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COMPARISON BETWEEN THE EFFICACY OF NEOSTIGMINE VERSUS SUGAMMADEX REVERSAL OF ROCURONIUM INDUCED NEUROMUSCULAR BLOCKADE IN PAEDIATRIC PATIENTS

By

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ABBREVIATIONS

ASA	American Society Of Anaesthesiologists
BP	Blood pressure
CI	Confidence interval
CMR	Closed manual reduction
DBP	Diastolic blood pressure
DBS	Double burst stimulation
EUA	Examination under anaesthesia
FB	Foreign body
HR	Heart rate
HUSM	Hospital Universiti Sains Malaysia
Hz	Hertz
kg	kilogram
LN	Lymph node
MAP	Mean arterial pressure
MD	Mean difference
mg	miligram
ml	mililitre
ms	miliseconds

n	Sample size
NMBAs	Neuromuscular blocking agents
PTC	Post-Tetanic Count
s	Seconds
SBP	Systolic blood pressure
SD	Standard deviation
SPO2	Pulse oxymetry saturation of oxygen
TOF	Train-of-four
T&S	Toilette and suturing
USM	Universiti Sains Malaysia
WD	Wound debridement

ABSTRAK

PERBANDINGAN ANTARA KEBERKESANAN NEOSTIGMINE DAN SUGAMMADEX DALAM PEMBALIKAN SEMULA KESAN RELAXAN OTOT DAN SARAF DISEBABKAN ROCURONIUM DALAM KALANGAN PESAKIT KANAK-KANAK

Pengenalan : Pesakit yang diberikan bius penuh (bius am) dengan ubat relaxan kerap kali diberikan ubat untuk mengembalikan fungsi otot dan saraf pada akhir pembedahan sebelum pesakit diekstubasi. Ubat neostigmine yang telah digunakan bertahun-tahun dalam amalan seharian anestesia menyebabkan kesan sampingan yang kurang menyenangkan pada pesakit. Sugammadex, ubat baru yang telah diperkenalkan dalam dekad yang lepas, menentang secara khusus tindakan ubat relaxan 'non-depolarizing neuromuscular blocking agents (NMBA)' kumpulan 'aminosteroidal'.

Objektif : Tujuan kajian ini adalah untuk membandingkan masa yang diambil untuk mengembalikan fungsi otot dan saraf, kestabilan hemodinamik dan kesan sampingan antara dua agen ini dalam menentang tindakan rocuronium (sejenis ubat relaxan NMBA kumpulan 'aminosteroidal') dalam populasi kanak-kanak.

Metodologi : Kajian ini berbentuk prospektif, 'double-blinded', 'randomized controlled trial' melibatkan 80 pesakit kanak-kanak berumur 2-12 tahun, yang

dijadualkan untuk menjalani pembedahan dengan pembiusan am (bius penuh), menggunakan ubat relaxan rocuronium. Pesakit-pesakit ini telah dibahagikan secara rawak kepada 2 kumpulan, di mana 40 pesakit menerima ubat neostigmine dan 40 pesakit menerima ubat sugammadex untuk membalikkan semula kesan relaxan rocuronium ke atas otot dan saraf. Semua pesakit diberikan gas sedutan bius sevoflurane, kemudian diletakkan branula saiz berpatutan. 2mcg/kg fentanyl diberikan dan TOF Watch Sx dipasangkan di tangan pesakit untuk mengukur tindakbalas ibu jari (otot adductor policis) melalui saraf ulnar. Seterusnya, TOF Watch Sx dikalibrasi dan bacaan diambil. 0.6mg/kg rocuronium diberikan dan intubasi trakea dilalukan apabila TOF kurang dari 1. Bacaan TOF dikekalkan 2 hingga 3 sepanjang pembedahan dengan memberikan 0.2mg/kg rocuronium jika TOF lebih dari 3. Bacaan parameter hemodinamik sebelum dan selepas pemberian neostigmine atau sugammadex diambil dan dicatatkan. Masa yang diambil untuk mencapai bacaan nisbah TOF 0.9 dari bacaan TOF 2 atau 3 setelah pesakit diberikan neostigmine atau sugammadex dicatatkan. Sebarang komplikasi yang dialami oleh pesakit didokumenkan.

Keputusan : Masa yang diambil untuk pembalikan semula fungsi otot dan saraf dari TOF 2 atau 3 ke nisbah TOF 0.9 lebih lama dalam kumpulan pesakit yang menerima ubat neostigmine dengan min masa 501.58 saat berbanding dengan kumpulan pesakit yang menerima sugammadex iaitu 84.45 saat. Min perbezaan antara dua kumpulan ini ialah 417.13 saat. Perbezaan antara 2 kumpulan ini adalah ketara dari segi statistik, dengan $p<0.05$. Perubahan parameter hemodinamik tekanan darah (sistolik, diastolik dan min tekanan arterial) adalah ketara dalam kedua-dua kumpulan jika dibandingkan sebelum dan selepas pemberian agen reversi. Namun begitu, min

perbezaan parameter hemodinamik dalam kumpulan sugammadex lebih rendah, iaitu -2.38 hingga -2.93 berbanding kumpulan neostigmine iaitu -4.85 hingga -6.80. Min degupan jantung sebelum dan selepas pemberian agen menunjukkan perubahan ketara dalam kumpulan neostigmine, tetapi tidak ketara dalam kumpulan sugammadex. Peratus kesan sampingan yang dialami oleh pesakit adalah lebih tinggi dalam kumpulan neostigmine iaitu 17.5% (7 pesakit) mengalami mual dan muntah manakala 2.5% (1 pesakit) berpeluh. Tiada kesan sampingan yang dilihat dalam kumpulan pesakit yang menerima sugammadex.

