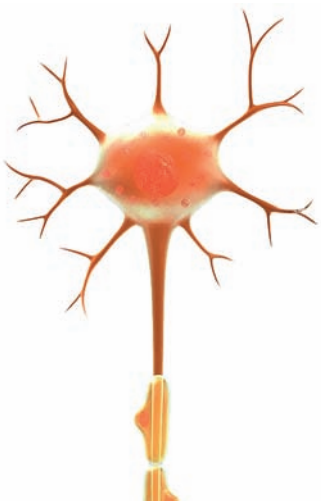
Deep neuromuscular blockade and neuromuscular reversal : applications and implications

Boon, M.

Chapter 1

Introduction and thesis outline



EVOLUTION OF NEUROMUSCULAR BLOCKADE IN ANAESTHESIA: FROM CURARE TO SUGAMMADEX

General anaesthesia is a pharmacologically induced state of the body that is characterized by unconsciousness (hypnosis), pain relief (analgesia) and muscle relaxation (paralysis). It allows patients to endure invasive surgical procedures without cognition and pain perception. Every pharmacologic component of anaesthesia is essential for success. Hypnosis and analgesia are induced by agents that depress the central nervous system at various levels. They prevent somatic and cognitive arousal and suppress the sympathetic response to painful (surgical) stimuli. The combination of both agents is sufficient to induce and maintain general anaesthesia; however they do not fully depress all motor reflexes in every circumstance.[1, 2] For example, even during adequate general anaesthesia, high intensity (surgical) stimuli can trigger reflexes that result in sudden movement of a patient. The addition of muscle relaxants to general anaesthesia prevents these sudden movements and ensures an immobile patient throughout a procedure.

The use of muscle relaxation as a routine part of general anaesthesia has historically not been an easy matter of course. The first muscle relaxing agents were direct derivatives of an agent called *curare*. Curare is naturally present in the jungle plants of the *Chondodendron* and *Strychnos* genus. Curare's deadly characteristics were long known by jungle tribes, who used it as a poison on their hunting arrows. Curare induces a flaccid paralysis of all skeletal muscles by blocking the signal transmission from the nerve-end to the muscle at the neuromuscular junction. This eventually causes death by respiratory arrest. Curare only exerts its muscle relaxing properties when it directly enters the bloodstream and is harmless when it is ingested by mouth. Hunted animals were therefore safe for consumption. Colonial expansion eventually brought curare to the attention of western scientists.[3] Experiments with curare began in the mid-1800 and were led by important discoveries on neuromuscular transmission by Claude Bernard and others.[4] Interestingly, these experiments took place at the same time ether and nitrous oxide inhalation anaesthesia became known.[5, 6] However, in contrast to the rapid adoption of these hypnotic agents, it would take nearly a 100 years longer for muscle relaxants to become a part of anaesthesia.

In 1942, Harold Griffith and Enid Johnson were the first to use a muscle relaxant (Intocostrin) during general anaesthesia.[7] They sought a way to provide optimal surgical working conditions during abdominal surgery by ensuring an immobile patient. At that time, the only way to ensure an immobile patient during surgery was to use high doses of anaesthetic agents to maintain a deep level of general anaesthesia. Deep anaesthesia,

although applicable, comes with a variety of disadvantages, most notably prolonged recovery times and hemodynamic collapse. Muscle relaxation allowed for a reduction in the depth of general anaesthesia, whilst maintaining an immobile patient and ensuring good surgical working conditions. Four main purposes for the use of muscle relaxants during general anaesthesia were recognized by that time[8]:

To provide muscular relaxation required for abdominal surgery
To facilitate respiratory control during thoracic procedures
To ensure freedom of laryngospasm
To reduce the amount of anaesthetic agents in whilst achieving the previous

