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# Reversal of residual neuromuscular block: complications associated with perioperative management of muscle relaxation

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## Abstract

The use of anticholinesterases to reverse residual neuromuscular block at the end of surgery became routine practice in the 1950s. These drugs could only be used when recovery from block was established [two twitches of the train-of-four (TOF) count detectable] and concern was expressed about their cholinergic side-effects. By the 1990s, it was recognized that failure to reverse residual block adequately to a TOF ratio (TOFR) >0.7 was associated with increased risk of postoperative pulmonary complications (POPCs) following the long-acting non-depolarizing neuromuscular blocking drug (NDNMBD) pancuronium. By 2003, and the introduction of acceleromyography, a TOFR ≥0.9 was considered necessary to protect the airway from aspiration before tracheal extubation. It was also considered that four, not two, twitches of the TOF should be detectable before neostigmine was given. Use of any NDNMBD was subsequently shown to be associated with increased risk of POPCs, but it was thought that neostigmine reduced that risk. Recently, there has been conflicting evidence that use of neostigmine might increase the incidence of POPCs. Although sugammadex has been shown to rapidly reverse profound neuromuscular block from aminosteroidal agents, there is currently no evidence that sugammadex is superior to neostigmine in its effect on POPCs. Other new antagonists, including cysteine to degrade CW002 and calabadion 1 and 2 to antagonize aminosteroidal and benzylisoquinolium NDNMBDs, are being studied in preclinical and clinical trials. Quantitative neuromuscular monitoring is essential whenever a NDNMBD is used to ensure full recovery from neuromuscular block.

**Key words:** neuromuscular blocking drugs; reversal; complications

## History

Seventy-five years ago, Griffith and Johnson[1] in Montreal, Canada first described the use of small doses of Intocostrin (extract of unauthenticated curare) to reduce muscle tone in 25 patients undergoing various types of abdominal surgery. Intocostrin had been used previously in humans to treat tetanus and for electroconvulsive therapy but this was the first report of its use during general anaesthesia. The patients were all breathing spontaneously with some manual assistance during cyclopropane anaesthesia. No postoperative complications were encountered. Intocostrin was a mixture of the alkaloids of curare, derived from the Indian rubber plant, *Chondrodendron tomentosum*, and prepared for commercial use by Squibb Inc. in the USA. It is difficult to ascertain the exact equivalent dose of d-tubocurarine (dtc) that each of these patients received, but at the most it was 25 mg. None of these patients underwent reversal of residual block at the end of surgery, although it was noted that the anticholinesterase, pyridostigmine, should be available for use if required.

T. Cecil Gray, a general practitioner in Liverpool, UK during World War II undertaking anaesthetic sessions, read this report by Griffith and Johnson.[1] He wrote to Griffith, asking for a supply of Intocostrin. This powder was brought by a Canadian air force pilot to a US air force base near Liverpool. As Intocostrin had proved difficult to standardize, Gray took the substance to the nearby Burroughs Wellcome pharmaceutical factory. Burroughs Wellcome were able to produce a commercial preparation of dtc from this powder.[2] Gray and Halton[3] went on to give much larger doses of dtc, up to 45 mg, to over 1000 adult patients. Only three patients received pyridostigmine at the end of the procedure. Thus, the Liverpool Anaesthetic Technique was born. In contrast to Griffith, Gray took over complete control of respiration, and only gave one, large intubating dose of dtc. The incidence of postoperative pulmonary complications (POPCs) was 12.5%, and two anaesthetic deaths were reported from early in the series, both determined at postmortem to be a result of myocardial ischaemia and hypoxia.

The popularity of the Liverpool Technique spread rapidly around the world, but in 1954 it almost came into disrepute. Beecher and Todd[4] in Boston, USA reported a retrospective study of 599 548 patients who had undergone various surgical procedures using many different techniques: regional blocks, local blocks and general anaesthesia either breathing spontaneously or with artificial ventilation using a muscle relaxant. The incidence of postoperative mortality was much higher in the group that had received a muscle relaxant: 1 in 370 *vs* 1 in 2100 patients.[4] On reading this report, Gray did not hesitate to introduce the routine use of a large dose of neostigmine, 5 mg in adults, into the Liverpool Technique, a practice that had already been advocated by others in the UK.[5] In an editorial to celebrate 50 yr since Griffith and Johnson[1] first described the use of Intocostrin, Utting[5] reviewed the lesser contributions made by Gray's contemporaries to the introduction of relaxant anaesthesia in the 1940s and 1950s.