Kesimpulan : Masa pembalikan fungsi otot dan saraf (dari TOF 2 atau 3 ke nisbah TOF 0.9) adalah jauh lebih singkat dalam kumpulan sugammadex berbanding kumpulan neostigmine. Sugammadex juga mempunyai profil hemodinamik yang lebih stabil berbanding neostigmine apabila digunakan untuk menentang kesan relaxan otot dan saraf ubat rocuronium. Sugammadex didapati mempunyai kurang kesan sampingan jika dibandingkan dengan neostigmine.

Carian : Rocuronium, Neostigmine, Sugammadex, TOF, Kanak-kanak

ABSTRACT

COMPARISON BETWEEN THE EFFICACY OF NEOSTIGMINE VERSUS SUGAMMADEX REVERSAL OF ROCURONIUM INDUCED NEUROMUSCULAR BLOCKADE IN PAEDIATRIC PATIENTS

Introduction : A reversal agent is commonly given to improve neuromuscular function after intra-operative administration of non-depolarizing neuromuscular blocking agents. The administration of conventional reversal agent neostigmine is associated with many undesirable side effects. For almost a decade, a new novel drug sugammadex has been used to specifically antagonize the effect of aminosteroidal neuromuscular blocking agents.

Objectives : The aim of this study is to compare the recovery time, haemodynamic stability and complications between these 2 reversal agents in antagonizing the effects of rocuronium in the paediatric population.

Methodology : This was a prospective, double-blinded, randomized controlled trial involving 80 paediatric patients aged between 2-12 years old scheduled for surgery under general anaesthesia requiring rocuronium induced neuromuscular blockade. They were randomized equally into two groups, 40 patients each group for reversal with neostigmine or reversal with sugammadex. All patients were induced with sevoflurane, intravenous access obtained, then 2mcg/kg of fentanyl was administered.

Neuromuscular function monitoring (acceleromyography) of the adductor pollicis muscle was done using train-of-four (TOF) method. TOF-Watch Sx was placed along the ulnar groove of the hand and calibrated. After a baseline TOF reading was taken, and 0.6mg/kg of rocuronium was given. Patients were intubated once TOF count was less than 1. TOF was monitored and maintained at count of 2-3 throughout the surgery by administering 0.2mg/kg of rocuronium once TOF count was more than 3. The haemodynamic parameters pre-reversal and post-reversal was documented. The neuromuscular recovery time, from reversal administration at TOF count 2 or 3 to TOF ratio 0.9 was documented. Any complications observed post-extubation were documented.

Results : The neuromuscular recovery time from TOF count 2 or 3 to TOF ratio 0.9 post-reversal was significantly higher in the neostigmine group, with a mean of 501.58 seconds as compared to only 84.45 seconds in the sugammadex group. The mean difference was 417.13 seconds. This difference was statistically significant evidenced by $p<0.05$. There were also significant changes in the means of systolic blood pressure, diastolic blood pressure and mean arterial pressure pre-reversal and post-reversal in both groups. However the mean differences were much lower in the sugammadex group, ranging from -2.38 to -2.93 as compared to the neostigmine group, which were from -4.85 to -6.80. The mean heart rate pre-reversal and post-reversal showed significant changes in the neostigmine group, but the changes were not significant in the sugammadex group. The incidence of complications post-reversal was higher in the neostigmine group with 17.5% (7 patients) post-operative nausea vomiting and 2.5% (1 patient) sweating. There were no complications noted in the sugammadex group.

Conclusion : Sugammadex has a significantly shorter recovery time (from TOF count of 2 or 3 to TOF ratio of more than 0.9) as compared to neostigmine. Sugammadex has a more stable haemodynamic profile as compared to neostigmine when used to reverse rocuronium induced neuromuscular blockade in paediatric patients. Sugammadex causes less complications or side effects when used in paediatric patients as a reversal for rocuronium induced neuromuscular bloackade.

Keywords : Rocuronium, Neostigmine, Sugammadex, TOF, Paediatrics

CHAPTER 1 : INTRODUCTION

Neuromuscular blocking agents (NMBAs) are frequently used during general anaesthesia to facilitate tracheal intubation, artificial ventilation, and adequate muscle relaxation for surgical procedures. Reversal agents are often administered at the end of surgery when there is evidence of return of neuromuscular function, to accelerate recovery from neuromuscular blockade and to prevent post-operative residual curarization (Plaud *et al.*, 2009).

Following the use of neuromuscular blocking agents for the various benefits it imposes during general anaesthesia, concerns have also been raised about the risks of postoperative residual neuromuscular blockade which may be associated with airway obstruction, pulmonary complications, hypoxia and increased mortality (Khuenl-Brady *et al.*, 2010). There are several ways to reduce the risk of developing residual block when using NMBAs. One approach is to wait for spontaneous recovery of neuromuscular block combined with clinical evaluation of recovery of neuromuscular function. However clinical tests such as leg lift, head lift or hand grip are not always accurate in predicting neuromuscular recovery and does not easily provide an objective evaluation of neuromuscular function. For example, a recent study found that 12% of patients who had good response to clinical tests were still at risk for residual block (Suy *et al.*, 2007).