The pioneering work of dr. T.C. Gray and others further shaped the technique of "light anaesthesia" with muscle relaxation and the control of respiration. This laid the basis of the well-known Liverpool anaesthetic technique.[9, 10] However, the increasing use of muscle relaxants soon unfolded major concerns. In 1954, Beecher and co-workers reported a six fold increase in anaesthesia related mortality in cases were muscle relaxants were used.[11] This association was noted in the period *after* anaesthesia and surgery had ended (*i.e.* the postoperative period). Incomplete recovery of neuromuscular block (NMB) after anaesthesia has ended (known as *postoperative residual curarization*) causes persistent general muscle weakness in the early postoperative period. This condition interferes with normal breathing and is strongly associated with adverse respiratory events in the recovery ward.[12] Postoperative residual curarization remains a common problem, even in the present day. Despite the availability of neuromuscular monitoring devices and reversal agents, incidences of 40-60% have been reported consistently in the literature over the last decades.[13]

From a pharmacological view, the potential for postoperative residual curarization to occur is evident. The paralyzing effect of muscle relaxants last much longer than the effects of the hypnotic agents. For instance, an induction dose of rocuronium, a commonly used muscle relaxant with an intermediate duration, has an average recovery time of 50-60 minutes.[14] In contrast, the time for a patient to awake after termination of a propofol and remifentanil infusion (a commonly used hypnotic and analgesic agent respectively) is less than 10 minutes.[15] In addition, the recovery time of muscle relaxants is unpredictable and displays a large variation between patients.[16] The use of muscle relaxants always bears a risk of incomplete recovery and the only way to fully preclude residual curarization is objective measurement of the level of neuromuscular block at the end of anaesthesia.

Neuromuscular monitoring is one of the corner stones to prevent residual curarization. Currently, multiple commercially available neuromuscular monitoring devices are avail-

able. In this thesis, *acceleromyography* of the adductor pollicis muscle (device: TOF watch SX, Organon, the Netherlands) or *compressomyography* of the biceps muscle (device: TOF cuff, RGB medical devices, Spain) were used. All these devices work by the same principle: a peripheral nerve is stimulated by a low voltage current, which evokes a contraction in a nearby muscle (see fig. 1 for schematic setup of the TOF watch). The magnitude of the evoked muscle contraction reflects the level of neuromuscular blockade. Several distinct stimulation modes exist, of which *train-of-four* and *post-tetanic-count* are the most common.[17, 18] *Train-of-four* (TOF) stimulation is used to assess shallow and moderate levels of neuromuscular bock. A train-of-four consists of four short electrical stimuli which evoke four short muscle contractions (*twitches*). With increasing level of neuromuscular block, the twitches will first reduce in strength and will eventually disappear.[18] In addition, the ratio of the fourth twitch relative to the first twitch (*TOF ratio*) has to be recovered to at least 0.9 or 90% before the end of anaesthesia, to ensure that muscle strength is adequate. . Any TOF ratio below 0.9 is called residual curarization by definition and poses patients at risk for postoperative respiratory complications.[19-21]

