A comparison of the potentiation by desflurane of the effects of rocuronium and cisatracurium.

by

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DECLARATION

By submitting this research assignment electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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ABSTRACT

Introduction:

Of the volatile anaesthetic agents, desflurane causes the greatest degree of potentiation of the neuromuscular blocking drugs (NMB). The purpose of this study was to determine whether desflurane prolongs the effects of 3xED_{95} doses of rocuronium and cisatracurium to the same degree. The two NMB represent potent and less potent classes respectively.

Methods:

Informed, written consent was obtained from 63 adult patients scheduled for routine surgery. They were randomly allocated to one of four groups to receive either desflurane-sufentanil (end-tidal partial pressure 4.0 kPa) or propofol-sufentanil anaesthesia and either rocuronium (0.9mg/kg) or cisatracurium (0.15mg/kg). All patients received a target-controlled sufentanil infusion (0.5 ng/ml). Neuromuscular blockade was recorded using accelerometry (TOF-GUARD®, Organon) while patients recovered spontaneously to a Train-of-Four ratio of 0.9 (TOFR0.9). Data were analysed using one- and two-way analysis of variance. The main effects were the types of anaesthetic and NMB on indices of recovery.

Results:

Compared with propofol-sufentanil anaesthesia, mean times to recovery to $T1_{25\%}$ and TOFR0.9, were prolonged by desflurane-sufentanil ($p<0.01$). There were no interactions.

Mean prolongation of time to TOFR0.9 was 41 min (SD 36) for cisatracurium and 26.6 min (SD 39) for rocuronium.

Discussion:

Whereas previous studies did not reveal prolongation of the duration of action of rocuronium by desflurane, we demonstrated a statistically significant prolongation of the spontaneous recovery times of both rocuronium and cisatracurium by desflurane. From the data we could not conclude that there was a difference between the two NMB. A power study revealed that in order to detect a difference between times to recovery to TOF0.9, a sample size of 101 subjects per group would be required.

Conclusion:

Desflurane prolongs the mean time to spontaneous recovery from neuromuscular blockade after $3xED_{95}$ doses of both cisatracurium (a potent NMB) and rocuronium (a less potent NMB). There was wide inter-individual variation in times to spontaneous recovery. Any difference in the mean prolongations between the different types of NMB is unlikely to be of clinical importance.

Keywords

Neuromuscular non-depolarizing agents, desflurane, rocuronium, cisatracurium, drug interactions, neuromuscular monitoring, train–of-four monitoring

OPSOMMING

Inleiding

Van al die vlugtige narkosemiddels veroorsaak desfluraan die grootste mate van potensiasie van die neuromuskulêre blokkeermiddels. Die doel van hierdie studie was om vas te stel of desfluraan wel die effek van driedubbel die ED_{95} dosis van rokuronium en cisatrakurium tot dieselfde mate sal verleng.

Metodiek

Geskrewe ingeligte toestemming is verkry van 63 pasiënte wat voorgedoen het vir roetiene chirurgiese prosedures. Pasiënte is lukraak in een van vier groepe ingedeel om of desfluraan-sufentaniel (eind-gety parsieële druk 4.0 kPa) of propofol-sufentaniel narkose en of rokuronium (0.9 mg/kg) of cisatrakurium (0.15 mg/kg) te ontvang. Alle pasiënte het 'n teiken-beheerde sufentaniel infusie (0.5 ng/ml). Neuromuskulêre blokkade is waargeneem met behulp van aksellerometrie (TOF-GUARD, Organon) terwyl pasiënte spontaan herstel het tot "reeks-van-vier" verhouding (Engels "Train-of-four" ratio) 0.9 (TOFR0.9). Data analise is gedoen met behulp van een- en tweerigting analise van variansie.

Resultate

Desfluraan-sufentaniel het die gemiddelde hersteltyd tot $T1_{25\%}$ en TOFR0.9 verleng in vergelyking met propofol-sufentaniel. Geen interaksies is waargeneem nie. Gemiddelde

verlenging van TOFR0.9 vir cisatrakurium was 41 minute (standaardafwyking 36) en vir rokuronium 26.6 minute (standaardafwyking 39).

Bespreking

Vorige studies kon nie vasstel of desfluraan die werkingsduur van rokuronium verleng nie. Ons het in hierdie studie vasgestel dat desfluraan wel 'n statisties beduidende verlenging in die hersteltyd van beide rokuronium en cisatrakurium veroorsaak. Ons kon egter nie 'n verskil tussen die twee neuromuskulêre agente aandui nie. 'n onderskeidingsvermoëstudie het getoon dat ten minste 101 pasiënte per groep benodig sou word om 'n beduidende verskil tussen die hersteltye tot TOFR0.9 te verkry.

Gevolgtrekking

Desfluraan verleng die gemiddelde hersteltyd tot spontane herstel van neuromuskulêre blokkade na driedubbele ED_{95} dosisse van beide cisatrakurium en rokuronium. Daar was egter groot interindividuele variasie ten opsigte van spontane hersteltyd. Enige verskille in die gemiddelde verlenging is onwaarskynlik van kliniese belang.

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But those who hope in the LORD will renew their strength.

Psalm 40:31

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LIST OF ABBREVIATIONS

ED_{50}	Effective dose to produce 50% effect
ED_{95}	Effective dose to produce 95% effect
ET_{Des}	End-tidal concentration of desflurane
GRCP	Good Clinical Research Practice
Hz	Hertz
IAA	Inhaled anaesthetic agent
MAC	Minimum alveolar concentration
N_2O	Nitrous-oxide
nAChR	Nicotinic acetylcholine receptor
NMB	Neuromuscular blocking drugs
NDMR	Non-depolarizing muscle relaxant
SNAP-25	Synaptosome-associated protein of 25kd
SNARE	Soluble N-ethylmaleimide-sensitive-attachment-protein receptors
T1	First twitch response
$T1_{25\%}$	First twitch response is 25% of the control height
$TI_{75\%}$	First twitch response is 75% of the control height
$T1_{90\%}$	First twitch response is 90% of the control height
$T1_{25\text{-}75\%}$	Recovery interval from $T1_{25\%}$ to $T1_{75\%}$
TIVA	Total intravenous anaesthesia
TOF	Train-of-four
TOFR	Train-of-four ratio

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INTRODUCTION

History of the potentiation of the effects of neuromuscular blockers by volatile anaesthetic agents

The effect of general anaesthetics on the neuromuscular junction has been studied for nearly a century. A study on the effect of ether inhalation upon the skeletal motor contraction mechanism was published as early as 1914. (1) Early animal model studies were later followed by clinical *in vivo* studies in an attempt to quantify this effect.

For more than four decades it has been well known that clinically less neuromuscular blocker is required to produce neuromuscular blockade in the presence of volatile agents. (2) Walts *et al.* studied the magnitude and duration of effect of curare in the presence of different anaesthetic agents and showed that, in comparison to an opioid-nitrous oxide anaesthetic, inhaled anaesthetic agents potentiated the twitch depression produced by curare. (3) Waud *et al.* demonstrated that the effect of volatile agents on mammalian muscle was concentration-dependent. (4)

Physiology and pharmacology of the neuromuscular junction

The physiology of the neuromuscular junction has been extensively studied and is well elucidated. (5)(6)(7) Interestingly, initial interest in this specific area was prompted by the desire to explain the mechanism of action of volatile agents.

Acetylcholine is produced in the cytoplasm of the nerve terminal and stored in vesicles. These vesicles are docked to the presynaptic membrane by means of specialized proteins, namely, soluble N-ethylmaleimide-sensitive-attachment-protein receptors (SNARE). These SNARE proteins include synaptobrevin, syntaxin and synaptosome-associated protein of 25kd (SNAP-25). Synaptobrevin (located on the vesicle membrane) attaches to syntaxin and SNAP-25 (which reside on the plasma membrane of the nerve terminal). Synaptotagmin (a protein on the vesicle membrane) stabilizes the vesicle in the docked state and acts as a calcium sensor. Depolarization of the motor nerve opens voltage-gated calcium channels (P-type) which allow an influx of calcium into the terminal button. The calcium facilitates exocytosis of the acetylcholine stored inside the docked vesicles. Under experimental conditions, the concentration of ionized calcium in the extracellular fluid is proportional to the amount acetylcholine released.

These acetylcholine molecules diffuse across the cleft between the terminal button and the muscle endplate and bind to nicotinic acetylcholine receptors (nAChR) on the post-synaptic membrane. The nAChR consists of 5 subunits (α2, β, γ, δ or Ɛ) that are arranged to form an ion channel with a central pore. Simultaneous occupation of the two binding sites for acetylcholine at the αƐ and αδ subunit borders results in a conformational change in the subunits and opening of the central pore to allow the flow of sodium, potassium and calcium cations along their individual concentration gradients. This ion flow results in an end-plate potential that triggers the activation of peri-junctional voltage–gated sodium channels which results in muscle membrane depolarization. The resultant action potential precipitates a sequence of events that ultimately result in muscle contraction.

After interacting with the binding sites on the nAChR, the acetylcholine molecules are released into the junctional cleft and are hydrolysed within one millisecond by acetylcholinesterase. Thus under normal conditions, one molecule of acetylcholine will only interact with one receptor before it is destroyed.

nAChR are also found on the presynaptic membrane at the neuromuscular junction. Nervous tissue does not contain the genes that code for the ɣ, δ or Ɛ subunits and thus these receptors differ from their postsynaptic counterparts, consisting of three α and two β subunits. Their function upon stimulation is to increase mobilization of vesicular acetylcholine so that more vesicles are readily available for docking and exocytosis of acetylcholine. This ensures that the neuromuscular junction is able to function effectively even during a state of high frequency impulses.

Non-depolarizing neuromuscular blockade is the result of competitive receptor antagonism at the acetylcholine binding sites on the postsynaptic nAChR. Non-depolarizing muscle relaxants (NDMR) occupy the nAChR binding sites for a slightly longer period of time than the normal lifetime of acetylcholine. The degree of block is therefore influenced by the relative concentration of acetylcholine and NDMR at the nAChR binding sites and the duration of time that the acetylcholine molecules reside in the junctional cleft.

NDMR also bind to the $\alpha_3\beta_2$ nAChR on the presynaptic membrane thus inhibiting the mobilization of acetylcholine vesicles in the terminal neuron. This is manifested clinically as

'fade', which is a phenomenon of progressively decreasing twitch heights seen with Train-of-Four and tetanic stimulation in the presence of NDMR.

If a single twitch stimulus is applied directly after a tetanic stimulus, in the presence of a NDMR, the twitch height of the single twitch will be significantly larger than the corresponding pre-tetanic twitch heights. This phenomenon of post-tetanic potentiation is explained by the increased concentration of calcium ions in the terminal neuron that occurs immediately after tetanus. Calcium ions enter the cytoplasm of the nerve with every stimulus. These ions cannot be removed from the cytoplasm as quickly as they enter during the tetanic stimulation and therefore the ions accumulate. The higher concentration of calcium ions in the cytoplasm results in more acetylcholine being released into the junctional cleft. In turn, the increased amount of acetylcholine momentarily partially antagonises the neuromuscular blockade by the NDMR and is demonstrated clinically as post-tetanic potentiation.

Evaluation of neuromuscular junction

Monitoring the neuromuscular junction involves the stimulation of a peripheral nerve using a supra-maximal stimulus and measuring the evoked muscular response. The most common method of applying the stimulus is by means of electrical nerve stimulation. The stimulus (fulfilling specified characteristics to prevent repetitive firing) must be of sufficient intensity to depolarise all the nerve fibres that supply the muscle simultaneously thereby causing a maximal motor response. To ensure a truly maximal response, a stimulus that is 20-25% greater than that which is necessary for a maximal response is required.

A variety of patterns of stimulation may be employed.