By 1980, the Liverpool Technique was receiving significant criticism. Many anaesthetists were using smaller doses of neostigmine than 5 mg in adults, and were using potent inhalational agents as well as nitrous oxide 70% in oxygen to ensure anaesthesia. When Payne and colleagues[6] described the possibility that excessive doses of neostigmine could potentiate residual neuromuscular block, albeit transiently, clinical practice changed in this respect in the UK. These results were obtained during halothane anaesthesia and the findings have never been fully validated. Nevertheless, neostigmine 2.5 mg became the standard dose to use in adults in the UK. In the USA and many parts of Europe, smaller doses of neostigmine were given on a weight-related basis: $<0.035$ mg kg$^{-1}$. In 1988, it was demonstrated that doses of neostigmine $<0.035$ mg kg$^{-1}$, given when recovery from neuromuscular block had commenced, potentiated a more rapid reversal than spontaneous recovery from atracurium and vecuronium.[7] As had been demonstrated previously, neostigmine 2.5 mg took up to 12 min for maximum effect. Neostigmine 1.25 mg and 0.625 mg were more efficacious than spontaneous recovery from either atracurium or vecuronium, although the effect was impracticable clinically: recovery took too long (Table 1). Baurain and colleagues[12] demonstrated that at 25–50% recovery of twitch height, a neostigmine dose of 0.04 mg kg$^{-1}$ was optimal. Larger doses led to less complete recovery.

There is now substantial evidence that the action of neostigmine displays a ceiling effect, as is commonplace with enzyme inhibition. When acetylcholinesterase inhibition approaches 100%, any increase in neostigmine dose will not produce an additional effect. Unfortunately, this degree of inhibition occurs within the clinical dose range so neostigmine only provides partial recovery. This effect has been discussed in detail in a review by Donati[13] in 2013. If neostigmine is given during profound block, time to full recovery is no shorter than spontaneous recovery.[13] All these findings demonstrate the limitations of using neostigmine and substantiate the need for accurate monitoring of neuromuscular block throughout anaesthesia (Table 2).

**Table 1** Times (min) to recovery of train-of-four ratio (TOFR) to 0.7 and 0.9 after neostigmine, sugammadex and cysteine used to reverse residual block from atracurium, vecuronium, cisatracurium, rocuronium or CW002. (*$P<0.01$, †$P<0.001$ compared with spontaneous recovery; ‡$P<0.0001$ sugammadex after rocuronium compared with neostigmine after cisatracurium). PTC, post-tetanic twitch

| | TOFR=0.7 | TOFR=0.9 |
|---|---|---|
| Neostigmine after atracurium 0.5 mg kg$^{-1}$ at TI/T0=10%[7] | | |
| 0.625 mg | 19.3* | |
| 1.25 mg | 14.2* | |
| 2.5 mg | 12.0† | |
| 5.0 mg | 11.2* | |
| Spontaneous | 32.3 | |
| Neostigmine after vecuronium 0.1 mg kg$^{-1}$ at T1/T0=10%[7] | | |
| 0.625 mg | 19.7 | |
| 1.25 mg | 10.4† | |
| 2.5 mg | 9.2* | |
| 5.0 mg | 5.6* | |
| Spontaneous | 24.2 | |
| Neostigmine 2.5 mg at T1/T0=0.2 after cisatracurium 0.1 mg kg$^{-1}$[8] | 5.1 | 9.0 |
| Sugammadex 2 mg kg$^{-1}$ at T1/T0=0.2 after rocuronium 0.6 mg kg$^{-1}$[8] | 1.4‡ | 1.9‡ |
| Sugammadex 8 mg kg$^{-1}$ at PTC 1–2 after rocuronium 0.6 mg kg$^{-1}$[9] | | 1.5 |
| Sugammadex 16 mg kg$^{-1}$ 3 min after rocuronium 1.2 mg kg$^{-1}$[10] | | 2.2 |
| Cysteine 50 mg kg$^{-1}$ after CW002 0.15 mg kg$^{-1}$ in monkey at 2% recovery of twitch[11] | | Spontaneous Recovery |
| 5–95% recovery | 2.1 | 11.2 |

## Neuromuscular monitoring

In 1970–1, Gray and colleagues[16–18] went on to produce a series of seminal papers describing for the first time a clinical tool for monitoring neuromuscular block perioperatively that, most importantly, did not require a control value to be determined before use. The train-of-four (TOF) twitch technique described the use of four electrical stimuli (T1, T2, T3 and T4) at 2 Hz, with an interval of at least 10 s between each TOF. The stimuli were applied to the ulnar nerve at the wrist, and contraction of the adductor pollicis muscle in the thumb was measured with a strain gauge transducer. After a non-depolarizing neuromuscular blocking drug (NDNMBD), the fourth twitch of the train reduced first, followed by the third, the second and finally the first. This effect came to be known as 'fade' or 'decrement' of

**Table 2** Appropriate doses of the reversal agents neostigmine and sugammadex according to the type of non-depolarizing neuromuscular blocking drug used and the degree of neuromuscular block.[14 15] PTC, post-tetanic twitch; TOF, train-of-four; TOFR, TOF ratio

| | Benzylisoquinoliniums | Aminosteroids | |
|---|---|---|---|
| | Neostigmine | Neostigmine | Sugammadex |
| Complete Block<br>No PTC detectable | Ineffective | Ineffective | 16.0 mg kg$^{-1}$ |
| Profound block<br>PTC <7 | Ineffective | Ineffective | 4.0–8.0 mg kg$^{-1}$ |
| Moderate block<br>TOF count 1–2 | 0.05 mg kg$^{-1}$ | 0.05 mg kg$^{-1}$ | 2.0 mg kg$^{-1}$ |
| Moderate block<br>TOFR <0.4<br>TOF count 2–3 | 0.02–0.05 mg kg$^{-1}$ | 0.02–0.05 mg kg$^{-1}$ | 2.0 mg kg$^{-1}$ |
| Residual block<br>TOF count=4<br>TOF fade detectable subjectively | 0.04 mg kg$^{-1}$ | 0.04 mg kg$^{-1}$ | 2.0 mg kg$^{-1}$ |
| No fade of TOF detectable subjectively or TOFR=0.4–0.9 | 0.015–0.025 mg kg$^{-1}$ | 0.015–0.025 mg kg$^{-1}$ | 2.0 mg kg$^{-1}$ |
| TOFR >0.9 on quantitative monitoring | No reversal agent required | No reversal agent required | |