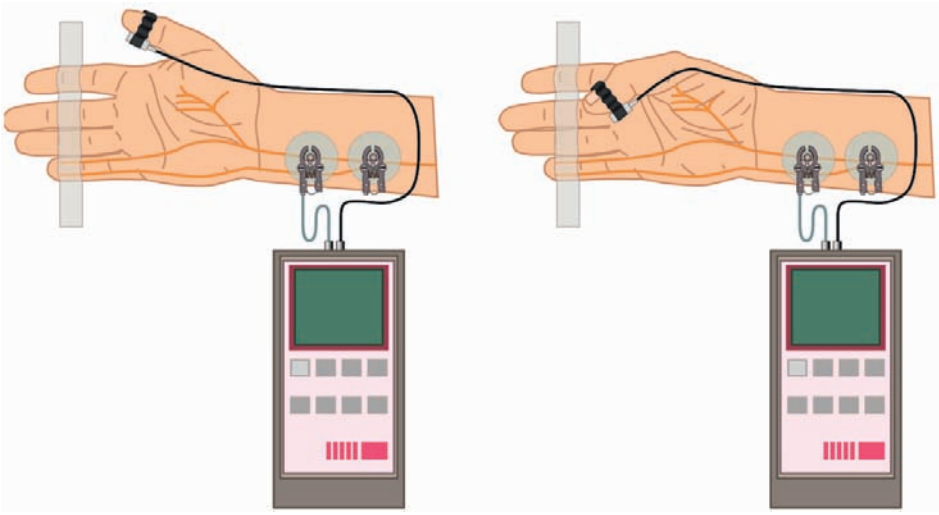


Figure 1: Schematic setup of the TOF watch at the adductor pollicis muscle. Two electrodes are placed adjacent to the ulnar nerve. A current of 30-60 mA administered at the ulnar nerve will evoke a muscle contraction of the adductor pollicis muscle at the base of the thumb. A piezoelectric sensor placed at the distal end of the thumb records the acceleration of the thumb that is caused by the muscle contraction. The magnitude of the acceleration is a reflection of the level of neuromuscular block.

During a deep neuromuscular block, the train-of-four will not yield any muscle responses (*i.e.* TOF = 0 twitches). In this instance, the *post-tetanic-count* (PTC) method can be used to determine the exact depth of neuromuscular block. The post-tetanic-count method differs from the train-of-four method in that this stimulation mode begins with

a prolonged current on the nerve (tetanic stimulus, 50Hz for 5 seconds). This results in a massive pre-synaptic release of acetylcholine in the neuromuscular junction. Acetylcholine is the neurotransmitter that is primarily responsible for signal transmission between a nerve end and a muscle fiber. The acetylcholine excess will exist for a short period of time, before it is broken down by the enzyme acetylcholinesterase. During this period, neuromuscular signal transmission is temporarily enhanced, so that 10 to 20 short stimuli following the tetanic stimulus may evoke muscle responses during a deep neuromuscular block. The number of detectable twitches add up to form the *post-tetanic-count*.[17] In this thesis, a deep neuromuscular block is defined as a *post-tetanic-count* of 1 to 2 twitches; a moderate neuromuscular block is defined as a *train-of-four count* of 1 to 3 twitches (see fig. 2). Further reading about depth of neuromuscular block can be found in chapter 7.

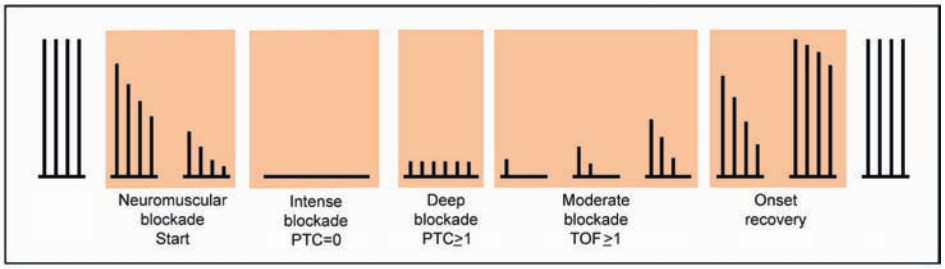


Figure 2: Schematic illustration of depths of neuromuscular block. The vertical bars represent the twitches of the thumb evoked by either TOF or PTC stimulation. The figure shows, from left to right, the typical course neuromuscular block (NMB) after a single administration of muscle relaxant. In the first orange square, the twitches of the train-of-four disappear after the administration of a muscle relaxant. As the NMB deepens in the first minutes after administration, all twitches of the TOF and PTC disappear (second square), leading to an intense NMB. When the muscle relaxant starts to wear off, the twitches return, first in the PTC (third square) and later on in the TOF (fourth and fifth square). Eventually, as the NMB has completely recovered, the twitches in the train-of-four will again have equal strength. TOF= train-of-four; PTC = post-tetanic-count.

