BJA Education, xxx(xxx): xxx (xxxx)

doi: 10.1016/j.bjae.2020.03.008
Advance Access Publication Date: XXX

Revalidation FOR ANAESTHETISTS RCA Revalidation matrix
Matrix codes: 1A02, 2A04, 3J03

Reversal of neuromuscular block

J.M. Hunter

University of Liverpool, Liverpool, UK

bja@liverpool.ac.uk

Keywords: neuromuscular block; reversal; sugammadex

Learning objectives

By reading this article, you should be able to:

- Detail the advantages and disadvantages of using neostigmine to reverse neuromuscular block.
- Detail the advantages and disadvantages of using sugammadex.
- Understand the risks associated with inadequate recovery from neuromuscular block at the end of anaesthesia.
- Have a basic knowledge of new reversal agents under development.

Key points

- Neostigmine takes at least 8 min to have its maximal effect and is only effective if recovery from neuromuscular block has commenced.
- Sugammadex, in the correct dose, can reverse any degree of neuromuscular block produced by rocuronium or vecuronium.
- Although rare, anaphylaxis is more common with sugammadex than neostigmine.
- Full recovery from neuromuscular block is more likely with sugammadex than neostigmine.
- Inadequate recovery from neuromuscular block after tracheal extubation is associated with an increased incidence of postoperative complications. The train-of-four ratio should be at least 0.9 before extubation.

Ideal properties of a reversal agent

Certain characteristics are prerequisites to developing a new reversal agent for antagonising neuromuscular block in the 21st century. These are listed in Box 1. To date, no reversal agent fulfils all these characteristics and hence the search continues.

Neostigmine: advantages and disadvantages

The pharmacology of the anticholinesterases has been described in detail in this journal.[1] The use of neostigmine is ubiquitous and has been for many decades. It is now the only anticholinesterase in routine use in the Western world. In most countries it is cheap (although not in the USA), but it does require the simultaneous use of an anticholinergic agent such as glycopyrrolate or atropine to prevent its muscarinic effects including bradycardia, bronchospasm, and increased intestinal motility. It is only efficacious if recovery from neuromuscular block has commenced: at least two twitches of the train-of-four (TOF) response should be detectable before it is given.[2] It also takes at least 8 min to have its maximum effect—a fact that is often forgotten by clinicians.[2] Neostigmine has a ceiling effect: increasing its dose does not necessarily increase its efficacy, which is a limitation of its use.[3] It may also cause depolarising block if given in excess. It is excreted in the urine and hence has a prolonged muscarinic effect in patients with renal insufficiency. Neostigmine has very little allergenicity; reports of anaphylaxis to neostigmine are very rare indeed. Only six proved cases have been described.

Jennifer M. Hunter MBE, PhD, FRCA, FCARCSI (Hon) is Emeritus Professor of Anaesthesia and senior research fellow in the University of Liverpool, UK. Her research interests are the pharmacodynamics and pharmacokinetics of neuromuscular blocking drugs and reversal agents in health and disease states. She was Editor-in-Chief of the BJA from 1997 to 2005, and Chair of the BJA Board from 2006 to 2012.

Accepted: 27 March 2020

Box 1
Ideal characteristics of a reversal agent to antagonise neuromuscular block.

- Can be used to reverse any neuromuscular blocking drug.
- Can be used to reverse any depth of neuromuscular block.
- A rapid onset of maximal effect (within a few minutes).
- No adverse cardiovascular effects.
- No adverse muscarinic effects (e.g. bradycardia, bronchospasm, abdominal pain, nausea and vomiting).
- No histamine release or risk of anaphylaxis.
- Not dependent on organ elimination.
- No ceiling effect.
- Does not produce depolarising block if given in excess.
- Low cost.
- Available as a solution.