Single twitch stimulation consists of a single supra-maximal stimulus being applied to a peripheral nerve. The frequency of the stimulation ranges from 1.0 – 0.1 hertz (Hz). The evoked force of the muscle response is measured and the amplitude of the twitch height is compared to the control response measured prior to neuromuscular blocker administration. The evoked response is expressed as a percentage of the control response e.g. the first twitch response is 25% of the control height ($T1_{25\%}$)

Tetanic stimulation involves electrical stimulation at a very rapid rate (30-100Hz) usually for a 5 second period. Fade of muscle contraction occurs during tetanic stimulation in the presence of NDMR, and this phenomenon has been used to demonstrate residual paralysis. However, the stimulation is painful and thus its use is limited to anaesthetized patients. Furthermore, repeated tetanic stimulation results in partial recovery of the stimulated muscle, which can be clinically confusing. More appropriate methods to detect residual neuromuscular blockade by NDMR include evaluation of fade during "double-burst" stimulation (8) and Train-of-Four stimulation (see below).

Train-of-Four (TOF) stimulation consists of four supra-maximal electrical stimuli applied at a frequency of 2Hz. The evoked muscle response is observed and, in the presence of NDMR, exhibits fade. The train-of-four ratio (TOFR) is calculated by dividing the amplitude of the 4^{th} response by the amplitude of the 1^{st} response. During control conditions, the TOFR will be 1.0 and in the presence of NDMR, fade is represented by a decreased ratio. Thus the TOFR varies inversely with the degree of blockade due to a non-depolarizing agent. This

method of stimulation is commonly used in clinical practice as it has the advantages of not requiring the control response to be assessed prior to the administration of the NDMR and it is less painful than tetanic stimulation.

In anaesthesia, four clinical levels of neuromuscular blockade may be demonstrated. (8) *Intense neuromuscular blockade* occurs within the first few minutes of administration. It is characterized by no response to nerve stimulation, regardless of the pattern of stimulation. During *deep neuromuscular blockade*, no response to TOF stimulation is elicited. However, after a tetanic stimulation, single twitches may be observed. *Moderate blockade* begins when a twitch response is demonstrated in response to the first stimulus during TOF stimulation. There is gradual return of four responses during this period and the number of responses elicited show a relationship with the degree of blockade. The presence of only one evoked response correlates with a 90-95% blockade of nAChR in the neuro-muscular junction and four evoked responses correspond with 60-85% neuromuscular blockade. The return of the fourth response indicates the *recovery phase.* A TOFR 0.7 corresponds clinically with a patient who is able to cough and lift his/her head for more than 5 seconds. However, it has been demonstrated that at TOFR < 0.9 patients may still have diplopia, pharyngeal dysfunction with danger of aspiration, and decreased carotid body chemosensitivity to hypoxia. (9) Thus, TOFR should be at least 0.9 to exclude residual paralysis.

Good Clinical Research Practice (GRCP) in pharmacodynamic studies of neuromuscular blocking agents was published with the aim to establish internationally acceptable guidelines for studies in neuromuscular blocking agents. (10) These guidelines suggest that all durations

and intervals should be referenced to a defined baseline control value. The clinical duration of block should be measured from the start of drug administration until 10% or 25% T1 recovery. The initial recovery phase should be described by the time from 25% twitch recovery to 75% twitch recovery, i.e. interval 25-75%. Complete recovery time should be described by the time from 25% twitch recovery to TOFR 0.8, i.e. interval 25% - TOFR0.8

A variety of methods are available to record evoked responses. (8)

Mechanomyography measures the evoked mechanical response of the muscle in response to a supramaximal stimulus applied to a peripheral nerve via cutaneous electrodes. Most commonly, the ulnar nerve is stimulated evoking a response in the *Adductor pollicis* muscle, which in turn acts on a force-displacement transducer that converts the mechanical signal into an electrical signal. A pre-requisite for reproducible measurements is that isometric muscle contraction should be evoked. This is achieved by applying a small preload (200-300g of resting tension) to the thumb. Mechanomyography has been used for many years for the precise quantification of neuromuscular blockade and may be considered to be the "gold standard". (10) However, early models were cumbersome and impractical for use in operating theatres.

Electromyography measures the evoked electrical response, that is, the compound action potentials produced in the muscle in response to a supra-maximal stimulus applied to the peripheral nerve via cutaneous electrodes. Electromyographic recording equipment is not as bulky as mechanomyography and easier to assemble. However, it is subject to numerous sources of inaccuracy, such as interference, direct muscle stimulation and signal drift. (11)

Acceleromyography measures the acceleration of the muscle in response to a supra-maximal stimulus applied to the peripheral nerve via cutaneous electrodes. (12) Newton's second law of motion states that force is directly proportional to acceleration (force = mass x acceleration). A piezoelectric ceramic wafer is simply taped to the thumb (an unchanging mass). Thus, evoked movement of the *Adductor pollicis* causes the piezoelectric wafer to generate an electric potential that is proportional to the degree of acceleration. A standardized elastic preload applied to the thumb with the acceleromyography transducer ensures that the thumb returns to its initial position after each response. Acceleromyography was developed as a more convenient method of monitoring the neuromuscular junction in operating theatres. The TOF-GUARD® monitor (Organon Teknika, Turnhout, Belgium) is a commercially available acceleromyographic monitor. Acceleromyography is not interchangeable with mechanomyography or electromyography and the temptation to directly compare results from different methods should be resisted. (13)

Kinemyography or piezoelectric neuromuscular monitoring utilizes a movement sensor and should be differentiated from acceleromyography. A piezoelectric polymer is placed between the thumb and forefinger. Movement of the thumb causes the redistribution of electrical charge on the sensor which is computed to a TOFR. (14)

Consideration of potential sources of error

It must be appreciated that the consistency of measurements made by the TOF-GUARD® may be compromised by sources of baseline signal 'drift'. Thus correct instrument

calibration, together with specific measures to limit individual variability and improve baseline stabilization, must be undertaken in order to obtain reliable measurements.

Repetitive indirect stimuli of skeletal muscle may cause potentiation of the evoked twitch tension. This effect has been termed the “staircase phenomenon” and is applicable to acceleromyographic as well as mechanomyographic monitoring techniques. (9) Kopman found that the magnitude of twitch augmentation is directly related to the frequency of stimulation. Sixty stimuli per minute (1 Hz) produce a larger effect than 16 stimuli per minute, which in turn produces a greater effect than six stimuli per minute (0.10 Hz). A five-second 50-Hz tetanus administered before initial twitch calibration has been shown to considerably shorten the time required to achieve baseline stability and thus reduce individual variability. (15) The staircase phenomenon is not manifested during the fade of twitch responses that occurs during TOF stimulation and therefore, does not affect the TOFR.

In the absence of neuromuscular block, TOFR may exceed values of 1.30, and in the absence of any preload applied to the thumb the TOFR ratio averages approximately 1.15–1.20. (9) Although the mechanism for this TOF augmentation has not been elucidated, it is reduced if a small elastic preload is applied to the thumb. (9) Dubois (16)(17) described a method to fix the arm and hand while creating a thumb preload within a “TOF tube" in order to optimize the accuracy and repeatability of accellerometry measurements.

Effects of interactions of volatile agents on NDMR

Individual volatile agents differ clinically in the magnitude by which they potentiate the neuromuscular blockade induced by NDMR. (2) For example, Miller *et al.* (18) demonstrated that 3.3 times more d-Tubocurarine was needed to obtain a 50% reduction in twitch height during halothane anaesthesia than during isoflurane anaesthesia.

The potentiation of non-depolarizing neuromuscular blockade by volatile agents includes the following three phenomena: (19)

- Decreased dose of neuromuscular blocker to produce similar clinical effect (i.e. increased potency)
- Shortened onset of action of neuromuscular blockade,
- Prolonged duration of action of the relaxant and prolonged recovery from the effects of neuromuscular blockade.

Numerous studies have investigated these aspects of the interaction between volatile anaesthetic agents and NDMR. Various investigators have attempted to quantify these effects. However varied results have been achieved. The pertinent studies are discussed in the following section and summarized in Table A1.

Studies investigating the effects of modern volatile anaesthetic agents on modern neuromuscular blockers

Rupp *et al.* (20) randomized 40 patients to receive 1.25 minimum alveolar concentration (MAC) halothane or enflurane (in 60% nitrous oxide) for 30 minutes prior to the administration of single bolus of atracurium (randomized to 50, 60, 70, 80, 90 or 100 μg/kg). They measured evoked twitch height responses of the A*dductor pollicis* using mechanomyography. They were unable to demonstrate a significant difference in the dose-response regression lines for halothane versus enflurane. However, when the results were analysed together with the results of a previously published study by the same lead author (21) that studied the effects of atracurium administered with 1.25 MAC isoflurane or fentanyl (both in 60% nitrous oxide), they demonstrated a statistically significant difference in the potency of atracurium administered in the presence of enflurane or isoflurane compared to a fentanyl-nitrous oxide anaesthetic. They estimated that the potentiation of atracurium by volatile agents was probably not more than 20%. They were unable to demonstrate any difference in the onset time of atracurium when administered in the presence of either one of the four different anaesthetics. Rupp *et al.* also measured the time from injection of the allocated single bolus of atracurium until the evoked twitch height of the *Adductor pollicis* was 95% of control as measured by mechanomyography. Using linear regression, they interpolated the plots of duration of action versus peak effect (defined as maximum percentage depression of twitch tension) for each group and then calculated the duration of a 50% block ($Duration_{50}$ – see Table 4). No significant difference in duration of action of atracurium was demonstrated between the enflurane and halothane groups. Again, the results of this study (comparing atracurium in halothane or enflurane) were analysed with the results of their previously published study (comparing atracurium in isoflurane or fentanyl). In this

manner they demonstrated a 33% increase in the duration of atracurium when administered together with enflurane compared to a fentanyl-nitrous oxide anaesthetic which is statistically significant.

These two studies (20)(21) therefore demonstrated that modern volatile anaesthetic agents increased the potency and duration of action of atracurium.

Ten years later, Wright *et al.* (22) performed a cross-over study in 16 patients to examine the effect of 1.25 MAC desflurane as well as 1.25 MAC isoflurane on vecuronium. The cross over design was intended to reduce the large inter-individual variation seen in the dose-response curve of vecuronium. All subjects were anaesthetized with the inhaled anaesthetic agents for >60 minutes prior to the administration of vecuronium to allow equilibration of the anaesthetic agents at the neuromuscular junction. They measured evoked *Adductor pollicis* twitch tension using mechanomyography. Fifty percent of participants were enrolled in potentiation studies in which 10µg/kg boluses of vecuronium were repeatedly administered until 90% twitch depression was achieved, at which point a vecuronium infusion was initiated and adjusted to maintain stable twitch depression at 80-90% of control. Wright *et al.* demonstrated that subjects displayed 20% greater twitch tension depression after administration of vecuronium when anaesthetized with desflurane compared to isoflurane. The remaining 50% of participants were enrolled in onset and duration studies in which a single bolus of vecuronium (100µg/kg) was administered and twitch tension was recorded until spontaneous recovery to 80-100% of control. Wright *et al.* demonstrated a faster onset time (defined as time from administration of vecuronium bolus to 12 seconds after last

detectable twitch response) for maximal muscle relaxation by vecuronium in the presence of desflurane versus isoflurane. They showed a significant increase in time for recovery to $T1_{25\%}$ and to $T1_{90\%}$ as well as the recovery interval from $T1_{25\%}$ to $T1_{75\%}$ ($T1_{25\text{-}75\%}$) of twitch height in the desflurane group versus the isoflurane group. This study (22) demonstrated that desflurane increased the potency, onset time and duration of vecuronium to a greater degree than isoflurane.

