Faculty of Medicine and Health Sciences
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Study on the Optimisation of Continuous Infusions of Neuromuscular Blocking Drugs During Anaesthesia

Thesis submitted to fulfil the requirements for achievement of the grade of Doctor in Medical Sciences

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I dedicate this thesis to my loved ones and thank everyone who participated in the realisation of it.

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Guy Cammu
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LIST OF ABBREVIATIONS

ABG *arterial blood gases*

ALDLTx *adult-to-adult living-donor liver transplantation*

ANOVA *analaysis of variance*

ASA *American Society of Anesthesiologists*

ATG *antithymocyte globulin*

AU *autologous blood*

BIS *bispectral index*

CABG *coronary artery bypass grafting*

CO *cardiac output*

CPB *cardiopulmonary bypass*

CS *cell saver*

CVP *central venous pressure*

ECG *electrocardiography*

ED_{95} *the dose causing 95% depression of control twitch height (=muscle relaxation) of the adductor pollicis*

EMG *electromyography*

HCC *hepatocellular carcinoma*

ICU *intensive care unit*

INR *international normalized ratio*

IV *intravenous*

MAP *mean arterial pressure*

MPAP *mean pulmonary artery pressure*

MRI *magnetic resonance imaging*

NA *not applicable*

NMBD *neuromuscular blocking drug*

NMT *neuromuscular transmission*

PA *pulmonary artery*

PCU *post-anaesthesia care unit*

POD *postoperative day*

PORC *postoperative residual curarisation*

RI *recovery index = the time in minutes needed for the T1 to increase from 25% to 75% or from 5% to 95%*

T1 *single twitch / first response to the train-of-four stimulus*

TCI *target-controlled infusion*

TEE *transoesophageal echocardiography*

TOF *train-of-four*

CONTENTS

Chapter 1

INTRODUCTION AND AIMS OF THE STUDY

INTRODUCTION

In 1942 Griffith and Johnson administered curare to a patient under general anaesthesia. Their report of the use of curare in 25 patients changed anaesthetic practice throughout the world and heralded the beginning of the modern era of anaesthesiology.[1] Until then, deep inhalational anaesthesia had been the only way of providing adequate muscle relaxation, but it was poorly tolerated by debilitated and/or aged patients. The introduction of curare allowed adequate muscle relaxation at a lighter, and therefore better tolerated, level of general anaesthesia. The use of neuromuscular blocking drugs (NMBDs) together with endotracheal intubation (to lessen the risk of aspiration) formed the basis for the current concept of 'balanced anaesthesia'– the combination of hypnosis, analgesia and muscle relaxation that results in fewer detrimental effects on the respiratory and cardiovascular systems. Inoperability at the extremes of age or in advanced pathology was virtually eliminated by the introduction of NMBDs. It is hard to imagine if and how, without the introduction of NMBDs, open-heart, transplant or intracranial surgery could have developed.

There are, however, potential unwanted side-effects when using NMBDs; they include:[2]

1. during the induction and maintenance of anaesthesia: aspiration; difficult or impossible airway management; cardiovascular effects (bradycardia, tachycardia, hypotension, rhythm disturbances); histamine release;
2. during emergence from anaesthesia and during recovery: postoperative residual curarisation (PORC) with possible hypoventilation and hypoxaemia/aspiration;
3. during and following the long-term administration of NMBDs: muscle weakness and convulsive effects of compounds or their metabolites.

The NMBDs generally produce few fatalities.[3] Death or complications related to failed endotracheal intubation or to aspiration during the induction of anaesthesia are also infrequent.[3, 4] Concerning NMBD-induced cardiovascular effects, it is known that succinylcholine-induced bradycardia and cardiac arrest have a relatively high incidence, particularly in high-risk patients (children, burns, spinal cord and other neuromuscular disorders).[5] NMBDs induce greater histamine release than do other drugs used in anaesthesia; the overall incidence of anaphylaxis is, however, low.[6] Succinylcholine appears to induce the highest incidence of serious, immunological histamine release.[7] Miscellaneous effects of NMBDs (mostly complications of succinylcholine[2]) include: fasciculation, myalgia, increased intracranial, intragastric and/or intraocular pressures, masseter muscle spasm, rhabdomyolysis/myoglobinaemia/myoglobinuria, and malignant hyperthermia. Muscle

weakness after the prolonged administration of NMBDs on the intensive care unit (ICU) and the convulsive effects of compounds or metabolites are more often encountered with non-depolarising NMBDs.[8, 9]

Whereas intraoperative surgical and anaesthetic conditions are greatly improved by the use of modern NMBDs, anaesthesiologists are still faced with preventing residual curarisation at the end of the procedure, even when reversal agents are used.[10] The side-effects of reversal agents originate from their combination with a vagolytic. This mixture of drugs may lead to several complications: cardiovascular effects, effects on the gastrointestinal system, and muscle weakness.[11] In contrast to most other complications, residual curarisation in the recovery room is a general problem with a high incidence, in particular with long-acting NMBDs (more than 40% of patients affected), but also with intermediate-acting NMBDs (more than 20%).[12, 13, 14, 15] Berg showed, in a prospective, randomised and blinded study, that residual curarisation in the recovery room caused by a long-acting NMBD is a significant risk factor for the development of postoperative pulmonary complications.[16] The time course of action for NMBDs is not only an intrinsic effect of the drug but also the result of the dose administered, the period and the method of administration (bolus or infusion), individual sensitivity, and interaction with drugs. Also, plasma clearance (liver uptake and excretion, renal excretion, and metabolism in plasma), active metabolites, and the effects of acidosis and hypothermia are important. An additional problem in determining clinically adequate recovery is its actual definition: ideally, pulmonary ventilation, airway protection and maintenance of airway patency should all be evaluated at the end of anaesthesia.[17, 18] Some variables of pulmonary ventilation, such as maximum inspiratory pressure and vital capacity, are used to determine adequate neuromuscular recovery;[19] this requires spirometry. It is, however, impossible to monitor airway protection and the maintenance of airway patency in clinical practice. Therefore, several other clinical indicators of sufficient recovery are used; these include the patient's ability to open their eyes, breathe deeply, cough, lift their head and/or legs against gravity, swallow, and to resist the removal of a spatula from between their clenched teeth.[20] These clinical tests are influenced by the effects of premedication and general anaesthetics, the degree of consciousness, the level of cooperation and postoperative pain. Thus there are contradictory findings on the correlation between clinically sufficient recovery and neuromuscular transmission (NMT) monitoring.[12] There are also conflicting results on the positive effect of such monitoring during anaesthesia on the incidence of postoperative residual curarisation (PORC).[21, 22, 23] Despite these inconsistencies, the recovery of a train-of-four (TOF) ratio, initially of 0.7 and nowadays of 0.9, is accepted as the level

that correlates with sufficient clinical recovery of muscle strength.[24, 25] The high sensitivity of the pharynx to NMBDs is the basis of the proposed new standard for residual block (TOF ratio = 0.9). Early recovery occurs in central respiratory muscles such as the diaphragm and in the larynx, whereas the muscles of the pharynx and the eyes recover much more slowly. Residual block is therefore more pronounced in the pharynx and the facial muscles. Recent findings suggest that even a residual TOF fade of up to 0.9 in the hand is associated with a pronounced dysfunction of the pharynx and the striated muscle of the upper oesophagus.[26] A TOF ratio below 0.9 can therefore be associated with a considerable risk of aspiration. Moreover, residual block disturbs the normal chemosensitivity of the carotid bodies by interaction with cholinergic transmission of the chemoreceptor in the glomus caroticum, causing an impaired hypoxic ventilatory response.[25]

Residual neuromuscular block is thus clearly a risk factor for developing postoperative pulmonary complications. However, in only a few published studies was PORC considered a separate risk factor and it is therefore impossible to specify the exact incidence of complications due to PORC; this is explained by the multifactorial aetiology of hypoventilation, upper airway obstruction and aspiration. Nevertheless, postoperative complications due to residual block can be life threatening and will substantially increase the total cost of a surgical intervention. The principal expense of surgery lies in potential side-effects and postoperative complications. Although the current drive to reduce the costs of medical care (made necessary by the concurrence of ageing populations and declining resources) should in no way interfere with the best care for the patient, improving safety by the use of NMBDs does also represent an important opportunity for reducing expenditure. Yet, in the 1990s and probably also in the first years of the millennium, patients still died as a result of PORC.[3] Four steps should therefore be followed to prevent residual block:

1. avoid long-acting NMBDs;
2. prevent hypothermia (which delays recovery);
3. use objective monitoring of neuromuscular block;
4. reverse any TOF ratio < 0.9.

Although NMT monitoring is indicated for all surgical interventions, it is particularly necessary in the following:[21, 27]

1. Long interventions: monitoring helps to avoid overdosing and the possibility of delayed recovery

2. Where there are altered pharmacokinetics/pharmacodynamics: a change in pharmacokinetics can be expected in patients with hepatic or renal diseases
3. Where no moving or straining is desired in certain interventions; monitoring helps maintain a sufficiently deep block
4. Where no reversal is preferred: in some patients, reversal agents may affect heart/lung function
5. In the presence of disturbed electrolyte and acid-base balance, which may alter the blocking effect of some NMBDs
6. When drug interactions are expected: the action of NMBDs can be potentiated or depressed by interaction with certain other drugs.

Despite large recent advances in the pharmacology of NMBDs, their effects, and onset and recovery times, remain unpredictable. The incidence of residual paralysis is still unacceptably high despite the introduction of new agents and monitoring techniques. In addition, the variable response of the individual patient makes it difficult to predict accurately the extent of the neuromuscular block, even more so in certain disease states or conditions (e.g. the pharmacokinetic parameters of NMBDs are altered in elderly people and those with impaired organs of elimination[28, 29]). Interactions between NMBDs and inhalational or local anaesthetics, antiarrhythmics, aminoglycosides and calcium-channel blockers, for example, can influence a patient's response to NMBDs and reversal agents.[30] In the light of this wide variability in the effects of NMBDs, optimisation of dosage, possible antagonisation and monitoring of NMT, and a thorough understanding of the limitations of these drugs and monitoring techniques, are invaluable for optimal patient care, especially if continuous infusions of NMBDs are to be administered. Fawcett et al. have demonstrated that the incidence of PORC is higher after infusions of atracurium or vecuronium than after bolus dosing.[13]

NEUROMUSCULAR BLOCKING DRUGS AND NEUROMUSCULAR TRANSMISSION MONITORING

The drugs studied

Cisatracurium

Cisatracurium besilate is a non-depolarising NMBD with an intermediate duration of action.[31] It is the R-cis, R'-cis isomer of atracurium besilate and is approximately 3-fold more potent

than atracurium.[31,32, 33] The ED_{95} (dose required to produce 95% suppression of the twitch response to nerve stimulation) for cisatracurium in adults is 0.05 mg/kg.[31, 33] The volume of distribution of cisatracurium at steady state ranges from 0.11 to 0.16 l/kg in healthy adults.[34] Cisatracurium is not associated with dose-related histamine release and, consistent with this, has demonstrable cardiovascular stability.[33, 35] It has a slightly longer onset time than atracurium. The degree and duration of neuromuscular block produced by cisatracurium increase and time to maximum block decreases in a dose-dependent manner.[31, 36] Cisatracurium 0.1 mg/kg (= 2 × ED_{95}) produces 99–100% twitch suppression within 4.6–5.8 min.[31, 33] The time to maximum effect was delayed by approximately 1 min in elderly patients and in those with renal failure, and shortened by almost 1 min in patients with endstage liver disease.[29, 37, 38, 39] The clinical duration of neuromuscular block (i.e., the time from injection to 25% twitch recovery) ranges from 33 to 45 min after cisatracurium 0.1 mg/kg.[31, 40] Once started, recovery (i.e., 5–95% or 25–75 % recovery indices) is independent of dose over the range 0.1–0.4 mg/kg.[31] The recovery rate is apparently unaffected by age, renal failure or endstage liver disease, but appears slower following the use of inhalational agents.[29, 30, 37, 38, 39] As with other non-depolarising agents, recovery from neuromuscular block with cisatracurium can be effectively accelerated by the administration of an anticholinesterase agent once recovery has begun.[33, 40]

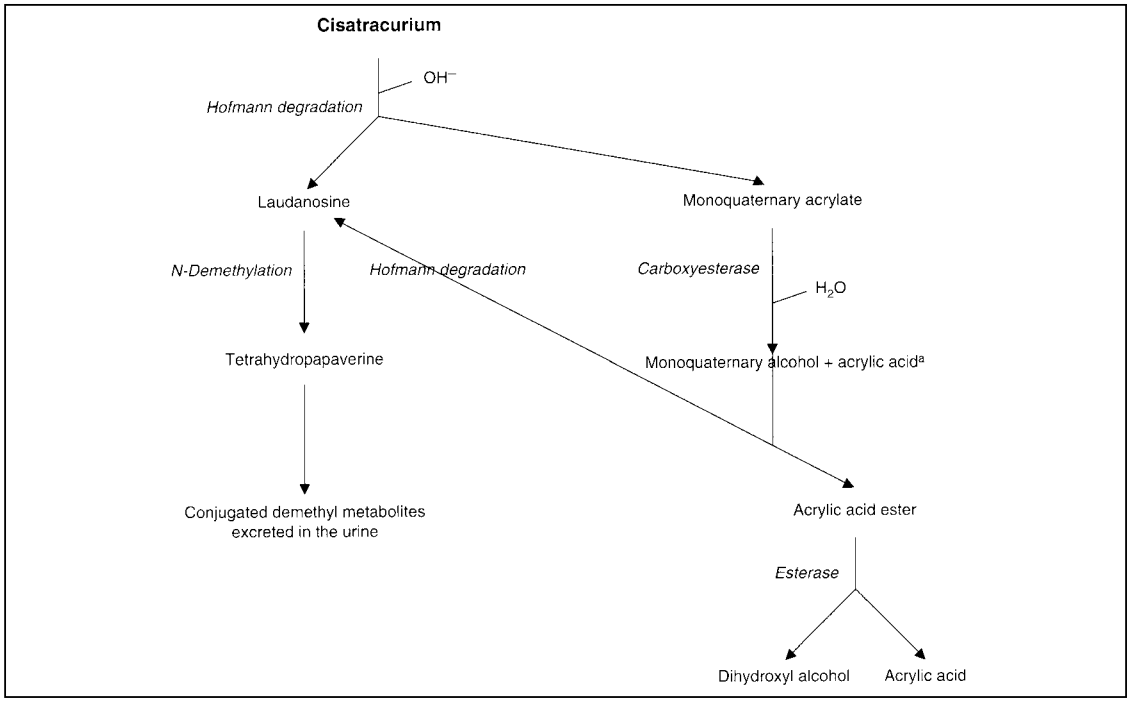

Fig 1. Suggested degradation pathway of cisatracurium. [a]Hofmann degradation of the monoquaternary alcohol occurs at a slower rate than that of cisatracurium. [Reproduced from: Bryson HM, Faulds D. Cisatracurium besilate *Drugs* 1997; 53: 848-66, with permission of Adis International Limited.]

Cisatracurium undergoes temperature- and pH-dependent chemical (Hofmann) degradation, the main route by which the drug is broken down, accounting for 77% of its total clearance (Fig 1).[41] Cisatracurium degrades to form laudanosine and the corresponding monoquaternary acrylate (which in turn is broken down to a monoquaternary alcohol and then laudanosine). Although the liver and kidneys play only a minor part in the excretion of cisatracurium, hepatic and urinary elimination pathways are important for the metabolites of laudanosine.[42] The effects of laudanosine on the behaviour of conscious mice, rats and dogs, and on cardiovascular function in conscious and anaesthetised dogs had been evaluated by Chapple et al. as early as 1987. In mice and rats, iv bolus doses of laudanosine 10-20 mg/kg, caused convulsions and hind limb extension. After the continuous infusion of laudanosine in conscious dogs, plasma concentrations of 1.2 µg/ml did not cause behavioural disturbances. In anaesthetised dogs, laudanosine plasma concentrations of more than 6 µg/ml caused hypotension and bradycardia, concentrations greater than 10 µg/ml induced epileptic EEG spiking and concentrations > 17 µg/ml produced prolonged seizures. However, Chapple et al. concluded that it was unlikely that the use of atracurium, in patients, would result in plasma concentrations of laudanosine capable of producing neurological or cardiovascular disturbances.[43] During the infusion of atracurium in the ICU, Yate et al. found in 1987 that the maximum plasma concentrations of laudanosine were 1.9-5 µg/ml and that there was no evidence of cerebral excitation.[44] Moreover, plasma laudanosine concentrations were lower in a cisatracurium (1.3 µg/ml) than in an atracurium (4.4 µg/ml) group. Indeed, because cisatracurium is three times more potent than atracurium, one would predict that plasma laudanosine concentrations following infusions of cisatracurium would be lower than those following equipotent doses of atracurium.[45]

Cisatracurium is cleared from the body at a rate of 0.27–0.34 l/kg per h, with an elimination half-life of 22–35 min. In adult patients undergoing elective surgery, the mean infusion rate of cisatracurium required to maintain a 95% block ranges from 1.2 to 1.5 µg/kg per min.[46] The 25–75 % recovery index ranged from 15 to 18 min in adults after a continuous infusion of cisatracurium; recovery appeared independent of duration of infusion or the number of maintenance doses administered.[31, 47] For prolonged surgery, significant reductions in the infusion rate should be considered.[48]

Rocuronium

Rocuronium is a non-depolarising, aminosteroid NMBD. Its most impressive feature is a rapid onset time. At a dose of 0.6 mg/kg (= 2 × ED_{95}), rocuronium has an onset to maximum

block approximately twice as rapid as equipotent doses of vecuronium and atracurium, and a duration of action similar to those agents. The potency of rocuronium is approximately six times less than that of vecuronium. Foldes et al. determined the ED_{50}, ED_{90} and ED_{95} of 0.17, 0.27 and 0.31 mg/kg rocuronium, respectively, for patients under balanced anaesthesia.[49] Rocuronium has a duration of action and a recovery index similar to that of the other intermediate-acting NMBDs. Cooper et al. found that the time to complete block decreased from about 1 min with a dose of 0.6 mg/kg to approximately 45 s with a dose of 0.9 mg/kg.[50] The clinical duration of action of rocuronium is proportional to the dose given. The duration of action provided by doses ranging from 0.45 mg/kg to 1.2 mg/kg is approximately 22 min and 73 min, respectively. After administering anticholinesterase drugs, at 25% recovery of T1 (the first response to the train-of-four stimulus), the neuromuscular blocking effect of rocuronium can be reversed (from 25% to 75% of T1) within 5 min. Rocuronium exhibits a low potential for systemic histamine release and for producing clinically significant cardiovascular changes in most patients. The effect of rocuronium is terminated predominantly by liver uptake and excretion through the bile, either degraded or undegraded. A small fraction of the administered dose (< 20%) is excreted via the kidneys.[51] The major metabolites are 17-desacetyl rocuronium and 16N-desallyl rocuronium. These putative metabolites have not been detected in any appreciable amount in plasma. They also have a very low neuromuscular-blocking potency.[52] Rocuronium is similar to most other non-depolarising NMBDs with respect to drug interactions; dose adjustments may therefore be necessary. The pharmacokinetics of rocuronium resembles that of vecuronium except for a smaller volume of distribution. The volume of distribution at steady-state varies from 0.20 to 0.22 l/kg, the plasma clearance is 3.7–5.2 ml/kg per min and the terminal half-life is 69–97 min.[28] The smaller distribution volume of rocuronium may be a reflection of its lower lipophilicity compared with that of vecuronium.[53] Within the clinical dose range, the termination of the effect of rocuronium is, like that of vecuronium, mainly dependent on distribution processes, one of which is hepatic uptake followed by biliary elimination. The infusion requirements to obtain a steady-state block of 90–95% with rocuronium during opioid-based IV anaesthesia can be expected to range between 0.3 and 0.8 mg/kg per h (mean 0.6 mg/kg per h).[54, 55] The spontaneous recovery index after a large single bolus is similar to that after a continuous infusion, based on identical pharmacokinetic parameters.[52, 56] The addition of volatiles significantly reduces the infusion requirements by 30–40%.[55] In a study by Sparr et al., a mean spontaneous recovery index of 16.7 min following a mean infusion time of 138 min was seen;[56] this was of the same order of magnitude as that observed after

single bolus injections of rocuronium. When administered by infusion, rocuronium has apparently no clinically significant cumulative effects in healthy adults.

Neuromuscular transmission monitoring

This technique is extensively described in the literature.[57]

Nerve stimulation

Intraoperatively, several factors may influence the intensity of the stimulus and thus the extent of the response. Changes in vascular flow influenced by anaesthetics, as well as changes in skin temperature, may lead to a change in skin resistance. To ensure that these factors do not falsify the measurement, the stimulation must be sufficient to trigger a response in the whole muscle. Therefore the stimulation of the nerve should be supramaximal, i. e., with a higher current than needed to trigger a maximal response in the muscle. Typically, a current of 50–60 mA is chosen.[58] The response of the nerve to electrical stimulation depends on three factors: the current applied, its duration, and the position of the electrodes. Therefore, clinically useful nerve stimulators should deliver a monophasic square wave having a pulse width of 200–300 μs and an adjustable output current to ensure that an adequate stimulus–response pattern is identifiable.