the response. Recovery occurred in the reverse order. Gray and colleagues[16–18] recommended that the train-of-four ratio (TOFR), the ratio of the fourth (T4) to the first twitch (T1), recover to at least 0.7 before extubation was effected. They also stipulated that an anticholinesterase should not be administered until all four twitches of the TOF were detectable, a recommendation that has been substantiated repeatedly since.[13] This level of recovery before extubation was demonstrated to equate with good recovery of muscle tone such that patients could, for instance, lift the head off the pillow for 5 s, cough and protrude the tongue, depressing a spatula with it. These clinical signs have been repeatedly questioned, however, and are now considered invalid.[13]

Although Gray and colleagues[16–18] recommended use of the TOF twitch technique clinically whenever a NDNMBD is used, such practice did not become routine in all institutions. Other clinical monitoring tools were described including the *post-tetanic twitch count (PTC)*, which is used to measure more profound degrees of neuromuscular block when the TOF count is undetectable. After a 5 s tetanic burst at 50 Hz and a 3 s interval, single twitch stimuli at 1 Hz are applied. In the early stages of recovery, one or two twitches may be detectable visually or on palpation. This degree of dense block may be necessary when using intermediate-acting NDNMBDs for certain surgical techniques, for instance, in neurosurgery, but it cannot be antagonized adequately with an anticholinesterase. When seven post-tetanic twitches are detectable, return of the TOF response is imminent.

Newer monitoring techniques include *double burst stimulation*, described in 1989, which was shown to be more accurate than the TOF pattern in detecting degree of fade subjectively during the later stages of recovery.[19] Two or three short bursts of 50 Hz tetanus separated by an interval of 750 ms are applied. Viby-Mogensen's group in Copenhagen demonstrated that even experienced neuromuscular researchers were unable to detect fade of the TOF by visual or tactile means when the TOFR had increased above 0.4, which is much lower than the then recommended level of 0.7 required for extubation.[20] In contrast, with the double burst technique, fade could be detected visually or by touch up to a TOFR of 0.6. However, this degree of recovery is still not sufficient for safe extubation.

By this time, the techniques of neuromuscular monitoring were changing. Gray had used mechanomyography in his first description, and subsequently electromyography became available although this was more of a research tool. With the introduction of acceleromyography in the 1990s, for the first time a readout of the TOFR was possible in clinical as well as research practice. It then became apparent that recovery of the TOFR to 0.7 was insufficient to confirm full recovery of the muscles of swallowing and the upper airway, sufficient to prevent pulmonary aspiration of stomach contents.[21] By 2003, Eriksson was stressing, as Viby-Mogensen[22] had done in 2000, that neuromuscular monitoring was essential throughout anaesthesia when a NDNMBD is administered and that reversal was necessary unless recovery of the TOFR to 0.9, and not 0.7, was confirmed before extubation (Table 2).[23] Hence, quantitative neuromuscular monitoring, which gives a measurement of the TOFR, should be used whenever a NDNMBD is given.

## Qualitative vs quantitative neuromuscular monitoring

As early clinical neuromuscular monitoring devices did not provide a readout of the TOFR, clinicians counted the number twitches visible or palpable and referred to this as the *train-of-four count*. Although this approach, known as qualitative monitoring, provided satisfactory guidance for administering incremental doses of NDNMBD or an anticholinesterase, there is little evidence that it reduces the risk of residual neuromuscular block

postoperatively or of POPCs.[24] In 1990, Pedersen and colleagues[25] found that use of qualitative monitoring perioperatively had no effect on the dose of NDNMBD given, the need for supplementary doses of anticholinesterase in the recovery room, or the presence of residual neuromuscular blockade evaluated clinically.

## Use of neuromuscular monitors

Clinical practice around the world varies significantly with respect to the use of intraoperative neuromuscular monitoring. In 2010, Naguib and colleagues[26] compared its use in Europe with American practice. They found that quantitative monitors were less frequently available to anaesthetists in the USA than in Europe (23% *vs* 70%). Routine reversal of residual block was more common in the USA than Europe, however (34% *vs* 18%). Concerns about cholinergic side-effects of neostigmine were given as the main reason for not using it. 19% of Europeans and 9% of Americans never used neuromuscular monitoring even though there is evidence that if the TOFR is greater than 0.7 on admission to the recovery room, duration of stay there is significantly shorter.[27] Most (80–90%) of the respondents believed they had never seen residual neuromuscular block in the recovery room. Kopman and Eikermann[14] have produced an algorithm recommending the dose of neostigmine to be used, according to the type of neuromuscular monitoring available and the TOF response obtained. They also detailed when use of a reversal agent was unnecessary (Table 2).[14]