Sugammadex

Drug design and pharmacology

The need to improve the efficacy of reversal of neuromuscular block led to the development of sugammadex. Sugammadex is a γ cyclodextrin (per-6-[2-carboxyethylthio]-per-6-deoxy-gamma-cyclodextrin sodium salt) that encapsulates or chelates aminosteroidal neuromuscular blocking drugs in a 1:1 ratio (Fig. 1). It consists of eight α-D-glucopyranoside units attached by α 1–4 linkages into a hollow ring-like structure known as a toroid. Sugammadex does not require coadministration of an antimuscarinic agent. It does not reverse residual block produced by other non-depolarising neuromuscular blocking drugs such as the benzylisoquinolinium compounds atracurium, cisatracurium and mivacurium. Its greatest affinity is for rocuronium, but it will also antagonise vecuronium at a slightly slower rate.[4] Sugammadex has been used to reverse the effects of pancuronium but this use is not indicated on its data sheet.[3]

Sugammadex has a lipophilic core and eight outer tails with a negative charge at their tips (Fig. 1).[2] These negative charges attract the positively charged quaternary ammonium group on the aminosteroid molecule, drawing the neuromuscular blocking drug into the more lipophilic core of the toroid and holding it there irreversibly. The attraction of sugammadex for rocuronium is as strong as the attraction of acetylcholine to the postsynaptic nicotinic receptor.[3] The rocuronium–sugammadex complex is excreted in the urine with a plasma clearance similar to the glomerular filtration rate.[5]

Pharmacodynamics

The onset of action of sugammadex at various degrees of neuromuscular block is dose dependent.[2,3] If sugammadex is to be beneficial, it must act much more rapidly than neostigmine. When moderate neuromuscular block is present, with only two twitches of the TOF response detectable, a dose of sugammadex 2.0 mg kg^{-1} will restore full recovery with a TOF ratio (TOFR) of at least 90% within 2 min. This is much faster than can be achieved with neostigmine. If profound (also called deep) neuromuscular block is still present, with no TOF count detectable and only a post-tetanic twitch response attainable, then the dose required is sugammadex 4–8 mg kg^{-1}. Neostigmine is ineffective at such deep levels of neuromuscular block. Theoretically, if immediate reversal of rocuronium is required after its administration, as in a failure to intubate situation, then sugammadex 16 mg kg^{-1} is advised. However several vials of sugammadex would need to be drawn up to obtain this dose in an adult, which is time-consuming to prepare.

It is now very well established that sugammadex is more efficacious in reversing neuromuscular block from the steroidal agents than neostigmine if given in the correct dose.[6] Because of pricing issues, some clinicians have used doses of sugammadex lower than those recommended on the data sheet, with inadequate recovery or transient worsening of the degree of neuromuscular block.[3] This approach is not to be recommended.

Advantages and disadvantages of sugammadex

The undoubted ability of sugammadex to reverse all depths of neuromuscular block produced by rocuronium or vecuronium is a useful characteristic of a reversal agent (Box 1). As the drug is a cyclodextrin, it would be expected to be an inert molecule with few adverse effects.

Sugammadex became available for clinical use in the UK in 2008. It was already available in many parts of Western Europe and Japan, but it took until December 2015 to be approved by the Food and Drug Administration (FDA) for use in the USA. In the UK, the price of sugammadex far exceeded that of neostigmine, an important factor in limiting its use. Price was not a controlling factor in other parts of Western Europe such as France, Germany, and Spain, and nor was it a problem in Japan. Hence the use of sugammadex became routine in those countries, whereas in the UK, the price of sugammadex often restricted its use to specific indications such as reversing profound neuromuscular block. A vial of neostigmine 2.5 mg with glycopyrrolate 0.5 mg costs less than £1 in the UK, whereas a dose of sugammadex 2 mg kg^{-1} for a 70 kg subject costs about £60.