Nerve stimulators

Basically, two different types of nerve stimulators may be used in clinical practice: devices that allow only a tactile or visual appreciation of the muscle response (qualitative or semiquantitative assessment), and those that actually measure the response and provide a quantitative assessment.

Stimulation patterns (Fig 2)

Single twitch

The simplest way to stimulate a nerve is to apply a single stimulus. Single-twitch stimulation examines the percent inhibition demonstrable after delivering a 0.2 ms stimulus every 0.5-1 s (1–2 Hz) and comparing the response to a control twitch. Single-twitch responses are dependent on the characteristics of the stimulus: the higher the frequency of the stimulus, the greater will be the apparent decrease from the control. To obtain clinical relevant information with this pattern of stimulation, the evoked responses must be calibrated and recorded before

the injection of the NMBD. Because a control is required, the clinical usefulness of this mode of stimulation is limited.[59]

Train-of-four

The TOF is the most frequently used stimulation pattern. It consists of four supramaximal stimuli given every 0.5 s (2 Hz). Each stimulus in the train causes the muscle to contract. The count of the responses to TOF stimulation and the fade in the response are the basis of the evaluation. Fade is the clinical response resulting from the reduced postsynaptic function due to the competitive inhibition produced by the NMBD. Dividing the amplitude of the fourth response by the amplitude of the first provides the TOF ratio. Obtaining a control value before the injection of the NMBD is unnecessary. In addition, neuromuscular recovery can be estimated using the TOF ratio. TOF stimulation can also evaluate the status of a depolarising blockade (phase I block) where all four responses are equally diminished (Fig 3).

The number of twitches can be correlated with the degree of neuromuscular blockade as pointed out in Fig 4.

Tetanic stimulation

In clinical practice a stimulus of 50–100 Hz for a duration of 5 s is usually selected. During a non-depolarising block, the peak muscle tension is reduced and the response of the muscle ‘fades’ if the stimulus is sustained. The degree of fade depends mainly on the extent of neuromuscular blockade and thus may be used to quantify its depth. Fade also varies proportionately with the frequency of the applied stimulus, being greater at higher frequencies.[59] Tetanic stimulation is painful.

Double-burst stimulation

This consists of two short bursts of 50 Hz tetanic stimulation separated by 750 ms.[60] In the partly paralysed muscle the second response is weaker than the first. The tactile evaluation of the response to double-burst stimulation is superior to that of the response to TOF stimulation.[61, 62, 63]

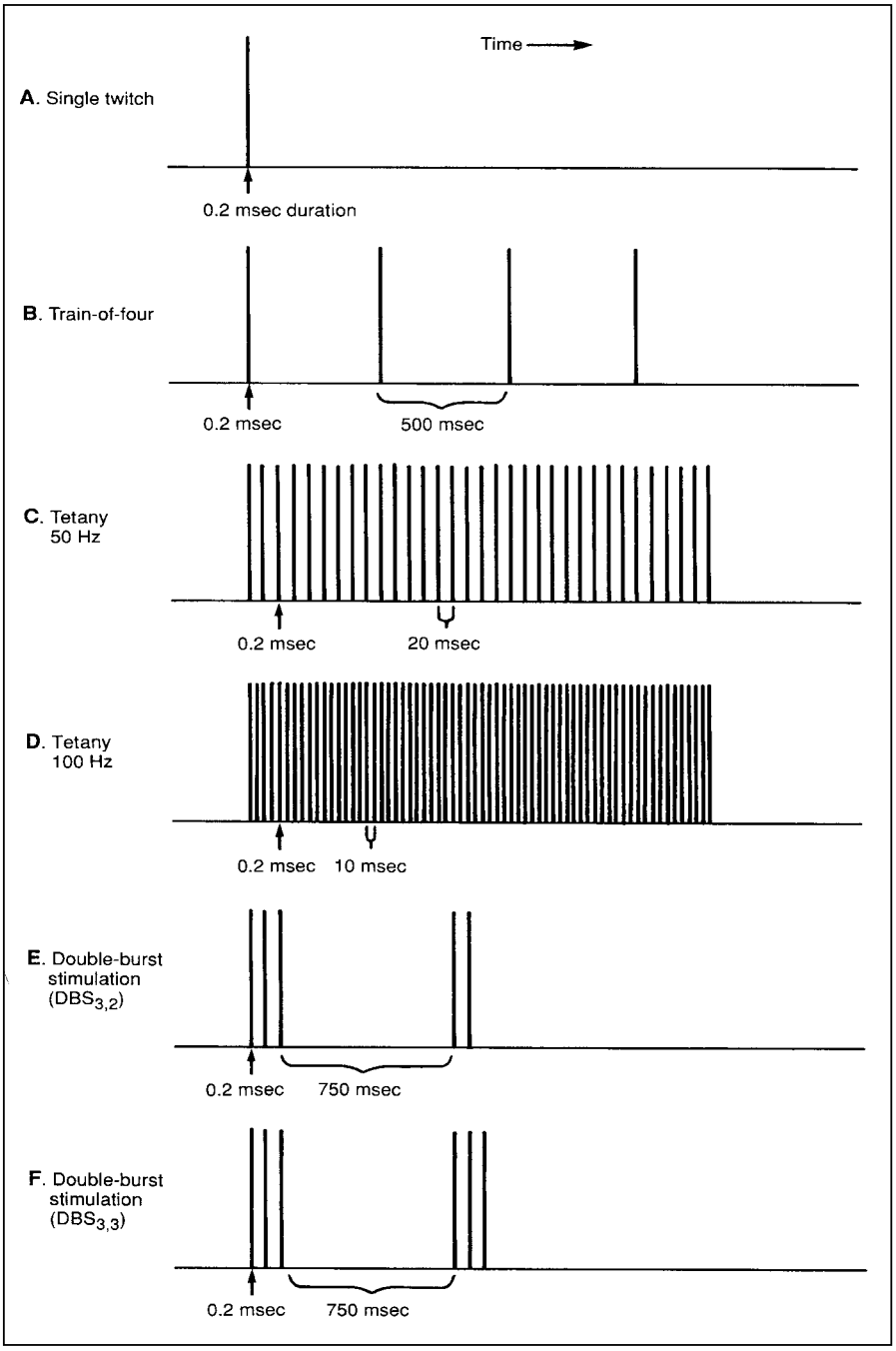

Fig 2. Neuromuscular transmission monitoring. *Single twitch*: supramaximal stimulation of the ulnar nerve provokes twitches of the thumb. *Train-of-four*: four supramaximal stimuli of the ulnar nerve (frequency 2 Hz) provoke four twitches of the thumb. Comparison of the fourth with the first is a good indication of the degree of neuromuscular block. No control values are needed with this mode of stimulation. *Tetany*: very rapid stimulation (50 or 100 Hz) of the ulnar nerve provokes vigorous contraction of all muscles of the hand. Tetanic stimulation is very painful in non-anaesthetised patients. *Double-burst stimulation*: a short burst of two to three twitches twice at a rate of 50 Hz, 750 ms apart. In the $DBS_{3,3}$ mode three stimuli are given twice; in the $DBS_{3,2}$ mode, three and two stimuli are given in each burst respectively.
[Reproduced from Morgan G, Mikhail M. *Clinical Anesthesiology*, with permission of the McGraw-Hill Companies.]

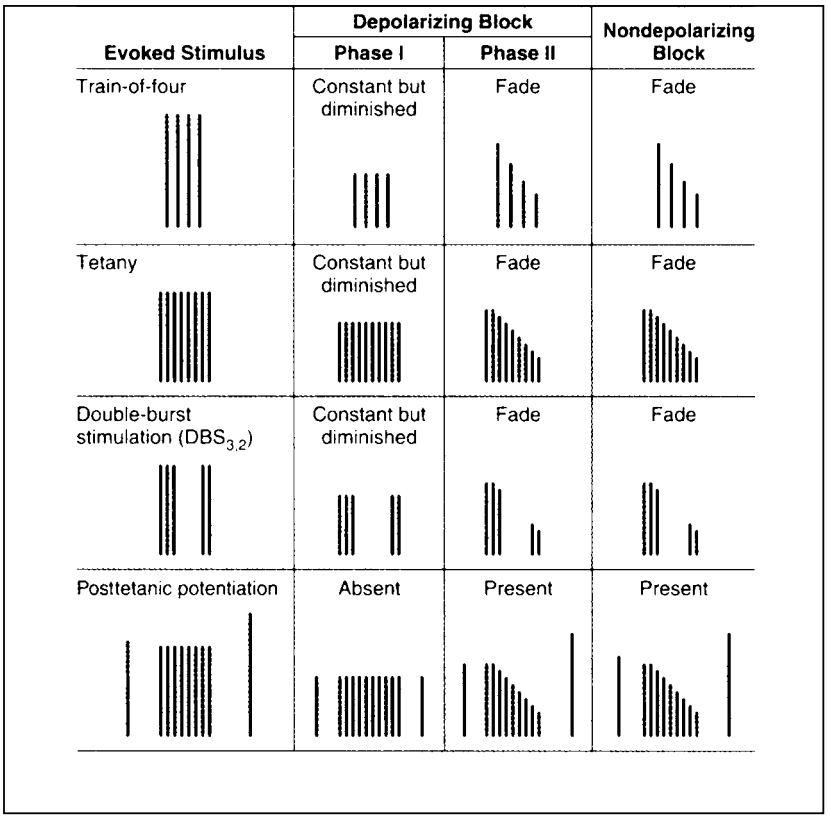

Fig 3. Fade during depolarising and non-depolarising block. According to the mechanism of binding to the post-junctional cholinoceptor, two types of NMBDs can be distinguished. The *depolarising NMBDs* are acetylcholine agonists and the paralysis they achieve is always preceded by strong stimulation of the motor endplates causing fasciculations of the muscles all over the body. *Non-depolarising NMBDs* act by competition with acetylcholine for the receptors in the motor endplate. They do not have an intrinsic stimulating action and therefore do not cause fasciculations. *Fade* is the decrease of muscle contraction with each next stimulus. Fade occurs when the readily releasable stores of acetylcholine in the endplates have been partly depleted by the prejunctional effect of the non-depolarising NMBDs. The prejunctional receptors, responsible for activating the main stores of acetylcholine vesicles, fail to do so under the influence of the NMBDs. The higher the frequency of stimulation, the sooner these depots will be emptied. The liberation of acetylcholine cannot cope with the increased demand at these high frequencies and acetylcholine is thus not available in sufficient quantities for normal neuromuscular transmission.
[Reproduced from Morgan G, Mikhail M. *Clinical Anesthesiology*, with permission of the McGraw-Hill Companies.]

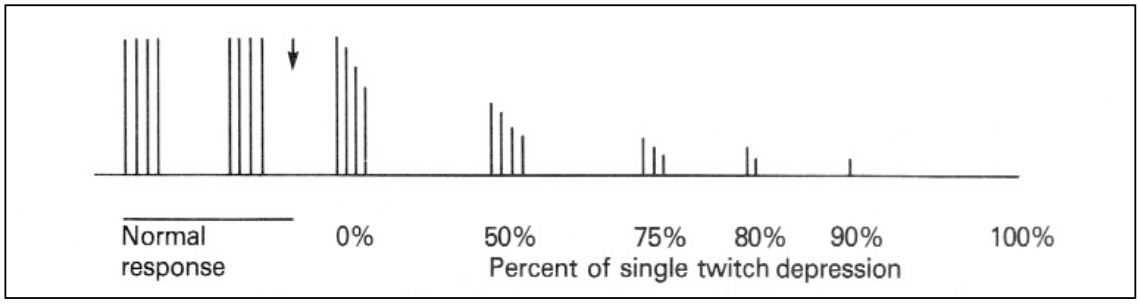

Fig 4. Single-twitch depression and train-of-four ratio. [Reproduced from Aitkenhead AR, Smith G. *Textbook of Anaesthesia*, with permission of Elsevier Ltd.]

Post-tetanic count

This comprises a 50-Hz tetanic stimulation of 5 s, followed 3 s later by single supramaximal stimuli (12–15) delivered once every second (= at a frequency of 1 Hz). Where the non-depolarising block is clinically profound, TOF or double-burst stimulation will evoke no neuromuscular response. However, the potentiation of neuromuscular transmission that occurs after tetanic stimulation may enable single stimuli to produce a response even during a profound non-depolarising block. Following tetanic stimulation there is mobilisation of acetylcholine from storage granules and the response of the twitch following tetanus is exaggerated. During a non-depolarising blockade, post-tetanic facilitation is followed by fade. The extent of fade quantifies the degree of muscle relaxation present.

Site of stimulation

From a practical standpoint, intraoperative access to a superficial nerve is most important. The ulnar nerve is most commonly used and the response of the adductor pollicis muscle monitored. This site is well suited for any assessment. Another advantage is that the muscle is on the lateral side of the arm whereas the site of stimulation is on the medial; there is thus little chance of direct muscle stimulation that might otherwise distort the assessment. Because different muscle groups have different sensitivities to NMBDs, results obtained for one muscle cannot necessarily be extrapolated to others.[64] The diaphragm and the laryngeal muscles are among the most resistant of all muscles to NMBDs. In general, the diaphragm requires 1.4–2 times as much relaxant as the adductor pollicis for an identical degree of blockade.[65] In addition, the onset time is normally shorter for the diaphragm than for the adductor pollicis and the diaphragm recovers from paralysis more quickly than do the peripheral muscles. Stimulation of the facial nerve produces contraction of the orbicularis oculi muscle. Onset of blockade is more rapid, and recovery occurs sooner, than at the adductor pollicis. In this regard, the time course of the blockade correlates well with that of other resistant muscles such as the diaphragm. The difference between muscle groups in their sensitivity to NMBDs is multifactorial in origin; it may include variable regional blood flow among muscle groups, differences in muscle temperature, differences in the density of receptors, as well as differences in muscle fibre composition.

Clinical application

Onset

After the induction of anaesthesia the intensity of neuromuscular blockade must be assessed to determine the optimum time for tracheal intubation. In this setting, excellent conditions depend on the relaxation of the laryngeal and respiratory muscles. Onset is much quicker in these muscles than in the adductor pollicis and they are less sensitive to the action of NMBDs.[66, 67] Thus the adductor pollicis is a poor guide to adequate intubating conditions. The orbicularis oculi, which, as described above, follows the profile of diaphragmatic and possibly laryngeal blockade, appears to be a more appropriate choice. TOF fade takes longer to develop than single-twitch depression and the TOF should be of little importance during onset. Thus single-twitch stimulation at 0.1 Hz is preferred during the onset of blockade.

Intraoperative use

The disappearance of the TOF at the adductor pollicis does not necessarily indicate paralysis of the vocal cords or the diaphragm. Consequently, it does not eliminate the possibility of hiccups or the extrusion of abdominal contents. Intense neuromuscular blockade (no TOF response at the adductor pollicis) may be evaluated by the post-tetanic count at the adductor pollicis. When profound neuromuscular blockade is not required, monitoring the adductor pollicis with the TOF is sufficient and surgical relaxation is usually adequate when fewer than two or three visible twitches of the train are observed. An advantage of keeping the neuromuscular blockade to a level of one or two responses to TOF stimulation is that antagonism of the block at the end of surgery is facilitated.

Recovery from neuromuscular blockade

A complete return of neuromuscular function at the end of surgery is desirable, unless mechanical ventilation is planned. Thus, monitoring is useful in determining whether spontaneous recovery has progressed to a degree that allows reversal and to assess the effects of reversal agents. The effectiveness of anticholinesterases depends directly on the degree of recovery present when they are administered. Preferably, reversal agents should be given only when four twitches are visible. In any event, the evaluation should be completed by clinical tests; the clinician must bear in mind that some of these investigations can be affected by pain, depth of anaesthesia and patient cooperation. For many years, a TOF of 0.7, measured at the adductor pollicis, was considered tantamount to adequate ventilatory function postoperatively. Then, new insights into the pathophysiogical consequences of residual

neuromuscular blockade demanded more rigorous criteria for determining the adequacy of neuromuscular recovery. A TOF of 0.7 can no longer be accepted as an indicator of sufficient recovery from neuromuscular blockade; it is now generally agreed that a TOF ratio of at least 0.9 is required.[25, 26, 68, 69, 70] Tactile and visual evaluation of the TOF ratio is no longer sufficient in this context because this technique allows detection only of residual paralysis corresponding to a TOF of about 0.3–0.4. Objective monitoring is the only way to determine neuromuscular recovery.[20, 71]

Recording the response

Visual and tactile evaluation

When electrical stimulation is applied to a nerve, the easiest and least expensive way to assess the response is to observe or feel the response of the muscle. Serious errors in assessment can, however, be made, especially during recovery. Several studies suggest that TOF ratios as low as 0.3–0.4 can remain undetected. The detection rate for tetanic fade is no better. With double-burst stimulation, fade can be detected reliably up to TOF ratios in the range of 0.5–0.6.

Measurement of force

A force transducer can overcome the shortcomings of the senses; it provides an accurate measurement of the response elicited by electrical stimulation of a peripheral nerve.

Mechanomyography measures evoked mechanical response; it monitors the isometric contraction of a muscle in response to, for example, ulnar nerve stimulation. The amplitude of the signal is proportional to the strength of muscle contraction. Due to its complexity, it is impractical for clinical use.

Electromyography

It is possible to measure the electrical instead of the mechanical response of the muscle. In practice, electromyographic recordings are limited to the muscles supplied by the ulnar nerve. Most electromyographic recording devices compute the area under the curve during a specified ‘time window’ after the stimulus has been applied. Some compute the amplitude of the signal. There is usually a good correlation between the EMG and the force of the adductor pollicis.

Accelerometry

Accelerometers respond to acceleration, which, according to Newton's law, should be proportional to force if mass remains unchanged. The device, containing a piezo-electric transducer, is usually attached to the tip of the thumb and a digital read-out is obtained. The set-up is sensitive to inadvertent displacement of the thumb. Because it measures isotonic muscle contraction, acceleromyography does not require that preload be maintained at the adductor pollicis. For clinical use, it is not obligatory to calibrate the accelerometer before injecting the NMBD. But, to obtain reliable results, the muscle must be able to move freely and to fall back into the starting position after each stimulation.[72] In addition, to eliminate the influence of gravity on the accelerometry the response of the stimulated muscle should be strictly horizontal. Consequently, the stimulated hand is typically fixed in supination.

In conclusion, mechanomyography measures the force of contraction of the appropriate muscles. Acceleromyography measures the equivalent acceleration caused by the contractions of the muscles. Electromyography measures the accompanying currents over the contracting muscles.

SOME IMPORTANT FACTORS AFFECTING NEUROMUSCULAR MONITORING AND NEUROMUSCULAR BLOCK

Age and gender

Neither age nor gender affected the degree of a suxamethonium-induced block.[73] But after a total dose of vecuronium of 80 µg/kg, the induced neuromuscular block was significantly longer in women than in men.[74] Xue et al. found that women were 30% more sensitive than men to rocuronium.[75] The routine dose of rocuronium should thus be reduced in women. According to another group of investigators, neuromuscular blockade after 0.45 mg/kg rocuronium is more pronounced in women compared to men.[76] The onset time was shortened and the clinical duration increased in female patients. In elderly people the volume of distribution of rocuronium is reduced and clearance diminished; this results in a slightly longer half-life than in younger adults.[77] Age and gender have significant effects on the dose response and time course of effect of atracurium.[78] Older patients and women are more sensitive to atracurium-induced neuromuscular blockade than are young patients and men. Finally, the population PK/PD model for cisatracurium revealed that anaesthesia type, gender, age, creatinine clearance, and presence of obesity were associated with statistically significant

(P<0.01) effects on the PK/PD parameters of cisatracurium. These covariants were not associated with any clinically significant changes in the predicted recovery profile of cisatracurium.[79]

Interactions of NMBDs

Many drugs interact with NMBDs and often enhance the induced block; this is of clinical importance for volatile anaesthetics, antimicrobials, magnesium and some more specific drugs. Difficulty in reversing the block occurs with calcium-channel blockers and polymyxin. Phenytoin, carbamazepine and other anticonvulsants may cause resistance to NMBDs. Moreover, clinically important interactions are found between individual NMBDs. In neurological diseases, resistance to NMBDs occurs with nerve damage, including peripheral nerve trauma, cord transection and stroke. The response to an induced block may be altered in patients under intensive care and those with cancer. Although the most important theoretical interactions of NMBDs are understood, the anaesthetist should be aware that pharmacological interactions can lead to an unpredictable induced neuromuscular block in many cases in daily clinical practice.[30] These issues are extensively described in chapter 2.

