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doi: 10.1016/j.bja.2020.03.017
Advance Access Publication Date: 20 May 2020

Sugammadex or neostigmine: should potential anaphylaxis be the overriding factor in the choice of a reversal drug? Comment on *Br J Anaesth* 2020; 124: 154–63

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Keywords: anaphylaxis; neuromuscular blockade; neostigmine; sugammadex

Editor—We read with interest the paper by Orihara and colleagues,[1] in which 49 532 patients from four tertiary hospitals in Japan were investigated to compare the incidence of anaphylaxis between sugammadex and neostigmine. Sugammadex is widely used in Japan: 18 cases of anaphylaxis were reported, of which six were attributable to sugammadex (0.02%; 95% confidence interval [CI], 0.007–0.044%) and none to neostigmine. The authors suggest that neostigmine is much less likely to cause anaphylaxis and that the choice of a reversal drug in Japanese practice should be reconsidered.[1]

Anaphylaxis related to general anaesthesia is a life-threatening complication and should be treated rapidly by well recognised management. The largest study of life-threatening perioperative anaphylaxis reported from the Royal College of Anaesthetists, 6th National Audit Project (NAP6), found an overall incidence of perioperative anaphylaxis (Grades 3–5) of 1:11 752 (95% CI, 10 422–13 303) and for sugammadex of 0.0016% (just one patient).[2] This is 10-fold less than that in the study by Orihara and colleagues,[1] although recently it has been argued that the two findings may not be dissimilar.[3] It is certainly difficult to ascertain the true incidence of any rare adverse event. The reported incidence of anaphylaxis to sugammadex in the literature is relatively low at 0.0016–0.039%.[1–5] Orihara and colleagues[1] stated that racial differences may be the cause of the lower incidence of sugammadex-induced anaphylaxis found in the NAP6 study. There are no data to support this statement. Furthermore, the exact mechanism of anaphylaxis from sugammadex alone or the sugammadex–rocuronium complex is still not well understood.[5] Previous sensitisation to sugammadex or similar compounds in the environment may also be a factor.[3]

The potential risk of anaphylaxis from any drug should be lowered by all possible means. Administration of a drug should be based on careful assessment of the indication and sugammadex is no exception. The only way to justify sugammadex administration and in particular its dose is to objectively monitor the level of neuromuscular block. There is some evidence from work in conscious volunteers that the risk of an allergic response to sugammadex increases with increasing dose.[6] However, no information is presented in the study by Orihara and colleagues[1] as to the doses of sugammadex used and whether neuromuscular monitoring had been undertaken in the patients. It is known that in clinical anaesthesia the application of neuromuscular monitoring is low globally and Japan is no exception.[7]

The incidence of anaphylaxis to neostigmine is unknown. According to the data sheet, neostigmine-induced anaphylaxis is rare to exceptional (<1/10 000). We performed a literature search in Medline (search criteria: 'neostigmine'/exp OR neostigmine AND 'anaphylaxis'/exp OR anaphylaxis, search date January 8, 2020) and identified 154 publications that met the search criteria. After screening the titles and abstracts, only six publications describing eight cases of anaphylaxis to neostigmine could be analysed.[8–13] In only five cases was neostigmine anaphylaxis confirmed by either measurement of plasma tryptase, skin testing, or both.[8–11] In the remaining three cases the suggested anaphylaxis to neostigmine was based on clinical signs only without further confirmation.[12,13] Hence, anaphylaxis from neostigmine is very rare, but it is not zero. However, from the existing data, it is impossible to even speculate on the incidence of anaphylaxis to this anticholinesterase. In cases of anaphylaxis after neostigmine administration, the drug should certainly be in the differential diagnosis as a potential trigger.

A recent Cochrane review showed that in comparison with neostigmine, sugammadex was able to reverse a rocuronium-induced neuromuscular block more rapidly regardless of the depth of the block.[4] Moreover, sugammadex reduced the signs of postoperative residual paralysis. Neostigmine is well recognised to take 10 min to reach its peak effect, and is unlikely to produce complete recovery from neuromuscular block.[14] Residual neuromuscular block after neostigmine is a contributing factor to the development of critical respiratory events in the PACU.[15]

The Cochrane review showed significantly fewer composite adverse events in the sugammadex group compared with the neostigmine group (risk ratio (RR), 0.60; 95% CI, 0.49–0.74; I^2=40%; 28 studies, n=2298; Grading of Recommendations Assessment, Development and Evaluation (GRADE), moderate quality).[4] It was shown that the risk of adverse events was 28% in the neostigmine group and 16% in the sugammadex group, which resulted in a number needed to treat to benefit (NNTB) of 8. Sugammadex appeared to have a better safety profile than neostigmine in many other aspects of reversal use. We acknowledge, however, that the Cochrane review reported on fewer patients (4206) compared with the Orihara and colleagues[1] study (49 532) or NAP6 (64 121). If the incidence of anaphylaxis to sugammadex is in the order of 0.02%,[1–3] then the Cochrane review may not have detected a case.

In contrast, the post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR) study, a prospective snapshot audit investigating European practice in neuromuscular monitoring, reversal and postoperative pulmonary complications in 22 803 patients, reported no differences in these outcomes when comparing patients receiving sugammadex *vs* neostigmine for antagonism of neuromuscular block.[16] Any allergic responses were not reported in this study. However, in a subsequent sub-study of POPULAR, the investigators found a significantly lower risk for postoperative pulmonary complications with more advanced neuromuscular recovery (train-of-four [TOF] ratio >95% *vs* TOF ratio >90%) especially when acceleromyography had been used for monitoring. They found that higher doses of sugammadex had been used more often when a TOF ratio >95% was reached, and that in the POPULAR cohort, a relative under-dosage of sugammadex may have explained the lack of positive effects on postoperative complications for sugammadex-based antagonism reported in the original POPULAR study.[17]

Hence, although the risk is low, we accept that sugammadex-induced anaphylaxis should not be underestimated. Nor can we factor into our comments the risk of postoperative pulmonary complications with either drug. Orihara and colleagues[1] may well be correct that neostigmine is safer than sugammadex in respect of the risk of anaphylaxis and should certainly be used in a high-risk patient. However, the risk of anaphylaxis alone should not be an over-riding factor in the choice of reversal drug, and the many other advantages of sugammadex compared with neostigmine should also be considered.

Declarations of interest

HDDB has received research grants and funding from MSD to participate in CME meetings. He is treasurer and member of the Executive Committee of the ERAS® Society. JMH has received funding from MSD in the past 5 yr to give international lectures and chair CME meetings. She was editor-in-chief of the *BJA* from 1997 to 2005, and chair of the *BJA* Board from 2006 to 12.

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doi: 10.1016/j.bja.2020.03.017
Advance Access Publication Date: 21 April 2020