Kumar *et al.* (23) randomized 68 patients to receive desflurane or isoflurane (both 1 MAC in 66% nitrous oxide). Ten minutes after stabilization of the end-tidal concentration of the volatile agent, all patients received a single bolus of rocuronium. The neuromuscular junction was monitored using mechanomyography and TOF stimulation. Seventy percent of the participants in the study were enrolled in the potentiation studies and were randomly allocated to single rocuronium boluses of 75, 150, 225 or 300 µg/kg. The different doses of NDMR administered allowed for construction of a dose-response curve (using least squares regression analysis). The curves for isoflurane and desflurane did not differ in their slopes or intercepts and thus indicating no difference in potentiation. The remaining thirty percent of the participants in the study were enrolled in onset and duration studies. These patients received a single bolus of 0.6mg/kg of rocuronium. Patients in the desflurane and isoflurane groups showed similar onset times by rocuronium (defined as time from administration to maximal effect). Kumar *et al.* implied that their study demonstrated longer recovery times ($T1_{25\%}$, $T1_{90\%}$, TOFR 0.7, recovery interval $T1_{25\%\text{-}75\%}$) in the presence of desflurane in nitrous oxide compared to isoflurane. However their results did not achieve statistically significance. On examining the data presented in their paper (Table 4, page 489), we calculated the 95% confidence intervals of the difference between means for time to spontaneous recovery to

TOFR 0.7 and it is -0.19 to 28,02 minutes. This interval includes zero indicating that there is no difference between the groups. However, the interval includes 28 minutes which could be a clinically significant difference. A power calculation based on the published data reveals that in order to demonstrate a difference with an alpha of 0.05 and a power of 80%, the study would need 18 patients per group. In this study only 10 patients were included in each group for the onset and duration studies and therefore it is probably underpowered. Ultimately, this study (23) could not demonstrate a difference in the potency, onset or duration of rocuronium in the presence of desflurane or isoflurane.

Lowry *et al.* (24) also studied rocuronium and randomized 102 patients anaesthetized with 66% nitrous oxide in oxygen to 1.5 MAC of sevoflurane or isoflurane, or a propofol infusion. *Adductor pollicis* muscle mechanomyography was utilized and the muscle relaxant was administered 10 minutes after initiation of the administration of the volatile agent. Seventy percent of subjects in the study were enrolled in the potentiation studies and were randomized to receive a single bolus of rocuronium (75, 150, 225 or 300 µg/kg) to construct a dose-response curve. No significant difference in the gradients of the dose-response curves was demonstrated. However, comparison of the estimated ED_{50} for rocuronium in each group demonstrated a significant difference between the sevoflurane and the propofol groups. Sevoflurane increased the potency of rocuronium in this study. Thirty percent of subjects in the study were enrolled in the onset and duration studies and received a single bolus of rocuronium (0.6mg/kg). There was no difference in onset time (defined as time from administration to maximal blockade). Lowry *et al.* did demonstrate significantly prolonged recovery (TOFR 0.8, $T1_{25\%-75\%}$) of rocuronium in the sevoflurane group versus the propofol and isoflurane groups. The isoflurane group demonstrated marginally prolonged duration

from administration of rocuronium to $T1_{90\%}$ recovery and time to TOFR 0.8. Therefore this study (24) demonstrated that sevoflurane increased the potency and duration of action of rocuronium compared to isoflurane and propofol. No difference in the onset of action was demonstrated

The contrasting results in these four studies may be explained by the difference in the duration of time that the patients were exposed to the volatile agents before the NDMR were administered. The former two studies (20)(22) allowed 30 and 60 minutes respectively to allow equilibration of the anaesthetic agents at the neuromuscular junction. In contrast, the latter two studies (23)(24) only allowed 10 minutes each for equilibration.

Wulf *et al.* (25) investigated rocuronium in 80 patients during anaesthesia with 1.5 MAC desflurane, sevoflurane, isoflurane or total intravenous anaesthesia (TIVA) using propofol/fentanyl (all in 70% nitrous oxide). While previous studies had prescribed a minimum mandatory interval between the onset of anaesthesia and administration of the muscle relaxant to allow for equilibration of the volatile agents in the neuromuscular junction, this was not done in this study. The authors argued that this was in keeping with clinical practice. They stabilized the arm using specialized arm board. TOF stimulation of the ulnar nerve was administered and the response of *Adductor pollicis* was assessed using acceleromyography (TOF-GUARD®). A cumulative bolus technique was used to ensure equivalent doses in terms of the end-point achieved in individual patients. The calculated ED_{50}s showed that desflurane and sevoflurane significantly increase the potency of rocuronium when compared to TIVA. They expressed the degree of potentiation of volatile

agent as the ratio of ED_{50} of rocuronium during TIVA divided by ED_{50} of rocuronium during volatile anaesthesia. In this study, the degree of potentiation was 1.6 for desflurane, 1.3 sevoflurane and 1.2 isoflurane. Recovery end-points were measured and did not show significant prolongation in the duration of action of rocuronium in the volatile anaesthetic groups.

In a similarly designed study, also using a cumulative bolus technique and acceleromyography, Wulf *et al.* (26) studied cisatracurium in 84 patients during anaesthesia with 1.5 MAC desflurane, sevoflurane, isoflurane or total intravenous anaesthesia (TIVA) with propofol and fentanyl (all in 70% nitrous oxide). There was also no minimum mandatory interval prescribed between the onset of anaesthesia and administration of rocuronium. They demonstrated a more pronounced depression of T1 in the volatile anaesthetic groups compared to the TIVA group and demonstrated that the degree of potentiation (ratio of ED_{50} during volatile anaesthesia/ED_{50} during TIVA) of cisatracurium was 1.4 for desflurane, sevoflurane and isoflurane. Recovery end-points were measured and also did not show significant prolongation in the duration of action of cisatracurium in the volatile groups. As repetitive incremental dosing was used in this study, the authors speculated that had the NDMR been given as equivalent single "bolus" doses, the differences in duration of action may have become evident.

Therefore these two studies (25)(26) demonstrated that the potency of rocuronium and cisatracurium was increased by several volatile anaesthetic agents compared to TIVA. Prolongation of the duration of action of the muscle relaxants was not demonstrated.

Amin *et al.* (27) randomized 80 patients to four groups to receive either cisatracurium or rocuronium, during anaesthesia with either 2 MAC sevoflurane or propofol TIVA (all in 50% nitrous oxide). The neuromuscular junction was monitored with acceleromyography and TOF stimulation. However the study does not comment on how the TOF-GUARD® was calibrated or set up technically. The NDMRs were administered incrementally until 95% twitch depression was achieved. They constructed cumulative dose-response curves and demonstrated that sevoflurane anaesthesia resulted in an approximately 20% decrease of the ED_{50} and ED_{95}. They found no difference in the degree of depression between the two muscle relaxants. Recovery end-points were measured and results demonstrated that the recovery index $T1_{25\text{-}75\%}$ and time to spontaneous recovery of TOFR of 0.70 were significantly prolonged in the sevoflurane groups compared to propofol groups. These endpoints were also significantly longer in the cisatracurium group compared to the rocuronium group. Therefore this study (27) demonstrated that the potency and duration of action of rocuronium and cisatracurium was increased by sevoflurane (at 2MAC) compared to propofol.

Using electromyography to monitor the neuromuscular junction, Bock *et al.* (28) randomized 84 patients to receive 1.25 MAC isoflurane, desflurane, sevoflurane or propofol (all in 60% nitrous oxide). Inhaled anaesthetic agents were administered for 40 minutes prior to the administration of rocuronium to allow equilibration of anaesthetic agents at the neuromuscular junction. At this point the electromyography was re-calibrated and a single dose of 0.1, 0.15 or 0.2mg/kg rocuronium was administered. After maximal depression of the twitch response was recorded a second dose of rocuronium was administered so that all subjects received a cumulative bolus dose of 0.3mg/kg of rocuronium. After recovery of T1

to 5% of control twitch height, a rocuronium infusion was initiated and adjusted to maintain T1 at 5-10% of control twitch height. Dose-response curves were constructed and used to calculate ED_{50} and ED_{90} for rocuronium. They demonstrated a leftward shift in the dose response curve of rocuronium when administered in the presence of isoflurane, desflurane and sevoflurane compared to propofol. The desflurane group had the lowest ED_{90}. They could not demonstrate a statistically significant difference in the ED_{50} or ED_{90} for rocuronium in the presence of any of the volatile groups compared to the propofol group, despite each group consisting of 21 patients. The infusion rate of rocuronium required to maintain T1 at less than 10% of control was reduced during the volatile anaesthetics compared to the propofol group, thus suggesting that the potency of rocuronium was increased by 30-40% in the presence of a volatile agent. Bock *et al.* measured recovery end points but could not demonstrate a statistically significant prolonged spontaneous recovery for rocuronium in the presence of desflurane, sevoflurane, isoflurane compared to propofol. Confidence intervals are not provided and a *posthoc* power analysis was not performed, thus it is possible that the study was underpowered. Therefore this study (28) demonstrated that volatile anaesthetic agents potentiate the potency of rocuronium.

Similarly, Hemmerling *et al.* (29) randomized 56 patients to receive isoflurane, sevoflurane, desflurane or propofol infusions. However, in contrast to the other studies where nitrous oxide was used, all anaesthetics in this study were administrated in oxygen and air. The neuromuscular junction was monitored using electromyography and TOF stimulation. Attention was paid to calibration of the instrument; however, this did not include a stabilising tetanic stimulus. There was no standardized time of anaesthesia prior to the administration of cisatracurium. They used a closed-loop feedback system to control administration of

cisatracurium to maintain the first twitch response to a TOF stimulus at 10% of its control value. Their results showed that, in comparison to propofol, the volatile anaesthetic agents resulted in a cumulative dose reduction of cisatracurium of 42% with sevoflurane, 41% with isoflurane and 60% with desflurane, all of which are statistically significant. The dose reduction demonstrated in the desflurane group compared to the other volatile anaesthetic agents is also statistically significant. Therefore this study (29) demonstrated that volatile anaesthetic agents increased the potency of cisatracurium compared to propofol.

Stout *et al.* (30) randomized 40 patients to receive either desflurane or propofol. All anaesthetics were supplemented by 50% nitrous oxide and intravenous boluses of fentanyl were administered at the discretion of the anaesthetist. After 3 minutes of calibration of the electromyographic neuromuscular junction monitoring equipment, a single rocuronium bolus (0.6mg/kg) was administered. After spontaneous recovery of the T1 to 10% of its control, an infusion of rocuronium was commenced and titrated to maintain T1 at 10%. They showed that the required infusion rates of rocuronium were 67% less in the desflurane group compared to the propofol group. This statistically significant difference became evident within the first 30 minutes of administration of the infusion. Onset times were measured in this study and were defined as the time from administration of rocuronium bolus to T1 10%. Surprisingly, they found that the onset times in the desflurane group were 67% longer than in the propofol group. This was attributed to the increase in sympathetic tone that may occur with sudden rapid increase in the end-tidal concentration of desflurane. They suggested that this resulted in superficial vasoconstriction and delay in delivery of rocuronium to the *Adductor pollicis* that was being monitored. The infusion of rocuronium was discontinued 30 min prior to the end of surgery and spontaneous neuromuscular recovery was recorded for as

long as possible. None of the recovery end-points measured (time from discontinuation of rocuronium infusion to $T1_{25\%, 50\%, 75\% \text{ and } 90\%}$) demonstrated statistically significant differences between the groups, although the study was probably underpowered to evaluate spontaneous recovery end-points. The authors noted that the number of patients that achieved $T1_{75\%}$ and $T1_{90\%}$ spontaneously in each group were too small for statistical comparison. Therefore this study (30) demonstrated that desflurane increased the potency of rocuronium compared to propofol.

Factors that affect the degree of potentiation of NDMR

As described above, various studies have attempted to quantify the potentiation of NDMR by inhaled anaesthetic agents and that these have yielded varied results. The inconsistencies in the studies may be explained by differences in study design and/or end-points examined.

The magnitude of potentiation is influenced by several factors:

- the partial pressure at which the volatile agent is administered,
- the duration of exposure to the volatile agent (before administration of NDMR),
- the specific muscle relaxant
- the specific volatile agent

These aspects are discussed in the following sections:

- ***The influence of volatile anaesthetic agent partial pressure***

The potentiation of muscle relaxants by volatile agents is dose-dependent. This has been demonstrated *in vitro* as well as *in vivo*. (3) Waud *et al.* (4) showed that volatile agents depress the ability of isolated mammalian muscle to undergo depolarization when exposed to a cholinergic agonist. This effect was concentration-dependent. Gencarelli *et al.* (31) administered a constant-rate infusion of d-Tubocurarine (adjusted to produce a constant twitch tension 10% of control) and an end-tidal concentration of enflurane (ET_{Enf}) at 2.2% for 60 minutes. While the infusion of muscle relaxant was continued at the same rate, the enflurane concentration was decreased to ET_{Enf} 1.35% for the following 60 minutes and then to ET_{Enf} 0.5% for the final 60 minutes. Blood samples were taken at 60 minute intervals and radioimmunoassays performed to measure serum d-Tubocurarine levels. While the serum d-Tubocurarine levels were demonstrated to remain constant (approximately 0.2µg/ml), the decreasing enflurane concentration resulted in a significant decrease in the degree of neuromuscular blockade. At ET_{Enf} 2.2% twitch tension (as measured by mechanomyography at the *Adductor pollicis* muscle) was 8% of the control twitch tension. At $ET_{Enf,}$ 1.35% twitch tension increased to 57% of control and at ET_{Enf} 0.5% it increased further to 91% of control.