## Residual block in the recovery room

There is substantial evidence of unrecognized residual block in patients in the recovery room who have received a NDNMBD perioperatively, regardless of whether or not a reversal agent has been used. Debaene and colleagues[28] (2003) showed that the incidence of a TOFR $<0.9$ in patients who had received only one dose of atracurium, vecuronium or rocuronium perioperatively but no reversal agent was as high as 45%. In 239 patients tested 2 h after admission, 10% still had TOFR $<0.7$ and 37% $<0.9$. The incidence was greater for shorter surgical procedures and if repeated boluses or an infusion of NDNMBD had been given.[28] McCaul and colleagues[29] showed that even if neostigmine had been used to reverse residual block from atracurium, the incidence of incomplete recovery of the TOFR to $<0.7$ in the postoperative care room was still 65%. In this study, 50% of patients had neuromuscular monitoring using a peripheral nerve stimulator. In the other 50%, clinical criteria only were used to manage reversal of residual block. The high rate of residual block could have been caused by failure to adequately monitor and by inappropriate doses of neostigmine. Again, residual block was more common in shorter surgical procedures, when larger doses of atracurium had been given, and with a shorter interval between the last incremental dose and extubation. Duration of surgery was the sole multivariate predictor of postoperative residual curarization. Baillard and colleagues[30] reported similar findings after vecuronium. Out of 568 patients who received no anticholinesterase, 42% had a TOFR $<0.7$ in the recovery room. Six of those patients had no TOF detectable and were reintubated. Once more, larger doses of NDNMBD and a shorter time between the last increment and extubation were significantly related to residual block. In a more recent study, Fortier and colleagues[31] (2015) investigated the incidence of residual block in the recovery room in 302 patients, 99% of whom received rocuronium and 72% received neostigmine. Using qualitative neuromuscular monitoring only, the incidence of residual block was 56%.

## Postoperative pulmonary complications

It has long been recognized that incomplete recovery from neuromuscular block is associated with postoperative respiratory failure. In a 1978 report on perioperative mortality in South Africa,[32] anaesthesia was considered to be responsible for 2.2% of perioperative deaths. After hypovolaemia, respiratory inadequacy following myoneural blockade was the second most common cause of anaesthetic death. It was thought to cause over 19% of the fatalities. Lunn and colleagues[33] demonstrated that respiratory failure was a contributing factor in at least 11 out of 32 anaesthetic-related deaths that occurred in the UK in 1981. Six of the fatal outcomes were associated with postoperative residual curarization. Cooper and colleagues[34] investigated anaesthesia-related complications leading to admission to an intensive care unit. Nearly half of the cases were associated with incomplete neuromuscular recovery. A survey in France in 1986 into the causes of anaesthetic-related deaths found that half of the 65 deaths were attributed to postoperative respiratory depression. Incomplete recovery from neuromuscular block was one of the main causalities.[35]

In 1997, Berg and colleagues[36] demonstrated that, if the TOFR was $<0.7$ in the recovery room in patients who had received pancuronium, there was a higher incidence of POPCs than when TOFR had recovered to $>0.7$ (Table 3). The same effect was not detected after use of atracurium and vecuronium. This report has led to extensive research into the incidence of POPCs in patients who had received a NDNMBD during general anaesthesia and the relationship to use of a reversal agent. In a meta-analysis in 2007, Naguib and colleagues[24] also suggested that the incidence of POPCs was significantly lower after use of intermediate- rather than long-acting NDNMBDs.

POPCs are more common in elderly patients.[42] In a prospective study of patients receiving rocuronium, Murphy and colleagues[42] found that 58% of elderly patients aged 70–90 yr had residual block postoperatively compared with 30% of younger patients aged 18–50 yr. Hypoxaemia, POPCs and length of hospital stay were all significantly increased in the elderly patients, and were more common in both groups when residual block had been detected. In elderly patients, however, unlike previous reports, the total dose of rocuronium administered was not related to residual neuromuscular block postoperatively. The causes and management of POPCs have recently been reviewed in detail by Miskovic and Lumb,[43] including commentary on the role of NDNMBDs in its evolution. These authors stressed the need for appropriate management of neuromuscular block in the prevention of POPCs, but acknowledged that the causes were multifactorial. Other events in the recovery room could contribute to development of POPCs such as accumulation of airway secretions and aspiration of gastric contents on tracheal extubation.