Specific uses

Major laparoscopic procedures

For major laparoscopic procedures such as laparoscopic nephrectomy or prostatectomy, there is evidence that the use of a continuous infusion of rocuronium will improve surgical operating conditions and allow the use of a low-pressure pneumoperitoneum, lessening postoperative pain and discomfort especially in the shoulder tip.[7,8] Such anaesthetic techniques, which use profound (deep) neuromuscular block with an undetectable TOF count and only a response to tetanic stimulation, require the use of quantitative neuromuscular monitoring throughout anaesthesia to provide measurements of the TOFR. The use of sugammadex is necessary to reverse profound neuromuscular block at the end of the procedure. These techniques have also been used successfully during laparoscopic bariatric surgery, although the benefits of such practices are being questioned. They are impossible to undertake if neostigmine is the only reversal agent available.

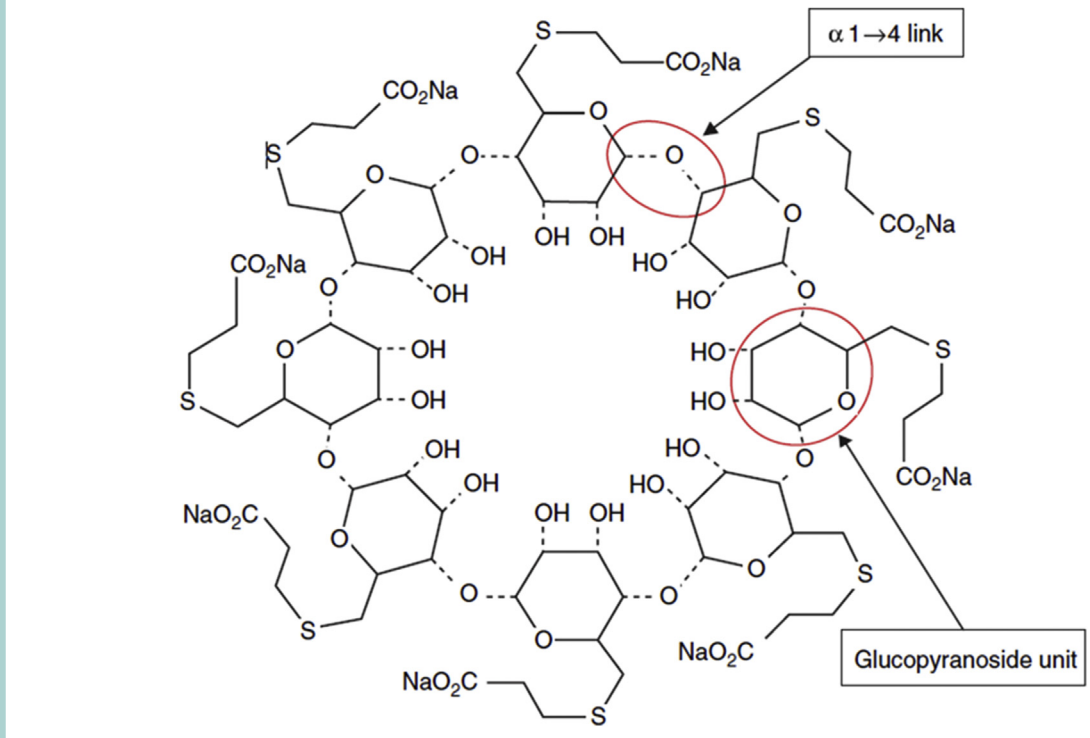

Fig 1 Structure of sugammadex showing eight glucopyranoside units linked together by α 1–4 linkages to maintain a ring shape.[2] One example of the glucopyranoside units and the α 1–4 linkages is encircled (accessible on https://en.m.wikipedia.org).

Treatment of anaphylaxis to rocuronium

There are reports of sugammadex being used successfully to treat anaphylaxis to rocuronium when first- and second-line treatment with adrenaline (epinephrine) and metaraminol has failed to resuscitate the patient.[9] Such treatment is not recommended on the manufacturer's datasheet for rocuronium. It has been postulated that the chelation of rocuronium by sugammadex causes the diffusion of unbound rocuronium back into the plasma down a concentration gradient, potentiating further chelation and reducing the amount of free drug available to enhance persisting anaphylaxis.