- ***The influence of the duration of administration of volatile anaesthetic agent***

The duration of exposure to the volatile agent influences the degree of potentiation displayed. Motamed *et al.* (32) demonstrated that there was a time-dependent potentiation of mivacurium induced neuromuscular blockade by sevoflurane and isoflurane compared with propofol. In this study, all patients were induced with propofol and fentanyl and after loss of consciousness, the neuromuscular junction was monitored with accelerometry and TOF stimulation. Details about calibration and stabilization of the monitored arm are not

available. All patients received an intubating dose of mivacurium (0.25mg/kg) and after tracheal intubation, were randomized to receive isoflurane (ET_{Iso} 1.2%) or sevoflurane (ET_{Sevo} 1.9%) or propofol (all in 50% nitrous oxide). After spontaneous recovery of T1 to 5% of its control, a mivacurium infusion was initiated at 10µg/kg/min and the infusion was manually adjusted to maintain T1 at 5-10% of its control value. The mivacurium requirements decreased progressively with time in all groups with the most meaningful changes occurring in the first 15 minutes after initiation of the mivacurium infusion. This early decrease in the mivacurium infusion rate was greater in the groups that received a sevoflurane or isoflurane anaesthetic. A statistically significant difference was demonstrated between the volatile anaesthetic agents and the propofol group at 15 minutes. The infusion requirements in the volatile groups continued to decrease, albeit at a slower rate, and at 90 minutes, the mivacurium infusion rate in the propofol group was four times higher than the infusion rate in the sevoflurane group.

- ***The influence of the type of muscle relaxant on the interaction between muscle relaxant and volatile anaesthetic agent***

The type of muscle relaxant used may influence the degree of potentiation measured. Rupp *et al.* (20) first suggested that different NDMR may be potentiated to different extents when they compared data from different studies by the same investigators and noted that atracurium and vecuronium appeared to be less affected by volatile agents than t-Tubocurarine or pancuronium. Work by Wulf *et al.* (25)(26) suggests that rocuronium may be more susceptible to potentiation by desflurane than cisatracurium. Amin *et al.* (27) directly compared the degree of potentiation exerted by sevoflurane on rocuronium and

cisatracurium and demonstrated that the duration of action of cisatracurium in the presence of sevoflurane was significantly longer than that of rocuronium.

- ***Influence of the type of volatile agent***

It appears that specific volatile agents differ with regard to the degree of potentiation that they exert on the effect of neuromuscular blockers. Not all studies yield identical results. This is attributed to differing methodologies and several of the studies lack statistical power. However, it seems that most studies agree on the order that the volatile anaesthetics may be ranked in terms of their potentiating effect on neuromuscular blockers. Desflurane has been shown to display the greatest degree of potentiation of NDMR, followed by sevoflurane > isoflurane > halothane > nitrous oxide-barbiturate-opioid or propofol anaesthesia. (22) (23) (25) (29)

Proposed mechanism by which volatile agents potentiate the effect of neuromuscular blockers

The exact mechanism of enhancement of non-depolarizing muscle relaxant-induced neuromuscular blockade by volatile anaesthetic agents is under debate. Postulated mechanisms are varied and include:

- direct synergistic effects at the level of the nAChR,
- prejunctional effects of inhaled anaesthetic agents,
- pharmacodynamic interaction by means of increased blood flow to muscles under anaesthesia, and

- centrally mediated relaxation by inhaled anaesthetic agents including the preferential effect of inhaled anaesthetic agents on the spinal cord and central pattern generator. (27) (33)

Using an isolated mammalian muscle model, Waud *et al.* (4) concluded that both neuromuscular blockers and volatile anaesthetics inhibit depolarization at the neuromuscular end-plate. While neuromuscular blockers prevent the interaction between acetylcholine and the nAChR, the volatile agents depress depolarization at a step distal to the receptor. They suggested that depolarization of the muscle membrane was inhibited in the presence of volatile agents despite the nAChR being stimulated by its agonist.

Early pharmacokinetic studies with rocuronium suggested that volatile anaesthetics did not significantly influence the pharmacokinetics of the muscle relaxant (i.e. did not change the rate of disappearance of rocuronium from the plasma) and that volatile anaesthetic-induced potentiation of the neuromuscular block could probably be explained by increased sensitivity of the neuromuscular junction for the relaxant (i.e. decrease in the EC_{50}). (34) Thus volatile agents probably influence muscle relaxants at a pharmacodynamic level.

Evidence in support of this supposition was produced by Paul *et al.* (6) who studied the inhibitory effects of two NDMR (d-Tubocurarine and vecuronium) in isolation and in the presence of two volatile anaesthetics agents (sevoflurane and isoflurane) in an *in vitro* model designed to evaluate their interaction at the nAChR level. Their work showed that exposure

of the model to volatile agents enhanced the inhibitory effects of the neuromuscular blockers on the nAChR and they suggested that volatile anaesthetics may enhance the affinity of the nAChR for NDMR. The augmentation of effect achieved statistical significance at all concentrations of muscle relaxant studied. This potentiation was most impressive at small concentrations of muscle relaxant.

The magnitude of potentiation is dependent on the aqueous concentration of the volatile agent. Motamed *et al.* demonstrated that the anaesthetic potency of the individual volatile agents (in terms of MAC) did not correspond to their muscle-relaxing properties. They suggested that the volatile agents when used clinically, are equipotent in their ability to affect the nAChR, but the more clinically pronounced effects of some volatile agents may be explained in terms of the aqueous concentration of the volatile anaesthetic achieved. Less potent anaesthetics (i.e., desflurane in contrast to isoflurane) appear to exert a greater effect because they are administered at greater partial pressures and therefore result in greater aqueous concentrations. In addition, desflurane and sevoflurane have low blood/gas and tissue/gas solubility which results in more rapid equilibration between the end-tidal partial pressure and the volatile agent tension at the neuromuscular junction compared to more soluble volatile anaesthetics. Thus a greater aqueous concentration at the nAChR is achieved more quickly, resulting in a greater clinical effect. (32)

Effect of propofol, sufentanil and nitrous oxide on neuromuscular function

It has been shown that propofol and sufentanil do not contribute to the effects of neuromuscular blocking agents. (35) While nitrous oxide (N_2O) (70% inspired) was

previously considered to not have an effect on neuromuscular blockade (36), recent evidence suggests that N_2O has a potentiating effect on neuromuscular block. It has been demonstrated to decrease the ED_{50} of rocuronium by approximately 20%. (37) It is interesting to note that most of the studies reviewed in this paper used nitrous oxide (N_2O) (50-70%) in all groups. This may have influenced their results, especially with regard to the studies investigating the relative potencies of the various volatile anaesthetics, of which some did not achieve statistical significance.

NDMR used in this study

NDMR are classified into two chemical classes, namely steroidal compounds and benzylisoquinolinium compounds.

Rocuronium is the least potent NDMR available commercially. It is a steroidal relaxant of intermediate duration, thus similar in structure to, but less potent than pancuronium and vecuronium. The ED_{95} of rocuronium is 0.3 mg/kg. The recommended dose for tracheal intubation is 0.6 mg/kg body weight (thus $2xED_{95}$) after which adequate conditions for laryngoscopy and tracheal intubation should be established within 90 seconds.

Cisatracurium is the most potent commercially available neuromuscular blocking agent with an ED_{95} of 0.05 mg/kg. It is a benzylisoquinolinium compound and is one of the 10 stereo-isomers of atracurium. Its onset time and duration of effect are slightly longer than that of atracurium. The recommended dose for tracheal intubation is 0.15 mg/kg body weight (thus

3xED_{95}) after which adequate conditions for laryngoscopy and tracheal intubation should be established within 3 minutes.

Studies have investigated and compared the duration of action of rocuronium and cisatracurium.

Scultz *et al.* (38) used mechanomyography to study the duration of action of rocuronium in the presence of TIVA (in 66%N_2O) and demonstrated the median time from administration of the NDMR to spontaneous recovery to TOFR 0.8 for rocuronium 0,9mg/kg was 73min (range 39-127, n=18). The very wide spread in the range of results should be noted. Addamus *et al.* (39) used kinemyography and compared the clinical duration and time to spontaneous recovery after rocuronium in young (age 20-40 years) and older patients (age 60-75 years) of both genders during TIVA. Statistically and clinically significant differences in the clinical duration of neuromuscular blockade and the complete recovery time were demonstrated between males and females, as well as between the young and the elderly. The longest times and most heterogeneous results were demonstrated in the elderly female group. [Time to TOFR0.9 after 2xED_{95} rocuronium: young males 59 min (interquartile range 51-67 min); elderly female 128 min (interquartile range 94-137 min) $p<0.05$]

The pharmacodynamics of cisatracurium were studied by Belmont *et al.* (40) in patients receiving a barbiturate and opioid anaesthetic in 70% N_2O. Using mechanomyography, the mean time from injection of cisatracurium to spontaneous recovery to TOFR0.7 was

determined. After cisatracurium 0.1mg/kg (thus 2xED_{95}), the mean time of this variable was 66.7min (SE±4.9, n=8) and after cisatracurium 0.2mg/kg (thus 4xED_{95}) was 89.9min (SE±3.4, n=10).

Adamus *et al.* (41) used kinemyography to compare the duration of action of cisatracurium and rocuronium in the presence of TIVA (no N_2O was used). They found no difference in the clinical duration of neuromuscular blockade or the complete recovery time after 3xED_{95} doses of rocuronium and cisatracurium.

Purpose of this study

In summary, volatile anaesthetic agents potentiate the potency (20)(22)(24)(25)(26)(27)(28)(29)(30) and the duration of action of NDMR. (20)(22)(23)(24)(27) Desflurane appears to cause the greatest degree of potentiation of the neuromuscular blocking drugs compared to other volatile anaesthetic agents. (23)(29) Studies conducted by Wulf *et al.* (25) (26) could not demonstrate significant potentiation of duration of action of the NDMR by volatile agents, but suggest that desflurane may have a more significant effect on rocuronium than cisatracurium in terms of potency. However, Amin *et al.* (27) showed that sevoflurane prolonged the time to recovery after cisatracurium more than after rocuronium. No previous study has compared the degree of potentiation exerted by desflurane on the highly-potent versus the less-potent NDMR. The purpose of this study was to determine whether desflurane (in an oxygen and air mixture) prolongs the effects of rocuronium and cisatracurium to the same or to a greater degree. The hypothesis was that there would be no difference.

METHODOLOGY

This prospective randomized clinical trial was conducted according to the principles of the declaration of Helsinki (42). Approval for the study (Project Number N06/02/017) was obtained from the research ethics committee of Stellenbosch University, Faculty of Medicine and Health Sciences. Informed consent was obtained from ASA I-III physical status patients, scheduled for elective surgery of expected duration 60 minutes or longer. Exclusion criteria included renal or hepatic dysfunction, myopathies and muscular dystrophies, patients receiving any medication known to interact with neuromuscular blocking agents (e.g. aminoglycoside antibiotics), patients with potential airway problems and body mass index greater than 35.

Anaesthesia

Patients received a diazepam 10 mg oral premedication two hours pre-operatively. In the operating room, routine monitors (electrocardiography, pulse oximetry, automated non-invasive blood pressure, capnometry, accelerometry) were prepared and an intravenous infusion of Ringer's Lactate was established after skin infiltration with lignocaine.