## Effect of reversal of residual block on POPCs

In a large retrospective study of the effect of anaesthetic management on perioperative morbidity and mortality in the Netherlands in 2005, Arbous and colleagues[44] demonstrated that lack of reversal of residual block intraoperatively was an independent risk factor for anaesthesia-related 24 h

Table 3 Incidence of postoperative pulmonary complications (POPCs) after use of non-depolarizing neuromuscular blocking drugs (NDNMBDs) and their relationship to the use of reversal with neostigmine. (*P<0.05 compared with TOFR >0.7; n.s.: not significant compared with reversal). TOFR, train-of-four ratio

| | d-Tubocurarine | Pancuronium | Atracurium or Vecuronium | |
|---|---|---|---|---|
| Gray and Halton, 1946[3] | 12.50% | | | |
| Berg and colleagues, 1997[36] | | | | |
| TOFR <0.7 | | 16.9%* | 4.20% | |
| TOFR >0.7 | | 4.80% | 5.40% | |
| | **No NDNMBD** | **NDNMBD** | **Reversal** | **No Reversal** |
| Grosse-Sundrup and colleagues, 2012[37] | | 1.36 | 1.32 | |
| Odds ratios (95% CI) | | (1.23–1.51, P<0.01) | (1.2–1.46) | |
| Sasaki and colleagues, 2014[38] | | | 2.10% | 1.4%, n.s. |
| McLean and colleagues, 2015[39] | | Up to 6.7% | 4.10% | 2.70% |
| Odds ratios (compared with no NDNMBD or no neostigmine) | | 1.28 | 1.19 | |
| (95% CI) | | (1.04–1.57) | (1.03–1.37) | |
| (total incidence POPC: 3.75%: dose-dependent) | | | | |
| Bulka and colleagues, 2016[40] (per 10 000 person-days at risk) | 5.22 | 9.0 | 1.88 | 4.22 |
| Bronsert and colleagues, 2017[41] | 1.40% | 5.70% | 3.60% | 13.50% |

Table 4 Effects of non-depolarizing neuromuscular blocking drugs (NDNMBDs) and reversal on postoperative pulmonary complications (POPCs) and postoperative mortality

| | Risk of POPCs after NDNMBD (compared with no relaxant) | Risk of POPCs after reversal with neostigmine | Risk of POPCs, no reversal agent | Effect on long-term mortality of reversal |
|---|---|---|---|---|
| Arbous and colleagues, 2005[44] | | Decreased | | Decreased |
| Grosse-Sundrup and colleagues, 2012[37] | Increased | Increased | | In-hospital mortality slightly increased |
| McLean and colleagues, 2015[39] | Dose-dependent increase | Dose-dependent increase | | |
| Bulka and colleagues, 2016[40] | Increased | Decreased | Increased | |
| Bronsert and colleagues, 2017[41] | Unchanged | Unchanged | Increased | No effect. Slight increase in 30 day mortality if not reversed |

postoperative morbidity and mortality. These findings were supported by Murphy and colleagues[45] in 2008. They showed that critical respiratory events were significantly more common postoperatively if the TOFR was <0.7 in the recovery room, and that they did not occur if the TOFR was greater than that value. These results have recently been substantiated by a single-centre study from Nashville, TN, USA, which also found that POPCs were less frequent if neostigmine had been used (Table 4).[40] Importantly, this study suggested that POPCs were more common in patients who had received a NDNMBD. From 13 100 cases, 1455 patients who had received an intermediate-acting NDNMBD were propensity score-matched to 1455 who had not. Patients who received a NDNMBD had a higher risk of POPCs (9.0 *vs* 5.2 per 10 000 person-days at risk). Patients who received a NDNMBD but not a reversal agent were 2.3 times more likely to develop POPCs than those who received neostigmine.

In 2017, a multicentre retrospective study of 11 355 adults in five Veterans Administration hospitals in the USA also suggested that use of neostigmine reduces the risk of POPCs. Not administering neostigmine was associated with a 70–75% increase in the odds of respiratory complications. But in this study, in contrast to the Nashville study, the risk of POPCs was not increased in patients who had received NDNMBDs and neostigmine compared with those who had not received a NDNMBD (Table 4).[41] There was a marginal increase in 30 day mortality in patients who did not receive neostigmine but no association with non-respiratory complications or long-term mortality. As these authors noted, they were reporting on a discrete population of mainly elderly, male veterans with multiple comorbidities, and the data were old (2003–8). Clinical practice does change subtly over time. Nevertheless, this report did substantiate many of the earlier reports on the benefits of neostigmine which, with the exception of Arbous and colleagues,[44] were from the USA.

## Questioning the use of neostigmine

By 2012, it was increasingly accepted that, although POPCs were probably more common if a NDNMBD had been given

perioperatively, their incidence was reduced if neostigmine had been used to antagonize residual block. This view was seriously questioned that year in a report from Massachusetts, USA. In a propensity score-matched study, Eikermann's group reported on 57 086 patients who had received either short- or intermediate-acting NDNMBDs (atracurium, mivacurium, vecuronium or rocuronium) or no muscle relaxant perioperatively.[37] Use of these NDNMBDs was associated with an increased risk of postoperative desaturation after tracheal extubation and an increased incidence of tracheal reintubation. These adverse effects were not reduced by use of subjective evaluation of neuromuscular monitoring. The use of neostigmine, in contrast to previous studies, *increased* the incidence of complications. This study was severely criticized,[46] but it strongly indicated the need for large-scale prospective studies of the incidence of POPCs after use of NDNMBDs and their antagonists. It was the first large study to implicate neostigmine in the increased incidence of POPCs. Further work from the same research group in 2014 suggested that neostigmine did not improve oxygenation in the recovery room and was associated with an increased incidence of postoperative atelectasis.[38] These researchers went on to suggest that the association between the use of intermediate-acting NDNMBDs and POPCs was dose-dependent. McLean and colleagues[39] suggested that the same relationship also existed between neostigmine and an increase in POPCs. *Post hoc* analysis demonstrated that appropriate use of neostigmine with subjective assessment of the TOF count eliminated the dose-dependent association between use of NDNMBDs and POPCs, however (Table 4). This is an important finding, as it may well be the cause of the wide discrepancies in these studies: it is almost impossible fully to allow for the effects of poor clinical practice on the analyses.