Patients with renal dysfunction

As the rocuronium–sugammadex complex is entirely excreted in the urine, the use of sugammadex in patients with kidney dysfunction is not advised in the UK datasheet. It has been repeatedly demonstrated that reversal of rocuronium-induced neuromuscular block with sugammadex is efficacious in patients with renal dysfunction; but it remains unclear as to the fate of the complex, which is still detectable in the plasma for up to 20 days after administration in these patients.[5]

Adverse effects of sugammadex

Anaphylaxis

The delay in obtaining approval in the USA by the FDA for the use of sugammadex resulted from the finding in a small number of conscious volunteers of allergic-type reactions to sugammadex including hypotension, skin flushing and bronchospasm. The FDA requested further studies on a larger number of subjects. Approval was given when further data had been gathered that suggested the incidence of such reactions was low.[10] But by 2010, reports had started to emerge of anaphylactic reactions after the use of sugammadex.[3] The reports were anecdotal and did not always fulfil all the criteria for anaphylaxis: the clinical presentation was convincing, but plasma tryptase concentrations had not always been determined, nor appropriate skin testing undertaken after the event. The mechanism for these reactions is not fully understood[11]; nor is the relevance of the rocuronium–sugammadex complex in this respect, rather than the individual drugs *per se*. Nevertheless, these reports have continued to occur, and an incidence of anaphylaxis to sugammadex of 0.02% has recently been reported in a second large retrospective study from Japan.[12] In contrast, in the same study, no reports of anaphylaxis to neostigmine were detected. In the RCoA NAP6 study, which reported in 2018, only one case of anaphylaxis to sugammadex was recorded out of 64,000 patients, an incidence of 0.0016%.[13] There were no reports of anaphylaxis from neostigmine in NAP6 either. The difference between the Japanese and the UK findings is difficult to explain, but could be caused by sensitisation to sugammadex in the Japanese population who have had a much greater exposure to the drug than in the UK.[12] However, this hypothesis is as yet unproven.

Cardiac effects

When the early reports of possible anaphylaxis to sugammadex were published, it became apparent that some of the adverse reactions did not fulfil all the diagnostic criteria.

