitivity became more likely following repeated administrations. They also sought to determine the underlying mechanism of hypersensitivity, and specifically whether this was an IgE- or IgG-mediated process. After completion of data collection in the first study[9], protocol deviations with the potential to introduce bias in the assessment of hypersensitivity were identified and this led to the repeat study[10].

Adverse events which might represent hypersensitivity were assessed by an independent and blinded committee. The authors defined hypersensitivity as: "objectively reproducible symptoms and signs of allergic disease initiated by exposure to a defined stimulus at a dose tolerated by non-hypersensitive persons". Anaphylaxis was further defined as: "acute onset of skin +/- mucosal symptoms, with at least one of either respiratory, cardiovascular or neurological compromise".

In the first study[9], the incidence of confirmed hypersensitivity was determined to be 0.7% in the 4 mg kg^{-1} group, 4.7% in the 16 mg kg^{-1} group, and 0% in the placebo group. One of the hypersensitivity subjects in the 16 mg kg^{-1} group was adjudicated to have suffered anaphylaxis. In the second study, 6.6% of the 4 mg kg^{-1} group were judged to have experienced hypersensitivity, 9.5% of the 16 mg kg^{-1} group, and 1.3% of the placebo group. Again, there was a single case of anaphylaxis in the 16 mg kg^{-1} group.

Overall between the two studies, among subjects who received at least one dose of sugammadex at either dose, there was an incidence of confirmed hypersensitivity of 5% (32/597). The incidence of anaphylaxis across all subjects given sugammadex was 0.3% (2/597). Both of the anaphylaxis cases occurred in the 16 mg kg^{-1} group, giving an incidence of anaphylaxis at this higher dose of 0.7% (2/298).

In six subjects (3 in each study) hypersensitivity occurred on the first dosing of sugammadex; all six subjects were in the 16 mg kg^{-1} groups. Two were allowed to continue in the study, the remainder discontinued the study. In the two who continued, one had experienced cough and widespread urticaria, while the other presented with flushing, urticaria and chest signs. Although the symptoms resolved

within a few hours without treatment there was a self evident risk of a more severe reaction on re-exposure, which could not be excluded by the investigators. It is not clear how this risk was communicated to the subjects.

On the basis of this work, an incidence of 1:20 mild or moderate hypersensitivity reactions could be expected for each exposure to sugammadex, and around 1:150 incidence of anaphylaxis when used at a dose of 16 mg kg^{-1}. These are alarming rates for anaesthetists. Compared to those drugs already widely used in the perioperative period, the increased risk of anaphylaxis would seem unjustifiable. For example, succinylcholine and teicoplanin, widely recognised to be relatively common causes of allergy, have an incidence of anaphylaxis of 11/100,000 and 16/100,000 respectively[11]. However, these high rates of hypersensitivity to sugammadex do not appear to translate into clinical practice. In Japan, the incidence of hypersensitivity was calculated from a national database audit, and a single centre study, at 1:34-40,000 and 1:2,500 respectively[8]. Based on the rates of confirmed anaphylaxis described in the papers by de Kam et al[9] and Min et al[10], one might have expected tens of thousands of cases in Japan alone, yet only 284 cases have been reported in total. In a one year study of peri-operative anaphylaxis in the UK, only one confirmed case of sugammadex anaphylaxis was reported from an estimated 64,000 administrations[11].

One explanation for the apparent discrepancy between these findings is under-reporting of peri-operative anaphylaxis, a problem which has been previously highlighted[12,13]. However, when new drugs are brought to market there is a tendency to over-report adverse reactions. This was noted with rocuronium, which initially appeared to be more allergenic than other NMBAs[14], but which has recently been demonstrated to be roughly equal to atracurium in its propensity to cause allergy[11]. It is unlikely that frequent episodes of serious allergic reactions would go largely unremarked for several years.