One of the more accurate, quantitative and feasable methods to monitor depth of neuromuscular blockade is using the train-of-four (TOF) counts or ratio. This assesses return of function at neuromuscular junction prior to reversal. Although it is

not routinely used in daily anaesthetic practice, it is essential and beneficial in ensuring lower incidence of residual blockade or incomplete recovery post-reversal, which may be associated with debilitating side effects. Many anaesthesiologists still rely on clinical judgement and seldom use objective monitoring of neuromuscular block. However, monitoring of neuromuscular function determines whether an antagonism of residual block is actually required and has been shown to be the only way to reduce the incidence of residual paralysis (Suy *et al.*, 2007).

Neostigmine, an anticholinesterase inhibitor has been widely used to reverse the effects of both aminosteroidal and benzylisoquinolone neuromuscular blocking agents since the 1970s. The use of acetylcholinesterase inhibitors for example neostigmine and endrophonium are associated with undesirable muscarinic side effects, which requires the use of a second drug in combination, which is an anticholinergic drug to counteract these side effects. In addition, there is a higher incidence of residual block in both adults and children. It is important to keep in mind that a recent study of upper airway dilator mucle activity and breathing showed that although the standard practice of reversal with cholinesterase inhibitors is relatively safe in patients who have residual block, but if these agents are given after complete spontaneous recovery, they can actually produce muscle weakness and possibly upper airway collapse (Eikermann *et al.*, 2008).

Sugammadex is a per-6-(2-carboxyethylthio)-per-6-deoxy-gamma-cyclodextrin sodium salt. Su- refers to sugar and –gammadex refers to the structural molecule ɣ-cyclodextrin. It is the first and only selective relaxant-binding agent to be introduced in the market since 2008, and is now gaining popularity. It has been

designed to reverse the aminosteroidal neuromuscular blocking drug, (rocuronium, vecuronium, pancuronium from the most sensitive to least sensitive respectively) in the plasma, creating a concentration gradient favouring the movement of rocuronium molecules from the neuromuscular junction into the plasma. It encapsulates and deactivates the rocuronium molecule forming a tight, inclusion, stable, water-soluble complex at a 1;1 ratio, causing the rocuronium to no longer be available to freely bind to the nicotinic receptors at the neuromuscular junction. This promotes liberation of the acetylcholine receptors, and muscle activity reappears rapidly. Because of the low dissociation rate, no muscle weakness has been reported in available human or animal studies.

The reversal of rocuronium induced neuromuscular blockade by sugammadex can be achieved using doses of 2mg/kg, 4mg/kg and 16mg/kg depending on the TOF readings. Studies have shown sugammadex achieves fast and efficient reversal of neuromuscular blockade, without the well-known undesirable cholinergic side effects associated with the use of cholinesterase inhibitors, such as bradycardia, hypersalivation, increased secretions, bronchoconstriction, abdominal cramps, nausea and vomiting.

Paediatric patients differ from adult patients as the pharmacokinetic and pharmacodynamic profiles of neuromuscular blocking agents may vary according to age. For example, the clinical duration of rocuronium is prolonged in infants as compared to children, whereas the potency of rocuronium is higher in infants but lower in children as compared to adults. Studies have also shown that residual paralysis occurs more commonly in children as compared to adults.

This study therefore was carried out to compare the reversal of rocuronium induced neuromuscular blockade with the conventional reversal neostigmine and the newly introduced novel sugammadex in paediatric patients. Sugammadex has not been widely studied in paediatric patients, most studies with sample sizes of 24 patients. A comparison study of the haemodynamic parametes and side effects also has yet to be done prior to this.

To further understand this study, one would need adequate understanding regarding the neuromuscular physiology, the role of TOF monitoring and the pharmacokinetics and pharmacodynamics if each drug used.

CHAPTER 2 : LITERATURE REVIEW

2.1 NEUROMUSCULAR PHYSIOLOGY

The neuromuscular junction consists of a presynaptic nerve terminal, the synaptic cleft, and post-synaptic nicotinic receptors on the muscle membrane. An electrical impulse is transmitted along the motor nerve causing presynaptic acetylcholine release with binding of the neurotransmitter to the post-synaptic acetylcholine receptor.

The presynaptic nerve terminal consists of the terminal part of the motor neurone which originates from the ventral horn of the spinal cord, losing its myelin as it nears the muscle fibre. Here, the Schwann cell anchors the nerve to the muscle membrane. Schwann cells play an important role in the maintenance of nerve homeostasis, providing stability and secreting growth and trophic factors, as well as axon development and synaptic formation. Schwann Cells control the number of neuromuscular junctions and remove superfluous presynaptic nerve terminals, especially during re-innervation, for instance, after crush injury. The presynaptic terminal also contains acetylcholine nicotinic receptors on the surface of the nerve membrane. Non-depolarizing and depolarizing neuromuscular blocking agents act on these receptors to mobilize acetylcholine, the former inhibit them and the latter stimulate them..

Acetylcholine is a neurotransmitter which is stored in vesicles. The release of acetylcholine on arrival of a nerve impulse results in sodium channel activation on the prejunctional nerve membrane. This in turn activates voltage-dependent calcium

channels (P-type fast channels) on the motor neurone causing an influx of calcium into the nerve cytoplasm that promotes further acetylcholine release. The calcium inflow is balanced by potassium ion outflow through potassium channels to maintain equilibrium across the nerve membrane.

The post-junctional membrane consists of multiple folds with shoulders bearing the high-density clusters of acetylcholine, and clefts containing voltage-gated sodium channels. The high density ensures that acetylcholine elicits sufficient depolarization across the muscle membrane for muscle contraction.