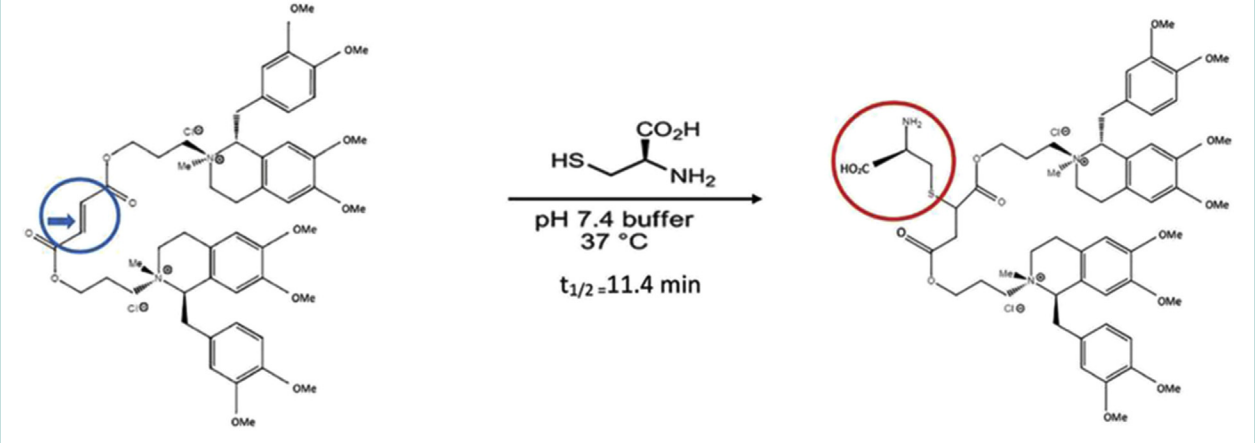

Fig 2 Breakdown of the chlorofumarate CW002 by the endogenous amino acid, L-cysteine. The left-hand circle shows the fumarate double bond that is the site of adduction of CW002 by L-cysteine. The circle on the right indicates where cysteine has been adducted onto CW002 to produce an inert molecule (accessible on https://en.m.wikipedia.org).[26]

Subsequently, an increasing number of reports of bradycardia and even cardiac arrest occurred without any proved evidence of an anaphylactic response. These were more common in patients with pre-existing cardiac problems, often receiving beta blocking drugs.[14] It is now accepted that sugammadex may have a vagal type of effect, although the mechanism is unclear. An antimuscarinic drug should always be available for use when sugammadex is given.

Residual neuromuscular block

Inadequate recovery from neuromuscular block with a TOFR less than 0.9 in the postoperative recovery room occurs in up to 45% of patients receiving neuromuscular blocking drugs during anaesthesia. There is increasing evidence of an association between inadequate recovery from neuromuscular block and respiratory complications in the immediate recovery period, such as arterial desaturation, obstruction of the upper airway, need for reintubation, and pulmonary aspiration.[15] Impaired hypoxic respiratory drive and even unexpected admission to the ICU may also ensue. Recovery from neuromuscular block should always be monitored at the end of anaesthesia using a quantitative monitor that gives a recording of the TOFR. Using a qualitative monitor in which the TOF response is only assessed visually or by touch is insufficient. Full recovery of the TOFR to more than 0.9 at tracheal extubation is less common after neostigmine than after sugammadex.[16] This results in fewer immediate respiratory complications if sugammadex is used. However, if neuromuscular block is not monitored, there is still a small risk of inadequate recovery even if sugammadex has been given.[17]

Postoperative pulmonary complications

The as yet unanswered question is whether this reduced incidence of immediate postoperative complications after sugammadex leads to a reduced incidence of postoperative pulmonary complications in the days after surgery. The evidence is accruing to support this hypothesis, although many of the data published so far are from underpowered, retrospective studies.[18] Statistically significant differences between sugammadex and neostigmine in terms of postoperative pulmonary complications (POPC) have not always been found, although odds ratios have suggested that sugammadex is superior in this respect. The recent results of a very large retrospective study of 45,712 patients in the USA from the Multicenter Perioperative Outcomes Group (MPOG) has found a significantly lower risk of POPC—a reduction of 30%—if sugammadex rather than neostigmine had been used, however.[18]

There is certainly evidence that POPC are more common if a neuromuscular blocking drug has been used during anaesthesia.[19] The incidence of POPC is in the order of 10–12% when neuromuscular blocking drugs are used, whereas it is only about 4% if the patient breathes spontaneously during general anaesthesia. In 2005, Arbous and colleagues demonstrated in a retrospective study that lack of reversal of residual neuromuscular block was an independent risk factor for anaesthetic-related morbidity and mortality in the 24 h after surgery.[20] But whether the use of a reversal agent reduces the risk of POPC in the days after surgery has been repeatedly questioned since Arbous and colleagues report.[21] There is evidence from the USA, but only from large retrospective studies when sugammadex was not yet available, that the use of neostigmine is associated with a higher incidence of POPC than if no antagonist is given after the use of a neuromuscular blocking drug.[21,22] In 2019, a very large, prospective, observational study in Europe (POPULAR) of more than 22,000 patients found no difference in the incidence of POPC between patients who received neostigmine or sugammadex.[23] Again, in the European study, reversal of neuromuscular block was found to be associated with an increased risk of POPC if a TOFR of 0.9 before extubation was taken as the cut-off point, as was the use of any neuromuscular blocking drug.[23] However, there is now a suggestion that, if the TOFR is allowed to recover to 0.95 rather than 0.9 before tracheal extubation, certainly when acceleromyographic monitoring is used, the incidence of POPC is reduced, whether or not a reversal agent has been used.[24]