It was also apparent by this time that no large-scale prospective studies had been carried out in Europe to compare with the increasing amount of American data. In 2014, the European Society of Anaesthesiology (ESA) therefore supported a prospective multicentre observational study to investigate the incidence of POPCs in patients who had received a NDNMBD perioperatively across Europe (POPULAR). Data on a control group who did not receive a NDNMBD were also obtained. It was recorded whether an antagonist to residual neuromuscular block had been given, and whether qualitative or quantitative neuromuscular monitoring was used throughout anaesthesia.[47] Postoperative mortality was noted. The initial findings from this study were described at the New York Society of Anesthesiologists Postgraduate Assembly meeting in December 2016 but have not yet been fully reported.

## Limitations of these studies

All of the studies discussed above are limited by the accuracy of the data collection, especially in respect of the use of neuromuscular monitoring and the definition of postoperative pneumonia. Many of them are retrospective. Qualitative monitoring has more commonly been used, with its questionable efficacy in detecting residual neuromuscular block. Postoperative residual neuromuscular block was rarely determined in the recovery room using quantitative monitoring. It is also impossible to account for all confounders such as: overdosing of NDNMBDs; incorrect use of monitoring; the varying doses of opioids administered between patients; and inaccurate interpretation of neuromuscular monitoring. In addition, it is almost impossible to do such studies with patients all undergoing the same operative procedure. Pneumonia is mainly determined by study of the medical records and not on clinical assessment. Milder cases may well have been missed because of a lack of radiographic or laboratory data. Statistical analysis of these large retrospective studies is also challenging. Appropriately, propensity scoring is often used with comparable patients in each group but even this technique varies between studies. The sensitivity or caliper used to ensure these patients are well matched can be of differing accuracy.

## Other antagonists of neuromuscular block

Although anticholinesterases may be considered by clinicians to be ideal drugs for the reversal of residual block, they do have unwanted side-effects, mainly because of their cholinergic effects.[48] As Gray emphasized, they can only be used to reverse residual block when recovery has commenced.[16–18] More recently, attempts have been made to develop more efficacious agents that could reverse profound block when the TOF was undetectable, and even when the PTC only measured 1–2. In addition to the need for safety and efficacy, a topical question in the development of new reversal agents is: do clinicians want an antagonist that reverses all NDNMBDs, or will they accept and utilize specific antagonists for individual muscle relaxants? A limitation of sugammadex is that it only antagonizes block induced by aminosteroidal NDNMBDs.

## Edrophonium

This short-acting anticholinesterase is less potent than neostigmine and can only be used when recovery from block is well established with, for instance, four twitches of the TOF detectable.[48] Its short duration of effect is because of the transient nature of the ionic bond that the drug forms with acetylcholinesterase. It has been successfully used to reverse residual block from mivacurium in both adults and children,[49] but is no longer available in the UK.

## Sugammadex

This encapsulating agent, a $\gamma$ cyclodextrin, became available for use in the UK in 2008. It was designed to encapsulate molecules of the aminosteroidal neuromuscular blocking drug, rocuronium, in a 1:1 ratio.[50] It is a cyclodextrin consisting of eight oligosaccharides attached by $\alpha$ 1–4 linkages into a circular arrangement to create a hollow toroid. A toroid is a geometric figure that can rotate around its axis without crossing the axis path. Cyclodextrins are hydrophilic on the outer surface because of tails of negatively charged hydroxyl groups and lipophilic on the inner surface. Lipophilic substances such as aminosteroidal NDNMBDs are encapsulated into the toroid,[15] where they are tightly held as a result of a combination of van der Waals forces and charge transfer.[15 50] The affinity of sugammadex for rocuronium is comparable with the affinity of acetylcholine for the postsynaptic nicotinic receptor ($10^7\,M^{-1}$). Sugammadex has slightly less affinity for vecuronium.[51] The affinity or association constant of rocuronium and sugammadex in commercial batches is $25\times10^6\,M^{-1}$, and for vecuronium and sugammadex is $10\times10^6\,M^{-1}$.[50] Sugammadex has also been shown in clinical studies to reverse pancuronium[52] and pipecuronium, albeit less efficaciously.[53] Recovery of the TOFR to 0.9 after sugammadex 2.0 mg $kg^{-1}$ given at recovery of T2 takes about 5 min with these longer-acting NDNMBDs. The

encapsulated complex is excreted entirely in the urine. It has a plasma clearance of 91 ml $min^{-1}$, which is equivalent to the glomerular filtration rate.[54] As yet, there is no evidence of an altered effect of sugammadex in patients with end-stage renal failure but the drug is not recommended for use in these patients on its data sheet. As sugammadex has no effect on acetylcholinesterase, co-administration of anticholinergic agents is not required.