Neuromuscular monitoring has proven to be essential in reducing the incidence of postoperative residual curarization,[22-24] but other strategies exist. One of these strategies is to *reverse* any residual neuromuscular block before the end of anaesthesia. Neuromuscular reversal may be of equal importance as neuromuscular monitoring and in practice these strategies go hand in hand. Reversal techniques are aimed to significantly speed up the recovery of neuromuscular block. Traditionally, this is achieved with the use of an acetylcholinesterase inhibitor (*e.g.* neostigmine). These agents reduce the breakdown of acetylcholine in the neuromuscular junction, resulting in enhanced neuromuscular signal transmission and competitive antagonism with the neuromuscular blocking agent.[25] However, acetylcholinesterase inhibitors have important intrinsic limitations. Reversal with these agents is often lengthy or incomplete and they cannot be used for reversal

of deep neuromuscular block.[26] Consequently, acetylcholinesterase inhibitors should be dosed well in anticipation of surgery-end and exclusively for reversal of shallow levels of neuromuscular block.[27] Inappropriate use of acetylcholinesterase inhibitors still yields a high incidence of residual curarization and the associated respiratory complications.[28]

To reduce the risk for residual curarization, the depth of the neuromuscular block *during* anaesthesia is often maintained at a shallow or moderate level to ensure prompt spontaneous recovery or easy reversal with an acetylcholinesterase inhibitor. In addition, a moderate depth of neuromuscular block is generally considered to be sufficient for abdominal muscle relaxation, ensuring good operating conditions (*i.e.* a *"surgical block")*. However, due to the evolution of surgical procedures from open to minimal invasive (laparoscopic) approaches, a moderate NMB may not be sufficient to maintain good surgical working conditions. To understand this, two things are important to realize. First, in laparoscopic surgery, space is often limited and muscle contractions can severely hamper the surgeon. Second, these muscle contractions can happen during a moderate NMB because the abdominal muscles and diaphragm are more resistant to muscle relaxants than other muscles in the body and require a larger dose to become fully paralyzed.[29-31] In practice, this means that a deep NMB must be applied to fully relax all these muscles.[1, 2, 30] Until recently, the application of a deep NMB was very unpractical for routine use. As a deep NMB cannot be reversed with acetylcholinesterase inhibitors, it came with very long recovery times and a high risk of postoperative residual curarization. The introduction of sugammadex, a novel, selective reversal agent, took away these disadvantages.

Sugammadex reversal is based on a new reversal principle, which substantially differs to the reversal principle of acetylcholinesterase inhibitors. Sugammadex is a modified, cyclic sugar molecule (y-cyclodextrin), which is able to *encapsulate* molecules of neuromuscular blocking agents with a steroidal structure (rocuronium, vecuronium and pancuronium).[32] Encapsulation renders the muscle relaxant molecules unable to exert their effect and quickly terminates the muscle relaxing effect. The encapsulation process takes place in the plasma, happens on a 1 to 1 basis (*i.e.* 1 molecule sugammadex encapsulates 1 molecule rocuronium) and is irreversible (see fig. 3). Unlike acetylcholinesterase inhibitors, sugammadex is able to completely reverse a deep neuromuscular block in a very short period of time.[33-35]

Sugammadex has opened the door for clinical application of deep neuromuscular block during general anaesthesia. The use of deep neuromuscular blockade may improve surgical working conditions over a standard (moderate) neuromuscular block during laparoscopic procedures. Especially in laparoscopic retroperitoneal prostatic and renal surgery, where space is very limited, surgical working conditions may largely depend