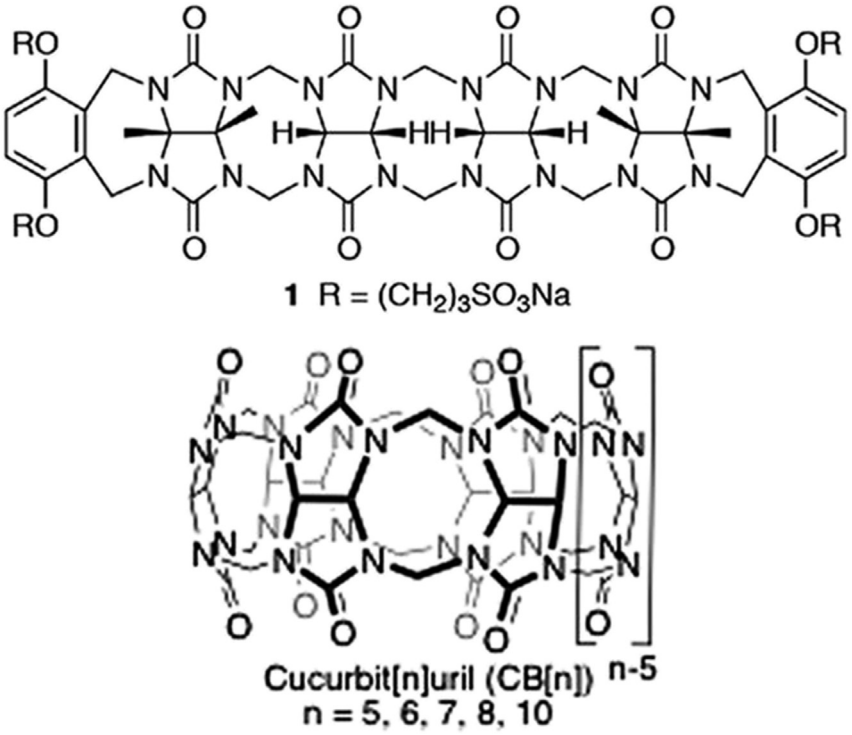

Fig 3 The chemical structure of one of the cucurbituril group of molecular containers, calabadion 1.[28] The bracketed section of the molecule on the right contains a variable number of nitrogen atoms. Calabadion 1 contains five nitrogen atoms, calabadion 2 contains six, etc. (accessible on https://en.m.wikipedia.org).

New developments

Chlorofumarates antagonised by L-cysteine

One ideal property of a neuromuscular blocking drug is that it breaks down, preferably spontaneously, in the plasma and therefore is not dependent on organ function, in particular the liver or kidney, for its elimination. In the search for such new neuromuscular blocking drugs, and in an attempt to shorten the onset time of non-depolarising agents without any adverse cardiovascular effects, Savarese and colleagues in the USA have developed a new group of benzylisoquinoliniums known as chlorofumarates.[25] These compounds undergo metabolism in the plasma by the endogenous amino acid, L-cysteine. The first chlorofumarate to undergo clinical trials was gantacurium (GW280430A).[25] Gantacurium had a comparable onset of action to rocuronium and a very short duration of effect similar to succinylcholine, but released sufficient histamine to deter its further development. However, two newer chlorofumarates, also metabolised by plasma L-cysteine, show more promise. In man, CW002 (now to be referred to as RP1000) has a similar onset of action to rocuronium at 90 s with a dose of 1.8 × ED_{95} (0.14 mg kg^{-1}), and a clinical duration of action similar to atracurium of 34 min.[26] CW002 can be rapidly antagonised by L-cysteine 50 mg kg^{-1} within 1 min of establishing neuromuscular block (Fig. 2). In contrast, neostigmine will not reverse profound block from CW002. CW002 is about to undergo Phase III clinical trials.