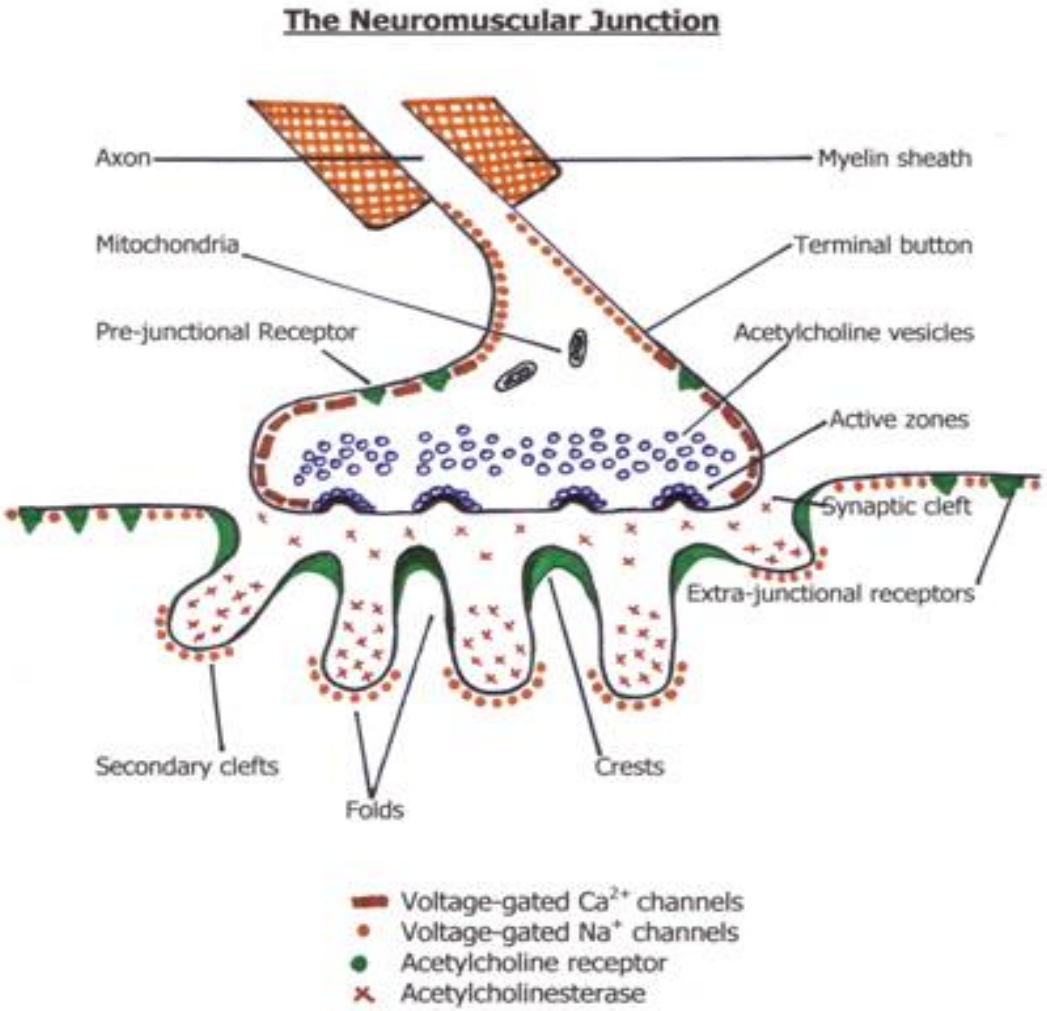

Figure 2.1 The Neuromuscular Junction. *Image adapted from* http://www.frca.co.uk

(Ackroyd and Gwinnutt, 2006)

2.2 ROCURONIUM

2.2.1 Overview of Neuromuscular Blocking Agents

Neuromuscular blocking agents are frequently used during anaesthesia to facilitate tracheal intubation, artificial ventilation and to provide adequate relaxation for surgical procedures.

There are many neuromuscular blocking agents currently used in daily practice of anaesthetists. These agents can be divided into depolarizing (for example succynylcholine) and non-depolarizing. Non depolaring muscle relaxants can be divided into 2 groups; aminosteroid (for example rocuronium, pancuronium, vecuronium) and benzylquinolones (for example atracurium, mivacurium, tubocurarine).

Neuromuscular blocking agents also can be divided according to their duration of action. Short acting agents are succynylcholine and mivacurium, intermediate agents are atracurium, cisatracurium, vecuronium and rocuronium, long acting agents are pancuronium, pipecuronium and doxacurium.

2.2.2 Molecular structure

Rocuronium is a monoquartenary aminosteroid non-depolarizing neuromuscular blocking agent. It was introduced in 1994. Below is its chemical molecular structure:

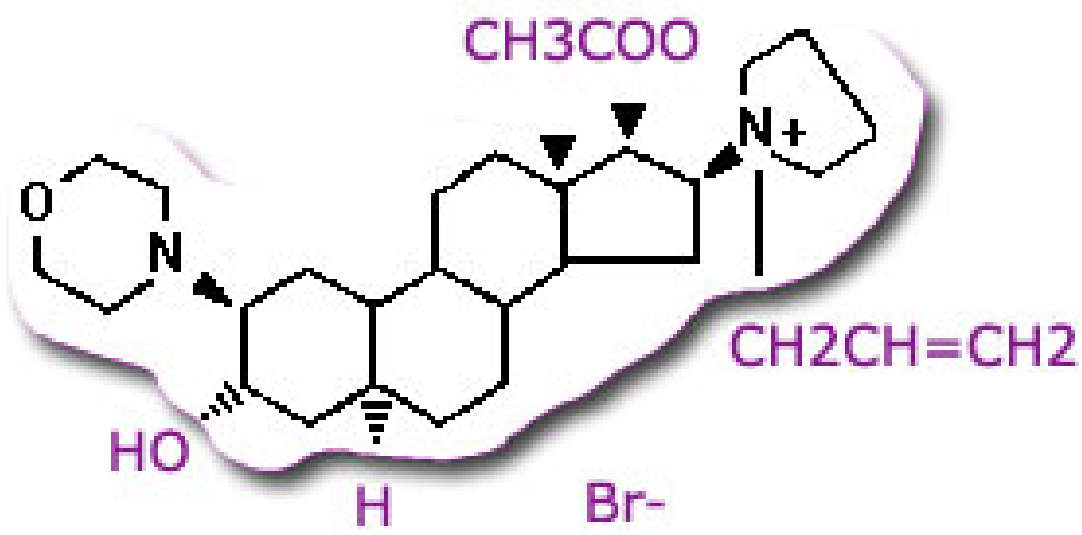

Figure 2.2 Rocuronium molecular structure. *Image adapted from www.frca.co.uk (2007b)*

2.2.3 Preparation

Rocuronium is a clear, colourless and odourless fluid prepared in a rubber sealed bottle. The preparation is 10mg/ml, available in 5ml and 10ml ampoules. It is mostly administered intravenously, but also can be administered intramuscularly.

2.2.4 Mode of Action of Rocuronium

When administered, rocuronium molecules act at neuromuscular junctions of the skeletal muscle. It inhibits the action of acethylcholine (neurotransmitted) at the neuromuscular junction by competitively binding to the alpha subunit of the nicotinic acetylcholine receptor on the post-junctional membrane. This binding does not cause activation or change in configuration of the ion receptor channels, as would be typically seen in the binding of acetylcholine to the receptor. The action potential is therefore inhibited, as acetylcholine is unable to bind to the acetylcholine receptors. Neuromuscular transmission is blocked only after 80-90% of the receptors have been occupied by rocuronium molecules.

2.2.5 Dosage, Onset and Duration of Action

Rocuronium has an ED95 of 0.3mg/kg. Intubating dose is 0.6mg/kg or 1-1.2mg/kg (3-4 times ED95) for rapid sequence induction. Its onset of action is roughly 90 seconds. Its duration of action lasts 20-35 minutes.

2.2.6 Pharmacokinetics

Rocuronium is mostly excreted in the unchanged form (up to 50%) in 2 hours in the bile. Renal excretion of rocuronium is roughly 30% in 24 hours. Liver diseases increases its volume of distribution, therefore may prolong its duration of action.

2.2.7 Side effects

Rocuronium is a fairly safe drug. It may cause minimal histamine release. It may also cause slight vagolytic effect. Patients may experience pain on injection (intravenous administration). There may be prolonged duration of action in patients with renal or liver impairment.

2.3 NEOSTIGMINE

2.3.1 Overview of anticholinesterase drugs

Anticholinesterase drugs are most often administered by anaesthesiologist to improve and speed the recovery of neuromuscular function after neuromuscular blockade by non-depolarizing neuromuscular blocking agents. It can also be used to treat certain illness for example myasthenis gravis, glaucoma and to non-specificly antagonize the central nervous system effects of certain drugs for example urinary retention and constipation.

Antichonisesterases can be classified according to its mechanism of action; easily reversible (endrophonium), formation of carbamylated enzyme complex (neostigmine, pyridostigmine, physostigmine) and irreversible inactivation by organophosphates.

2.3.2 Molecular structure

Neostigmine is a quartenary amine which is an ester of an alkyl carbamic acid. It has been used since the early 1930s. Its structure is as below :

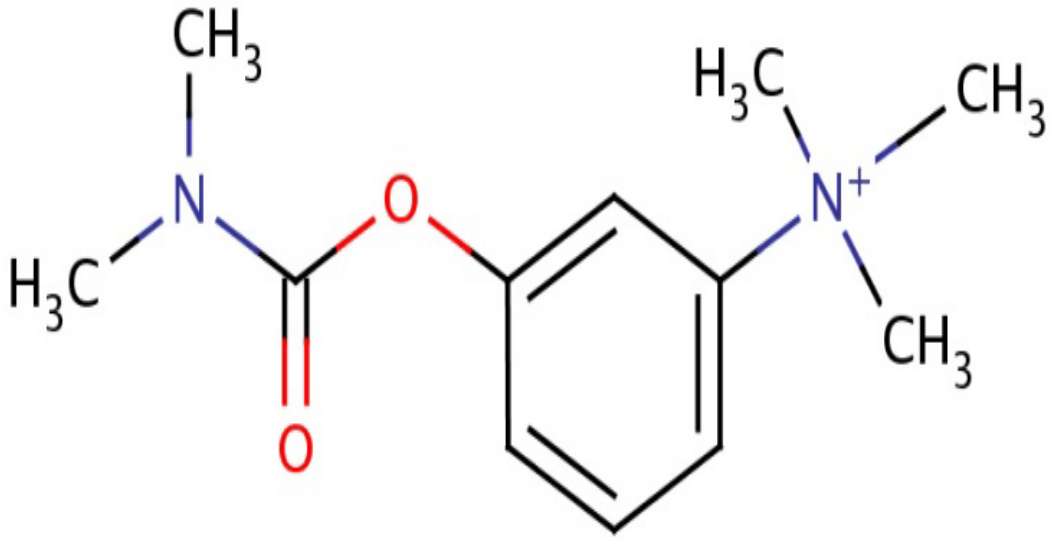

Figure 2.3 Neostigmine molecular structure. *Image adapted from* www.frca.co.uk *(2010)*

2.3.3 Preparation

Neostigmine is available is tablets and in solution for intravenous injection. The intravenous form used widely in anaesthetic practice is clear, colorless and odourless in a 1ml ampoule. Its preparation is 2.5mg/ml.