Temperature, pH and electrolytes

The influence of temperature on the sensitivity of a muscle to neuromuscular blockade is complex. The effect of hypothermia on the sensitivity of the neuromuscular junction to an induced block will vary with the species studied, with different muscle relaxants, and at different temperatures. Hypothermia has direct effects on skeletal muscle function, with reduced contractility and muscle weakness.[80] Moreover, changes in temperature will affect the interpretation of the results of monitoring neuromuscular blockade. In general, hypothermia decreases the response to NMBDs. The force of contraction of the adductor pollicis decreases by 10–16% for every ºC decrease in muscle temperature below 35.2°C during both nitrous oxide/isoflurane and nitrous oxide/fentanyl anaesthesia.[81, 82] Thus, if the monitored hand is cold, the degree of paralysis will appear to be increased.[83] To keep the muscle temperature above 35.2°C, the central temperature must be maintained at > 36.0 °C.[80, 84, 85]

Mild hypothermia significantly prolongs the duration of action of NMBDs in humans:[84, 86] the influence of hypothermia on the metabolism of elimination organs, as well as on Hofmann elimination, is responsible for the prolongation of steroidal NMBDs as well as benzylisoquinolines.[86, 87] As hypothermia invariably lengthens the duration of block,

maintaining a normal temperature, both centrally and in the limb being monitored, will improve precision. Finally, disturbances of acid–base balance, as well as change in electrolytes, will make an induced neuromuscular block unpredictable.[30]

Hepatic and renal failure

As described earlier, atracurium and cisatracurium are almost independent of liver and renal function for their elimination; cistatracurium, like atracurium, is cleared by Hofmann elimination.[34] Accumulation is thus unlikely. As the metabolism of (cis)atracurium is independent of liver function, it is the NMBD of choice in liver failure,[29, 88] but a metabolite, laudanosine, may accumulate in liver disease. It was demonstrated that only 23% of the elimination of cisatracurium occurs via organs, in contrast to 90–95% for rocuronium.[41, 89] Accordingly, it might be reasoned that, during the course of an anaesthetic, rocuronium will tend to accumulate at receptor sites (neuromuscular junctions) to an extent that, for example, infusions would have to be progressively decreased to maintain the same level of block. The fact that this requirement was not observed in many published studies might be because the infusions were not administered for long enough to saturate the body's clearance systems. The onset of action for rocuronium is delayed by an enlarged volume of distribution in patients with severe liver disease.[90] However, although its elimination kinetics are unaltered, the time to recovery is also prolonged because of a markedly impaired hepatic elimination. Thus, rocuronium predominantly depends on hepatic biotransformation and should be used with great care, if at all, in hepatic failure. Rocuronium also depends in part on renal elimination, and maintenance doses must be decreased in chronic renal failure or titrated carefully to effect. In patients with reduced renal function, rocuronium has only a slightly longer time course of neuromuscular blockade than in those with normal renal function.[53, 91] Although rocuronium may accumulate with continuous infusion, its single-dose pharmacokinetics are, nevertheless, little changed in anephric patients. In contrast, patients with liver failure have a prolonged duration of clinical block and an increased recovery time, with a wide interindividual variation due to a decreased elimination rate.[90, 92]

Finally, drugs with active metabolites that are eliminated by the liver and/or kidneys, e.g. laudanosine from atracurium (and cisatracurium) metabolism, also need to be used with care in hepatic/renal failure.[9, 93]

MAINTENANCE OF NEUROMUSCULAR BLOCKADE

Neuromuscular blockade having been secured and the trachea intubated, the maintenance of paralysis is the next consideration. If surgery lasts longer than about 60 min and neuromuscular blockade has to be maintained, then three methods can be used in order for continued muscle relaxation [94].

Large initial bolus

If a large initial bolus is administered, the duration of action is extended as well as the rate of onset being increased. The question remains whether such a large initial bolus is safe regarding cardiovascular side-effects and histamine release. Moreover, where there is unusual sensitivity or reduced clearance, an extended block may occur. It is, furthermore, difficult to anticipate the exact length of the operation and it will thus remain doubtful if this technique will be sufficient to overcome relaxation problems during interventions that take several hours. Tullock (1990) describes the onset and duration of vecuronium up to 0.4 mg/kg ($8 \times ED_{95}$) and Belmont (1995) does the same for cisatracurium ($8 \times ED_{95}$), but no accounts have been traced on how these large boluses will behave in organ failure or special types of surgery [31, 95].

Incremental boluses

Incremental boluses result in a fluctuating block, sometimes too deep and sometimes inadequate. Moreover, the action of repeating boluses often requires the anaesthetist's attention at a critical moment. This technique, although used in clinical practice, is often too cumbersome and thus can cause specific problems.

Continuous infusions

When it is desired to maintain a constant level of effect of an agent, the most logical approach is to administer it in such a way that there remains a constant activity at the receptor site. Such activity is usually related exactly to concentration at the receptor site, except where there is an alteration in the receptor or in the drug–receptor complex. This may result in the appearance of tachyphylaxis or increased sensitivity. In the use of non-depolarising NMBDs in clinical practice, there is no evidence of the development of such a phenomenon. Suxamethonium is the exception because its interaction with the receptor changes with time. On the assumption that the concentration at the neuromuscular junction is the determining factor, maintenance of a constant degree of neuromuscular blockade should be possible if that

concentration is held constant. NMBDs are all polar and water-soluble, and diffuse freely throughout the extracellular fluid; it would therefore be expected that the concentration at the neuromuscular junction will be reflected in the plasma concentration. Maintenance of a constant plasma concentration should therefore produce a constant degree of neuromuscular blockade [96].

The NMBDs are given where it is most convenient to the surgeon that a constant degree of neuromuscular blockade should be maintained throughout the majority of the procedure. It is also useful if this degree of blockade can be attained without delay, altered relatively easily and is reversible without problems at the end of surgery. In order to maintain a constant plasma concentration and thus a constant effect, the most appropriate technique of administration would be to administer a continuous infusion. If the rate of delivery of the drug is equal to its rate of clearance from the plasma at steady state, then this will be achieved. The bolus/infusion technique (bolus dose = volume of distribution × plasma concentration and infusion rate = plasma concentration × clearance) is in practical terms a great improvement over the simple infusion technique. In fact, because tracheal intubation requires a greater degree of neuromuscular blockade than does surgery, it is usual to administer a bolus loading dose, wait for recovery to the desired level and then to begin an infusion. It is obviously not possible always to use an exact formula and so it can be useful to know the approximate rates of usage of each NMBD when given by infusion. If an infusion is started at a recommended rate, the desired level of neuromuscular blockade should be maintained in most patients, although adjustments will be necessary to allow for patient variability. An alternative method of continuous NMBD infusion is to use a computer-controlled system relying on neuromuscular transmission monitoring [54, 97]. At present this remains a research tool.

Disadvantages of the infusion technique are the need for preparation of the infusion, the availability of equipment (syringe drivers) and need for a dedicated intravenous line.

HYPOTHESIS AND PRESENTATION OF THE PUBLISHED MATERIAL

For the maintenance of a neuromuscular block during long interventions, incremental boluses of NMBDs are probably not a favourite choice, for practical reasons. Is a large initial bolus of NMBD an alternative during protracted surgery or will its effect end too early? Furthermore, how will this large bolus behave pharmacodynamically in the presence of impaired organ

function or in specific types of surgery? When we choose a continuous infusion of NMBDs in order to maintain muscle relaxation, how will the dose requirements evolve with time and how can PORC be avoided when NMBD infusions are administered during protracted surgery, in liver failure and during hypothermic cardiopulmonary bypass surgery?

This thesis describes studies on the optimisation of continuous infusions of the newer NMBDs, cisatracurium and rocuronium. The risk with this method of NMBD administration is indeed PORC, a consequence of misinterpretation of the dose–effect relation, which is influenced by the 'time' component in the continuous administration of drugs – the so-called pharmacological context of administration. The factor 'time' is responsible for drug accumulation and disturbs the dose–effect relation when a fixed dose is infused. Possible solutions include the use of pharmacokinetic models, such as are employed when hypnotics and/or opioids are administered continuously, but with NMBDs there is the great advantage that there exists an extensively validated,[98] direct-effect monitor. So, to avoid problems with the continuous administration of NMBDs, one can:

1. optimise the dose requirement over time, as a fixed dose regimen has a high PORC rate;
2. measure the effect by means of NMT monitoring and selectively antagonise the neuromuscular block at the end of surgery;
3. routinely antagonise the neuromuscular block at the end of surgery (but the classical antagonists may be harmful).

Unfortunately, NMT monitors are only seldom used in daily clinical anaesthesia.[99] This thesis will further demonstrate the necessity of NMT monitoring as well as the clinically important role of optimisation techniques for continuous infusions of the NMBDs studied. By optimising the dose in relation to duration via NMT monitoring, the total anaesthesiological management of the patient can be improved, especially when the dose–effect relation is unpredictably disturbed by pathology or type of surgery. This improvement is here confirmed in anaesthesia for liver and cardiac surgery, where those two factors (pathology and surgery) play an important part.

We investigated in healthy patients the value of NMT monitoring in guiding continuous infusions as well as preventing PORC. We next investigated some pathological conditions in which the 'fixed-dose' rule is even more compromised, such as in liver and heart surgery, and we studied outcomes when techniques for optimising NMBD infusions were used.

This thesis thus describes the effects of the continuous administration of cisatracurium and rocuronium, and the need for NMT monitoring, during protracted, major surgery without routine pharmacological reversal in patients who do not have organ failure. We also studied patients with organ failure and/or undergoing special surgical techniques: dose requirements for continuous infusions of cisatracurium and rocuronium in cardiac surgery with hypothermic CPB. We draw a parallel in studying, by means of NMT monitoring, the dose requirements for an infusion of cisatracurium, the preferred NMBD in liver surgery, during liver transplantation. Relying on NMT monitoring, we then optimised the management of anaesthesia and of the continuous infusion of cisatracurium in right-lobe living-donor liver surgery.

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Chapter 2

INTERACTIONS OF NEUROMUSCULAR BLOCKING DRUGS

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INTERACTIONS OF NEUROMUSCULAR BLOCKING DRUGS

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SUMMARY

Many drugs interact with neuromuscular blocking drugs and often enhance the induced block; this is of clinical importance for volatile anaesthetics, antimicrobials, magnesium and some more specific drugs. Difficulty in reversing the block occurs with calcium-channel blockers and polymyxin. Phenytoin, carbamazepine and other anticonvulsants may cause resistance to neuromuscular blocking drugs. Moreover, clinically important interactions are found between individual neuromuscular blockers. Giving succinylcholine after a non-depolarizing neuromuscular blocking drug prolongs the onset of succinylcholine; when non-depolarizing drugs are administered after succinylcholine their effects are prolonged. The succinylcholine block is prolonged when the drug is administered during recovery from pancuronium or following neostigmine reversal. Drugs or diseases that decrease the activity of plasma cholinesterase may prolong a succinylcholine-induced block. Finally, liver dysfunction, renal failure, disturbances of acid-base balance, change in temperature and neurological diseases all have an effect on the profile of the neuromuscular blocking drugs; the response to an induced block may be altered in patients under intensive care and those with cancer. Although knowledge of the most important theoretical interactions of neuromuscular blocking drugs is favourable, the anaesthetist should be aware that pharmacological interactions can lead to an unpredictable induced neuromuscular block in many cases in daily clinical practice. Therefore anaesthetists should become familiar with the use of neuromuscular transmission monitoring in order to manage the block correctly.

Keywords: ANAESTHESIA, general; BLOCKING AGENTS, neuromuscular; Drug interactions.

Interactions between neuromuscular blocking drugs and several anaesthetic and non-anaesthetic drugs have been described. Although some interactions have been confirmed in controlled trials and are of real clinical importance, many others remain as isolated case reports or are theoretical. Moreover, investigators did not always succeed in explaining whether interactions occurred at a pharmacokinetic or a pharmacodynamic level. Except for some benzylisoquinolines, the effect of most non-depolarizing neuromuscular blocking drugs depends on liver and renal function because their pharmacokinetics are strongly dependent on these organs; hepatic and/or renal dysfunction may thus be of importance in this context. Temperature and pH changes also have an effect on the profile of neuromuscular blocking drugs.

Interactions with anaesthetic agents

1. INHALATIONAL AGENTS

Vapours potentiate neuromuscular blocking drugs: in 1971 already, Miller et al. described the comparative neuromuscular effects of pancuronium, gallamine and succinylcholine during isoflurane and halothane anaesthesia in man (1). Later, additional material was published suggesting enhancement of induced neuromuscular blockade by volatile anaesthetic agents (2, 3, 4, 5, 6). In general, volatile anaesthetics potentiate drug-induced neuromuscular blocks in a dose-related fashion, but the results of the Suzuki trial indicate that the duration of sevoflurane anaesthesia also influences the dose-response of vecuronium (7). Moreover, neostigmine was found to reverse a vecuronium-induced but not a sevoflurane-induced neuromuscular block (8). Although it is doubtful if there are clinical implications, d-tubocurarine and pancuronium appear to be more influenced by enflurane and isoflurane than halothane, while enflurane potentiated a vecuronium-induced block more intensely than did halothane or isoflurane (4). However, the background anaesthetic appears to have less effect on an atracurium-induced neuromuscular blockade (9). In children receiving a continuous infusion of atracurium, Brandom et al. found a 30% decrease in dose requirement when halothane or isoflurane was used (10). Also, the newer neuromuscular blocking drugs, cisatracurium and rocuronium, are potentiated by inhalational anaesthetics (11, 12): rocuronium appears to be more influenced by enflurane and isoflurane than halothane (13); and in a recent study by Bock et al. there was a satistically significant reduction in the ED_{90} of rocuronium by desflurane, sevoflurane and isoflurane compared with propofol, but no significant differences between the three inhalational anaesthetics in relation to the potency,

infusion requirements or recovery characteristics of rocuronium (14). Nakata et al. compared vecuronium-induced neuromuscular blockade during xenon or sevoflurane anaesthesia in humans and found that the mean time from the administration of vecuronium to 25% recovery of the first twitch of the train-of-four response was significantly shorter in the xenon than the sevoflurane group (15). Cara et al. report three cases of prolonged paralysis resulting from rapacuronium in the presence of sevoflurane (16).

Not only non-depolarizing neuromuscular blockers but also the depolarizing succinylcholine block are potentiated by nitrous oxide and volatile agents (1, 17). A precise explanation for this phenomenon has not been formulated: prejunctional mechanisms have been proposed, but others suggest that muscle blood flow is increased by isoflurane, increasing the delivery of the relaxant and the consequent neuromuscular block (18).

2. INTRAVENOUS ANAESTHETICS

Slight potentiation of an induced neuromuscular block by most intravenous induction agents has been shown in a number of animal studies (19). Recently, it was demonstrated that propofol significantly enhances d-tubocurarine-induced twitch depression in animals (20). Although this effect could probably be extrapolated to man, it is of little clinical significance.

3. LOCAL ANAESTHETICS

Local anaesthetics have neuromuscular blocking properties of their own. They also potentiate the effects of neuromuscular blocking drugs (21) and, in combination with certain drugs, some of them seem to have additive neuromuscular blocking properties: gentamicin and lidocaine (lignocaine) have such effects, producing a profound neuromuscular block after d-tubocurarine (22).

Interactions with neuromuscular blocking drugs

Several investigators have studied pancuronium – vecuronium, d-tubocurarine – metocurine and atracurium - mivacurium interactions and found additive effects (23); a pancuronium - metocurine combination appeared to potentiate the neuromuscular blockade (24). Studying the interaction between vecuronium and pancuronium, Okamoto et al. noticed that duration of action of the supplemental relaxant was largely modified by the initial one (25). Also, Erkola

et al. demonstrated that a shorter-acting neuromuscular blocking drug (mivacurium), if administered after a longer-acting one (pancuronium), took on the characteristics of the first drug (26). The only justifiable clinical reason for combined administration of neuromuscular blocking drugs is in trying to blunt undesirable haemodynamic effects; but as the newer neuromuscular blockers lack haemodynamic instability it is therefore far from evidence-based to combine them. Naguib et al. found that the interaction between rocuronium and cisatracurium or mivacurium was synergistic (27, 28). The interaction between cisatracurium and mivacurium, vecuronium or rocuronium was also synergistic, but the interaction between cisatracurium and atracurium was additive. Synergy between cisatracurium and vecuronium or rocuronium was greater than between cisatracurium and mivacurium (29). The mechanism by which combined neuromuscular blocking drugs act is difficult to explain. In contrast to what some had earlier suggested, combinations of neuromuscular blocking drugs did not affect the degree of protein binding by each drug and, consequently, the amount of unbound drug (30). Others held that one drug would act presynaptically while the other would have a postsynaptic effect (31). Probably, the interaction is of postsynaptic origin, i.e., the explanation is to be sought in the binding properties of the different relaxants to the α-subunits of the acetylcholine receptor (32, 33).

The combination of a non-depolarizing with a depolarizing neuromuscular blocking drug has intrinsic antagonistic effect. In order to prevent fasciculation, some clinicians administer a non-depolarizing neuromuscular blocker before succinylcholine is given; succinylcholine then appears to be less potent and has a shorter duration of action (34, 35). Pancuronium appears to be an exception, as the duration of succinylcholine action increases when pancuronium is administered first; the cholinesterase-inhibiting properties of pancuronium probably explain this phenomenon (36). The potency of a non-depolarizing block, except by rocuronium or cisatracurium, increases when preceded by succinylcholine (12, 37, 38). The effect of prior administration of succinylcholine on an atracurium block depends on the state of recovery from succinylcholine (39). Finally, succinylcholine can reverse a non-depolarizing block by enhancing the release of acetylcholine (40). Following the administration of an anticholinesterase, the succinylcholine effect increases by inhibition of plasma cholinesterase. However, data from Fleming et al. suggest that other mechanisms in addition to cholinesterase inhibition may contribute to this drug interaction (41).

Interactions with antibiotics, anticonvulsants, magnesium and other agents

Interactions between β-lactam antibiotics, particularly acylaminopenicillins, and vecuronium lead to prolonged neuromuscular blockade (42). However, Condon et al. showed that cefoxitin and piperacillin, administered pre- or intraoperatively, are not associated with a clinically important prolongation of neuromuscular block induced by vecuronium (43). Aminoglycosides, especially neomycin and streptomycin, potentiate a depolarizing as well as a non-depolarizing block (44); moreover, this block is enhanced by magnesium. The blockade can be antagonized by calcium and by anticholinesterases. Initially, these antibiotics appeared not to have effect on a rocuronium block (45), but a clinical report from 1996 describes the failure of rocuronium reversal in a patient who had received oral neomycin (46). Polymyxins have a postjunctional effect that is difficult to reverse. Lincosamines, clindamycin and lincomycin, have pre- and postjunctional effects: no reversal is possible with calcium or anticholinesterases. The management of this kind of block is thus difficult.

Patients on chronic phenytoin or other anticonvulsant therapy show resistance to pancuronium, pipecuronium (47), vecuronium (48) and rocuronium (49, 50, 51), but not to atracurium (52). However, Tempelhoff et al. demonstrated that atracurium, when used on epileptic patients requiring long-term anticonvulsant therapy, had a shorter duration of action than in non-epileptic patients (53). Others have shown that chronic carbamazepine therapy does not influence the onset time and duration of action of atracurium-induced neuromuscular blockade (54).

Up-regulation of the acetylcholine receptor is probably responsible for this pharmacological resistance (55, 56). The prolonged duration of succinylcholine in patients receiving anticonvulsants is also consistent with a mild, anticonvulsant-induced up-regulation of acetylcholine receptors (57). Because of an enhancement of the neuromuscular blocking effect it was concluded that succinylcholine, pancuronium and vecuronium should be used with caution in those receiving lithium or other alkali metals; this enhancement was not confirmed for alcuronium, metocurine or d-tubocurarine (58). Curiously, phenytoin, acutely administered, augments the neuromuscular blockade produced by rocuronium (59).

Induced neuromuscular block is potentiated in the presence of α_2-agonists (60), ß-agonists and calcium blockers (release of acetylcholine from presynaptic nerve endings requires calcium) (61, 62, 63, 64); South Korean investigators showed that, in animals, esmolol

decreased plasma cholinesterase activity, antagonized the neuromuscular blocking potency of mivacurium and prolonged its neuromuscular blocking effect (65). Abnormal reactions, mostly block potentiation, occur in combinations of neuromuscular blocking drugs with corticoids (66), immunosuppressants (cyclosporine) (67), H_2 antagonists (interaction at the presynaptic level) (68) and proton-pump inhibitors (69). Some cardiovascular agents (70) and psychotropic drugs (71) antagonize induced neuromuscular blockade. Finally, concerning more 'exotic' drugs, ulinastatin, a protease inhibitor, delayed the onset time and hastened recovery from a vecuronium-induced neuromuscular block, probably because of an acetylcholine-releasing effect by this drug (72).

A need for larger doses of vecuronium was found in smokers, probably caused by enhanced nicotine-induced biotransformation, but these findings were not confirmed for rocuronium (73). On the other hand, many neuromuscular blocking drugs interact pharmacokinetically with alcohol, the liver being the site where both alcohol and many such drugs are metabolized, frequently by the same enzymes (74).