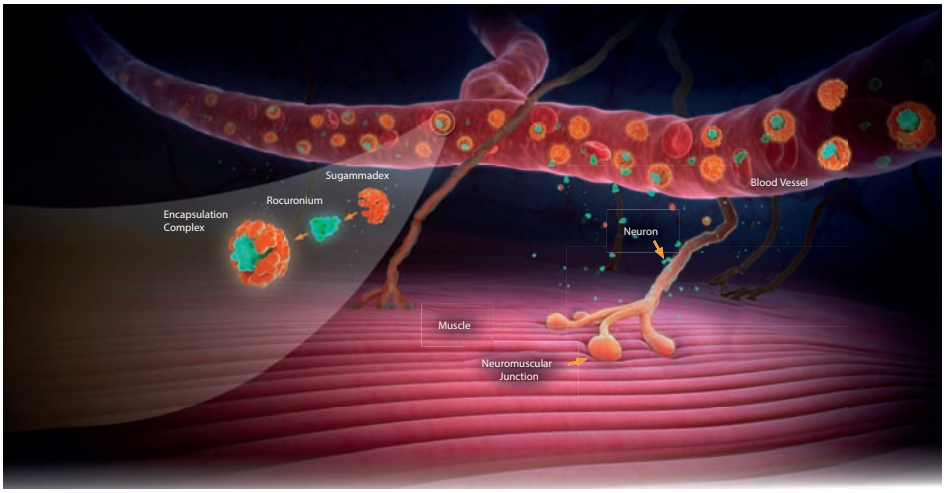


Figure 3. Schematic illustration of neuromuscular transmission at the neuromuscular junction and the encapsulation of rocuronium by sugammadex in the blood plasma. Courtesy of MSD, not authorized for reproduction.

on a deep neuromuscular block. In addition, the intensity of sugammadex reversal compared to neostigmine reversal may reduce the occurrence of postoperative residual curarization. In this thesis, these two hypotheses were tested. Additionally, the effect of deep neuromuscular block and reversal of neuromuscular block with sugammadex on postoperative outcomes was assessed.

THESIS OUTLINE

This thesis is divided in four subsections.
Section 1 presents two prospective studies about the effect of deep neuromuscular block on surgical conditions during laparoscopic retroperitoneal surgery (chapters 2 and 3).

The effect of deep neuromuscular block and of sugammadex reversal on postoperative outcome is presented in *section 2* (chapters 4 and 5).

The methods and use of surgical rating scales in laparoscopic surgery are discussed in *section 3* (chapter 6).

Section 4 presents an overview of recent literature and places the results of this thesis in perspective (chapter 7). Finally, conclusions and applications and implications of the results of this thesis are presented in chapter 8.

REFERENCES

1 Fernando PU, Viby-Mogensen J, Bonsu AK, Tamilarasan A, Muchhal KK, Lambourne A. Relationship between posttetanic count and response to carinal stimulation during vecuronium-induced neuromuscular blockade. Acta anaesthesiologica Scandinavica 1987; 31: 593-6

2 Werba A, Klezl M, Schramm W, et al. The level of neuromuscular block needed to suppress diaphragmatic movement during tracheal suction in patients with raised intracranial pressure: a study with vecuronium and atracurium. Anaesthesia 1993; 48: 301-3

3 Raghavendra T. Neuromuscular blocking drugs: discovery and development. Journal of the Royal Society of Medicine 2002; 95: 363-7

4 Bernard MC. Lecons sur les effets des substances toxiques et medicamenteuses. Cours du medicine du college de France 1857: 311-25

5 Wells JG. A history of the discovery of the application of nitrous oxide gas, ether and other vapors, to surgical operations. Hartford, Conneticut. 1847

6 Bigelow HJ. Insensibility during surgical operations produced by inhalation. Boston Medical Journal 1846; 35: 309-17

7 Griffith HR JG. The use of curare in general anesthesia. Anesthesiology 1942; 3: 418-20

8 Gray TC. The Use of D-Tubocurarine Chloride in Anaesthesia: Lecture delivered at The Royal College of Surgeons of England on 17th April, 1947. Ann R Coll Surg Engl 1947; 1: 191-203

9 Gray TC, Halton J. A milestone in anaesthesia? (d-tubocurarine chloride). Proc R Soc Med 1946; 39: 400-10

10 Gray TC, Halton J. Technique for the use of d-tubocurarine chloride with balanced anaesthesia. Br Med J 1946; 2: 293-5

11 Beecher HK, Todd DP. A study of the deaths associated with anesthesia and surgery: based on a study of 599, 548 anesthesias in ten institutions 1948-1952, inclusive. Annals of surgery 1954; 140: 2-35

12 Berg H, Roed J, Viby-Mogensen J, et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. Acta anaesthesiologica Scandinavica 1997; 41: 1095-103