2.3.4 Mode of action

Neostigmine functions by inhibiting the enzyme acetylcholinesterase, which hydrolyzes the neurotransmitter acetylcholine. Inhibition of this enzyme results in greater availability of acetylcholine at the sites of action, including preganglionic sympathetic and parasympathetic nerve ending in the neuromuscular junction. This enables more acetylcholine to competitively bind at the acetylcholine receptors of the neuromuscular junction. Therefore more miniature end plate potentials are produced, eventually producing an action potential. The increase in acetylcholine concentration also causes autonomic cholinergic effects like bradycardia and salivation, therefore it is often administered with an anticholinergic agent for example atropine or glycopyrrolate.

Neostigmoine produces reversible inhibition of acetylcholinesterase enzyme by forming a carbamyl ester complex at the esteratic site of the enzyme. Both acetylcholine and carbamate esters are hydrolysed by acetylcholisterterase enzymes. However acetylcholine acetylates the enzyme, while carbamate esters produce a carbamylated anzyme, which has a much slower rate of hydrolysis. This is also the reason why neostigmine is known as an acid transferring or time dependant acetylcholinesterase enzyme inhibitor. This carbamylated acetylcholinesterase cannot

hydrolyse acetylcholine until the carbamate-enzyme bond dissociates. Carbamylated acetylcholinesterase has a half-time of 15-30 minutes.

Neostigmine also inhibits plasma cholinesterases.

2.3.5 Dosage, onset, duration of action

The dosage of neostigmine for reversal of neuromuscular blockade by non-depolarizing muscle relaxants is 0.05mg/kg. In the treatment of myasthenia gravis, the dosage is 15-30mg orally. Its onset is intermediate, about 7-11 minutes, and duration of action is up to 1 hour.

2.3.6 Pharmacokinetics

Neostigmine has a large volume of distribution 0.7litres/kg. Its elimination half time is 77 minutes. 50% is metabolized in the liver and 50% is cleared in the kidneys. Neostigmine has poor lipid solubility

2.3.7 Side effects

Neostigmine side effects are mainly parasympathetic, for example increased secretions, salivating, abdominal cramps, vomiting, bronchospasm and bradycardia.

2.4 SUGAMMADEX

2.4.1 Introduction

Sugammadex is a modified gamma-cyclodextrin. It is the first selective relaxant binding agent to be introduced. It was previously known as Org 25969. It has a lipophilic core and hydrophilic

2.4.2 Molecular structure

Sugammadex was introduced in 2008. The molecular structure is as below :

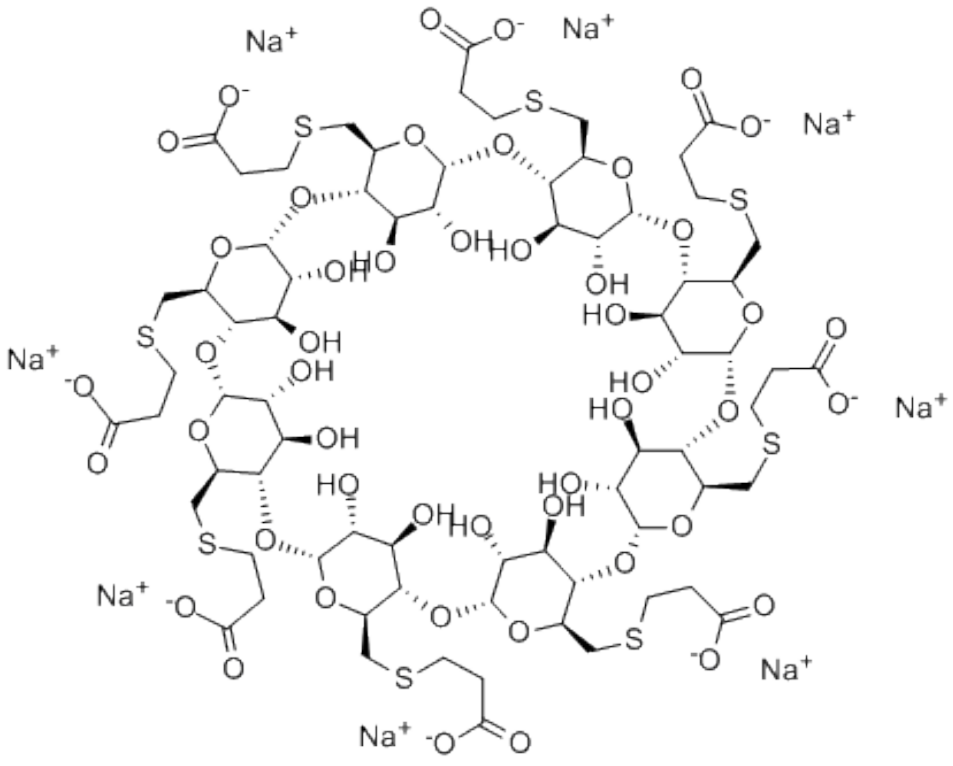

Figure 2.4 Sugammadex molecular structure. *Image adapted from www.chemicalbook.com(2007a)*