The effects of neuromuscular blockade by rocuronium or cisatracurium were measured using a nerve stimulator and accelerometry according to the guidelines of Good Clinical Research Practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents (10). Electrodes of a TOF-GUARD® accelerometric neuromuscular monitor (Organon Teknika,

Turnhout, Belgium) were attached to the skin overlying the ulnar nerve at the wrist. The arm, fingers and hand were immobilized on a modified "TOF tube" (17)(16) and the accelerometer transducer was taped to the thumb, to which a small preload had been applied using a light elastic band. (Figure 1)

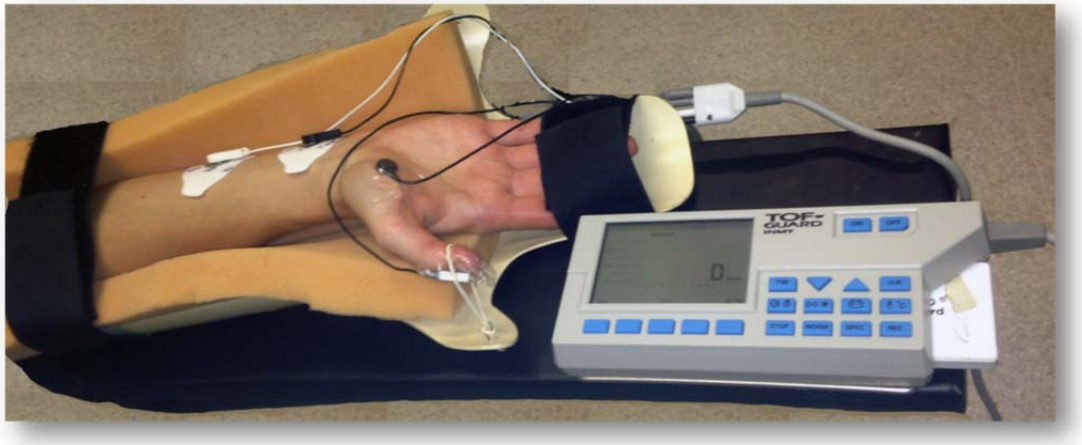

Figure 1: TOF-Guard® monitor and modified "TOF tube

After pre-oxygenation via face mask, sufentanil 0.25 µg/kg (actual body weight) was administered, followed immediately by an infusion of 0.5 µg/kg/hour using a syringe pump (Graseby model 3400). Calculated blood and effect-site concentrations were monitored using pharmacokinetic simulation software (StelSim)♣ employing the pharmacokinetic parameter-set of Gepts *et al.* (43). After approximately 5 minutes, when the simulated sufentanil effect-site concentrations had reached approximately 0.5 ng/mg, anaesthesia was induced with propofol 1-2mg/kg. Following loss of consciousness, a 50Hz tetanic stimulation of 5 seconds

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duration was applied to the ulnar nerve in order to avoid the “staircase effect" (15). Immediately thereafter, monitoring of responses by the *Adductor pollicis* muscle to twitch stimuli (50 mA) using the TOF-GUARD® monitor at one-second intervals was begun. In order to establish comparable control values, the twitch responses were allowed to achieve stable values before the monitor was calibrated. After calibration of the TOF-GUARD® monitor, a $3xED_{95}$ of either rocuronium (0.9 mg/kg) or cisatracurium (0.15 mg/kg) was administered and a stopwatch was started. Patients’ lungs were ventilated manually via facemask until the twitch responses had decreased to 10% of the control value, whereupon tracheal intubation was performed.

Anaesthesia was maintained with either desflurane or propofol. Group DR patients received rocuronium during desflurane-sufentanil anaesthesia; Group DC patients received cisatracurium during desflurane-sufentanil anaesthesia. Desflurane end-tidal partial pressures were maintained at 4 kPa, while adjusting the sufentanil infusion rates according to patient requirements. Groups PR and PC patients underwent TIVA using propofol and sufentanil. Propofol was administered by a separate infusion pump using the regimen of Roberts *et al.*(44) This comprises infusion rates of 10 mg/kg/h for 10 minutes, followed by 8 mg/kg/h for 10 minutes and 6 mg/kg/h thereafter. Estimated propofol blood concentrations were monitored by a separate instance of the pharmacokinetic software StelSim, employing the pharmacokinetic parameter set of Marsh *et al*. (45) Sufentanil and propofol infusion rates were adjusted according to patient requirements for suppression of autonomic responses during surgery. Rocuronium and cisatracurium were administered to Groups PR and PC respectively.

After intubation, the TOF-GUARD® monitor was set to apply TOF supramaximal stimuli at 12 second intervals throughout the course of anaesthesia and surgery. The neuromuscular block was allowed to recover spontaneously to a TOFR of 0.9 after which additional neuromuscular blocking agent (0.5 x ED_{95}) was administered if judged to be necessary for continued surgery. All data were stored in the memory card of the TOF-GUARD® monitor for subsequent transfer to a personal computer and offline analysis.

The sufentanil administration was terminated at the beginning of wound closure and propofol administration during skin-closure. Desflurane administration was terminated after skin-closure. If the TOFR was not ≥ 90%, residual neuromuscular blockade was reversed during skin closure using neostigmine (0.04 mg/kg) and glycopyrollate (0.08 mg/kg).

Estimation of sample size and patient enrolment

We regarded a clinically relevant difference in duration of effect to be 15 minutes (SD 12). Calculation of the required sample size for four groups required to ensure a power of 0.8 with an alpha value of 0.05 revealed that each group should consist of at least 15 subjects. Patients were randomly allocated to one of the four designated groups by means of a table of random numbers (www.randomization.com). In order to ensure that the required minimum number of patients with complete datasets be enrolled into each group the following procedure was followed if reversal of neuromuscular blockade was required before spontaneous recovery to TOFR90%: the patient was disqualified from the study and the next study patient was allocated to the disqualified patient's group.

Statistical analysis

Data were visualized using box-and-whisker plots and tests for group differences were performed using one-way analysis of variance (Medcalc Statistical Software (version 12.3.0.0), Mariakerke, Belgium, http://www.medcalc.org/). If analysis of variance detected a significant result then *posthoc* pairwise group-comparisons were done using the Student-Newman-Keuls Method. If the group data did not meet the criteria for equal variances (Levene's test), then nonparametric tests were performed (Kruskal-Wallace) and the posthoc test for pairwise comparison of subgroups were done according to Conover. (46) Confidence interval analysis was done using the software package CIA (Trevor Bryant, University of Southampton). An alpha value of 0.05 or less was regarded as indicating statistical significance.

RESULTS

Of the 81 patients who were recruited into the study, 63 recovered spontaneously to a TOFR of 0.9. The reason for the dropouts was that the surgery was completed before spontaneous neuromuscular recovery was complete, thus necessitating reversal of neuromuscular blockade and termination of anaesthesia.

Table 2: Demographic data

	DC	*DR*	*PC*	*PR*	
N	15	15	17	16	
Female/Males	13/2	11/4	13/4	13/3	
Age (years)	44.8±8.8	43.8±12.2	47.2±11.4	43.1±15.2	p=0.791
BMI	25.3±4.9	25.3±4.5	26.24±4.9	23.2±4.1	p=0.311

DC = desflurane-cisatracurium group; DR = desflurane-rocuronium group; PC = propofol-cisatracurium group; PR = propofol-rocuronium group. BMI = body mass index

The differences among the groups are not great enough to exclude the possibility that the difference is due to random sampling variability. More females than males were included in all the groups.

A typical recording from the TOF-GUARD® is presented in Figure 2.

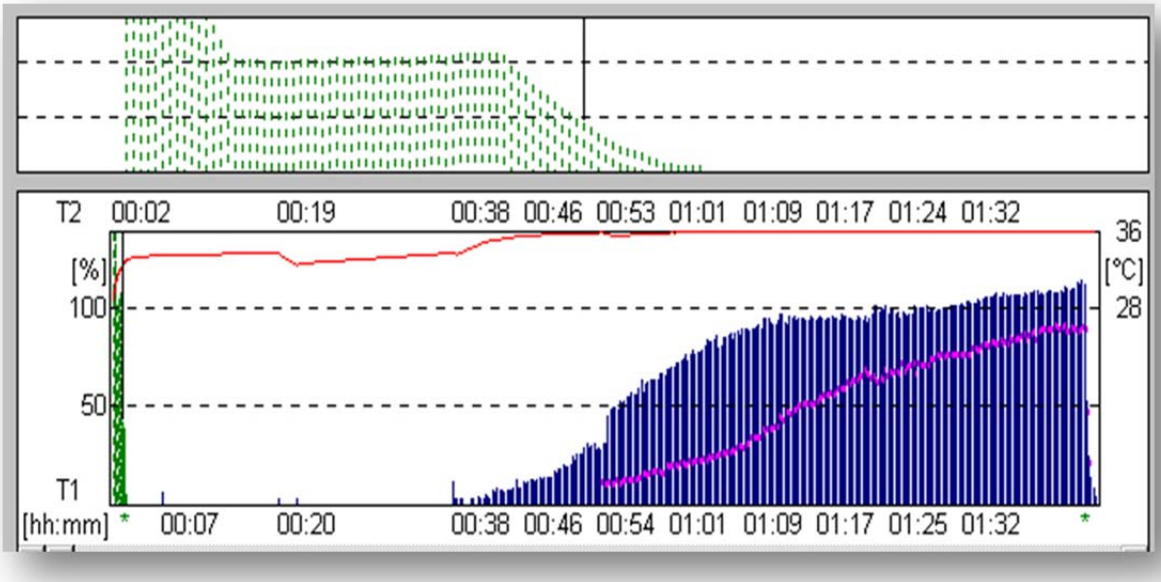

Figure 2: Graphical representation of a recording of a single study patient from the TOF-GUARD®

x-axis = time, *y*-axis = twitch height (as a percentage of control), Green lines displayed on the upper level are an expansion of the green lines on the lower level, Green lines = twitch response from single twitch, Blue lines = twitch response from TOF twitches, Purple dots = TOFR, Red line = temperature measured at *Adductor pollicis*

Accelerometry data of spontaneous recovery times are depicted graphically in Figures 3 to 5 and results of the one-way ANOVA are depicted in Table 2. In the box-and-whisker plots, the central box represents the values from the lower to upper quartile (25^{th} to 75^{th} percentile). The middle line represents the median. The red square within the square depicts the mean value. The vertical line extends from the minimum to the maximum value, excluding outside and far out values, which are displayed as separate points. An outside value is defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range (inner fences). A far out value is defined as a value that is smaller than the lower quartile minus 3 times the interquartile range, or larger than the upper quartile plus three times the interquartile range.