## Reversal of neuromuscular block

In contrast to neostigmine, sugammadex in appropriate doses can reverse profound block produced by aminosteroidal agents.[9] Sugammadex 2 mg $kg^{-1}$ rapidly reverses moderate neuromuscular block from rocuronium (recovery of T1/T0 to 0.2) within 2 min,[8] which is much quicker than the action of neostigmine (Table 1). Profound neuromuscular block when the TOF is undetectable and only a post-tetanic count of 1–2 can be elicited can be reversed with sugammadex 4–8 mg $kg^{-1}$ (Table 1).[9] Neostigmine is ineffectual at this degree of neuromuscular block (Table 2). This technique is proving to be useful during major laparoscopic procedures, providing good surgical access throughout anaesthesia with rapid recovery from residual block.[55] Recently, such benefits have been questioned in obese patients undergoing laparoscopic bariatric procedures. In a small study comparing surgical conditions during deep neuromuscular block compared with moderate neuromuscular block, no difference was found, and pulmonary function was substantially impaired in both groups postoperatively.[56] However, a meta-analysis and systematic review of 12 studies has recently substantiated the benefits of deep neuromuscular block, which improves surgical conditions, although not substantially, and facilitates use of a low-pressure peritoneum, which is probably the reason for lower pain scores postoperatively.[57]

Larger doses of sugammadex up to 16 mg $kg^{-1}$ can reverse block immediately after administration of rocuronium.[10] This approach could be advantageous in a 'cannot intubate, cannot ventilate' scenario, but it has impracticalities. In an adult, it may require several ampoules of the drug to be drawn up, which has time limitations. Other anaesthetic agents such as benzodiazepines and opioids would also need to be antagonized to allow the patient to adequately breathe spontaneously.

There are few clinical trials reported in the English language of the use of sugammadex in children, which have been reviewed recently by Tobias.[58] Only a dose of 2 mg $kg^{-1}$ to reverse moderate neuromuscular block is recommended on the sugammadex data sheet for use in paediatric practice in the UK, and the drug does not yet have approval in this country for use in neonates.

## Residual block

The incidence of residual neuromuscular block in the recovery room is much lower if sugammadex rather than neostigmine has been used.[59] In a prospective study, Brueckmann and colleagues[59] found that none of the 74 patients given sugammadex had TOFR <0.9 on admission to the recovery room. In contrast, 33 out of 76 (43%) patients given neostigmine did. Cammu and colleagues[60] reported similar findings in 2012. In a study of 624 patients, 15% of those who received no reversal agent developed residual block (TOFR <0.9) as did 15% of those who received neostigmine. Only one of the 44 patients who received sugammadex had residual block. Gaszynski and colleagues[61] reported a lower incidence of residual curarization in morbidly obese patients (BMI >40 kg $m^{-2}$) given sugammadex 2 mg $kg^{-1}$ to reverse moderate block (TOF count=2) compared with a similar group given neostigmine 0.05 mg $kg^{-1}$. It is as essential that neuromuscular block is monitored when sugammadex as well as neostigmine is used, as residual block will otherwise be a risk.[62] Kotake and colleagues,[62] in an observational study, reported that the incidence of a TOFR <0.9 after extubation was 24% after neostigmine and 4.3% after sugammadex if routine clinical practice without neuromuscular monitoring was used. Uncalibrated acceleromyography was used in the recovery room to determine the TOFR. As yet, there is no evidence that the incidence of POPCs is lower after use of sugammadex rather than an anticholinesterase. Ledowski and colleagues[63] showed that postoperative nausea and vomiting were less after sugammadex than neostigmine but the evidence for sugammadex decreasing the incidence of POPCs was weak and mainly related to elderly patients. Ultimately, whatever the anaesthetic technique, if the TOFR = 1.0 is determined before tracheal extubation, then residual block will not be encountered.

## Low doses of sugammadex

Doses lower than those recommended in the data sheet have been used to reverse residual block produced by rocuronium during the later stages of recovery.[64] Schaller and colleagues[64] showed that only sugammadex 0.22 mg $kg^{-1}$ was required to reverse residual block at a TOFR of 0.5, with a similar recovery profile to neostigmine 0.034 mg $kg^{-1}$. Kaufhold and colleagues[65] used small doses of sugammadex to effectively reverse moderate block produced by rocuronium. Sugammadex 0.49 and 0.26 mg $kg^{-1}$ induced recovery of TOFR to >0.9 within 5 and 10 min of administration at a TOFR of 0.2. Although faster in action than neostigmine, these slower rates of recovery detract from the benefits of sugammadex over neostigmine in reversing residual neuromuscular block. Baumuller and colleagues[66] administered sugammadex 1 mg $kg^{-1}$ at a TOFR of 0.9 in conscious patients in the recovery room and compared the effect on voluntary grip strength and fine motor function to a placebo group. They found a minimal beneficial effect on these recovery characteristics from sugammadex at this late stage of recovery. In both groups there was some improvement in grip strength and motor function but they did not return to preoperative baseline values.[66] These findings could have been a result of the ongoing spontaneous recovery from the NDNMBD. Care must be taken if lower doses of sugammadex are used often in an effort to reduce cost. Quantitative monitoring is essential throughout. Eleveld and colleagues[67] noted a transient decrease in the height of T1 and the TOFR after reversal of rocuronium 0.9 mg $kg^{-1}$ with sugammadex 0.5 mg $kg^{-1}$ administered 42 min later at a post-tetanic count of 1. The TOFR subsequently recovered to 0.9, 60 min later, with no adverse effect, but such practice is unacceptable.