Magnesium deserves special attention as clinicians are regularly confronted with cases of hypermagnesaemia ($[Mg^{2+}] > 2.5$ mg.dl^{-1}), caused by, for example, magnesium in antacids, enemas or parenteral nutrition; especially in patients with impaired renal function one must be cautious about induced hypermagnesaemia. On the other hand, hypermagnesaemia is therapeutic in pregnant women being (pre)eclamptic. Hypermagnesaemia antagonizes the release and effect of acetylcholine at the neuromuscular junction and, consequently, depresses skeletal muscle function, leading to neuromuscular blockade. Magnesium potentiates the action of neuromuscular blocking drugs and decreases potassium release in response to succinylcholine. During pregnancy, the non-organ-dependent elimination of (cis-)atracurium results in an unchanged clinical duration of action, but in contrast the clinical duration of vecuronium is dramatically increased in magnesium-pretreated pregnant women (75). Among women undergoing a caesarean section who were pretreated with magnesium, the infusion rate of mivacurium required to obtain relaxation was lower than that among women who did not receive pretreatment (76). The umbilical : maternal vein concentration ratio of non-depolarizing neuromuscular blocking drugs varies from 7 to 26% and clinical doses of these drugs may consequently induce partial residual curarization in neonates. Despite the decreased plasma pseudocholinesterases, the clinical duration of succinylcholine, 1mg kg^{-1}, is unchanged in pregnant women. At clinical doses, transplacental passage of succinylcholine is insufficient to produce curarization of neonates. As already mentioned, magnesium sulphate

enhances the effects of non-depolarizing neuromuscular blocking drugs, but will have no effect on the characteristics of recovery from succinylcholine (77). Moreover, the incidence of succinylcholine-associated fasciculations was significantly lower in a magnesium-treated group than a control group (78). For rocuronium, prolongation of the block due to a magnesium effect is well known, certainly when using the 'rapid sequence dose' of 0.9 mg kg^{-1}. Therefore, one must perhaps not reject succinylcholine, but rather keep in mind that its use in this context is rational (79, 80). Moreover, in contrast to vecuronium, magnesium does not shorten the onset time of rocuronium; therefore, a rapid sequence dose of 0.9 mg kg^{-1} is probably required for safety (81, 82).

Altered responses to neuromuscular blocking drugs

Patients in the intensive care unit often receive a conglomerate of drugs; interactions between neuromuscular blocking drugs and methylprednisolone, aminoglycosides, cyclosporin and others have been investigated and found important (83). Electrolyte, acid-base and temperature disorders may interfere with the profile of neuromuscular blocking drugs (84, 85). In patients in intensive care, a marked prolongation of recovery following steroidal drug as well as atracurium infusions has been noted (83, 86); a decrease in organ-specific excretion (liver and kidneys) due to multiple organ failure, and the circulation of active metabolites, have been proposed as explanations for the disproportionate residual curarization in patients under intensive care who have received a continuous infusion of neuromuscular blocking drug. However, many other issues should not be overlooked when attempting to explain this pharmacological phenomenon in the intensive care unit: possible drug overdosing, disorders of acetylcholine synthesis and/or release, concomitant administration of calcium blockers, postjunctional membrane dysfunction, and up- or down-regulation of the acetylcholine receptor (87). Finally, critical-illness neuropathy itself is synonymous with neuromuscular weakness and can obviously interact with recovery from a pharmacologically induced neuromuscular block. The complex state of the critically ill patient dictates that the effects of neuromuscular blocking drugs will be unpredictable (88, 89, 90). Although only a few controlled clinical trials have been performed, it is important that when neuromuscular transmission was monitored, no prolonged blockade was found following continuous infusions of neuromuscular blocking drugs in intensive care (91, 92).

Probably the same conclusions about unpredictability can be drawn in relation to patients with cancer, in whom not only is serum cholinesterase activity depressed but also

chemotherapy sometimes increases the dose requirements for neuromuscular blocking drugs while often also potentiating an induced block. Possible hepatic and renal impairment contributes to the obscurity of the neuromuscular blocking drug profile in patients with cancer (93).

Patients suffering from myasthenia gravis are usually resistant to succinylcholine (94) and highly sensitive to non-depolarizing neuromuscular blocking drugs (95, 96). Patients with myotonia show sustained contracture in response to succinylcholine; they have normal responses to non-depolarizing drugs. In muscular dystrophy, succinylcholine is contraindicated (97). There are reports of hyperkalaemia in response to succinylcholine in certain neurological diseases. Hyperkalaemia following succinylcholine administration is reported in patients with hemiplegia/paraplegia, but they are sometimes resistant to non-depolarizing neuromuscular blocking drugs. Burn injury causes hyperkalaemia in response to succinylcholine; there is resistance to the effects of non-depolarizing drugs (98).

CONCLUSIONS

Drug interactions involving neuromuscular blocking drugs may have clinical importance. Volatile anaesthetics are known for their dose-dependent potentiation of all neuromuscular blockers; local anaesthetics also potentiate the effects of all of them. Non-depolarizing drugs, when combined, produce synergistic or additive effects, depending on the combination, but the clinical significance of this is doubtful. The response to non-depolarizing/depolarizing drug combinations depends on the sequence of administration; a non-depolarizer given before succinylcholine interferes with the succinylcholine blockade, whereas the block by a non-depolarizer given after succinylcholine is potentiated. Antibiotics, especially aminoglycosides and polymyxins, and magnesium tend to potentiate neuromuscular blocking drugs. Anticonvulsants are most likely to induce resistance to non-depolarizing drugs. Although knowledge of the most important clinical interactions of neuromuscular blocking drugs is favourable, the anaesthetist must be aware of the unpredictability of an induced neuromuscular blockade in ill patients with disturbed liver or renal function receiving all kinds of drugs that sometimes, theoretically, may potentiate or counteract it. Perhaps such interactions occur even in the majority of our daily practice, as we all routinely use a basket of drugs, each of them having their own pharmacological profile. Therefore, the monitoring of neuromuscular transmission, ideally quantitative, should become routine practice in managing neuromuscular blockade and thus in titrating the required amount of drug.

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Chapter 3

POSTOPERATIVE RESIDUAL CURARIZATION WITH CISATRACURIUM AND ROCURONIUM INFUSIONS

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POSTOPERATIVE RESIDUAL CURARIZATION WITH CISATRACURIUM AND ROCURONIUM INFUSIONS

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SUMMARY

Background and aim Monitoring of neuromuscular blockade still relies often on clinical judgement; moreover, there are substantial national differences in the use of reversal agents. We investigated recovery characteristics and incidence of postoperative residual curarisation after cisatracurium and rocuronium infusions for long duration interventions without systematic reversal.

Methods In 30 patients undergoing major surgery, we have measured infusion dose requirements for rocuronium and cisatracurium during propofol anaesthesia. Infusions were discontinued at the beginning of surgical closure; spontaneous recovery of neuromuscular function was awaited in both groups. Neostigmine (50 µg/kg) was administered only when a patient started to wake without a train-of-four ratio of 0.9.

Results In the cisatracurium and rocuronium groups, four (27 %) and one (7 %) patients, respectively, had a train-of-four ratio of 0.9 at the end of surgery. The train-of-four ratio in each group at that time was 51 ± 32 % for cisatracurium and 47 ± 31 % for rocuronium (P = 0.78). Six patients (40 %) in the cisatracurium group and seven (47 %) in the rocuronium group required neostigmine. The train-of-four ratio at time of reversal was 63 ± 7 % for cisatracurium and 40 ± 19 % for rocuronium (P = 0.01). The time interval between end of surgery and a train-of-four ratio of 0.9 was 10 ± 9 min for cisatracurium and 18 ± 13 min for rocuronium (P = ns).

Conclusion Patients receiving a cisatracurium or rocuronium infusion have a high incidence of postoperative residual curarisation, when the block is not antagonised. When ‘reversal’ is not attempted, cisatracurium seems to be safer than rocuronium.

Keywords NEUROMUSCULAR BLOCKING AGENTS, neuromuscular non-depolarising agents; NEUROMUSCULAR BLOCK, cisatracurium, rocuronium.

INTRODUCTION

Monitoring and/or antagonising the effects of a muscle relaxant-induced neuromuscular block is a widely accepted standard in clinical practice. However, the reality is that there are international differences in this practice and, in many departments throughout the world, clinicians do not have access to equipment for measuring the degree of a neuromuscular block [1]. Moreover, many anaesthetists do not routinely antagonise the neuromuscular block and, in some patients, reversal agents may affect heart or lung function or both [1,2]. In daily clinical practice, residual block can be excluded only by objective methods providing a quantitative measure of neuromuscular recovery. However, it is not possible to exclude clinically important residual paralysis either by clinical evaluation or tactile/visual evaluation of the response to peripheral nerve stimulation [3]. Neuromuscular blocking drugs are commonly given by incremental boluses or by continuous infusion during major abdominal and thoracic surgery. In the absence of monitoring, or when irrational dosage regimens are used, or in absence of routine ‘reversal’, continuous infusions for lengthy interventions can cause overdosing and may delay recovery.

The study measured the infusion dose requirements for rocuronium and cisatracurium during propofol anaesthesia for major surgery in 30 patients. Infusions were discontinued at the beginning of surgical closure. As closure of the abdomen or thorax can often be achieved with the aid of deep anaesthesia or some mild degree of paralysis only, many anaesthetists tend to switch off the muscle relaxant infusion at this particular moment. Spontaneous recovery of neuromuscular function in both groups was awaited and we recorded the recovery characteristics after the infusions had been discontinued. We investigated whether patients receiving a rocuronium or a cisatracurium infusion presented less residual curarisation. Implications for safety from the differences observed are discussed.

METHODS

Organisation and recruitment

After Institutional Review Board approval and written informed consent, we studied 30 ASA class I–III patients undergoing abdominal or thoracic surgery. Using data from previously published material, we performed a power analysis (two group t-test of equal means) that revealed a sample size of 14 in each group having 80% power to detect a difference in train-of-four (TOF) ratio of 10% using a two group t-test with a 0.05 two-sided significance level [4]. The patients were allocated randomly by drawing lots to group 1 (n = 15; cisatracurium) or group 2 (n = 15; rocuronium). Exclusion criteria were pregnancy; evidence of renal, hepatic, metabolic or neuromuscular disorders; and a history of medication interfering with neuromuscular transmission.

Neuromuscular function

Neuromuscular transmission was monitored on the right arm by the EMG response of the adductor pollicis muscle to TOF stimulation of the ulnar nerve, using surface electrodes (M-NMT™ module; Datex-Ohmeda, Helsinki, Finland). The TOF response to a supramaximal stimulus was obtained before the initial bolus of neuromuscular blocking drug. The TOF was measured at 1-min intervals, using a square-wave, constant-current stimulus pulse with a width of 200 μs.

Induction and maintenance of anaesthesia

All patients were premedicated with lorazepam 2.5 mg 1 h before induction. After 3 min of preoxygenation, anaesthesia was induced with propofol 5 ml min^{-1} until loss of consciousness and sufentanil 0.3 μg kg^{-1} i.v. As soon as the eyelid reflex was absent, assisted ventilation by facemask was started with oxygen 100%. After equipotent bolus doses of cisatracurium 0.1 mg kg^{-1} or rocuronium 0.6 mg kg^{-1}, endotracheal intubation was performed as soon as the first response to the TOF stimulus (T1) fell below 10%. Normocapnic ventilation was established with an ADU ventilator (Datex-Ohmeda; Helsinki, Finland). Anaesthesia was maintained with oxygen 40% in air, propofol 3–6 mg kg^{-1} per h and supplemental boluses of sufentanil. No inhalation anaesthetics were used. Routine monitoring included ECG, pulse oximetry, invasive and/or non-invasive blood pressure and central venous pressure. Temperature was monitored in the oesophagus and on the area of the skin on the right arm where neuromuscular transmission monitoring electrodes had been applied. We used a forced

air-warming system (Bair Hugger™; Augustine Medical, Inc., Eden Prairie, MN, USA) at the lower body surface to keep the oesophageal temperature between 35.5 and 37°C [5].

After recovery of T1/T0 to 10%, patients were given either cisatracurium or rocuronium at an infusion rate of 1.5 and 10 μg kg^{-1} per min, respectively. The rate was manually adjusted to maintain T1/T0 at 10%. The concentration of the solutions used for infusion was 0.2 and 1 mg ml^{-1} for cisatracurium and rocuronium, respectively, so that even small changes in infusion rate led to significant changes in the volume delivered and, thus, to a quick alteration in effect [4]. The infusion was discontinued at the beginning of surgical closure, whereas the administration of propofol was stopped when the surgeon started closing the skin.

Recovery of neuromuscular function

When surgery had been accomplished, the TOF ratio was assessed, and once it had recovered spontaneously to 0.9, the awakening patient's neuromuscular function was assessed clinically. The patient's response to the clinical tests was recorded. Neostigmine (50 μg kg^{-1}) was administered only when a patient started to wake with a TOF ratio < 0.9. When the TOF ratio had recovered to 0.9, patients were extubated when they were breathing spontaneously, were fully awake and able to follow commands. All clinical tests were completed within 1 min and repeated within 5 min of the patient's arrival in the postanaesthesia care unit (PCU). In contrast to most studies published on this matter, we extubated our patients when the TOF had recovered to 0.9. The evidence that residual effects of neuromuscular blocking drugs may persist until a TOF ratio of 0.9 is reached, enforced this strategy [6]. Moreover, Eriksson suggested an effect of vecuronium on carotid body hypoxic chemosensitivity at a TOF ratio of 0.7, thus impairing the hypoxic ventilatory response [7]. In another study by Eriksson, TOF values below 0.9 were accompanied by a reduced ability to protect the airway [8]. Return of the TOF ratio to 0.9 at the thumb is thus probably necessary to counteract any residual block in the pharynx and the facial muscles.

Data collection

The results of monitoring the neuromuscular transmission and of all other vital parameters were displayed on an AS/3™ monitor (Datex-Ohmeda; Helsinki, Finland) and stored in a spreadsheet on a PC (Compaq™; Houston, TX, USA). Infusion rate and duration were recorded throughout the procedure for each patient. The mean infusion rates in both groups were computed. We derived the patient characteristics and calculated the body surface area in both groups. The number of patients having a TOF ratio of 0.9 at the end of surgery was

recorded, as well as the mean TOF ratio in each group at that time. Also, the number of patients needing neostigmine and the time-points, as well as the mean TOF ratio at which reversal was attempted, were derived. The time intervals between discontinuing the infusion and the end of surgery and between the end of surgery and a TOF ratio of 0.9 were recorded. Additionally, the time interval between the end of surgery and extubation, as well as between the end of surgery and arrival at the PCU, were computed. We looked at unplanned admissions to the intensive care unit (ICU), as well as other adverse postoperative events. Finally, we investigated the following potential confounding factors: the infusion duration and the period between discontinuing the neuromuscular blocking drug infusion and the end of surgery.

Statistical analysis

Statistical analysis (GraphPad™ InStat®, San Diego, CA, USA) was performed to compare both groups and to investigate significant differences. A Kolmogorov and Smirnov normality test and an unpaired t-test were performed to compare body surface area. The calculated T1/T0 was compared with the preset value (T1/T0 = 10%) by means of a Kolmogorov and Smirnov test to assess normality and a one-sample t-test. We compared the duration of surgery as well as the infusion duration using a non-parametric Mann-Whitney test. The recovery time intervals, as well as the TOF ratio at the end of surgery and at the time of reversal were compared between cisatracurium and rocuronium groups using a non-parametric Mann-Whitney test. A Fisher's exact test compared the results of the clinical neuromuscular function tests between cisatracurium and rocuronium groups at two different time-points. Results are presented as mean ± SD. Significance was set at a level of $P<0.05$.

RESULTS

In the cisatracurium group, one patient suffered from bronchospasm following intubation, and another developed atrial fibrillation requiring intraoperative electrical conversion. In the rocuronium group, surgery in one patient was complicated by significant blood loss (<2000 ml). Another patient in the rocuronium group lost 2000 ml of blood and required a small dose of norepinephrine infusion intraoperatively (<200 ng kg^{-1} per min). Eight minutes after surgery, this patient had a neuromuscular transmission count of 1 and a T1% = 9. It was decided to continue sedation and to transfer the patient to the intensive care unit for postoperative ventilation. Because of infiltration on the chest radiograph and fever, this patient was not extubated until 3 days later, and was excluded from the recovery analysis. Anaesthesia was uneventful in all other patients.

The duration of surgery in the cisatracurium and rocuronium groups was 242 ± 83 and 212 ± 137 min, respectively (P = 0.10). Table 1 shows the physical characteristics of the patients in the cisatracurium and rocuronium groups. The body surface area in the cisatracurium and rocuronium groups was 1.74 ± 0.18 m^2 and 1.82 ± 0.24 m^2, respectively (P = 0.30). In the cisatracurium group, T1/T0 during the infusion was 10.3 ± 3.5 %; this mean was not significantly different from the preset value (T1/T0 = 10%) (P = 0.76). The infusion rate of cisatracurium required to keep T1/T0 at 10% was 1.0 ± 0.3 µg kg^{-1} per min. In the rocuronium group, the T1/T0 during the infusion was 10.0 ± 6.3 %; this was not significantly different from the preset value (T1/T0 = 10%) (P = 0.99). The infusion rate of rocuronium required to keep T1/T0 at 10% was 5.6 ± 2.6 µg kg^{-1} per min. The infusion duration was 174 ± 67 min for cisatracurium and 159 ± 142 min for rocuronium (P = 0.15).

Table 2 shows the recovery time intervals. In the cisatracurium and rocuronium groups, four (27%) and one (7%) patients, respectively, had a TOF ratio of 0.9 at the end of surgery. The TOF ratio in each group at that time was 51 ± 32 % for cisatracurium and 47 ± 31 % for rocuronium (P = 0.78). Six (40%) patients in the cisatracurium group and seven (47%) in the rocuronium group required neostigmine; for cisatracurium, neostigmine was administered 10 ± 5.5 min after the end of surgery and for rocuronium, it was given 11.4 ± 7.2 min after the end of surgery. These time-points were comparable between both groups (P = 0.72). The TOF ratio at the time of reversal was 63 ± 7 % for cisatracurium and 40 ± 19 % for rocuronium (P = 0.01). Patients requiring neostigmine recalled no undesirable experiences while awakening.

Table 3 shows the results of the neuromuscular tests in the operating room and at arrival in the PCU. There was some variation in correspondence between the different neuromuscular tests and a TOF ratio of 0.9 in the operating room, as well as in the PCU. However, at both time-points there were no significant differences in the results of the clinical neuromuscular function tests between cisatracurium and rocuronium groups.

DISCUSSION

Baillard et al. reported the incidence of postoperative residual curarisation in the PCU after a vecuronium bolus-induced neuromuscular block without the use of a nerve stimulator and without reversal [9]. The results were alarming: 30–40% of patients had a TOF ratio < 0.7. Viby-Mogensen also formulated some evidence-based guidelines [10]. Subsequently, we sought to investigate the incidence of postoperative residual curarisation after infusions of the newer muscle relaxants, cisatracurium and rocuronium, during lengthy interventions (3 to 4 h), without attempting systematic 'reversal'. It is routine clinical practice for many anaesthetists to administer a continuous infusion of a muscle relaxant during protracted abdominal or thoracic surgery. Most often, anaesthetists discontinue the infusion at the start of surgical closure, as this moment is a recognisable event during the procedure and the method is close to common clinical practice. Throughout the world, there are differences in the practice of antagonising a neuromuscular block; in many countries, systematic 'reversal' is not attempted routinely and especially in abdominal surgery, many anaesthetists do not use cholinergic drugs in order to avoid stress on the intestinal anastomoses [1]. Moreover, anticholinesterases may induce serious adverse effects [2]. Although there was a rational intraoperative dosage regimen for the muscle relaxant infusions, we still found dramatic results: at the end of surgery, only one patient in the rocuronium group and four in the cisatracurium group recovered spontaneously to a TOF ratio of 0.9. This TOF level is apparently needed for safety [6,7,8]. In the other patients in both groups, we found important time intervals between the end of surgery and recovery to a TOF ratio of 0.9. Achieving spontaneous recovery of neuromuscular function took so long that six patients in the cisatracurium group and seven in the rocuronium group required pharmacologic reversal, meaning that they began to wake while their TOF ratio was < 0.9. As it only takes seconds before the onset of the effect of neostigmine, there was probably no risk that these patients would become conscious without full recovery of neuromuscular function [2,11]. Moreover, none of our patients recalled undesirable experiences while awakening. However, if partial curarisation had not been recognised by monitoring or if pharmacological reversal had not been attempted, there would have been a risk of evolution to full awakening with partial paralysis in these patients, and to a much more serious extent for rocuronium than for cisatracurium. These numbers of postoperative residual curarisation were, however, the result of rational dosage regimens of these muscle relaxants. We administered cisatracurium at 1 µg kg^{-1} per min and rocuronium at 6 µg kg^{-1} per min, regimens that are in accordance with those

reported in other investigations [11,12]. If overdosing had occurred, the recovery results would be probably even worse.

The possible confounding factors in this study were not important: there was no difference in duration of infusion/surgery between the cisatracurium and the rocuronium groups. Moreover, there was no difference in the time interval between discontinuing the infusion and the end of surgery. We found some variable correspondence between the different clinical and neuromuscular tests, and a TOF ratio of 0.9 in the operating room as well as in the PCU. It is well known that clinical signs, which require patient cooperation during recovery from anaesthesia, offer partial degrees of reliability. Moreover, head lifting causes pain in patients with an abdominal incision and is notoriously useless. Beemer et al. described an inherent incidence of incomplete antagonism when only clinical methods were used [13]. In the present study we could only confirm the lack of a relationship between the results of the clinical neuromuscular tests and a TOF ratio of 0.9.

