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Clinical Practice

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