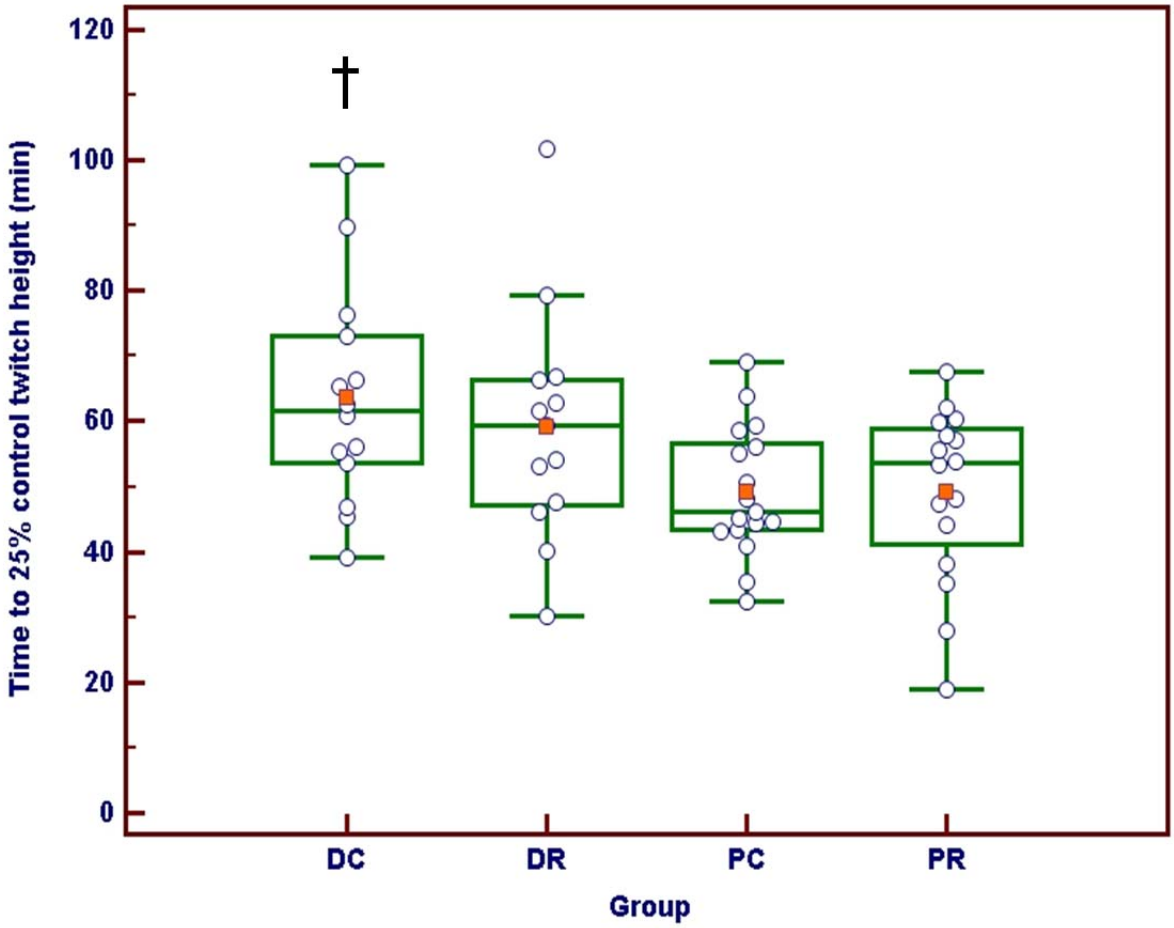

Figure 3: Box and whisker plot of times to recovery to $T1_{25\%}$

"Time to 25% control twitch height" = Time from administration to spontaneous recovery of T1 to 25% twitch in minutes, DC = desflurane-cisatracurium group; DR = desflurane-rocuronium group; PC = propofol-cisatracurium group; PR = propofol-rocuronium group.

† = significantly different from PC ($p < 0.05$).

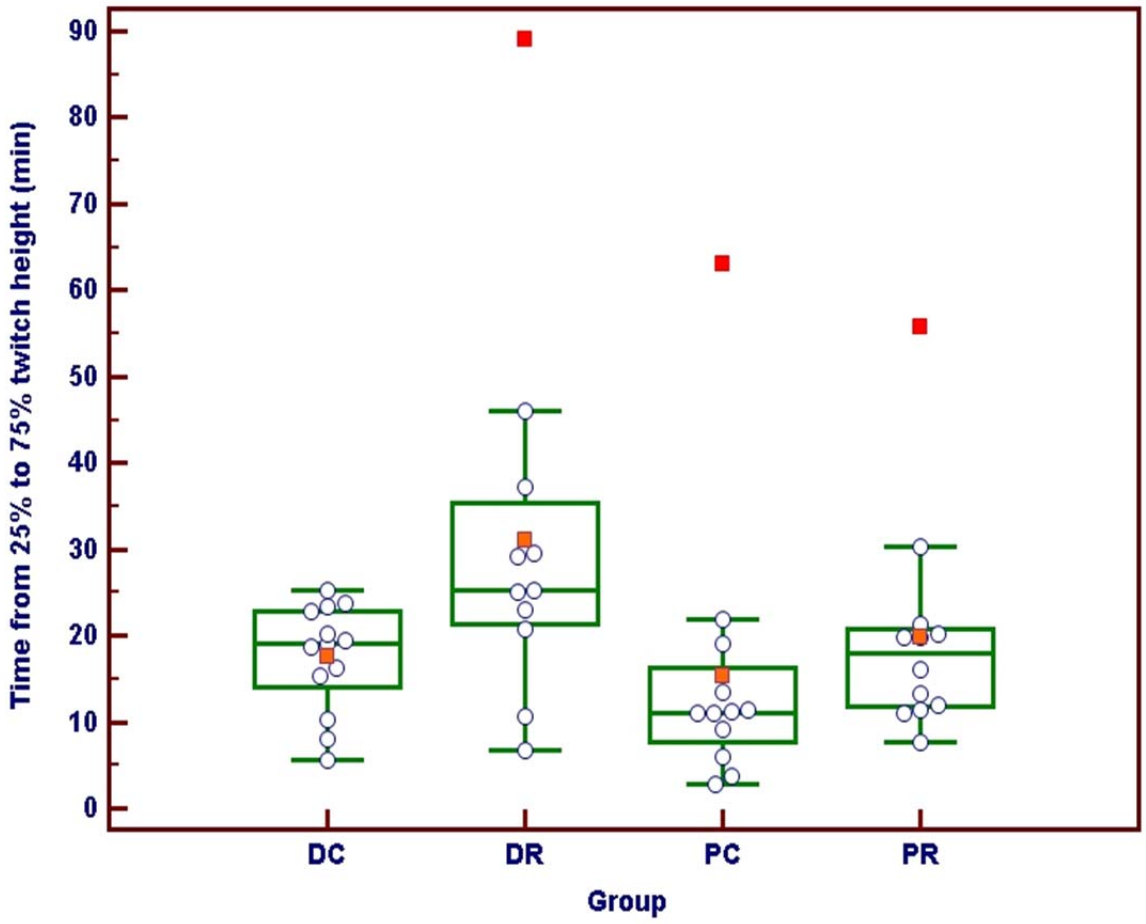

Figure 4: Box and whisker plot of times to recovery of $T1_{25\%-75\%}$

"Time from 25% to 75% twitch height" = Time from administration to spontaneous recovery of $T1_{25\%-75\%}$ in minutes, DC = desflurane-cisatracurium group; DR = desflurane-rocuronium group; PC = propofol-cisatracurium group; PR = propofol-rocuronium group.

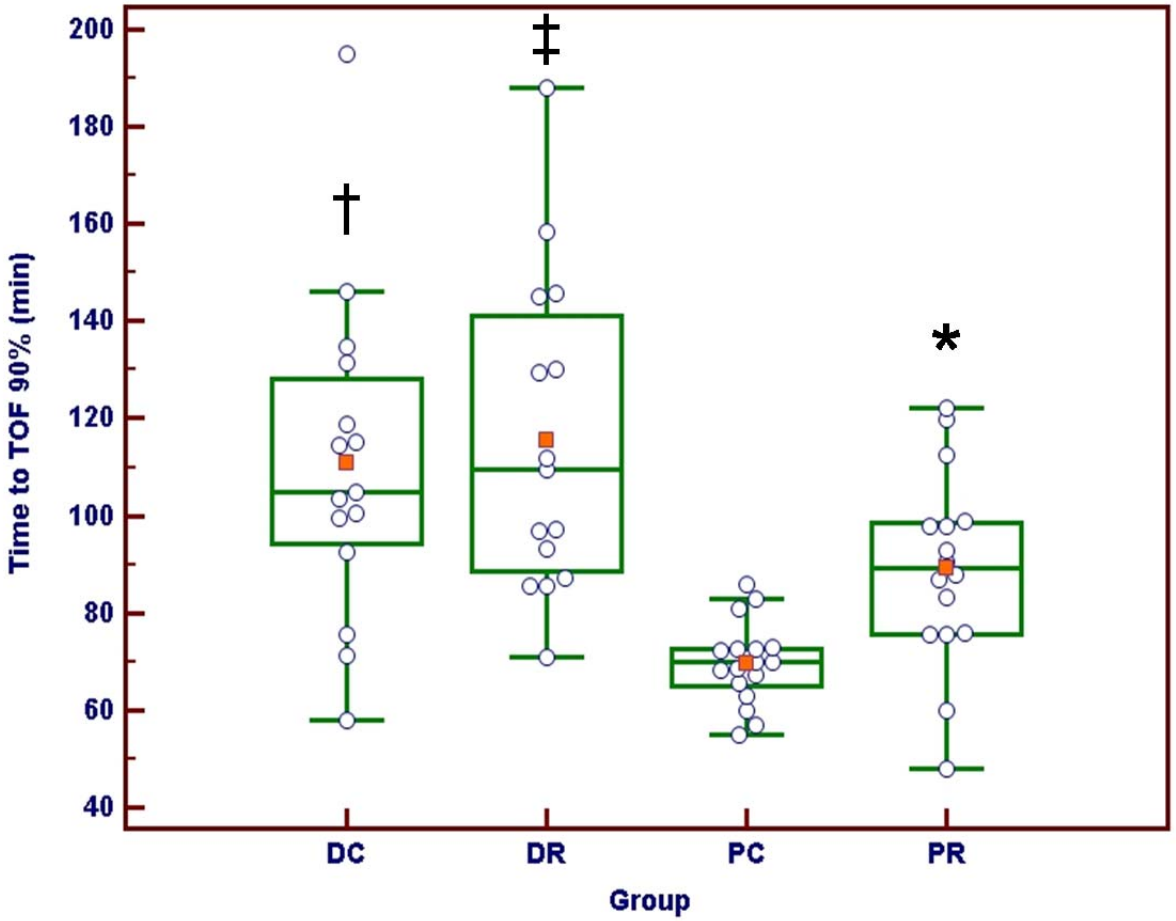

Figure 5: Box and whisker plot of times to recovery to TOFR 0.9

"Time to TOF 90%" = Time from administration to spontaneous recovery to TOFR 0.9 in minutes, DC = desflurane-cisatracurium group; DR = desflurane-rocuronium group; PC = propofol-cisatracurium group; PR = propofol-rocuronium group.

† = significantly different from PC ($p < 0.05$); ‡ = significantly different from PR ($p < 0.05$); * = significantly different from PC ($p < 0.05$).

Table 2: Times to various stages of recovery from neuromuscular blockade after a dosage of 3xED$_{95}$ of cisatracurium or rocuronium during propofol or desflurane anaesthesia

	n	*Group*	*Median or mean*	*25th to 75th percentile or SD*	*P (ANOVA)*	*Significant differences between groups (p<0.05)*
Spontaneous Recovery of T1 to 25% twitch (min)	17 16 14 13	PC PR DC DR	49.2 49.2 63.6 59.2	9.9 13.3 16.8 18.1	0.017	DC DC PC, PR
Spontaneous Recovery of T1 from 25% to 75% twitch (min)	12 12 13 11	PC PR DC DR	15.3 19.9 17.5 31.1	16.0 12.8 6.2 22.1	0.073	
Spontaneous Recovery TOFR 0.9 (min)	17 16 15 15	PC PR DC DR	69.9 89.3 104.7 109.6	64.9 - 72.7 75.6 - 98.4 94.2 - 128.2 88.6 - 141.3	<0.0001	PR, DC, DR PC, DC, DR PC, PR PC, PR
Time to intubation (min)	27 32	Roc Cis	0.94 2.09	0.58 0.76	<0.001	

n = number of patients; PC = propofol & cisatracurium; PR = propofol & rocuronium; DC = desflurane & cisatracurium; DR = desflurane & rocuronium, 25%-75% = 25th to 75th percentile; SD = standard deviation of the mean; ANOVA = one-way analysis of variance; Roc = rocuronium; Cis = cisatracurium

The following statistically significant differences in spontaneous recovery indices were found between the four groups:

Mean times for the first TOF twitch response to recover to 25% of control values: There were no statistically significant differences between PC and PR as well as DC and DR. There was a significant difference between PC and DC, but not between PR and DR.

Mean times for the first TOF twitch response times to recover from $T1_{25\%}$ to $T1_{75\%}$: No statistically significant differences were demonstrated between the four groups.

Mean times for the first TOF twitch response to recover to 90% of control values: There were no significant differences between the groups, however the data were considered to be too sparse to infer a meaningful result and that variable is not further reported or commented upon.