When comparing recovery characteristics between cisatracurium and rocuronium, we found that there was no significant difference in TOF at the end of surgery. However, the difference in time interval between the end of surgery and a TOF ratio of 0.9 was obvious but not statistically significant. Of importance to us was the significant difference in TOF in those patients who received neostigmine: when patients began to awaken, those in the cisatracurium group had a TOF ratio of nearly 0.7, whereas those in the rocuronium group had a TOF ratio of only 0.4, a value that is associated with a much more dangerous degree of inadequate ‘reversal’ of neuromuscular function. At time points thereafter, there was no longer a difference in effect between cisatracurium and rocuronium: the time intervals between the end of surgery and tracheal extubation and between the end of surgery and leaving patients safely in the PCU. One patient in the rocuronium group had to be transferred to the ICU due to an unforeseen event requiring prolonged mechanical ventilation of the lungs; a possible explanation may have been the extremely long surgical procedure (544 min). Although there were intra- and postoperative complications in this patient, postoperative residual curarisation may have contributed to the multifactorial causes of this expensive ICU transfer.

In summary, we recorded the recovery characteristics of cisatracurium and rocuronium infusions and looked at the safety implications for postoperative residual curarisation in the event that the infusions were discontinued at the beginning of surgical closure and no routine ‘reversal’ was attempted. We found alarming numbers of residually curarised patients at the

end of surgery. The time needed for spontaneous recovery was longer for rocuronium compared with cisatracurium. In both groups, some patients were given neostigmine as an escape. At that moment, the TOF ratio in the cisatracurium group was in a safer range than in the rocuronium group. In the rocuronium group, there was one unforeseen admission to the ICU. Postoperative residual curarisation can perhaps be avoided by discontinuing the neuromuscular blocking drug infusion earlier than at the beginning of surgical closure or by systematically antagonising the neuromuscular block at the end of surgery. When ‘reversal’ is not attempted or not indicated, the choice of cisatracurium seems to be safer than rocuronium, as spontaneous recovery is longer with rocuronium. However, both drugs are unsuitable for continuous relaxation in abdominal/thoracic surgery when relaxation is mandatory until the abdomen/thorax is started to be closed and the patient has to be extubated at the end of surgery. In order to administer rational dosage regimens and to recognise possible postoperative residual curarisation, the only objective and reliable guide is to use the neuromuscular transmission monitor [14,15]. Moreover, neuromuscular transmission monitoring must provide a quantitative TOF, as the present study confirms the relative uselessness of clinical recovery tests and previous reports have shown a discordance between TOF and visual/tactile fade detection [3].

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Table 1. Patient characteristics in Cisatracurium and Rocuronium groups

	Cisatracurium group (n=15)	Rocuronium group (n=15)
Age (yr)	53 ± 13	58 ± 13
Gender (male/female)	9/6	7/8
Weight (kg)	66 ± 13	73 ± 20
Height (cm)	168 ± 8	170 ± 9

Values are mean ± SD, except for gender.

Table 2. Recovery time intervals in Cisatracurium and Rocuronium groups

	Cisatracurium group (n=15)	Rocuronium group (n=14)	P
Time interval between discontinuing the infusion and the end of surgery (min)	28.3 ± 9.1	24.5 ± 9.5	ns
Time interval between end of surgery and a TOF ratio of 0.9 (min)	10.1 ± 9.0	18.2 ± 13.2	ns
Time interval between end of surgery and extubation (min)	18.8 ± 10.2	20.3 ± 12.4	ns
Time interval between end of surgery and safely leave patients in the postanaesthesia care unit (min)	26.9 ± 10.6	28.1 ± 13.4	ns

Values are mean ± SD.

Table 3. Clinical assessment of neuromuscular function in Cisatracurium (n=15; CIS) and Rocuronium (n=14; ROC) groups: number of patients scoring 'positive' for the respective test in the operating room and postanaesthesia care unit. None of the parameters were significantly different between study groups in the operating room, as well as in the postanaesthesia care unit.

Clinical tests of neuromuscular function	Operating room		Postanaesthesia care unit	
	CIS	ROC	CIS	ROC
Ability to sustain a head lift for 5 s	10	6	10	10
Ability to sustain a leg lift for 5 s	13	12	13	12
Hand grip strength for 5 s	11	12	12	13
Sustained tongue depressor test	14	12	14	12
Ability to breathe deeply	15	14	15	14

Chapter 4

LARGE BOLUS DOSE VERSUS CONTINUOUS INFUSION OF CISATRACURIUM DURING HYPOTHERMIC CARDIOPULMONARY BYPASS SURGERY

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LARGE BOLUS DOSE VERSUS CONTINUOUS INFUSION OF CISATRACURIUM DURING HYPOTHERMIC CARDIOPULMONARY BYPASS SURGERY

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SUMMARY

Background and objective: We investigated whether a high bolus dose of cisatracurium (8 × ED_{95}) given at induction can provide muscle relaxation for the major part of a cardiac procedure with hypothermic cardiopulmonary bypass, avoid important postoperative residual curarization and cause no waste of product.

Methods: Twenty patients were randomly assigned either to group 1 (n = 10) or group 2 (n = 10). Those in group 1 were given cisatracurium in a high bolus dose (0.4 mg kg^{-1}). Those in group 2 received cisatracurium 0.1 mg kg^{-1} at induction; after 30 min a continuous infusion of cisatracurium was begun. As an escape for patients' moving, bolus doses of cisatracurium 0.03 mg kg^{-1} were given if gross movement occurred.

Results: In group 1 (large cisatracurium bolus dose), the clinical duration of effect ($T1/T0$ = 25%) was 110 min. Six out of 10 patients in group 1 required additional boluses of cisatracurium intraoperatively. Four of these six had received an additional bolus near the end of surgery and had a train-of-four ratio = 0 at the end. The other four patients in group 1 had a final train-of-four ratio > 0.9. In group 2 (continuous cisatracurium infusion), only two patients had a train-of-four ratio > 0.9 at the end of surgery; no patient had moved and, obviously, none received additional boluses. The total amount of cisatracurium used in the bolus and infusion groups was 34.5 ± 7.8 mg and 21.3 ± 5.7 mg, respectively (P = 0.0004).

Conclusions: For continued neuromuscular block during hypothermic cardiac surgery, a high bolus dose of cisatracurium is, although safely used, not an alternative to a continuous infusion, as its neuromuscular blockade does not cover the intraoperative period and a high incidence of movements occurs. In the patients who received a high bolus dose of cisatracurium, important postoperative residual curarization appeared after additional boluses had been given. The consumption of cisatracurium by high bolus was significantly greater than with continuous infusion.

Keywords: hypothermia; neuromuscular block; heart surgery.

INTRODUCTION

Neuromuscular blocking drugs are commonly used during cardiac surgery. Their advantages are that they aid mechanical ventilation, decrease anaesthetic requirements, prevent patient movement and decrease oxygen consumption. Because the elimination of cisatracurium is organ-independent and because it lacks cardiovascular side-effects during high-dose opioid anaesthesia [1], it may have advantages for cardiosurgical procedures.

Drug elimination may be reduced by relative hypoperfusion of the liver and kidney or by hypothermia during cardiopulmonary bypass (CPB) [2]; this is true for atracurium [3] and for rocuronium [4]. Moreover, as the clearance of cisatracurium, one of the stereoisomers of atracurium, is highly dependent on Hofmann degradation [5], the temperature and pH changes associated with CPB could possibly affect its pharmacokinetics more than those of other neuromuscular blocking drugs.

In a previous study we sought a rational dosage regimen for the infusion of cisatracurium or rocuronium during hypothermic CPB: infusion rates for cisatracurium were halved during CPB and even after CPB the requirements were reduced. The same tendency occurred with rocuronium but the changes in infusion rate were not statistically significant [6]. There may be waste of product when a continuous infusion is used, a syringe pump is obviously needed, and there was a high incidence of postoperative residual curarization after continuous infusions of neuromuscular blocking drugs, even when they were discontinued early [7]. One can argue that it is always possible to reverse the block and that there is no problem with residual curarization as these patients are ventilated in the intensive-care unit (ICU). However, reversal agents can cause harm [8] and an earlier recovery may be important in fast-tracking and minimally invasive cardiac procedures, as it may allow earlier extubation. Avoiding an excessively prolonged neuromuscular blockade may also decrease the incidence of awareness during the first hours in the ICU. Therefore, we now investigated whether a large bolus dose of cisatracurium ($8 \times ED_{95}$), given at induction, can provide muscle relaxation for the major part of the procedure, avoid important postoperative residual curarization and cause no waste of product. This dose of cisatracurium was safely used earlier [9]. A possible advantage of a single large bolus dose is decreased opioid-induced rigidity at the induction of anaesthesia.

METHODS

With ethics committee approval for the experiment and after giving written informed consent, 20 patients were randomly assigned either to group 1 (n = 10) or group 2 (n = 10). Those in group 1 were given cisatracurium in a large bolus dose (0.4 mg kg^{-1}). Those in group 2 received cisatracurium 0.1 mg kg^{-1} at induction; after 30 min a continuous infusion of cisatracurium was begun at a rate of 1 µg kg^{-1} min^{-1} before CPB, 0.75 µg kg^{-1} min^{-1} during CPB, and 1 µg kg^{-1} min^{-1} following CPB [6]. All patients were ASA physical status III and IV and scheduled for cardiac surgery with hypothermic CPB (28°C): coronary artery bypass grafting, valve surgery, multiple valve surgery or valve surgery combined with coronary artery bypass grafting. The exclusion criteria were evidence of renal, hepatic, metabolic or neuromuscular disorders; and a history of medication that interferes with neuromuscular transmission.

All patients were premedicated with oral lorazepam 2.5 mg 1 h before induction. After 3 min of preoxygenation, anaesthesia was induced with diazepam 0.15 mg kg^{-1} and sufentanil 2.5 µg kg^{-1} i.v. As soon as the eyelid reflex was absent, assisted ventilation by facemask was started with 100% oxygen. After the appropriate bolus dose of cisatracurium, intubation was performed as soon as the first response to the train-of-four (TOF) stimulus (T_1) fell below 10%. Normocapnic ventilation was established with an Aestiva 3000 ventilator (Datex-Ohmeda, Helsinki, Finland). Anaesthesia was maintained with 40% oxygen in air, propofol 1–3 mg kg^{-1} h^{-1} and boluses of sufentanil (0.3 µg kg^{-1} i.v.). Propofol was adjusted in 0.5 mg kg^{-1} h^{-1} steps according to bispectral index (BIS) monitoring (A-2000; Aspect Medical Systems, Natick, MA, USA); the BIS was kept between 45 and 55%. Routine monitoring included ECG, pulse oximetry, invasive arterial pressure (right radial artery), central venous pressure (right jugular vein) and transoesophageal echocardiography. Temperature was monitored at the following sites: oesophagus, rectum, skin of the forehead and the area of skin on the left arm where electrodes for monitoring neuromuscular transmission were applied.

The bypass circuit was of standard construction. Blood temperature was measured at the venous site of the bypass circuit and kept constant at 28°C during hypothermia. Rewarming to a rectal temperature of 37°C was started as soon as the surgeon had completed the last distal anastomosis and/ or the last valve suture. Alpha-stat pH management was used.

Neuromuscular transmission was monitored on the left arm, at 1-min intervals, by the acceleromyographical response of the adductor pollicis muscle to TOF stimulation of the ulnar nerve, using surface electrodes (TOF-Watch® SX; N.V. Organon, Oss, The Netherlands). The TOF response to a supramaximal stimulus was obtained before the initial bolus of neuromuscular blocking drug.

As an escape for patients' moving, bolus doses of cisatracurium 0.03 mg kg^{-1} were given if gross movement occurred. In group 2 the cisatracurium infusion was discontinued when the surgeon began closing the pericardium. Spontaneous recovery from neuromuscular blockade was allowed in the operating theatre and/ or ICU. Vital measures were displayed on a Datex S/5 monitor and, together with the results of monitoring intraoperative neuromuscular transmission, stored in a spreadsheet on a PC.

The duration of surgery, pre-CPB time, CPB time, as well as the duration of cisatracurium infusion, were calculated. Time of arrival in the ICU, extubation, and discharge from ICU and hospital were recorded. Intraoperative complications were noted. In group 2, the mean T_1/T_0 during cisatracurium infusion was derived. In both groups, the TOF ratio at the end of surgery and the time-point at which it reached 0.9 were evaluated. The following recovery variables were derived before registration of neuromuscular transmission monitoring was discontinued (i.e. before transfer of the patient to the ICU): T_1/T_0 = 25%, T_1/T_0 = 95%, TOF ratio > 0.7, TOF ratio > 0.9, 25–75% and 5–95% recovery indices. Any unforeseen movements by the patients during surgery were registered, as well as the need for additional boluses of cisatracurium. Finally, the total amount of neuromuscular blocking drug administered in both groups was derived. Data from groups 1 and 2 were compared using *GraphPad* (InStat®, San Diego, CA, USA). A Kolmogorov and Smirnov test was performed to assess normality: an unpaired *t*-test was used to determine the significance of normally distributed parametric values. Non-normally distributed data were compared in a non-parametric U-test. Results are presented as means ± SD, except for extubation time, ICU and hospital discharge times (median and ranges). Significance was set at $P < 0.05$.

RESULTS

Table 1 shows the patients' characteristics and main findings in group 1 (large cisatracurium bolus dose) and group 2 (continuous cisatracurium infusion). There were no significant differences between groups 1 and 2. We did not observe any stigmata of histamine release, hypotension or other side effects of cisatracurium.

In group 2, the mean T_1/T_0 % during infusion was 12 ± 9 %. In group 1, six patients received additional cisatracurium boluses intraoperatively at a TOF ratio = 0.82 ± 0.20. None of the patients recalled any intraoperative event, nor did the BIS exceed 55% at the occasion of the additional boluses. Explanations for giving additional boluses were: diaphragmatic movement (n = 3); abdominal muscle strain at wound closure (n = 2); another patient moved their legs twice intraoperatively and concomitantly had low mixed venous oxygen saturation. Four out of these six patients had received an additional bolus of cisatracurium near the end of surgery and had a TOF = 0 at the end of surgery. One patient reached a TOF ratio > 0.9 as additional boluses had been given earlier intraoperatively and another recovered to a TOF ratio = 0.35 for the same reason. The other four patients had a TOF ratio > 0.9 at the end of surgery: they had received no additional boluses of cisatracurium.

In group 2, only two patients had a TOF ratio > 0.9 at the end of surgery; in the other eight the final TOF ratio was 0.18 ± 0.18. Seven out of the eight patients did not reach a TOF ratio > 0.9 during registration; in one patient only the TOF ratio reached > 0.9 at 51 min after stopping the cisatracurium infusion. In group 2, no patient moved or had diaphragmatic contractions and, obviously, none received additional boluses.

Table 2 shows the mean ± SD of the recovery characteristics of patients in the cisatracurium bolus and infusion groups reaching different time-points during registration (i.e., before transfer to the ICU). In group 1, the 95% confidence limits for T_1/T_0 = 25% and for a TOF ratio > 0.7 were 92–128 min and 126–148 min, respectively.

The total amount of neuromuscular blocking drug used in the bolus and the infusion groups was 34.5 ± 7.8 mg and 21.3 ± 5.7 mg, respectively (P = 0.0004) [0.43 ± 0.03 mg kg^{-1} vs 0.28 ± 0.06 mg kg^{-1} (P < 0.0001)].

DISCUSSION

In this study we evaluated the recovery profile of an 8 × ED_{95} bolus dose of cisatracurium during cardiac surgery with hypothermic CPB and compared it with the recovery profile of a cisatracurium infusion administered according to an earlier-described protocol [6].

During hypothermic CPB, complex changes in drug pharmacokinetics occur, prolonging the duration of action of many non-depolarizing neuromuscular blocking drugs [2]. The impairment of the metabolic function of the kidney as a result of hypoperfusion during CPB is expected to decrease renal elimination [10]. Moreover, decreased hepatic blood flow, decreased concentration of binding proteins and decreased intrinsic activity of the liver are assumed to diminish hepatic clearance during bypass [10]. Hypothermia itself can alter the pharmacokinetics of drugs during CPB: it influences the enzymatic processes involved in drug metabolism in the liver and kidneys [2]. The half-life of cisatracurium is presumably prolonged during hypothermic CPB, as its breakdown is particularly dependent on temperature and pH. One might thus expect that not only the duration of action of infusion doses but also of a large bolus dose of cisatracurium would be prolonged in hypothermic CPB. However, the mean T_1/T_0 = 25% in the population given 8 × ED_{95} in the study by Belmont and co-workers (91 min) lies only slightly beyond the lower confidence interval of our bolus group; moreover, the mean TOF ratio > 0.7 reported by Belmont's group (126 min) was between the confidence limits of our study. Thus, we cannot conclude from our study that recovery from a high bolus dose of cisatracurium during CPB takes significantly longer than in a non-CPB group [9]. Surprisingly, hypothermia seems not to contribute to a prolonged recovery from a 8 × ED_{95} bolus of cisatracurium; a possible explanation for this phenomenon might be that the pre-CPB time, when the patient is normothermic, covers the clinical duration of effect, i.e., the time from the injection of 8 × ED_{95} of cisatracurium to the return to T_1/T_0 = 25%. It was already known that the consistent pattern of recovery independent of size of bolus dose suggests that cisatracurium displays non-cumulative pharmacodynamics, with recovery always occurring during the drug's elimination phase. Cisatracurium's intermediate duration of action and lack of cumulative neuromuscular-blocking effects are probably due to its decomposition and metabolism by Hofmann elimination, which is independent of hepatic or renal function [9]. This conclusion is also suggested by our finding that the mean clinical duration of effect in the Belmont 8 × ED_{95} group (91 min) lies only slightly beyond the lower confidence interval of our bolus group.

Recovery from a large bolus dose of cisatracurium reached a TOF ratio > 0.9 after 148 ± 10 min; on the one hand this period covers an important part of many cardiac procedures, but on the other a large bolus of cisatracurium seems insufficient to cover neuromuscular blockade during the complete intraoperative period. One may argue that it is not strictly necessary to administer neuromuscular blocking drugs during cardiac surgery; however, in this study, a majority of our patients either moved or had diaphragmatic contractions in the absence of continuous administration of neuromuscular blocking drugs and despite an adequate level of anaesthesia. On the other hand, in the group receiving a continuous infusion of cisatracurium, a high incidence of postoperative residual curarization was observed. One should not forget, however, that 5/10 patients in group 1 (bolus) also had postoperative residual curarization because an additional bolus of neuromuscular blocking drug was given. It is important to notice that postoperative residual curarization was studied only between the end of surgery and transfer of the patient to the ICU. When considering the total amount of drug used, the consumption of cisatracurium in the bolus group was significantly greater than in the infusion group, indicating that there is no economic benefit of a high bolus over a continuous infusion.

No intraoperative events that could be related to the use of a high bolus of cisatracurium were recorded. There was a tendency towards longer ICU and hospital stays in group 2 (continuous); this was probably due to their more complicated perioperative course.

In conclusion, for continued neuromuscular block during hypothermic cardiac surgery, a high bolus dose of cisatracurium is, although safely used, not an alternative to a continuous infusion, as its neuromuscular blockade does not cover the intraoperative period, and, most importantly, a high incidence of movements occurs in these patients. Neuromuscular transmission had not returned to normal by the end of surgery in a significant number of patients in both groups. This waived the benefit expected from a large bolus dose at the beginning of surgery, i.e., the absence of postoperative residual curarization. Consumption of cisatracurium in a high bolus was also significantly greater than when a continuous infusion was administered, making a large bolus less economically valuable than a continuous infusion.