Another, shorter-acting chlorofumarate, CW 1759-50 (to be known as RP3000 in future studies), has an onset of action in rhesus monkeys similar to rocuronium. *In vitro*, it is adducted by L-cysteine within 2.3 min. The duration of action of CW 1759-90 is similar to succinylcholine at 7.4 (1.9) min.[27] Administration of L-cysteine shortens recovery after a bolus dose or an infusion of CW 1759-50. Neither of these compounds seems to have adverse cardiovascular effects in Phase I or II studies. They can also be reversed once recovery is established by neostigmine. However, reversal with i.v. L-cysteine has a more rapid effect. Marketing of a suitable proprietary preparation of L-cysteine is being considered. The amino acid is already available for use in parenteral nutrition, but the doses used in that clinical setting are inappropriate for its use as a reversal agent.

Calabadion 1 and 2

In an attempt to develop a reversal agent that is effective in antagonising both aminosteroidal and benzylisoquinolinium neuromuscular blocking drugs, a new group of acyclical compounds have been investigated. The cucurbituril family of molecular containers have a similar mode of action to sugammadex (Fig. 3). Their structure consists of a methylene-bridged glycouril tetramer capped by two *o*-xylylene rings. The four sulfonate groups on the bridging units point away from the cavity making the drug into a C-shape to bind the neuromuscular blocking drug. Early studies in rats showed that

calabadion 1 was equally efficacious in reversing rocuronium and cisatracurium, but it had less of an affinity for rocuronium than sugammadex. However, in a rat model, calabadion 2 rapidly reverses profound block from rocuronium, vecuronium, and cisatracurium in a dose-dependent manner. It is more efficacious than sugammadex in reversing profound block from rocuronium.[28] Calabadion 2 has 89 times more affinity for rocuronium than sugammadex. It is excreted in the urine. Studies of all these new compounds in humans are awaited.

Declaration of interests

JMH has received funding from Merck Sharp & Dohme to give lectures and chair CME meetings in the past 5 years. She was Editor-in-Chief of the *BJA* from 1997 to 2005, and Chair of the *BJA* Board from 2006 to 2012.

MCQs

The associated MCQs (to support CME/CPD activity) are accessible at www.bjaed.org/cme/home for subscribers to BJA Education.