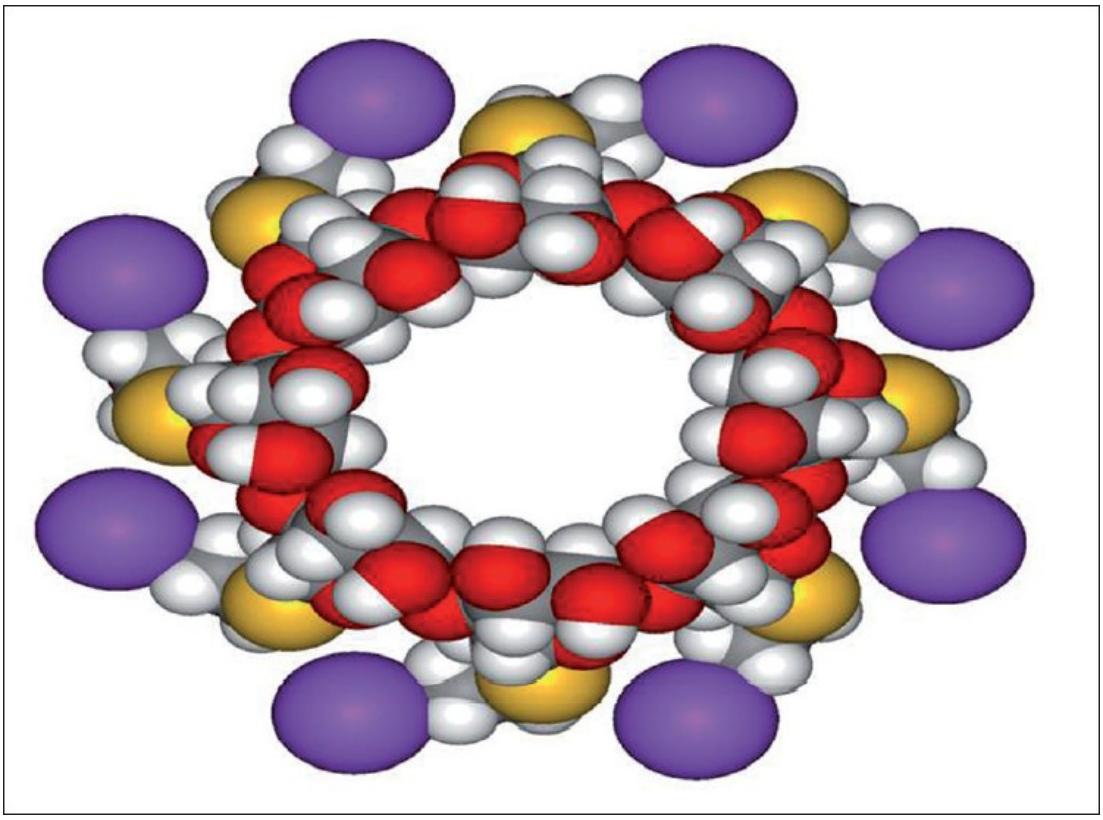

Figure 2.5 Tri-dimensional structure of sugammadex (space-filling, ring shaped) *Image adapted from Annals Of Cardiac Anaesthesia (Hemmerling et al., 2010)*

2.4.3 Preparation

Sugammadex is prepared in a clear, colourless and odourless liquid, in a rubber-sealed ampoule. Its prepared in 100mg/ml.

2.4.4 Mode of action

Sugammadex has a unique mode of action which differs from other reversal agents. It specifically encapsulates the aminosteroidal non-depolarizing neuromuscular blocking agent, rocuronium. It has an inert doughnut shape. The eight side chain of sugammadex elongate the central cavity to ensure complete encapsulation of rocuronium, while the negatively charged carboxyl groups at the end of each chain enhances electrostatic binding to the positively charges nitrogen atom of rocuronium. This reduces the amount of rocuronium molecules readily available at the neuromuscular junction, allowing acetylcholine to occupy acetylcholine receptors to produce an action potential.

2.4.5 Dosage, onset, duration of action

Sugammadex can be given in different doses, according to the degree of neuromuscular blockade. 2mg/kg is given for moderate blocks (at reappearance second twitch T2), 4mg/kg is given for deep blocks (TOF count less than 1, PTC 1 or 2) and 16mg/kg is given for profound blocks (PTC 0) or for immediate reversal when rocuronium has just been administered. Its onset of action is 30-60 seconds.

2.4.6 Pharmacokinetics

Sugammadex has a volume of distribution of 0.2Litres/kg. It is not metabolized, but excreted unchanged in the kidneys. Elimination half life is 2.2 hours.

2.4.7 Side effects

As of date, there is no clear known side effects of sugammadex. However, it is avoided or used with caution in patients with renal impairment. There have been reports of possible prolongation of the QT interval of the electrocardiogram after sugammadex, and hypertension and hypotension have been reported after large doses (32 mg/kg). One report described accidental administration of a very large dose of sugammadex (40 mg kg^{-1}), however, without any adverse effect on the cardiovascular system.

2.5 ROLE OF REVERSAL OF NEUROMUSCULAR BLOCK

Reversal agents are administered at the end of surgery when muscle relaxation or neuromuscular paralysis is no longer desired. Reversal agents help accelerate the recovery of the neuromuscular function post-administration of a non-depolarizing NMBA. The practice of administering neuromuscular blocking agents is very popular among anaesthetist worldwide, to avoid unwanted complications post-extubation for example residual paralysis or recurarization, which may lead to debilitating effects.