Median times for the TOFR to recover to 90%: Relations between the times to recovery were as follows: PR > PC; DC > PC; DR > PR.

With regard to the spontaneous recovery of the TOFR to 0.9 during propofol-opioid anaesthesia (the control groups), the median duration of action of rocuronium was longer than that of cisatracurium. In order to establish whether the relative prolongation by desflurane of one NDMR was greater than the relative prolongation of the other and whether there was an interaction between the type of NDMR and the type of anaesthetic, two-way analysis of variance was performed. The main effects were the types of anaesthetic and NDMR on indices of recovery. The results are depicted graphically in Figure 6. The effect of the type

of anaesthetic on TOFR0.9 was statistically significant ($p < 0.01$) whereas the effect of the type of relaxant was not ($p = 0.063$). There was no interaction ($p = 0.26$).

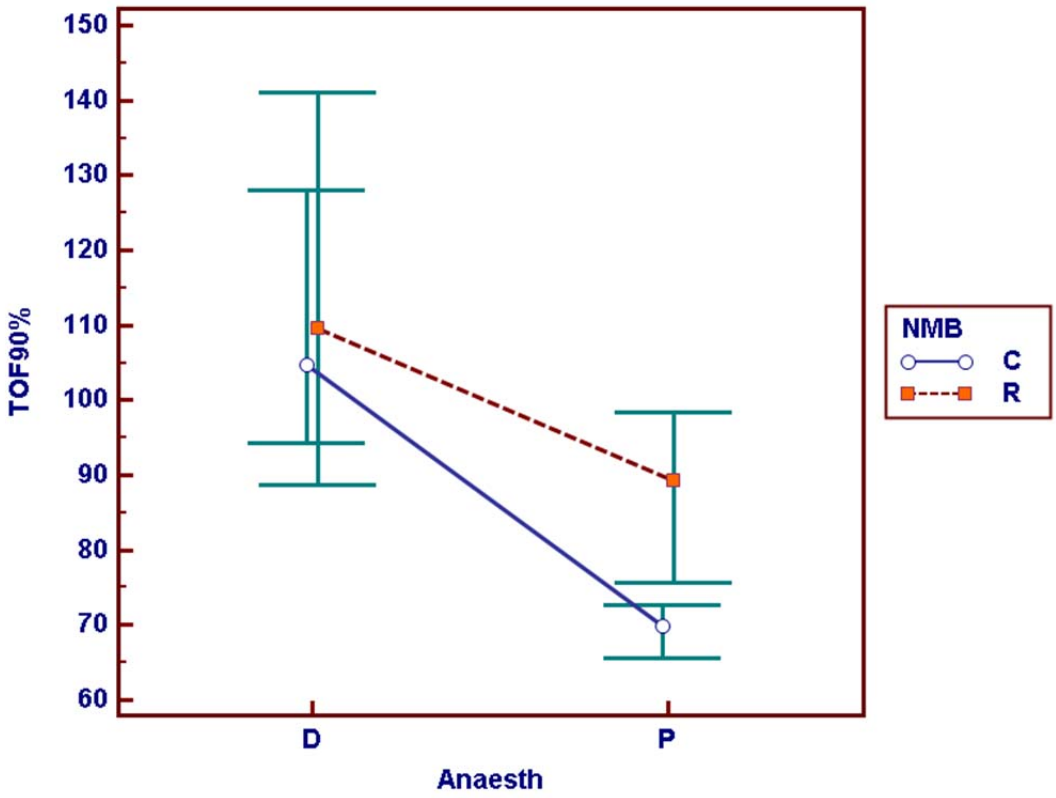

Figure 6: Interaction diagram of TOFR 0.9

TOF90% = time to recovery to a TOFR of 90% (minutes), Anaesth = type of anaesthetic; D = desflurane; P = propofol; C = cisatracurium; R = rocuronium;

Error bars indicate 95% confidence intervals of the mean values.

CONCLUSIONS

Desflurane significantly prolonged the time to spontaneous recovery after administration of NDMR compared to the control.

There was no difference demonstrated between the two muscle relaxants with regard to the mean prolongation by desflurane.

DISCUSSION

The purpose of this study was to determine whether desflurane prolongs the duration of action of rocuronium and cisatracurium to the same degree. This study demonstrated that, compared to TIVA, desflurane (0.6-0.7 MAC) - opioid anaesthesia prolongs the time to spontaneous recovery to $T1_{25\%}$ and TOFR 0.9 after both cisatracurium ($3xED_{95}$) and rocuronium ($3xED_{95}$). We cannot conclude from our data that there was a difference between the two muscle relaxants.

Closer examination of the data (Figures 3 to 5) and of the statistical analysis (Table 2) reveals that there was wide scatter of the data, including some prominent outliers, so that it is likely that the study was underpowered to demonstrate a difference, if it exists. Table 3 presents the 95% confidence intervals of the mean prolongation times of the two muscle relaxants. The difference in mean prolongation time is 14.5 minutes (95% confidence interval -11.8 to 40.9), which reflects the wide inter-individual variation. A *posthoc* sample size calculation reveals that in order to detect a real difference, if it exists, with 80% power and alpha 0.05 would require 101 subjects per group. Considering the prolonged mean times to recovery in the presence of desflurane (105 and 110 minutes), the mean difference in prolongation of 14.5 minutes and the presence of wide scatter in the data, it is unlikely that the difference between the two NDMR is of clinical importance. This is in contrast to a study (27) that used sevoflurane (2 MAC) and demonstrated that the time to spontaneous recovery to TOFR 0.7 was significantly prolonged in the cisatracurium group compared to the rocuronium group.

To our knowledge, no other study has investigated whether desflurane (in an oxygen and air mixture) prolongs the effects of rocuronium and cisatracurium to the same degree or not.

Table 3: 95% confidence intervals of the mean prolongation times of cisatracurium and rocuronium

Comparison (Welch's t-test)	*Mean prolongation of time to TOFR90%*	*Standard deviation*	*95% CI of difference*
PC vs. DC	41.1	33.6	23.9 to 59.9
PR vs. DR	26.6	39.2	6.2 to 46.9

PC = propofol & cisatracurium; DC = desflurane & cisatracurium; PR = propofol & rocuronium; DR = desflurane & rocuronium,

The effects of desflurane on a single bolus of rocuronium (23) as well as cumulative bolus techniques (25)(28)(30) have been explored. Cumulative bolus techniques have also been used to study the effects of desflurane on cisatracurium (26)(29). These studies have investigated the effect of desflurane on the action of either rocuronium or cisatracurium using an array of neuromuscular monitoring equipment. Not one study has demonstrated a statistically significant increase in the duration of action of either one of these NDMR in the presence of desflurane. However, this has been attributed to insufficient data regarding the effect of desflurane on the time to spontaneous recovery to TOFR 0.75-0.9 after a fixed

single dose of NDMR. (26)(25) In the current study, all patients were allowed to recover spontaneously to TOFR 0.9 after receiving equivalent $3xED_{95}$ doses of NDMR.

A secondary finding of this study is that during propofol-opioid anaesthesia, the time to spontaneous recovery to TOFR 0.9 after rocuronium ($3xED_{95}$) is greater than that of cisatracurium ($3xED_{95}$). This is in contrast to a study by Adamus *et al.* (41) that used kinemyography to compare the duration of action of cisatracurium and rocuronium in the presence of TIVA and demonstrated no difference between the recovery times of the two NDMR. Their study compared the times from administration of the NDMR ($3xED_{95}$ doses) to $T1_{25\%}$ as well as the times from $T1_{25\%}$ to TOFR 0.9. The time to $T1_{25\%}$ was identical in both groups [rocuronium 52min (SD 12, n=30); cisatracurium 52min (SD 7, n=30)]. In comparison, our study also demonstrated identical times to recovery to $T1_{25\%}$ between the two NDMR in the presence of TIVA. Adamus *et al.* demonstrated no difference between the two NDMR when they compared the times from $T1_{25\%}$ to TOFR 0.9 [rocuronium 56,7min (SD 12.9, n=15); cisatracurium 52.5min (SD 7, n=15)]. In contrast, our study found that the median time for interval from administration of rocuronium (in the presence of TIVA) to spontaneous recovery to TOFR 0.9 was 19.4 min longer than for the same parameter in the cisatracurium group. The two measurements are not the same and therefore cannot be compared.

There are few studies that investigate the duration of action of $3xED_{95}$ doses of rocuronium or cisatracurium. As discussed above, Adamus *et al.* (41), using kinemyography, demonstrated the mean time from administration of cisatracurium 0.15mg/kg to $T1_{25\%}$ in the

presence of TIVA was 52min (SD 7, n=30). In comparison our study demonstrated a mean time to $T1_{25\%}$ in the cisatracurium group administered in the presence of TIVA of 49.2 min. Lightall *et al.* (47), using accelerometry, demonstrated the mean time to $T1_{25\%}$ after cisatracurium 0.15mg/kg was 60min (range 36-76, n=10) in the presence of isoflurane (0.6-1%) in 50% N2O. In comparison, our study demonstrated a mean time to $T1_{25\%}$ in the cisatracurium group administered in the presence of desflurane of 63.6 min. Scultz *et al.* (38) used mechanomyography to study the duration of action of rocuronium in the presence of TIVA (in 66%N2O). They demonstrated a median time from administration of rocuronium 0,9mg/kg to recovery to $T1_{25\%}$ was 41min (range 23-72, n=32). Using kinemyography, Adamus *et al.* (41) demonstrated the mean time from administration of rocuronium 0.9mg/kg to $T1_{25\%}$ was 52min (SD 12, n=30) in the presence of TIVA (no N2O was used). In comparison our study demonstrated a mean time to $T1_{25\%}$ in the rocuronium group administered in the presence of TIVA of 49.2 min. Majorian *et al.* (48) used mechanomyography to demonstrate the mean time from injection of rocuronium 0.9mg/kg to recovery to $T1_{25\%}$ was 53min (range 35-88, n=9) in the presence of 0.7-1.3% isoflurane (60% N2O). Using accelerometry, Lightall *et al.* (47) demonstrated the mean time from administration of rocuronium 0.9mg/kg $T1_{25\%}$ in the presence of isoflurane (0.6-1%) in 50% N2O was 64min (range 32-85, n=10). In comparison, our study demonstrated a mean time to $T1_{25\%}$ in the rocuronium group administered in the presence of desflurane of 59.2 min.

It is important to note the wide range of results demonstrated in these studies that investigate the duration of action of $3xED_{95}$ doses of rocuronium or cisatracurium. It appears that more heterogeneity is demonstrated in the rocuronium groups than the cisatracurium groups. Very wide inter-individual variation was also demonstrated in our study. The influence of age and

gender on the duration of action of rocuronium has recently been demonstrated for the first time. (39) Our study included a high percentage of female patients and a wide range of ages. It appears to be common practice for studies that investigate the duration of action of NDMR to include participants from both genders (unmatched) and a wide range of age groups, as this is representative of clinical practice. It would be enlightening to confirm the effect of age and gender on duration of action of NDMR. Future studies should consider including these parameters in their criteria to match their groups.

The relevance of this study in clinical practice is the implication that more NDMR will be required when using TIVA techniques compared to inhalational techniques. Nevertheless the wide variation in individual patients' clinical responses to a single fixed dose of NDMR emphasizes the need to monitor the effects of the neuromuscular block by means of a peripheral nerve stimulator for safe practice.

This study is representative of clinical practice: a 3xED_{95} dose of NDMR was administered, the desflurane was initiated after administration of the NDMR and 0.8 MAC (in O2 and air mixture) was targeted. This is in contrast with studies that used cumulative bolus techniques, had minimum mandatory period of volatile agent administration before initiation of the neuromuscular blockade, administered greater partial pressures (>1 MAC) and in which the presence of nitrous oxide was a confounding factor. We also paid attention to calibration of the TOF-GUARD® monitor and took specific measures to avoid sources of baseline signal drift.