13 Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. Anesth Analg 2010; 111: 120-8

14 Cooper RA, Mirakhur RK, Maddineni VR. Neuromuscular effects of rocuronium bromide (Org 9426) during fentanyl and halothane anaesthesia. Anaesthesia 1993; 48: 103-5

15 Vuyk J, Mertens MJ, Olofsen E, Burm AG, Bovill JG. Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. Anesthesiology 1997; 87: 1549-62

16 Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology 2003; 98: 1042-8

17 Viby-Mogensen J, Howardy-Hansen P, Chraemmer-Jorgensen B, Ording H, Engbaek J, Nielsen A. Posttetanic count (PTC): a new method of evaluating an intense nondepolarizing neuromuscular blockade. Anesthesiology 1981; 55: 458-61

18 Ali HH, Utting JE, Nightingale DA, Gray C. Quantitative assessment of residual curarization in humans. Br J Anaesth 1970; 42: 802-3

19 Eriksson LI, Lennmarken C, Wyon N, Johnson A. Attenuated ventilatory response to hypoxaemia at vecuronium-induced partial neuromuscular block. Acta anaesthesiologica Scandinavica 1992; 36: 710-5
20 Eriksson LI, Sato M, Severinghaus JW. Effect of a vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. Anesthesiology 1993; 78: 693-9
21 Eriksson LI, Sundman E, Olsson R, et al. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. Anesthesiology 1997; 87: 1035-43
22 Gatke MR, Viby-Mogensen J, Rosenstock C, Jensen FS, Skovgaard LT. Postoperative muscle paralysis after rocuronium: less residual block when acceleromyography is used. Acta anaesthesiologica Scandinavica 2002; 46: 207-13
23 Baillard C, Clec'h C, Catineau J, et al. Postoperative residual neuromuscular block: a survey of management. Br J Anaesth 2005; 95: 622-6
24 Todd MM, Hindman BJ, King BJ. The implementation of quantitative electromyographic neuromuscular monitoring in an academic anesthesia department. Anesth Analg 2014; 119: 323-31
25 Katz RL. Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. Anesthesiology 1967; 28: 327-36
26 Morita T, Kurosaki D, Tsukagoshi H, Shimada H, Sato H, Goto F. Factors affecting neostigmine reversal of vecuronium block during sevoflurane anaesthesia. Anaesthesia 1997; 52: 538-43
27 Brull SJ, Murphy GS. Residual neuromuscular block: lessons unlearned. Part II: methods to reduce the risk of residual weakness. Anesth Analg 2010; 111: 129-40
28 Sasaki N, Meyer MJ, Malviya SA, et al. Effects of neostigmine reversal of nondepolarizing neuromuscular blocking agents on postoperative respiratory outcomes: a prospective study. Anesthesiology 2014; 121: 959-68
29 Hemmerling TM, Donati F. Neuromuscular blockade at the larynx, the diaphragm and the corrugator supercilii muscle: a review. Can J Anaesth 2003; 50: 779-94
30 Kirov K, Motamed C, Dhonneur G. Differential sensitivity of abdominal muscles and the diaphragm to mivacurium: an electromyographic study. Anesthesiology 2001; 95: 1323-8
31 Donati F, Antzaka C, Bevan DR. Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. Anesthesiology 1986; 65: 1-5
32 Bom A, Bradley M, Cameron K, et al. A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. Angew Chem Int Ed Engl 2002; 41: 266-70
33 de Boer HD, Driessen JJ, Marcus MA, Kerkkamp H, Heeringa M, Klimek M. Reversal of rocuronium-induced (1.2 mg/kg) profound neuromuscular block by sugammadex: a multicenter, dose-finding and safety study. Anesthesiology 2007; 107: 239-44
34 Puhringer FK, Rex C, Sielenkamper AW, et al. Reversal of profound, high-dose rocuronium-induced neuromuscular blockade by sugammadex at two different time points: an international, multicenter, randomized, dose-finding, safety assessor-blinded, phase II trial. Anesthesiology 2008; 109: 188-97
35 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