Residual paralysis poses a significant risk to a patient post-extubation. The residual presence of volatile anaesthetic agents, benzodiazepines and narcotics in the tissue compartments contribute to this risk. Residual paralysis increases the risk of passive regurgitation of gastric contents because of pharyngeal and laryngeal muscle dysfunction, in spite of adequate diaphragm recovery. There is also evidence that NMBAs may interfere with hypoxic ventilatory control. The hypoxic ventilatory response is reduced by about 30% in awake volunteers when the TOF ratio is only 0.7. The mechanism behind this interaction seems to be a reversible depression of carotid body chemoreceptor activity during hypoxia. This may potentiate postoperative brain injury. Postoperative pulmonary complications, especially atelectasis and pneumonia, are also associated with incomplete reversal. Atelectasis occurs during anaesthesia and is compounded in the postoperative period by any degree of residual paralysis (Srivastava and Hunter, 2009).

Many studies have proven that patients who received NMBAs but no reversal agents experienced postoperative residual paralysis, whether in the aminosteroidal groups such as pancuronium, vecuronium and rocuronium or the benzylquinolones

group such as atracurium and cisatracurium. The incidence of residual curarization was much higher when infusions of NMBAs were used but no reversal agents were given. After a single dose of an intermediate-duration NMBA and no reversal, residual paralysis is common, even more than 2 hours after its administration.

Recurarization is defined as an increase in neuromuscular block after a variable period of recovery. Recurarization was particularly common with the older NMBAs such as gallamine, *d*-tubocurarine and pancuronium. The problem was reduced with the introduction of atracurium and vecuronium. This is also contributed by improved neuromuscular monitoring. Recurarization may occur when a long-acting NMBA is antagonized with an anticholinesterase that has a shorter duration of action. There may be an initial period of recovery from block, as acetylcholine concentrations increase as compared to NMBA concentrations post-administration of acetylcholinesterase inhibitors. As the anticholinesterase is redistributed and metabolized, its concentration falls at the NMJ, but the NMBA is still present. This effect is increased by respiratory acidosis and inadequate renal function, both of which potentiate the duration of effect of the older agents.

Several techniques may be used to reduce the risk of postoperative residual paralysis, including avoidance of long-acting NMBAs, use of neuromuscular monitoring in the operating theatre, and reversal of block at a TOF count of at least 2.

Ideally, any new reversal agent would have a more rapid onset of action, be efficacious irrespective of the degree of neuromuscular block, and have an improved side-effect profile. Only until recently, a selective relaxant binding agent sugammadex was introduced to the market, which fits these desirable criterias.

2.6 NEUROMUSCULAR MONITORING METHODS

The anaesthetist can assess neuromuscular recovery muscle power by a variety of clinical tests, such as the ability to sustain head lift for 5 seconds or the ability to hold a tongue depressor between the teeth. These are a crude assessment of neuromuscular function, and can be influenced by many factors, for example, residual sedation or inability to follow instructions. In 1958, Christie and Churchill-Davidson described the use of a nerve stimulator to monitor neuromuscular block. However, it was not until the TOF pattern of stimulation was described in 1970, that such equipment came into routine clinical use (McGrath and Hunter, 2006).

There are many methods of neuromuscular monitoring in anaesthesia. This is done using a device that delivers a desired magnitude and duration of electrical current (supramaximal stimuli) to stimulate a group of peripheral nerves to produce an action potential, whereby the associated muscular response is measured. Examples neuromuscular monitoring stimuli are Single Twitch stimulation, Tetanic stimulation, Double Burst Stimulation (DBS), Post-Tetanic Count (PTC) and Train Of Four (TOF) stimulation.

Neuromuscular monitoring is an essential tool in anaesthetic practice, to ensure good neuromuscular recovery prior to extubation and to avoid undesired post-operative adverse events. There is increasing evidence that residual neuromuscular block is common, and also that it may adversely affect patient outcome.

Although there is no evidence that residual neuromuscular block leads to increased mortality, significant pulmonary morbidity has been demonstrated after using longer-acting agents such as pancuronium. As well as interfering with pulmonary mechanics, residual neuromuscular block impairs the ventilatory response

to hypoxia. At low doses, these drugs significantly impair pharyngeal function and lead to an increased risk of tracheal aspiration and airway obstruction (McGrath and Hunter, 2006).

When neuromuscular monitoring is used, visual or tactile evaluation of the degree of neuromuscular block is unreliable. Even experienced anaesthetists are unable to detect fade when the TOF ratio is >0.4. It is now thought that significant residual curarization is still present if the TOF ratio is <0.9 (not 0.7 as previously suggested). It is clear that as well as monitoring neuromuscular block clinically, we should be using quantitative techniques to assess the degree of recovery (McGrath and Hunter, 2006).

The following are basic principles regarding Single Twitch Stimulation, Tetanic Stimulation, Post-Tetanic Count and Double Burst Stimulation. Train Of Four Stimulation will be discussed under the TOF Watch Sx subheading.

2.6.1 Single Twitch Stimulation

A single square wave supramaximal stimulus (0.1-1 Hertz) is applied to a peripheral nerve for a period of about 0.2 ms, at regular intervals (1-10 seconds), and the evoked response is observed. The twitch response will only be depressed when a neuromuscular blocking agent occupies 75% of the post-synaptic nicotinic receptors. Twitch depression will need to be more than 90% in order to provide good conditions for abdominal surgery. The most useful time to apply the single twitch pattern of nerve stimulation is at the onset of neuromuscular block. The onset and recovery from depolarizing and non-depolarizing block monitored using single twitches have a similar pattern, differing only in timescale. The major limitation to this technique is the need to measure a control twitch before administering the neuromuscular blocking agent.