The question we asked was whether the relative prolongation of one muscle relaxant by the volatile was greater than the relative prolongation of the other muscle relaxant. Thus a cross-over or matched pair design would have been ideal. A 3xED_{95} dose is large; therefore the duration of muscle relaxation was prolonged. This resulted in 18 recruited patients dropping out of the study and this may have biased the results towards patients who had a quicker recovery. A smaller dose may have demonstrated a significant difference in the prolongation of neuromuscular block between the two NDMR. Thus to elucidate the prolongation of desflurane on cisatracurium and rocuronium further, the study should be expanded to include the effect after administration of a 1 and 2x ED_{95} doses of the muscle relaxants.

The current study was unable to demonstrate an interaction between the type of NDMR and the degree of potentiation on its duration of action by the volatile agent. Thus, any differences in the potentiation of duration of action of the potent and less potent NDMR by desflurane are unlikely to be of clinical importance.

ADDENDUM

Table A1: Studies investigating the effects of modern volatile anaesthetic agents on modern neuromuscular blockers

Study	NMB	Dosage	Volatile/ IVdrug	N_2O	Exposure to volatile before NDMR	Measuring technique	Results		
							Potency	**Onset time**	**Duration of recovery**
Rupp *et al.*1985 (Rupp *et al.*1983)	**Atracurium**	Randomly allocated to receive single bolus of 50, 60, 70, 80, 90 or 100µg/kg to construct a dose-response curve	1.25 MAC: **Halothane Enflurane** (included 0.6 MAC contribution from N2O) Results compared with data from a previous study using identical techniques by same lead author: 1.25 MAC: **Isoflurane**; **Fentanyl** 7-10µg/kg bolus with induction	60%	30 min	Mechano-myography Twitch height	ED_{50}: Halothane: 77µg/kg Enflurane: 70µg/kg* Isoflurane: 68µgkgl* Fentanyl: 83µg/kg (* Different from Fentanyl P<0.05) ***Thus:*** - No difference Halothane vs. Enflurane - Enflurane and Isoflurane significantly increased the potency of atracurium vs Fentanyl	No difference	$Duration_{50}$: Halothane: 25.5 min Enflurane: 34.2 min* Isoflurane: 25.5 min Fentanyl: 21.6 min (* Different from Fentanyl P<0.05) ***Thus:*** - No difference Halothane vs Enflurane - 33% increase by Enflurane vs Fentanyl

Table A1 (continued):

Study	NMB	Dosage	Volatile/ IVdrug	N_2O	Exposure to volatile before NDMR	Measuring technique	Results		
							Potency	**Onset time**	**Duration of recovery**
Wright *et al.* 1995	**Vecuronium**	*Potentiation studies*: Dose-response *Onset and duration studies:* 100µg/kg 50% of participant involved in potentiation studies and 50% involved in onset and duration studies All participants crossover 6 days apart	1.25 MAC: **Desflurane Isoflurane**	70% Potentiation studies: N20 added after 90% twitch suppression achieved by NDMR	60 min	Mechano-myography Twitch tension	ED_{50}: Desflurane: 8.7µg/kg Isoflurane: 10.7µg/kg Vecuronium infusion requirements to maintain same twitch height: Desflurane: 0.65µg/kg/min Isoflurane: 0.79µ/kg/min ***Thus:*** Desflurane 20% > Isoflurane	Time to maximum blockade: Des: 62 sec Iso: 73 sec (P< 0.05) ***Thus:*** Desflurane significantly faster than Isoflurane	Time (min) until: Des Iso 25% recovery 69 55 90% recovery 135 110 (P <0.01) T1 25%-75% 41 34 (P<0.05) ***Thus:*** Desflurane prolonged recovery vs Isoflurane
Kumar *et al.* 1996	**Rocuronium**	*Potentiation studies:* Randomly allocated to receive a single bolus of 75, 150, 225, or 300µg/kg *Onset and duration* studies: 0.6mg/kg	1.0 MAC: **Desflurane Isoflurane**	66%	10 min	Mechano-myography Twitch height TOFR	ED_{50}: Desflurane: 138µg/kg Isoflurane: 126µg/kg ***Thus:*** - No difference Desflurane vs Isoflurane	Time to maximum blockade Des: 1.0 min Iso: 1.1 min (P=0.09) ***Thus:*** - Desflurane non-significantly faster than Isoflurane	Time (min) until: Des Iso 25% recovery 36 31 90% recovery 54 45 (P>0.1) TOFR 0.7 66 52 (P>0.05) T1 25%-75% 14 10 (P>0.05) ***Thus:*** - Non-significant prologation of recovery times with Desflurane vs Isoflurane

Table A1 (continued):

Study	NMB	Dosage	Volatile/ IVdrug	N_2O	Exposure to volatile before NDMR	Measuring technique	Results		
							Potency	**Onset time**	**Duration of recovery**
Lowry *et al.* 1998	**Rocuronium**	*Potency studies*: Randomly allocated to receive a single bolus of 75, 150, 225, or 300µg/kg *Onset and duration* studies: 0.6mg/kg	1.5 MAC: **Sevoflurane Isoflurane Propofol** 6-12mg/kg/hr	66%	10 min	Mechano-myogr Twitch height TOFR	ED_{50}: Sevofllurane: 142µg/kg* Isoflurane: 165µg/kg Propofol: 183µg/kg (* Different from Propofol P<0.05) ***Thus:*** - Significant difference with Sevoflurane vs Propofol	Time to maximum blockade Sevo: 0.96 min Iso: 0.9 min Prop: 1.02 min ***Thus:*** - No difference	Time (min) until: Sevo Iso Prop 25% recovery 45 35 35 90% recovery 83 56 55 TOFR 0.8 103* 69 62 T1 25%-75% 26* 12 14 (* P<0.01 for sevoflurane vs isoflurane and propofol)) ***Thus:*** - Sevoflurane prolonged recovery to TOFR 0.8 and recovery from 25% twitch height to 75% twitch height vs Isoflurane and Propofol
Wulf *et al.* 1998	**Rocuronium**	Cumulative bolus	1.5 MAC: **Desflurane Sevoflurane Isoflurane TIVA with Propofol/Fentanyl** (doses not specified)	70%	Not specified	Accellero-metry Twitch height TOFR	ED_{50}: Desfllurane: 95µg/kg* Isoflurane: 130µg/kg Sevoflurane: 1 20µg/kg* TIVA: 150µg/kg (* P<0.05) ***Thus:*** - Desflurane and Sevoflurane reduced the ED_{50} vs propofol TIVA	Not studied	Time (min) until: Des Iso Sevo Prop 25% recovery 13.2 13.9 15.5 13.9 TOFR 0.7 26.9 26.3 31.0 27.5 T1 25%-75% 12.7 10.7 11.4 11.3 ***Thus:*** - No prolongation by the volatiles
Wulf *et al.* 1998	**Cisatacurium**	Cumulative bolus	1.5 MAC: **Desflurane Sevoflurane Isoflurane TIVA with Propofol/Fentanyl** (doses not specified)	70%	Not specified	Accellero-metry Twitch height TOFR	ED_{50}: Desfllurane: 15µg/kg* Isoflurane: 15µg/kg* Sevoflurane: 15µg/kg* TIVA: 21µg/kg (* P<0.05) ***Thus:*** - Volatiles reduced the ED_{50} vs propofol	Not studied	Time (min) until: Des Iso Sevo Prop 25% recovery 19 20 19 16 TOFR 0.7 43 41 44 35 T1 25%-75% 18 14 19 12 ***Thus:*** - No prolongation by the volatiles

Table A1 (continued):

Study	NMB	Dosage	Volatile/ IVdrug	N_2O	Exposure to volatile before NDMR	Measuring technique	Results		
							Potency	**Onset time**	**Duration of recovery**
Amin *et al.* 2009	**Cisatracurium** **Rocuronium**	Cumulative bolus	2 MAC: **Sevoflurane** **Propofol** 100µg/kg/min	50%	10-15 min	Accellero-metry Twitch height TOFR	ED_{50}: Roc+Sevo: 124µg/kg Cis + Sevo: 17µg/kg Roc + Prop: 150µg/kg* Cis + Prop: 23µg/kg# (* P<0.01 compared with Roc + Sevo group) (# P<0.01 compared to Cis + Sevo group) ***Thus:*** - Sevoflurane reduced ED_{50} vs propofol by 20% in both NMB	Not studied	Time (min) until: RS CS RP CP 25% recovery 18 19 15 16 TOFR 0.7 36* 44*# 29 34# T1 25%-75% 13* 18*# 9 14# (* P <0.05 same NDMR< different anaesthetic) (# P<0.05 same anaesthetic, different NDMR) ***Thus:*** - Prolonged recovery 25%-75% & TOFR 0.7 of Cisatracurium > Rocuronium

Table A1 (continued):

Study	NMB	Dosage	Volatile/ IVdrug	N_2O	Exposure to volatile before NDMR	Measuring technique	Results		
							Potency	**Onset time**	**Duration of recovery**
Bock *et al.* 2000	**Rocuronium**	Randomly allocated to receive single bolus of 0.1, 0.15 or 0.2mg/kg to construct a dose-response curve After maximal depression recorded, a supplementary dose of rocuronium given so that all subjects received cumulative dose of 0.3mg/kg After recovery of T1 to 5% of control, rocuronium infusion started and adjusted to maintain T1 5-10% twitch height.	1.25 MAC: **Desflurane** **Sevoflurane** **Isoflurane** **Propofol** (4-6mg/kg/hr)	60%	40 min	Electro-myography Twitch height TOFR	ED_{50} Propofol: 169µg/kg Isoflurane: 126µg/kg Desflurane: 136µg/kg Sevoflurane: 121µg/kg ED_{90} Propofol: 358µg/kg* Isoflurane: 288µg/kg Desflurane: 250µ/kg Sevoflurane: 289µg/kg (*P<0.05) ***Thus:*** - No difference in ED50 - Significant difference in ED90 for propofol compared to volatiles - Showed leftward shift of dose response curve for volatiles vs propofol - And a 30-40% decrease in the infusion rate of rocuronium during volatile anaesthesia compared to propofol	Not studied	Time (min) Prop Iso Des Sevo TOFR 0.25-0.7 22 27 26 28 ***Thus:*** - No prolongation with volatiles Recovery index defined as TOFR 0.25-0.70 Compared to all other studies (and the GCPR guidelines) that defined Recovery index as T1 25%-75%

Table A1 (continued):

Study	NMB	Dosage	Volatile/ IVdrug	N_2O	Exposure to volatile before NDMR	Measuring technique	Results		
							Potency	**Onset time**	**Duration of recovery**
Hemmerling *et al.* 2001	**Cisatracurium**	Closed-loop control to 10% twitch height Infusion rate of cisatracurium used to estimate the Effective Therapeutic index (µg x m^2BSA x min^{-1})	1.3 MAC: **Desflurane Sevoflurane Isoflurane Propofol** (6-8mg/kg/hr)	None	Volatile started after NDMR – induced T1% < 5%i Only study to start volatile after administration of NDMR	Electro-myography Twitch height	Effective Therapeutic index Propofol: 61.7µg.m^{-2}.min^{-1} * Desflurane: 23.8 µg.m^{-2}.min^{-1}# (*P<0.002 for Propofol vs all volatiles) (#P<0.02 for Des vs Prop, Sevo, Iso) ***Thus:*** - Volatiles significantly decreased the infusion rate required - Desflurane significantly increased the potency of cisatracurium compared to other volatiles studied	Not studied	Reduced cumulated dose requirements compared to Propofol: Desflurane 60% Sevoflurane 42% Isoflurane 41% (p<0.002 for Propofol vs all volatiles) (p<0.02 for Des vs prop, sevo, iso)
Stout *et al.* 2006	**Rocuronium**	Single bolus 0.6mg/kg) then infusion (10-12 µg/kg/min) to maintain T1 at 10%	**Desflurane** (ET_{Des} 3-8%) **Propofol** (100-150µg/kg)	50%	Not specified	Electro-myography Twitch height	Rocuronium infusion rate 67% less with Desflurane than Propofol	Time to T1 10% Des: 198 sec Prop: 118 sec (p = 0.034) ***Thus:*** - Onset was prolonged by Desflurane.	Time (min) until: Des Prop T1 25% 19 16 T1 50% 27 21 T1 75% 44 28 (P>0.05) T1 90% 68 46 (number too small for statistical comparison)

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