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Table 1 Patient characteristics in cisatracurium bolus and infusion groups

	Bolus group (*n*=10)	**Infusion group (n=10)**
Sex (male/female)	6/4	10/0
Age (years)	66 ± 14	67 ± 13
Weight (kg)	82 ± 22	75 ± 8
Height (cm)	170 ± 9	171 ± 5
Type of surgery	CABG (*n* = 2)	CABG (*n* = 4)
(*n* = number of patients)	AVR (*n* = 3)	CABG + AVR (*n*=1)
	CABG + AVR (*n* = 2)	REDO CABG + AVR (*n* = 1)
	DAVID procedure (*n* = 1)	DAVID procedure (*n* = 1)
	CABG + ASD (*n* = 2)	CABG + MVP (*n* = 2)
		MVP + TVP (*n* = 1)
Duration of surgery (min)	273 ± 75	272 ± 77
Pre-CPB time (min)	112 ± 43	92 ± 34
CPB duration (min)	119 ± 56	126 ± 50
Infusion duration (min)	NA	214 ± 70
Arrival at the ICU (min after end of surgery)	21 ± 8	26 ± 8
Extubation time in ICU (h)	12 [4–21]	14 [6–288]
ICU stay (h)	23 [18–96]	56 [24–384]
Hospital stay (days)	8 [7–22]	10 [7–23]

ASD, atrial septal defect; AVR, aortic valve replacement; CABG, coronary artery bypass graft; DAVID, valve-sparing aortic root replacement; MVP, mitral valve plasty; TVP, tricuspid valve plasty

CPB, cardiopulmonary bypass; ICU, intensive care unit; NA, not applicable

Values are means ± SD, except for extubation time, ICU and hospital stays (median and ranges)

Table 2 Recovery characteristics of patients in groups 1 (large cisatracurium bolus dose) and 2 (continuous cisatracurium infusion) reaching different time-points during registration (i.e., before transfer to the intensive care unit)

	Group 1	**Group 2**
T_1/T_0 = 25%	110 ± 25 (*n* = 10)	11 ± 18 (*n* = 8)
T_1/T_0 = 95%	129 ± 40 (*n* = 4)	36 ± 15 (*n* = 3)
TOF ratio > 0.7	137 ± 13 (*n* = 8)	26 ± 16 (*n* = 6)
TOF ratio > 0.9	148 ± 10 (*n* = 7)	29 ± 24 (*n* = 3)
RI 25-75%	30 ± 22 (*n* = 5)	18 ± 6 (*n* = 6)
RI 5–95%	49 ± 30 (*n* = 4)	36 ± 15 (*n* = 3)

Time-points in group 1 are minutes after induction; in group 2 minutes after stop infusion

TOF = train-of-four; RI = recovery index. Values are means ± SD

n = number of patients reaching the time-point during registration

Chapter 5

DOSE REQUIREMENTS OF INFUSIONS OF CISATRACURIUM OR ROCURONIUM DURING HYPOTHERMIC CARDIOPULMONARY BYPASS

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DOSE REQUIREMENTS OF INFUSIONS OF CISATRACURIUM OR ROCURONIUM DURING HYPOTHERMIC CARDIOPULMONARY BYPASS

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SUMMARY

We investigated the influence of mild hypothermic cardiopulmonary bypass (CPB) on the dose requirements of cisatracurium and rocuronium used as a continuous infusion. We studied 8 patients given cisatracurium and 9 given rocuronium. They were ASA class III and IV and scheduled for elective coronary artery bypass grafting. Neuromuscular transmission was monitored electromyographically. After recovery of T1/T0 to 10%, a cisatracurium infusion or a rocuronium infusion was started at a rate of 1.5 or 10 μg kg^{-1} min^{-1}, respectively, and adjusted to maintain T1/T0 at 15%. Infusion rate and duration were recorded before, during and after CPB in each patient and the mean infusion rates were calculated. One-way ANOVA showed a statistically significant difference between the cisatracurium infusion rates before, during and after CPB: a T1/T0 of 15% could be achieved with a mean infusion rate of 1.1, 0.75 and 0.98 μg kg^{-1} min^{-1} before, during and after CPB, respectively. There was no significant difference between the rocuronium infusion rates before, during and after CPB. The mean rocuronium infusion rate required to maintain T1/T0 at 15% throughout the procedure was 4.1 μg kg^{-1} min^{-1}. Cisatracurium infusion rates should be halved during CPB. Even after CPB, requirements are reduced. The same tendency occurs with rocuronium, but the changes in infusion rate were not statistically significant.

Keywords

Hypothermia; neuromuscular block, rocuronium; neuromuscular block, cisatracurium; surgery, cardiovascular

Neuromuscular blocking drugs are commonly used during coronary artery bypass grafting (CABG). Their advantages are that they aid mechanical ventilation, decrease anaesthetic requirements, prevent patient movement and decrease oxygen consumption. Cisatracurium and rocuronium generally lack cardiovascular side effects during high-dose opioid anaesthesia[1 2] and thus have advantages for use during CABG procedures. These advantages may not, however, be observed in different clinical conditions[3]. During CABG and, more particularly, during cardiopulmonary bypass (CPB), cisatracurium and rocuronium requirements have not been studied in detail.

Drug elimination may be reduced by relative hypoperfusion of the liver and kidney or by hypothermia during CPB[4]. This is true for atracurium[5] and for rocuronium[6]. Moreover, as the clearance of cisatracurium, one of the stereoisomers of atracurium, is highly dependent on Hofmann degradation[7], temperature and pH changes associated with CPB are likely to affect its pharmacokinetics more than those of other neuromuscular blocking drugs. As data for the newer neuromuscular blocking drugs are scarce, cisatracurium and rocuronium infusion rates during and after CPB are adjusted empirically.

A more rational dosage regimen may reduce waste and, consequently, the cost of using these expensive new drugs. Moreover, a more predictable recovery may be important in fast tracking and minimally invasive cardiac procedures, as it may allow early extubation. Avoiding an excessively prolonged neuromuscular block may also decrease the incidence of awareness during the first hours on the intensive care unit (ICU).

METHODS

After Institutional Review Board approval and written informed consent, we studied eight patients given cisatracurium followed by nine given rocuronium during CABG with mild hypothermic CPB (33°C). All patients were ASA class III and IV. Exclusion criteria were: left ventricular ejection fraction <50%; evidence of renal, hepatic, metabolic or neuromuscular disorders; and history of medication interfering with neuromuscular transmission.

All patients were premedicated with lorazepam 2.5 mg 1 h before induction. After 3 min of preoxygenation, anaesthesia was induced with diazepam 0.15 mg kg^{-1} and sufentanil 5 µg kg^{-1} i.v. As soon as the eyelid reflex was absent, assisted ventilation by facemask was started with oxygen 100%. After equipotent bolus doses of cisatracurium 0.1 mg kg^{-1} or rocuronium 0.6 mg kg^{-1} intubation was performed as soon as the first response to the train-of-four (TOF) stimulus (T1) fell below 10%. Normocapnic ventilation was established with a Servo 900C (Siemens Elema; Stockholm, Sweden). Anaesthesia was maintained with oxygen 50% in air, propofol 1-3 mg kg^{-1} h^{-1} and supplemental boluses of diazepam or sufentanil. No potent inhalation anaesthetics were used. Routine monitoring included ECG, pulse oximetry, invasive arterial pressure (left radial artery) and central venous pressure (right jugular vein). Temperature was monitored at the following sites: oesophagus, rectum, skin of the forehead and the area of skin on the right arm where neuromuscular transmission monitoring electrodes had been applied.

The bypass circuit was of standard construction. Blood temperature was measured at the venous site of the bypass circuit and kept constant at 33°C during hypothermia. Rewarming to 37°C was started as soon as the surgeon had completed the last distal anastomosis. Alpha-stat pH management was used.

Neuromuscular transmission was monitored on the right arm by the EMG response of the adductor pollicis muscle to TOF stimulation of the ulnar nerve, using surface electrodes (M-NMT module; Datex-Ohmeda, Helsinki, Finland). The right arm was wrapped in a protective towel. The TOF response to a supramaximal stimulus was obtained before the initial bolus of neuromuscular blocking drug. The stimulus current range during supramaximal stimulation was 10-70 mA. The TOF was measured at 1 min intervals, using a square wave, constant current stimulus pulse with a pulse width of 200 µs.

After recovery of T1/T0 to 10%, patients were given either cisatracurium or rocuronium, at an infusion rate of 1.5 and 10 µg kg^{-1} min^{-1}, respectively. These dosages were based on data obtained during major non-cardiac surgery[8 9]. The infusion rate was adjusted to maintain T1/T0 at 15%. The concentration of the solutions used for infusion was 0.2 and 1 mg ml^{-1} for cisatracurium and rocuronium, respectively, so that even small changes in infusion rate led to significant changes of volume delivered and, thus, to a quick alteration in effect. The infusion was discontinued just before the completion of surgery. Bolus doses of cisatracurium 0.03 mg kg^{-1} or rocuronium 0.15 mg kg^{-1} were given if gross movement occurred. Spontaneous recovery from neuromuscular blockade was allowed on the ICU. The results of monitoring neuromuscular transmission and all other vital parameters were displayed on a Datex AS/3 monitor and stored in a spreadsheet on a PC (Compaq).

Infusion rate and infusion duration were recorded before, during and after CPB for each patient. The mean infusion rates in both groups were derived before, during and after bypass. Statistical analysis included one-way analysis of variance (ANOVA). Significance was set at a level of $p<0.05$. A one-sample t-test was performed to assess if the derived mean (actual T1/T0%) was significantly different from the theoretical mean (T1/T0 = 15%). Results are presented as mean (SD).

RESULTS

Anaesthesia was uneventful in all patients. No patient moved and no diaphragmatic contractions were observed. There was no need for any escape bolus dose of neuromuscular blocking drug. Patients did not sweat and their eyes did not water. They did not recall the operation. One patient in the cisatracurium group suffered from opioid-induced rigidity during induction. Although assisted ventilation was initially difficult, oxygenation was well maintained and induction was otherwise uneventful.

Table 1 shows the physical characteristics of the patients in the cisatracurium and rocuronium groups. The mean (SD) time between starting the initial infusion of cisatracurium at a rate of 1.5 µg kg^{-1} min^{-1} and the first adjustment to a lower dose was 34.5 (19.1) min. In the cisatracurium group, mean (SD) T1/T0 during the procedure was 14.6 (9.9) %. This actual mean was not significantly different from the preset value (T1/T0=15%) (p=0.7). Table 2 shows the one-way ANOVA of cisatracurium infusion rates during CABG. The means differ significantly (p=0.01), with the highest rate before and the lowest during CPB.

The mean (SD) time between starting the rocuronium infusion at the initial infusion rate (10 µg kg^{-1} min^{-1}) and the first adjustment to a lower dose was 20.2 (13.3) min. In the rocuronium group, the mean (SD) T1/T0 during the procedure was 14.2 (7.1) %; this was not significantly different from the preset value (T1/T0=15%) (p=0.2). Table 2 shows the one-way ANOVA of rocuronium infusion rates during CABG. There was no statistically significant difference between these means (p=0.5). The mean (SD) infusion rate of rocuronium required to keep T1/T0 at 15% throughout surgery was 4.1 (1.6) µg kg^{-1} min^{-1}.

DISCUSSION

During hypothermic CPB, complex changes in drug pharmacokinetics occur, prolonging the duration of action of many non-depolarising neuromuscular blocking drugs [4]. The serum concentration of neuromuscular blocking drugs may decrease when bypass is started, as a result of haemodilution[10 11], or it may increase secondary to decreased clearance and altered drug distribution[12 13].

The impairment of the metabolic function of the kidney, as a result of hypoperfusion during CPB is expected to decrease renal elimination[14]. Moreover, decreased hepatic blood flow, decreased concentration of binding proteins and decreased intrinsic activity of the liver are assumed to diminish hepatic clearance during bypass[14]. These phenomena may result in a steady increase in the serum concentration of neuromuscular blocking drugs during hypothermic CPB[14]. Hypothermia itself can alter the pharmacokinetics of drugs during CPB: it influences the enzymatic processes involved in drug metabolism in the liver and kidneys[4].

Finally, since neuromuscular blocking drugs may redistribute significantly to the lungs, they can accumulate there before bypass begins. These drugs can thus become trapped in the lungs during CPB, as circulation to the lungs during that period is restricted to the bronchial vessels. When pulmonary artery blood flow is restored during weaning from CPB, the serum concentration of these drugs may suddenly increase[4 14].

Rosen and Rosen[4] concluded that pharmacokinetics during CPB depend mainly on the composition of the oxygenator, the physical properties of the drug, the use of pulsatile or non-pulsatile flow and hypothermia. Drugs with a smaller distribution volume are more affected. The oxygenator binds lipophilic drugs more avidly than those that are hydrophilic. Neuromuscular blocking drugs generally have a rather small distribution volume: cisatracurium has a slightly greater volume of distribution than atracurium[15], while rocuronium has a smaller one than vecuronium[16].

In clinical practice, serum concentrations of neuromuscular blocking drugs are not available. The degree of muscle relaxation can only be assessed by monitoring neuromuscular transmission. However, neuromuscular monitoring during hypothermia is complicated by the fact that cooling affects nerve conduction, neuromuscular transmission and muscular activity[17]. The evoked response obtained in a peripheral muscle during CPB may be

influenced by peripheral and core temperature gradients and alterations in skeletal muscle blood flow. Nevertheless, in the presence of hypothermia, pH disturbances and the side-effects of vasoactive drugs, neuromuscular monitoring is superior to simple clinical judgment[18].

It has been shown that, for various neuromuscular blocking drugs, the duration of action is prolonged by CPB[10-14 19]. The half-life of cisatracurium is presumably prolonged during hypothermic CPB, as its breakdown is even more dependent on temperature and pH than that of atracurium, for which a reduced dose requirement has been observed during CPB[5]. The remainder of the drug, about 15%, is cleared by the kidneys[15]. The pharmacokinetics of rocuronium resemble those of vecuronium, except that the former has a smaller volume of distribution[16]. The termination of the effect of rocuronium is similar to vecuronium and mainly dependent on redistribution, by hepatic uptake, followed by biliary elimination. A smaller proportion, <20%, is excreted renally[20]. Smeulers and colleagues found that hypothermic CPB prolonged the duration of action of maintenance doses of rocuronium[6].

In a preliminary study[21], we concluded that a cisatracurium infusion, administered at half the initial rate (0.75 µg kg^{-1} min^{-1}) during hypothermic CPB, resulted in clinically acceptable conditions. Discontinuation of the cisatracurium infusion at the start of CPB, on the contrary, led to an unacceptably high incidence of movement, suggesting that it is preferable to use a continuous infusion of neuromuscular blocking agent during CABG and CPB. In the current study, we confirmed our previous findings that a cisatracurium infusion rate of 0.75 µg kg^{-1} min^{-1} was appropriate during CPB. Moreover, we found that a T1/T0 of 15% could be achieved before CPB with a dose < 1.5 µg kg^{-1} min^{-1}. Even after the bypass, cisatracurium infusion rates were lower than those before bypass, probably because of a further fall in body temperature, a tendency described in previous reports for other neuromuscular blocking drugs[5]. Less rocuronium was required during and, to a lesser extent, after CPB compared with before CPB, but the differences in infusion rates were not statistically significant. In the rocuronium group, we also observed a temperature after-drop in the period after the bypass.

We have searched for a practical and adequate infusion regimen for the two latest commercially available neuromuscular blocking drugs, cisatracurium and rocuronium, during cardiac surgery with mild hypothermic CPB. For cisatracurium, we found that a significant reduction to half of the initial infusion rate during CPB was appropriate in clinical practice. As with atracurium, the cause is probably related to the temperature-dependent inactivation of

cisatracurium. For rocuronium, a lower infusion rate was used in our study than in previous reports[9]. Further reduction during CPB was not necessary. The degree of cooling during CPB may explain the discrepancy between our results and those of other investigators: while Smeulers and colleagues[6] cooled patients to 25-28°C, we used only mild hypothermia (33°C).

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Table 1 Patient characteristics in cisatracurium and rocuronium groups

	Age, yr mean (range)	**Weight, kg mean (SD)**	**Heigth, cm mean (SD)**	**Gender male/female**
cisatracurium group (n = 8)	71 (62-80)	76 (19)	162 (11)	4 / 4
rocuronium group (n = 9)	70 (62-77)	73 (15)	166 (10)	7 / 2

Table 2. Mean (SD) cisatracurium and rocuronium infusion rates during coronary artery bypass grafting (one-way ANOVA; significance at $p<0.05$)

	Infusion rate, μg kg^{-1} min^{-1}			
	Before bypass	**During bypass**	**After bypass**	**P**
Cisatracurium	1.10 (0.24)	0.75 (0.24)	0.98 (0.17)	0.01
Rocuronium	4.42 (1.83)	3.57 (1.54)	4.24 (1.45)	0.5

Chapter 6

Chapter 6 is based on the following manuscript:

IMPLICATIONS OF THE USE OF NEUROMUSCULAR TRANSMISSION MONITORING ON IMMEDIATE POSTOPERATIVE EXTUBATION IN OFF-PUMP CORONARY ARTERY BYPASS SURGERY

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IMPLICATIONS OF THE USE OF NEUROMUSCULAR TRANSMISSION MONITORING ON IMMEDIATE POSTOPERATIVE EXTUBATION IN OFF-PUMP CORONARY ARTERY BYPASS SURGERY

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SUMMARY

Background and objective: When continuous infusions of neuromuscular-blocking drugs are administered during lengthy interventions and no routine reversal is applied, there is a dramatic incidence of residual curarization. We have examined whether the use of neuromuscular transmission monitoring results in differences in the incidence of postoperative residual curarization, the use of reversal agents, and the extubation rate and outcome after continuous infusion of rocuronium in patients undergoing off-pump coronary artery bypass surgery.

Methods: Twenty patients were assigned to group 1 (n = 10, non-blinded neuromuscular transmission monitoring) or group 2 (n = 10, blinded neuromuscular transmission monitoring). In group 1, patients were given rocuronium at an infusion rate of 6 μg kg^{-1} min^{-1}. The rate was manually adjusted in order to maintain T1/T0 at 10%. In group 2, a rocuronium infusion was started 30 min after induction, at a rate of 6 μg kg^{-1} min^{-1}; this rate was left unchanged during surgery. The rocuronium infusion was discontinued on completion of all vascular anastomoses; propofol was stopped at the beginning of closure of the subcutis and piritramide 15 mg i.v. was administered. Remifentanil was discontinued at the beginning of skin closure and neostigmine (50 μg kg^{-1}) administered at the end of surgery when the train-of-four was < 0.9 in group 1, and routinely in group 2. A 20-min test period for spontaneous ventilation was allowed once surgery had been accomplished. When the train-of-four ratio was ≥ 0.9 (group 1), patients were extubated when breathing spontaneously, fully awake and able to follow commands. When they met the clinical criteria for normal neuromuscular function after induced blockade, patients in group 2 were extubated when fully awake and able to follow commands.

Results: In group 1 the rate of rocuronium infusion required to keep T1/T0 at 10% was 5 ± 1.9 μg kg^{-1} min^{-1}; this rate was not significantly different from the fixed rate in group 2 (P = 0.15). One patient in group 2 was excluded. Eight out of 10 and eight out of nine patients in groups 1 and 2, respectively, reached the extubation criteria. Three out of eight and five out of eight patients from groups 1 and 2, respectively, were extubated in the operating room. At that extubation, all three patients from group 1 but only four out of the five patients from group 2 had a train-of-four ≥ 0.9. In group 2, one patient was reintubated in the intensive care unit. The incidence of pharmacological reversal was high in group 1.

Conclusions: Although we found no additional benefit of using neuromuscular transmission monitoring, it seems an absolute necessity for safety reasons. Pharmacological reversal was

mandatory. However, in our opinion, it is not wise routinely to perform immediate postoperative extubation in off-pump coronary artery bypass surgery.

Keywords:
NEUROMUSCULAR BLOCKING AGENTS, neuromuscular non-depolarizing agents; NEUROMUSCULAR BLOCK, rocuronium; SURGERY, thoracic.

INTRODUCTION

We know that worldwide there are different traditions in monitoring induced neuromuscular blocks; moreover, not all anaesthesia services have access to monitoring devices. Also, individual anaesthetists tend to have different ideas about antagonizing the block [1]. When continuous infusions of neuromuscular-blocking drugs are administered during lengthy interventions and no routine reversal is applied, there is a dramatic incidence of residual curarization [2].

For years, anaesthetists and intensivists have been extubating their cardiosurgical patients early because there is no sense in keeping them ventilated for a long time when the perioperative course is uncomplicated; postoperative mechanical ventilation has evolved as a result of tradition and not as a result of evidence-based medicine [3]. Early extubation (1–6 h) may reduce ventilator-dependent pathologies, and intensive care and hospital stays [4]. With the introduction of off-pump coronary artery bypass (OPCAB) surgery and the consequent avoidance of hypothermic cardiopulmonary bypass, these cardiosurgical patients can probably be extubated even earlier, possibly while still in the operating room; a further decrease in the length of stay in the intensive care unit (ICU) and hospital is thereby projected [3, 5]. Work by London et al. supports the contention that we need not preselect patients for early extubation: it is the intra- and postoperative morbidity rates that will ultimately determine the feasibility of early extubation and the length of stay in the ICU [5].

The primary problems of anaesthetic management for immediate postoperative extubation in cardiac surgery are keeping patients normothermic and providing adequate postoperative analgesia: the relatively recent development of warming devices [6] and the administration of strong painkillers [7] has made immediate postoperative extubation realistic. Finally, the anaesthetic drugs used intraoperatively must enable early emergence and ambulation: among the hypnotics and analgesics the combination of remifentanil and propofol by target-controlled infusion (TCI) allows anaesthetists to schedule the time of extubation in patients undergoing cardiac anaesthesia [8]. For the neuromuscular-blocking drugs, continuous infusions are commonly used during coronary artery bypass grafting. The advantages of their use are that they aid mechanical ventilation, decrease anaesthetic requirements and prevent patient movement [9]. It is believed that neuromuscular transmission monitoring could be an aid to the timing of extubation in OPCAB patients.

Therefore, in this prospective study, we have examined whether the use of neuromuscular transmission monitoring results in differences in the incidence of postoperative residual curarization, the use of reversal agents, and the extubation rate and outcome after continuous infusion of rocuronium in patients undergoing OPCAB surgery.

METHODS

Organization and recruitment

With ethical committee approval and written informed consent, we studied 20 consecutive ASA II–III patients undergoing OPCAB surgery. Using data from previously published material [2], we performed a power analysis (two-group unpaired t-test of equal means), which revealed that a sample size of 10 in each group would have 80% power to detect a difference in extubation time of 15 min using a two-group unpaired t-test with a 0.05 two-tailed significance level (alpha). In a prospective, randomized, double-blind study, patients were assigned either to group 1 (n = 10, non-blinded neuromuscular transmission monitoring) or group 2 (n = 10, blinded neuromuscular transmission monitoring). The patients enrolled had no evidence of hepatic insufficiency, were not receiving drugs that interact with neuromuscular transmission, and had no known diseases affecting that transmission.