## Side-effects

Although sugammadex has been shown *in vitro* to encapsulate other steroidal compounds, both endogenous and exogenous, such as oestrogen-type compounds, flucloxacillin and antifungal agents, there is no evidence of this phenomenon being of relevance *in vivo*.[68] In the sugammadex data sheet, however, it is advised that additional contraception is required for 7 days after the administration of sugammadex if a hormonal

contraceptive is being used. Large doses of sugammadex have been associated with hypotension and prolongation of the Q–T interval of the ECG but the clinical significance of these findings is limited.[69] There has also been an indication from volunteer studies of increases in blood clotting times after sugammadex, but this has not been reported in clinical studies.[69] There is evidence from a study in rats that sugammadex has less effect on upper airway dilator activity than neostigmine, which should have an advantageous effect in reducing POPCs.[70] Neostigmine after complete recovery of T4/T1 following rocuronium decreased upper airway dilator muscle activity to 30% of baseline and decreased tidal volume, but sugammadex had no effect on either variable in this small animal study. In clinical practice in the UK, the much higher price of sugammadex than neostigmine has been a limiting factor in its clinical use, together with the fact that it only reverses aminosteroidal NMBAs.

*Anaphylactic reactions* to sugammadex have, somewhat surprisingly for a dextrin compound, been reported albeit rarely.[71] The occasional occurrence of histaminoid reactions in conscious volunteers delayed approval of the drug by the FDA in the USA until 2015. It is interesting that, in contrast, sugammadex has been used to treat anaphylaxis to rocuronium when first-line management with epinephrine and metaraminol has failed,[72] although this indication is not recommended on its data sheet.

## CW002 and cysteine

In an attempt to develop a NDNMBD with a rapid onset and a short duration of action that does not cause histamine release or other autonomic effects, Savarese and colleagues have reported the clinical pharmacology of CW002, a fumarate belonging to a family of tetrahydroisoquinolinium compounds.[73] This drug is degraded in the plasma by endogenous L-cysteine.[11] In doses of 1.8 × $ED_{95}$, it has a mean onset of action of 200 s in humans.[73] Clinical duration of action is about 34 min, which is similar to atracurium and vecuronium. This early report of its use in healthy patients suggests that CW002 does not release histamine and has few autonomic effects in the normal dose range.[73] Profound block from CW002 can be reversed with exogenous cysteine (Table 1). CW002 is not yet available for clinical use. Consideration is being given to commercial production of cysteine, which is already available for use in parenteral nutrition, to reverse profound block induced by CW002.

## Calabadion 1 and 2

In an attempt to develop a reversal agent that was an efficacious antagonist to both benzylisoquinolinium and aminosteroidal NDNMBDs, animal studies have been reported of the actions of calabadion 1 and 2.[74 75] These drugs are acyclic members of the cucurbituril family of molecular containers with the potential to form host–guest complexes with NDNMBDs, comparable with the encapsulation of rocuronium by sugammadex. Early studies in rats suggest that to variable extents, these drugs will reverse both rocuronium and cisatracurium. Calabadion 1 reverses rocuronium, vecuronium and cisatracurium, although its *in vitro* binding affinity for rocuronium is less than the affinity of sugammadex for rocuronium. Calabadion 2 rapidly reverses profound block from rocuronium, vecuronium and cisatracurium in a dose-dependent manner. The antagonism of rocuronium is more rapid than that produced by sugammadex in this animal model.

## Conclusions

Despite the routine use of neostigmine to reverse residual neuromuscular block for over 60 yr, data are accumulating to suggest that use of this anticholinesterase is associated with an increased incidence of POPCs, largely from one research group in the USA. Not all reports support these findings and it is difficult accurately to interpret the conflicting data (Tables 3 and 4). POPCs are certainly thought to be more frequent if a NDNMBD is used during anaesthesia but it is difficult to ascertain whether poor standards of clinical practice are responsible for these findings. If excessive doses of NDNMBDs are used, and if neuromuscular monitoring is not carried out or is not interpreted correctly, then these factors could confound the research findings, as could an inaccurate diagnosis of pneumonia. Certainly, there has been little improvement in the incidence of POPCs over 70 yr (Table 3). It is still advised that quantitative neuromuscular monitoring is carried out whenever a NDNMBD is given, that a reversal agent is used unless full recovery from block has been established (Table 2), and that the TOFR should reach 0.9 before tracheal extubation. Guidelines have been well described for good practice in this respect.[76] As Naguib, Dexter and Brull[77] have recently commented, further large scale prospective studies are required to try and elucidate these vexatious questions.

## Declaration of interest

J.M.H. has received funding from MSD in the last five years to give national and international lectures, and to chair CME symposia.

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