References

1. Priya Nair V, Hunter JM. Anticholinesterases and anticholinergic drugs. *CEACCP* 2004; **4**: 164–8
2. Srivastava A, Hunter JM. Reversal of neuromuscular block. *Br J Anaesth* 2009; **103**: 115–29
3. Hunter JM. Reversal of residual neuromuscular block: complications associated with perioperative management of muscle relaxation. *Br J Anaesth* 2017; **119**(S1): i53–62
4. Duvaldestin P, Kuizenga K, Saldien V *et al*. A randomized, dose-response study of sugammadex given for the reversal of deep rocuronium or vecuronium-induced neuromuscular blockade under sevoflurane anesthesia. *Anesth Analg* 2010; **110**: 74–82
5. Staals LM, Snoeck MMJ, Driessen JJ *et al*. Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study. *Br J Anaesth* 2010; **104**: 31–9
6. Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. *Cochrane Database Syst Rev* 2017; **8**: CD0121763
7. Martini CH, Boon M, Bevers RF, Aarts LP, Dahan A. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate v deep neuromuscular block. *Br J Anaesth* 2014; **112**: 498–505
8. Bruintjes MH, van Helden EV, Braat AE *et al*. Deep neuromuscular block to optimize surgical space conditions during laparoscopic surgery: a systematic review and meta-analysis. *Br J Anaesth* 2017; **118**: 834–42
9. McDonnell NJ, Pavy TJG, Green LK, Platt PR. Sugammadex in the management of rocuronium-induced anaphylaxis. *Br J Anaesth* 2011; **106**: 199–201
10. Min KC, Bondiskey P, Schulz V *et al*. Hypersensitivity incidence after sugammadex administration in healthy subjects: a randomised controlled trial. *Br J Anaesth* 2018; **121**: 749–57
11. de Kam PJ, Nolte H, Good S *et al*. Sugammadex hypersensitivity and underlying mechanisms: a randomized study of healthy non-anaesthetised volunteers. *Br J Anaesth* 2018; **121**: 758–67
12. Orihara M, Takazawa T, Horiuchi T *et al*. Comparison of incidence of anaphylaxis between sugammadex and neostigmine: a retrospective multicentre observational study. *Br J Anaesth* 2020; **124**: 154–63
13. Harper NJN, Cook TM, Garcez T *et al*. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
14. Hunter JM, Naguib M. Sugammadex-induced bradycardia and asystole: how great is the risk? *Br J Anaesth* 2018; **121**: 8–12
15. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth Analg* 2008; **107**: 130–7
16. Brueckman B, Sasaki N, Grobara P *et al*. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. *Br J Anaesth* 2015; **115**: 743–51
17. Kotake Y, Ochiai R, Suzuki T *et al*. Reversal with sugammadex in the absence of monitoring did not preclude residual neuromuscular block. *Anesth Analg* 2013; **117**: 345–51
18. Bartels K, Hunter JM. Neostigmine vs. sugammadex: the tide may be turning, but we still need to navigate the winds. *Br J Anaesth* 2020; **124**: 504–7
19. Bulka CM, Terekhov MA, Martin BJ, Dmochowski RR, Hayes RM, Ehrenfeld JM. Nondepolarising neuromuscular blocking agents, reversal, and risk of postoperative pneumonia. *Anesthesiology* 2016; **125**: 647–55
20. Arbous MS, Meursing AE, van Kleef JW *et al*. Impact of anesthesia management characteristics on severe morbidity and mortality. *Anesthesiology* 2005; **102**: 257–68
21. Grosse-Sundrup M, Henneman JP, Sandberg WS *et al*. Intermediate-acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study. *Br Med J* 2012; **345**: e6329
22. Sasaki N, Meyer MJ, Malviya SA *et al*. Effects of neostigmine reversal of nondepolarizing neuromuscular blocking agents on postoperative respiratory outcomes. *Anesthesiology* 2014; **121**: 959–68
23. Kirmeier E, Eriksson L, Lewald H *et al*. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study. *Lancet Resp Med* 2019; **7**: 129–40
24. Blobner M, Hunter JM, Meistelman C *et al*. Use of a train-of-four ratio of 0.95 *versus* 0.9 for tracheal extubation: an exploratory analysis of POPULAR data. *Br J Anaesth* 2020; **124**: 63–73
25. Belmont MR, Lien CA, Tjan J *et al*. Clinical pharmacology of GW280430A in humans. *Anesthesiology* 2004; **100**: 768–73
26. Heerdt PM, Sunaga H, Owen JS *et al*. Dose-response and cardiopulmonary side effects of the novel neuromuscular-blocking drug CW002 in man. *Anesthesiology* 2016; **125**: 1136–43

27. Savarese JJ, Sunaga H, McGilvra JD *et al*. Preclinical pharmacology in the rhesus monkey of CW 1759-50, a new ultra-short acting nondepolarizing neuromuscular blocking agent, degraded and antagonized by L-cysteine. *Anesthesiology* 2018; **129**: 970–8

28. Haerter F, Simons JC, Foerster U *et al*. Comparative effectiveness of calabadion and sugammadex to reverse non-depolarizing neuromuscular blocking agents. *Anesthesiology* 2015; **123**: 1337–49