Neuromuscular function

Neuromuscular transmission was monitored on the left arm, at 1-min intervals, by the acceleromyographical response of the adductor pollicis muscle to train-of-four (TOF) stimulation of the ulnar nerve, using surface electrodes (TOF-Watch® SX; N.V. Organon, Oss, The Netherlands). The TOF response to a supramaximal stimulus was obtained before the initial bolus of neuromuscular-blocking drug.

Induction and maintenance of anaesthesia

All patients were premedicated with lorazepam 2.5 mg, 1 h before induction. After 3 min of preoxygenation, anaesthesia was induced with propofol TCI (target 3 μg ml^{-1}; induction time 3 min), remifentanil 0.2 μg kg^{-1} min^{-1} and rocuronium 0.6 mg kg^{-1}. Normocapnic ventilation was established with an Aestiva 3000 ventilator (Datex-Ohmeda, Helsinki, Finland). Routine monitoring included electrocardiography (ECG), pulse oximetry, invasive arterial pressure (right radial artery), central venous pressure (via the right jugular vein) and transoesophageal echocardiography (TEE). We maintained oesophageal and rectal temperatures at 36–37.5°C using the Allon 2001-system® (MTRE Advanced Technologies Ltd., Israel). Anaesthesia was maintained with oxygen 40% in air, propofol TCI and remifentanil 0.1–0.5 μg kg^{-1} min^{-1}. Propofol was adjusted in 0.5 μg ml^{-1} target steps according to bispectral index (BIS)

monitoring (A-2000; Aspect Medical Systems, Natick, MA, USA); BIS was kept between 45 and 55%. Remifentanil administration was guided by the haemodynamics and changed in 0.1 µg kg^{-1} min^{-1} steps in response to variations in systolic blood pressure of 20 mmHg. Increasing preload and placing the patient in the Trendelenburg position prevented hypotension upon dislocation of the heart. Noradrenaline was given in steps of 0.05 µg kg^{-1} min^{-1} where the systolic blood pressure was lower than 80 mmHg for at least 5 min. After mobilization of the internal mammary arteries, 1.5 mg kg^{-1} of heparin was administered to obtain an activated clotting time > 250 s. A cellsaver was used in order to reduce homologous blood transfusion.

In group 1, endotracheal intubation was performed as soon as the first response to the TOF stimulus (T1) fell to < 10 %. After T1/T0 had recovered to 10%, patients were given rocuronium at an infusion rate of 6 µg kg^{-1} min^{-1}. The rate was manually adjusted in 50% steps each time T1% was < 5 or > 15, in order to maintain T1/T0 at 10%.

In group 2, the investigator was blinded to the neuromuscular transmission monitoring and the trachea was intubated 3 min after the administration of the rocuronium bolus. A rocuronium infusion was started 30 min after induction, at a rate of 6 µg kg^{-1} min^{-1} [2]; this rate was left unchanged during surgery.

Recovery from anaesthesia

Figure 1 shows the decision tree for the recovery from anaesthesia in groups 1 and 2. In both groups, the rocuronium infusion was discontinued when all vascular anastomoses had been completed; intraoperative criteria were then evaluated in all the patients (Table 1). If one or more criteria were not fulfilled, patients were excluded from immediate postoperative extubation and were further ventilated in the ICU. In the others, propofol was stopped at the beginning of closure of the subcutis and piritramide 15 mg i.v. was administered. An escape bolus of propofol (0.5 mg kg^{-1}) was given where the BIS exceeded 60% before surgery had been completed. Remifentanil was discontinued at the beginning of skin closure and neostigmine (50 µg kg^{-1}) administered at the end of surgery, in group 1 when the TOF was < 0.9 and routinely in group 2. For those patients still scheduled for immediate extubation, a 20-min test period for spontaneous ventilation was allowed once surgery had been accomplished.

When the TOF ratio was ≥ 0.9 (group 1), patients were extubated when breathing spontaneously (Table 2), fully awake and able to follow commands. If not, ventilation was continued in the ICU. When they met the clinical criteria for normal neuromuscular function after induced blockade [10], patients in group 2 were extubated when they fulfilled the criteria shown in Table 2, and when fully awake and able to follow commands. If not, they too were ventilated in the ICU.

Data collection

All vital measures were displayed on a S/5® monitor (Datex-Ohmeda, Helsinki, Finland) and stored in a record-keeping system; the results of monitoring neuromuscular transmission were saved in a spreadsheet on a Compaq® PC (Houston, TX, USA). We derived the characteristics for patients in both groups and calculated the neuromuscular-blocking drug infusion rate in group 1, as well as the mean T1/T0 during infusion in both groups. We registered the time interval between induction and the onset of the infusion in group 1, and computed the T1/T0 at the discontinuation of the infusion in both groups. We derived the durations of infusion and surgery, and the time interval between discontinuing the infusion and the end of surgery. The TOF at the end of surgery and at extubation, the number of patients needing neostigmine, and the time point of TOF = 0.9 were calculated. We investigated how many patients reached the extubation criteria, and how many were extubated in the operating room and had a TOF ≥ 0.9 at extubation; the extubation time in the operating theatre or the ICU was also derived. We sought explanations for extubation failure and for reintubation. Length of stay in the ICU and hospital were calculated, and general outcome described.

Statistical analysis

Results are presented as means ± SD, except for the TOF ratios at extubation (median and range). Significance was set at $P < 0.05$. Data from groups 1 and 2 were compared to investigate significant differences using GraphPad (InStat®, San Diego, CA, USA). A Kolmogorov and Smirnov test was performed to assess normality: an unpaired t-test or a one-sample t-test, when appropriate, was used to determine the significance of normally distributed parametric values. Non-normally distributed data were compared in a non-parametric U-test. A two-sided Fisher exact test was used to perform univariate analysis of

immediate postoperative extubation versus blinded or non-blinded neuromuscular transmission monitoring.

RESULTS

Study groups

In group 1 the rate of rocuronium infusion required to keep T1/T0 at 10% was 5 ± 1.9 μg kg^{-1} min^{-1}; this rate was not significantly different from the fixed rate in group 2 (P = 0.15). Table 3 shows the physical characteristics of the patients in groups 1 and 2. Each surgeon contributed to approximately the same number of cases and used the same operative strategies in both groups. Tables 4 and 5 show the most important data in groups 1 and 2. In group 2, one patient was excluded because of intraoperative conversion to cardiopulmonary bypass; during the routine intraoperative TEE examination, we identified a preoperatively unknown thrombus in the left atrial appendix and it was decided to open the heart to remove it. In group 1, one patient had a combined repair of a groin aneurysm; in group 2, one patient's operation was prolonged by a carotid endarterectomy and another by the repair of a groin aneurysm. Finally, eight out of 10 and eight out of nine patients in groups 1 and 2, respectively, reached the extubation criteria (Table 1). Three out of eight and five out of eight patients from groups 1 and 2, respectively, were extubated in the operating room. At that extubation, all three patients from group 1 had a TOF ≥ 0.9, as this was a condition for extubation in that group; however, only four out of the five patients from group 2, despite reversal, had a TOF ≥ 0.9. Although the clinical criteria for extubation seemed satisfactorily fulfilled, unblinding revealed that one patient in that group had been extubated at a TOF of 0.55. The median and range of TOF ratios at extubation were 1.12 (1.01-1.13) and 1.00 (0.55-1.11) in groups 1 and 2, respectively. No patient required reintubation in group 1, while in group 2 one patient, not the one with the low TOF at extubation, was reintubated in the ICU for excessive pain and CO_2 retention. The incidence of pharmacological reversal was high in group 1 (8/10): moreover, of the only two patients in group 1 who did not receive neostigmine, one of them would normally have had it but had not reached the intraoperative extubation criteria. As this particular patient had respiratory and cardiac problems at that time, the anaesthetist decided not to give neostigmine. Hence, this patient did not reach a TOF ≥ 0.9 during registration.

Explanations for extubation failure were ischaemia during awakening in one patient and respiratory failure in four patients in group 1. In group 2, two patients were not fully awake at the end of the 20-min test period for spontaneous breathing and one did not reach the respiratory extubation criteria. In both groups, the general outcome was not uneventful (Table 4).

Operating room-extubated versus ICU-extubated patients: univariate associations

Of the eight patients who were extubated in the operating room, five had had blinded neuromuscular monitoring while three had not; in the 11 patients who were extubated in the ICU, monitoring had been blinded in four and not blinded in seven (P = 0.37) (Table 6).

DISCUSSION

Continuous infusions of neuromuscular-blocking drugs are often used during OPCAB surgery. We found a high incidence of residual curarization (i.e., TOF < 0.9) at the end of surgery after a rocuronium block in our two study groups: the necessity of reversing the neuromuscular block was thus obvious. Even in group 1 the need for neostigmine was high, which reveals the importance of reversing a block caused by a continuous infusion of a neuromuscular-blocking drug, as monitored by neuromuscular transmission. Moreover, although the neuromuscular-blocking infusion was started later in group 1 than group 2, and thus less product was required, no difference was found in the recovery from the induced block. Also, the infusion rate in the group of patients not monitored blind was the same as the fixed rate of neuromuscular-blocking infusion in group 2. Moreover, the extubation rate in the group not monitored blind did not differ from that in the group whose neuromuscular monitoring had been blinded. So, at first glance, we could find no additional benefit for using neuromuscular transmission monitoring in OPCAB surgical patients who were to undergo planned extubation in the operating room. Nevertheless, it appeared unsafe not to perform this monitoring, as clinical criteria for extubation were found to be misleading and one patient was extubated at a dramatic TOF. However, this patient was not reintubated.

In this study, 50% of the patients who reached the intraoperative criteria were extubated in the operating room, where the extubation time was about 20 min. Although immediate postoperative extubation of OPCAB patients is feasible, the results of this study make it debatable whether this practice should become routine. There was the case of ischaemia and the often encountered respiratory failure during awakening, as well as the reintubation in the ICU; although we did not systematically measure pain scores in our patients, the immediately extubated patients had significant postoperative pain, despite piritramide administration before awakening. Previous reports have already suggested that, although it is possible to extubate on the operating table some patients who have undergone coronary surgery, the early risks of hypothermia, bleeding and cardiorespiratory instability probably outweigh the potential benefits [11]. Moreover, the practice of operating-room extubation has not been associated with a significant reduction in the length of stay in the ICU or hospital [12]. We draw the same conclusion from our study. Also, one must not forget the delay and the costs of the time required fully to awaken and extubate patients in the operating room. Others have demonstrated that early extubation (1–6 h) is safe and cost-effective, and can improve resource utilization in cardiac surgery by shifting the high ICU costs to the lower ward costs

[13]. Moreover, early extubated patients (1–6 h) recovered to baseline performance in the mini-mental state test 24 h before conventionally extubated patients [4] and displayed fewer depressive symptoms on the third postoperative day [14].

Advocates of OPCAB state that omitting the cardiopulmonary bypass reduces the complications of extracorporeal circulation and aortic cross-clamping, and, because stabilizers can reach all sides of the heart, even triple-vessel revascularization can be successfully performed; however, most of the reports are not based on randomized, prospective trials [15, 16]. Some investigators have concluded that OPCAB reduces blood loss, hospital costs, postoperative length of stay and morbidity, and is associated with excellent graft patency and less postoperative renal dysfunction than coronary surgery with cardiopulmonary bypass [15, 16, 17, 18]. Although some reports on OPCAB surgery even show less myocardial cell damage, less inotropic support, a lower incidence of low-output syndrome and lower rates of myocardial infarction, eliminating the cardiopulmonary bypass did not significantly reduce postoperative morbidity [18, 19]. The risks of embolic neurological complications due to manipulation of a severely atherosclerotic ascending aorta in cardiac surgical patients have been well documented, and the contribution of cardiopulmonary bypass to the occurrence of cerebral complications appears significant [20]. Consequently, a lower incidence of cognitive dysfunction after OPCAB surgery is described in the literature [21]. However, during proximal anastomoses in OPCAB surgery, the risk of emboli due to manipulation of the aorta is probably as high. In our study, there was one case of postoperative stroke; we must stress that here the immediately postoperative extubation of the patient was without doubt beneficial. If this patient had been ventilated in the ICU, the stroke would probably have been described as an intraoperative, instead of a postoperative, event. Finally, we should state that the overall postoperative morbidity in our study population appeared unrelated to the different monitoring or extubation protocols.

In summary, if NMT monitoring had not been applied, then one would not have known that an extremely large proportion of the patients (in the non-blinded group) needed pharmacological reversal to reach an adequate TOF. Moreover, in both groups, a significant incidence of PORC was found; this deleterious phenomenon could obviously be detected in the non-blinded group and consequently treated with appropriate antagonists. If one had not antagonized routinely in the blinded group (blinding is virtually the same as not monitoring a neuromuscular block), then a dramatic number of patients would have had PORC. Anaesthetists do not all routinely antagonize a neuromuscular block, and, finally, extubating a

patient at a TOF of 55% is far from evidence-based and is potentially hazardous. Although we found no additional benefits of using neuromuscular transmission monitoring in OPCAB surgical patients whose extubation was planned to be in the operating room, it appears to be an absolute necessity to use neuromuscular transmission monitoring for reasons of safety when practising this extubation strategy. Moreover, due to the high incidence of residual curarization, pharmacological reversal is mandatory if extubation on the table is to be performed. However, in our opinion, it is unwise to extubate these patients routinely on the operating table: as the necessity of prolonged ventilation is primarily determined by intra- or postoperative complications, an uncomplicated recovery can also be achieved by an early-extubation protocol without extubation on the operating table. Physicians must ensure that patients' best treatment is based on scientific evidence rather than on methods dictated by ever-increasing economic pressures.

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Figure 1. Decision tree for the recovery from anaesthesia in groups 1 and 2. ICU, intensive care unit; BIS, bispectral index; TOF, train-of-four.

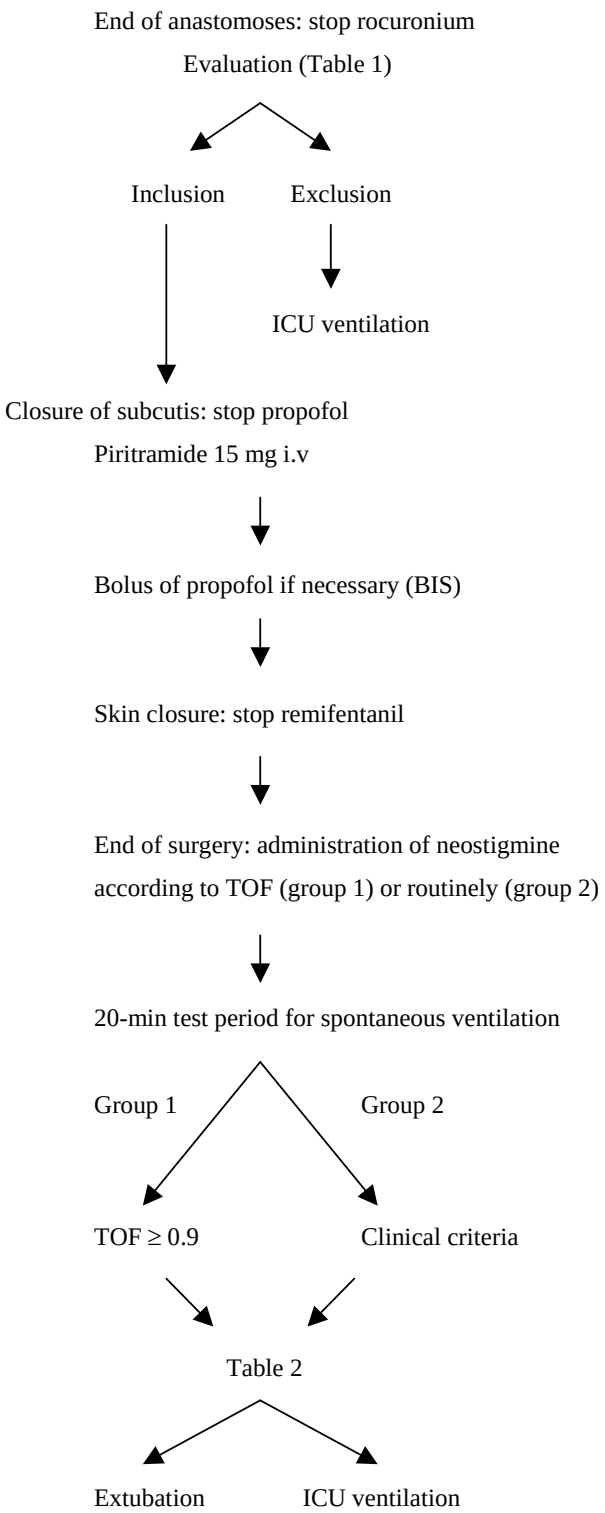

Table 1 Intraoperative criteria for immediate postoperative extubation after OPCAB grafting

1. Normal pH
2. Alveolar–arterial oxygen gradient < 200 mmHg
3. No overt clinical bleeding
4. Haemodynamically stable [defined as no noradrenaline infusions > 0.2 μg kg^{-1} min^{-1}]
5. No uncontrolled arrhythmia
6. No intra-aortic balloon pump
7. Oesophageal and rectal temperatures between 36 and 37.5°C

Table 2 Respiratory extubation criteria

1. Respiratory rate < 35 min^{-1}
2. SPO_2 > 90%
3. Tidal volume > 4 ml kg^{-1}
4. No respiratory distress (two of the following):
Heart frequency > 120% of baseline during > 5 min
Use of accessory muscles
Abdominal paradox
Sweating

Table 3 Patient characteristics in groups 1 and 2

	Group 1 (n = 10)	Group 2 (n = 10)
Age (years)	68 ± 12	67 ± 11
Sex (male/female)	6/4	9/1
Weight (kg)	78 ± 15	79 ± 7
Height (cm)	169 ± 7	175 ± 5

Values are means ± SD, except for sex

Table 4 Main findings in groups 1 and 2

	Group 1	Group 2
n (one excluded for conversion to CPB)	10	10
Extubation criteria reached	8/10	8/9
Neostigmine at the end of surgery	8/10	9/9
Extubation in the OR	3/8	5/8
TOF ≥ 0.9 at extubation	3/3	4/5 (1/5: TOF = 55%)
Explanation for extubation failure	Ischaemia (n = 1) Respiratory failure (n = 4)	Not fully awake (n = 2) Respiratory failure (n = 1)
Reintubation in OR/ICU	0/3	1/5 (ICU)
General outcome	Sacral decubitus (n = 1) Atrial fibrillation (n = 3) Postoperative myocardial infarction (n = 1) Sternitis (n = 1)	Atrial fibrillation (n = 5) Stroke (n = 1) Ventricular tachycardia (n = 1)

CPB, cardiopulmonary bypass; OR, operating room; TOF, train-of-four; ICU, intensive care unit

Table 5 Detailed results in groups 1 and 2

	Group 1 (n = 10)	Group 2 (n = 9)	P
Surgery duration (min)	214 ± 33	211 ± 46	0.86
Start infusion (min after induction)	49 ± 25	30	0.04
Mean T1/T0 during the infusion (%)	10 ± 7	12 ± 12	0.66
T1/T0 at stop infusion (%)	8 ± 8	8 ± 12	0.99
Infusion duration (min)	132 ± 51	145 ± 47	0.56
Surgery duration post-infusion (min)	33 ± 15	36 ± 11	0.68
TOF at the end of surgery (%)	41 ± 37	60 ± 45	0.30
Time point of TOF = 0.9:			
End of surgery (number of patients)	1	3	0.40
Min after end of surgery	5 ± 3	3 ± 3	0.31
Not reached during registration (no. of patients)	1	3	0.40
Extubation time in:			
OR (min)	23 ± 9	18 ± 8	0.45
ICU (h)	22 ± 25	7 ± 5	0.19
ICU stay (h)	37 ± 33	40 ± 58	0.90
Hospital stay (days)	15 ± 11	10 ± 8	0.31

Values are means ± SD, except for numbers of patients; significance set at $P < 0.05$

TOF, train-of-four; OR, operating room; ICU, intensive care unit

Table 6 Univariate analysis of immediate postoperative extubation versus blinded neuromuscular transmission monitoring or not

	Immediate postoperative extubation		
	Yes	No	Total
Group 1	3	7	10
	15.8 %	36.8 %	52.6 %
Group 2	5	4	9
	26.3 %	21.1 %	47.4 %
Total	8	11	19
	42.1 %	57.9 %	100 %

% values are % of total population

Chapter 7

DOSE REQUIREMENTS AND RECOVERY PROFILE OF AN INFUSION OF CISATRACURIUM DURING LIVER TRANSPLANTATION

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This manuscript is accompanied by an article on the immediate postoperative extubation of these patients: "*Criteria for Immediate Postoperative Extubation in Adult Recipients Following Living-related Liver Transplantation under Total Intravenous Anesthesia"*.
G Cammu, J Decruyenaere, R Troisi, B de Hemptinne, F Colardyn, E Mortier.
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DOSE REQUIREMENTS AND RECOVERY PROFILE OF AN INFUSION OF CISATRACURIUM DURING LIVER TRANSPLANTATION

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ABSTRACT

Study Objective: To examine the dose requirements and recovery profile of an infusion of cisatracurium during liver transplantation.