Another explanation is that mild or moderate cases of hypersensitivity are not deemed to be clinically relevant during the peri-operative period, or not severe enough to be recognised. Hypersensitivity is not an all-or-nothing response, but is on a spectrum of severity. Milder cases can manifest in the awake patient as feeling unwell, itchy, or anxious; these symptoms will be missed in anaesthetized patients. Objective signs

such as tachycardia, flushing, or mild bronchospasm, may be attributed to the effects of anaesthesia and airway manipulation, or be physically obscured by surgical drapes. It is also possible that the now routine use of dexamethasone as an anti-emetic further reduces the severity of hypersensitivity. However, general anaesthesia provides many of the co-factors which are thought to worsen or precipitate anaphylaxis (and in particular non-allergic anaphylaxis). The co-administration of several large and complex molecules, effects of surgical and emotional stress, heat, and concurrent infection, can all act to destabilise mast cells and produce systemic histamine release. It would be reasonable to think that the cough seen in an awake subject given sugammadex, may manifest in the anaesthetized patient as profound airway irritation and is likely to be exacerbated by airway manipulation. This would mean that general anaesthesia would increase, not decrease, the risk of hypersensitivity. The severity of hypersensitivity reactions is essentially unpredictable, and the likelihood of reactions which are apparently mild in a research setting, translating into severe reactions clinically, is unknown. Studies of food and venom allergy indicate that the severity of reactions cannot be reliably predicted on the basis of previous reactions, or time elapsed since these[15-17].

We should be neither falsely reassured by the apparent mildness of most reactions nor too alarmed by the rate of reactions in these two studies, as it remains unclear how this translates into clinical practice. We do, however, find it hard to agree with the implication that the greater risk of anaphylaxis when higher doses are used is mitigated by the immediate availability of an anaesthetist and resuscitation equipment[10]. The onset of anaphylaxis during any anaesthetic is a critical event with associated morbidity and mortality. The need for higher doses of sugammadex is most likely to arise in already fraught clinical scenarios (e.g., the failed rapid sequence induction); anaphylaxis as an additional critical event could be overwhelming for both patient and anaesthetist regardless of the proximity of key personnel and equipment.

Our understanding of the likelihood of harmful hypersensitivity reactions might be helped by elucidating the underlying mechanisms and de Kam et al[9] and Min et al[10] have performed exploratory work on this. To the best of our knowledge, there is no other mechanistic work in this area. First, they looked for evidence of mast cell degranulation, through serial serum mast cell tryptase (MCT) measurements. None of

the subjects demonstrated a dynamic change in MCT, including the two with confirmed anaphylaxis. This raises the possibility of a mechanism for the clinical picture of anaphylaxis not involving mast cell degranulation. Possibilities include complement or basophil-mediated mechanisms, or other non-elucidated mechanisms. Alternatively, a rise in MCT was not seen because the reaction was not severe enough to generate this, or the MCT results were falsely negative. MCT is not 100% sensitive[18] and negative results do not preclude a diagnosis of anaphylaxis.

Evidence of IgE-(or IgG) sensitisation in subjects with and without clinical evidence of hypersensitivity was also sought by de Kam et al[9] and Min et al[10] using assays for sugammadex-specific IgE or IgG antibodies, as well as skin testing. Skin testing, in the presence of appropriate negative and positive controls, suggests a specific IgE mediated effect against the compound being tested. Neither serum nor skin test evidence of anti-sugammadex antibodies 'proves' allergy, since not all patients with specific antibodies will exhibit a clinical picture of allergy on exposure[19]. Both testing modalities lack reproducibility, and neither have 100% specificity or sensitivity. For many drugs, the negative predictive value of these tests is low, and positive predictive value not 100%[20]. Further work is needed in order to validate skin and serum testing for sugammadex antibodies before conclusions about these results can be drawn. The papers by de Kam et al[9] and Min et al[10] also describe basophil activation testing (BAT) as a marker of hypersensitivity, as well as studies to determine whether complement or contact activation had occurred. These are largely research tools although there is some evidence from Japan for the clinical utility of BAT[21].

In conclusion, the work presented by de Kam et al[9] and Min et al[10] leaves us with perhaps more questions than answers. The discrepancy between their findings of high rates of hypersensitivity, and the clinical evidence for peri-operative hypersensitivity, remains difficult to rationalise. There is undisputed evidence of an allergy risk with sugammadex, but it is too early to precisely quantify that risk. However, on the basis of current knowledge, it would at least be prudent to avoid the use of sugammadex in the treatment of suspected rocuronium allergy. Administration of a potentially highly allergenic drug, to treat an ongoing anaphylaxis, seems at very best a triumph of hope over evidence.

As the pricing structure of sugammadex changes, we are likely to see a significant expansion in its use. With this, predictably, will be an increase in severe adverse reactions. What remains unknown, is whether this will be at the rates predicted by de Kam et al[9] and Min et al[10].

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