Design: Open-label, descriptive study.

Setting: University hospital.

Patients: 6 ASA physical status III and IV patients with end-stage liver disease, undergoing liver transplantation.

Interventions: Neuromuscular transmission was monitored electromyographically. After recovery of T1/T0 to 10%, cisatracurium was infused at an initial rate of 1.5 µg/kg/min. The infusion rate was adjusted to maintain T1/T0 at 10%. At the end of surgery, spontaneous recovery from the neuromuscular block was awaited.

Measurements and Main Results: The infusion rate of cisatracurium was 1.6 ± 0.4 µg/kg/min. Before the anhepatic phase this rate was 1.5 ± 0.4 µg/kg/min, during the anhepatic phase it was 1.7 ± 0.5 µg/kg/min, and after reperfusion it was 1.9 ± 0.4 µg/kg/min. There was a significant difference between the cisatracurium infusion rates before and after the anhepatic phase ($p < 0.05$). Following termination of the infusion, the time to 25% recovery of T1/T0 was 19.2 ± 6.1 min, the recovery index (25%-75%) was 28.8 ± 7.0 min, and the time for the train-of-four (TOF) ratio to reach 0.7 was 50.2 ± 7.1 min. The time for the TOF ratio to reach 0.9 was 61.4 ± 6.6 min. There was no difference in body temperature or pH during the consecutive stages of transplantation.

Conclusions: The infusion dose requirement for cisatracurium during liver transplantation tended to be higher than previously reported in healthy patients; recovery appeared prolonged. In continuous infusion of cisatracurium during liver transplantation, the tendency towards higher dose requirements, the protracted duration of infusion, the non-Hofmann elimination and/or other pharmacokinetic changes during transplantation might influence recovery from the neuromuscular block. Potential temperature or pH change during surgery seemed irrelevant to explain delayed recovery.

Keywords: Liver: disease; liver: transplantation; neuromuscular block: cisatracurium; pharmacodynamics: cisatracurium; pharmacokinetics: cisatracurium.

INTRODUCTION

A continuous infusion of a neuromuscular-blocking drug is often used during liver transplantation. In the presence of end-stage liver disease, cisatracurium is an advantageous choice of block because of its organ-independent elimination. Although cisatracurium predominantly undergoes spontaneous degradation by Hofmann elimination, changes in its pharmacokinetics, pharmacodynamics, or both may occur with liver disease. Its volume of distribution at steady state and plasma clearance are higher in patients with end-stage liver disease than in healthy patients.[1] The relatively minor differences in the pharmacokinetics of cisatracurium in end-stage liver disease are, however, not associated with any clinically significant differences in the recovery profile following a single bolus.[1] To the best of our knowledge, there are no published studies of the use of a continuous infusion of cisatracurium during liver transplantation. Therefore, we undertook this study to examine the dose requirements and recovery profile. Moreover, this study seems important to us now that immediate postoperative extubation of liver transplant patients becomes more common practice.[2]

We also searched for differences in dose requirements during the different stages of the transplantation (pre-anhepatic, anhepatic, and post-reperfusion). For atracurium, infusion requirements were found to be less during the anhepatic period and greater after reperfusion of the new liver.[3]

MATERIALS AND METHODS

We studied six patients, aged 18–65 years, after study approval was granted from the Ethics Committee of the Ghent University Hospital and after receiving patients' written informed consent. All patients were ASA physical status III and IV, had end-stage liver disease, and were undergoing liver transplantation. They had no evidence of renal insufficiency (serum creatinine < 1.8 mg/dL), were not receiving aminoglycosides or antihistaminics, and had no diseases affecting neuromuscular transmission. Patients with acute liver failure or encephalopathy were excluded from the study.

After 3 minutes of preoxygenation, anesthesia was induced with midazolam 0.02 mg/kg, remifentanil 0.2 µg/kg/min, and propofol 300 mL/h until loss of consciousness. As soon as the eyelid reflex was absent, assisted ventilation with 100% oxygen by facemask was begun. After a bolus dose of cisatracurium 0.15 mg/kg, intubation was performed as soon as the first response to the train-of-four (TOF) stimulus (T1) decreased below 10%. Normocapnic ventilation was established with an ADU ventilator (Datex-Ohmeda, Helsinki, Finland). Anesthesia was maintained with 50% oxygen in air, propofol 2–6 mg/kg/h, and remifentanil 0.1–0.3 µg/kg/min. No inhalation anesthetics were used. Routine monitoring included electrocardiography (ECG), pulse oximetry, invasive arterial pressure (left radial and right femoral artery), central venous pressure (CVP) and pulmonary artery pressure (right jugular vein), and continuous cardiac output (CO). Temperature was monitored at the pulmonary artery and at the skin area where neuromuscular transmission-monitoring electrodes were applied (right arm). We used a forced air-warming system (Bair Hugger™; Augustine Medical, Inc., Eden Prairie, MN) at the lower and upper body surface to keep body temperature between 35.5 and 37°C. Bispectral index (BIS) monitoring (A-2000, Aspect Medical Systems, Natick, MA) was used to assess depth of anesthesia and to guide propofol requirements accordingly. Remifentanil administration was adjusted according to hemodynamic values.

Neuromuscular transmission was monitored at the right arm by the electromyographic (EMG) response of the adductor pollicis muscle to TOF stimulation of the ulnar nerve, using surface electrodes (M-NMT module; Datex-Ohmeda, Helsinki, Finland). The TOF response to a supramaximal stimulus was obtained before the initial bolus of neuromuscular blocking drug. The TOF was measured at one-minute intervals, using a square-wave, constant-current stimulus pulse with a pulse width of 200 µs. After recovery of T1/T0 to 10%, cisatracurium

was infused at an initial rate of 1.5 μg/kg/min. The infusion rate was manually adjusted to maintain T1/T0 at 10%. The concentration of the solution used for infusion was 0.2 mg/mL, so that even small changes in infusion rate resulted in important changes of volume delivered and thus in a quick alteration of the effect. The cisatracurium infusion was discontinued at the beginning of the biliary anastomosis. The propofol infusion was stopped at the completion of the biliary anastomosis and piritramide 15 mg IV was administered. Remifentanil was discontinued at the beginning of skin closure. Spontaneous recovery from neuromuscular block was awaited. When the TOF ratio had recovered to > 0.9, patients' tracheas were extubated when they were breathing spontaneously, fully awake, and able to follow commands, provided that they fulfilled our institutional criteria for immediate postoperative extubation: good donor liver function, < 10 U packed red blood cells administered, hemodynamic stability, and alveolar–arterial oxygen gradient < 200 mmHg. Two patients were not extubated in the operating room (OR) because of alveolar–arterial oxygen gradient disorder.

Results for neuromuscular transmission monitoring as well as all other intraoperative parameters were displayed on a Datex AS/3 monitor and stored in a spreadsheet on a PC (Compaq™; Houston, TX).

We evaluated the recovery profile of cisatracurium in each patient: the time to 25% recovery of T1/T0, the recovery index (25%–75%), and the time needed for recovery to a TOF ratio of 0.7 and 0.9 were averaged. Cisatracurium infusion rate (μg/kg/min) and duration (min) were recorded during the pre-anhepatic, anhepatic and post-reperfusion stages of surgery for each patient. Body temperature and pH data were collected during the different phases of transplantation. Hemodynamics and fluid replacements during liver transplantation were described. Additionally, blood transfusion requirements were derived.

Statistical analysis was performed using a software package (GraphPad™ InStat®, San Diego, CA). We used the Kolmogorov and Smirnov method to test if the data were sampled from normally distributed populations. To measure the success of infusion titration, the calculated T1/T0 was compared with the preset value (T1/T0 = 10%) by a Wilcoxon signed rank test. We investigated significant differences between the infusion rates during the different stages of liver transplantation by repeated measures analysis of variance (ANOVA), followed by a Tukey-Kramer multiple comparisons test, if appropriate. Significant differences in body temperature during the respective stages of surgery were assessed using

repeated measures ANOVA with a Tukey-Kramer post test, if appropriate. The same statistical analysis was performed for pH data. Results are presented as means ± SD (ranges). We computed the lower and upper 95% confidence limits for the different infusion rates as well as for the recovery index and the time for TOF = 0.7. Significance was set at a level of $p < 0.05$.

RESULTS

The physical characteristics of the six patients are given in Table 1. Two patients scored Child-Pugh B, while four patients were Child-Pugh C. Indications for liver transplantation were: hepatitis C-related cirrhosis in three patients, hepatocellular carcinoma on hepatitis C-related cirrhosis in one patient, and alcoholic cirrhosis in the other two patients. No veno-venous bypass was used during liver transplantation. All data were normally distributed (Kolmogorov and Smirnov test passed). The duration of surgery was 801 ± 235 (566-1158) minutes. The duration of infusion was 644 ± 218 (439-911) minutes. The T1% during the infusion of cisatracurium was 12.8 ± 2.0 (10.1-15.7) %. This calculated T1% did not differ significantly from the preset T1% ($p = 0.06$). The infusion rate of cisatracurium during surgery was 1.6 ± 0.4 (1.1-2.0) µg/kg/min. Before the anhepatic phase this rate was 1.5 ± 0.4 (1.0-2.0) µg/kg/min, during the anhepatic phase it was 1.7 ± 0.5 (0.9-2.3) µg/kg/min, and after reperfusion it was 1.9 ± 0.4 (1.3-2.3) µg/kg/min. The lower and upper 95% confidence limits were 1.0-2.1, 1.0-2.3, and 1.4-2.4 µg/kg/min, respectively. Statistical analysis showed a significant difference between the cisatracurium infusion rates before, during, and after the anhepatic phase ($p = 0.03$). The post-test revealed a significant difference between pre-anhepatic and post-reperfusion infusion rates ($p < 0.05$); no significant differences were found between pre-anhepatic and anhepatic infusion rates or between anhepatic and post-reperfusion infusion rates. Pre-anhepatic pH averaged 7.41 ± 0.03 (7.37-7.44); during the anhepatic stage pH was 7.43 ± 0.02 (7.40-7.46) and after reperfusion of the new liver it was 7.40 ± 0.02 (7.37-7.43) ($p = 0.17$). Blood temperature was 35.9 ± 0.4 (35.2-36.3), 36.1 ± 0.8 (35.4-37.3) and 36.2 ± 0.9 (35.4-37.6) °C during the consecutive stages of the transplantation ($p = 0.62$). Hemodynamics were stable in all patients: no periods of hypotension (mean arterial blood pressure < 60 mmHg) were recorded, except for the transient hypotension immediately after reperfusion, countered with small doses of epinephrine. Mean arterial blood pressure was 76 ± 10 (67-95) mmHg. Intraoperatively, two patients received 1 to 2 units of vasopressine per hour; one patient received a dobutamine infusion of 4 µg/kg/min because of low cardiac output and a normal systemic vascular resistance. Intraoperative fluid replacement was with 6830 ± 1530 (5500-8500) mL of crystalloids (5% dextrose, NaCl 0.45% and/or 0.9%, and Plasma-Lyte™ A; Baxter Healthcare Ltd., Norfolk, U.K.), 1330 ± 610 (800-2000) mL of 4% albumin (SOPP, CAF-DCF, Brussels, Belgium), and 22 ± 4 (18-26) units of fresh frozen plasma. During liver transplantation, 4.2 ± 3.6 (0-8) units of packed red blood cells were transfused. Table 2 shows the pharmacodynamic recovery variables. Following termination of the infusion, the time to 25% recovery of T1/T0 was 19.2 ± 6.1 (12-

28) minutes, the recovery index (25%–75%) was 28.8 ± 7.0 (23-41) minutes, and the time for the TOF ratio to reach 0.7 was 50.2 ± 7.1 (39-56) minutes. The time for the TOF ratio to reach 0.9 was 61.4 ± 6.6 (51-67) minutes. The lower and upper 95% confidence limits for the recovery index and for the time for TOF = 0.7 were 20.1-37.5 minutes and 41.4-59.0 minutes, respectively.

DISCUSSION

The liver plays an important part in the pharmacokinetics of neuromuscular blocking drugs with regard to the offset of the block. Studies of these drugs in patients with liver disease show that their duration of action is often prolonged, owing to a lengthening of the elimination half-life that results from a reduced plasma clearance and, depending on the character and severity of the liver dysfunction, an increased volume of distribution, possibly due to a substantial increase in extracellular fluid.[4] Atracurium and cisatracurium seem to be favourable exceptions because of their unique breakdown mechanism. However, the elimination half-life of their potentially toxic metabolites in patients with severe liver disease is decelerated.[5] Ward and Weatherley [6] found that the pharmacokinetics of atracurium in liver failure were not significantly different from those in patients with normal liver function, but Gyasi and Naguib [7] report a case of prolonged atracurium-induced block in liver failure. For cisatracurium, small increases in volume of distribution (21%) and clearance (16%) have been found in patients with liver disease, but no difference in its elimination half-life or change in its recovery profile; and no apparent effect of liver disease on its urinary excretion. All these findings were, however, based on a single bolus of cisatracurium.[1] Although the liver seems to play only a minor part in the elimination of cisatracurium, it is a primary pathway for the elimination of metabolites.[6] These metabolites, however, do not possess neuromuscular blocking activity, but laudanosine can be harmful.[8] Because cisatracurium is three to four times as potent as atracurium and its dose requirements are thus less, a considerably lower concentration of laudanosine is achieved following cisatracurium.[9] Consequently, the margin of safety relating to the laudanosine concentration is greater than with atracurium, especially if the drug is needed by continuous infusion.[10]

From continuous infusions of atracurium used during liver transplantation, it appeared that the atracurium requirements were less during the anhepatic period and greater after removal of the vascular clamps on the new liver. The rate of atracurium infusion during liver transplantation, however, was not different from that needed in patients with normal hepatic function.[3] In our investigation, cisatracurium dose requirements during liver transplantation tended to be higher than previously reported infusion rates of cisatracurium in healthy subjects (1.4 μg/kg/min); however, the mean infusion rate in the referred group was not beyond the lower 95% confidence limit of the infusion rates in our investigation.[11] However, the T1/T0 in the reports by Belmont et al [12] and Mellinghoff et al [13] was kept at 5% during the infusion, which makes us expect that their infusion needs were relatively greater and,

consequently, the difference from our results (T1 = 10%) even more important. The higher dose requirement perhaps can be explained by an increased volume of distribution for cisatracurium in patients with liver disease, assuming this explanation can be extrapolated from single bolus data.[1] We also found significant differences in the infusion rates of cisatracurium during the consecutive periods of liver transplantation. However, a post-test revealed a significant difference only between the pre-anhepatic cisatracurium infusion rate and the dose requirement once the new liver had been reperfused. The increased infusion rate after reperfusion may reflect the albeit small (7%) contribution of the liver to the breakdown of cisatracurium.[14]

When looking at the pharmacodynamics of spontaneous recovery after a cisatracurium infusion during liver transplantation, we found that recovery was longer than previously reported in healthy patients. As Smith et al. [10] maintained a T1/T0 of 5% during infusion (versus 10% in our investigation), it is hard to compare the times to 25% recovery of T1/T0; the recovery index, however, indicates a slower rate of recovery in liver transplant than in healthy patients - 28.8 ± 7.0 min vs. 15.9 ± 5.2 min, 15.0 ± 0.6 min and 17.9 ± 10.9 min.[12, 13] The referred mean recovery index data are beyond the 95% confidence limits of the liver transplant data. These findings contrast with those of Belmont et al. [12], who state that the rate of recovery following cisatracurium administration was independent of the dose once recovery began. Also, the time to a TOF ratio = 0.7 was prolonged: 50.2 ± 7.1 minutes in our investigation versus 40.7 ± 14.1 minutes and 38.7 ± 6.4 minutes; these mean values were beyond the lower 95% confidence limit of our data.[10, 13] The time course of spontaneous recovery in healthy patients following the termination of a cisatracurium infusion was independent of the duration of infusion and similar to that following single doses.[12] In liver transplant patients, however, the recovery index (25-75%) for continuous infusions is different from that for single boluses: the mean value for a single bolus is smaller than the lower 95% confidence limit for a continuous infusion (15.4 vs. 20.1 min).[1] It is, however, inappropriate to compare the duration of infusion in our liver transplantations with the duration in other surgical procedures in healthy patients, where mean durations of 109 minutes, 122 minutes and 79 minutes have been reported.[10,12,13] One can argue that it would be more ideal having applied our protocol to a negative control group, but it is extremely hard to find a control group with similar duration of surgery. Moreover, it isn't liver failure alone that makes liver transplant patients different from healthy patients: ascites, serum albumin disorders, diuretic and/or beta blocker therapy, intraoperative fluid shifts, secondary

hyperaldosteronism, and portopulmonary hypertension are common in the liver transplant patient and are all likely to influence pharmacokinetics and pharmacodynamics of drugs.

Finally, temperature and pH may be very deranged in the anhepatic (low pH) and post-reperfusion (low temperature) phases of liver transplantation. However, potential effects of temperature or pH change on the recovery profile of cisatracurium were not found to be of relevance in our study. On the other hand, it is possibly reasonable to consider the importance of non-Hofmann elimination in the clearance of cisatracurium so as to explain delayed recovery from a cistatracurium infusion administered during liver transplantation.

To conclude, it is probable that in continuous infusions of cisatracurium during liver transplantation the tendency towards higher dose requirements, the protracted duration of infusion, the non-Hofmann elimination, and/or other pharmacokinetic changes during transplantation influence recovery from the neuromuscular block. Moreover, the degree of hepatic dysfunction possibly affects the degree of pharmacokinetic disorder. Potential temperature or pH change during surgery seemed irrelevant to explain delayed recovery. Thus, to avoid underdosing or overdosing and postoperative residual curarization when administering cisatracurium during liver transplantation, it is essential to titrate this drug against effect, which means that neuromuscular-transmission monitoring is of extreme importance in this setting. Multiple conditions make, however, pharmacokinetics and pharmacodynamics unpredictable during liver transplantation.

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Table 1. Patients' Characteristics

Gender ratio; M:F	5:1
Age (yrs)	57 ± 5 (49-62)
Height (cm)	165 ± 11.8 (145-175)
Weight (kg)	81 ± 9.3 (70-95)

Note: Data are means ± SD (ranges).

Table 2. Recovery Variables After Cisatracurium Infusion During Liver Transplantation

Time to 25% recovery of T1/T0 (min)	19.2 ± 6.1 (12–28)
Recovery index: (25-75%) (min)	28.8 ± 7.0 (23–41)
Time to TOF ratio = 0.7 (min)	50.2 ± 7.1 (39–56)
Time to TOF ratio = 0.9 (min)	61.4 ± 6.6 (51–67)

Note: Data are means ± SD (ranges).

TOF = train-of-four.

Chapter 8

ANAESTHETIC MANAGEMENT AND OUTCOME IN RIGHT-LOBE LIVING LIVER-DONOR SURGERY

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ANAESTHETIC MANAGEMENT AND OUTCOME IN RIGHT-LOBE LIVING LIVER-DONOR SURGERY

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SUMMARY

Background and objective: We reviewed retrospectively the anaesthetic management and perioperative course of eight right hepatectomies for living liver donation.

Methods: After preoperative psychiatric evaluation, eight ASA class I-II individuals donated the right lobe of their liver to a family member. A graft-recipient body weight ratio of 0.8-1.0 % was required for patient selection. Indications for liver transplantation were: hepatitis C viral-related cirrhosis in six patients; combined hepatitis C and B viral cirrhosis in one patient; multifocal hepatocellular carcinoma -four lesions, involving both liver lobes- of hepatitis C virus-related cirrhosis in another patient. Indication for adult-to-adult living-donor liver transplantation was retained in the latter because of rapid deterioration of the liver disease, rare recipient's blood group and extended, unresectable hepatocellular carcinoma. Hepatitis C viral-related cirrhosis was casually the primary indication for adult-to-adult living-donor liver transplantation in this group. The condition of the donated hepatic lobe was optimised by appropriate drug and perfusion management. Preoperative investigations included: blood tests (full cell count and film, thyroid function tests, pregnancy tests, full virological tests and bacteriological cultures, and immunological typing), chest radiograph, electrocardiogram plus Doppler cardiac ultrasound, spirometry, aminopyrine breath test, liver Doppler examination, magnetic resonance imaging, angiography and cholangiography and a volumetric study of the whole liver and the right lobe. Haemoglobin and lactate concentrations, liver function tests and international normalized ratio were measured before and after operation. The volume and weight of the resected right lobe was calculated. Anaesthesia was induced with propofol 300 ml h^{-1} and sufentanil 0.3 µg kg^{-1} intravenously; cisatracurium, 0.15 mg kg^{-1}, was given to facilitate tracheal intubation. Anaesthesia was maintained during normocapnic ventilation of the lungs with oxygen 40% in air, isoflurane 1-1.5 MAC and sufentanil. Routine anaesthetic monitoring included electrocardiography, pulse oximetry, invasive blood pressure, central venous pressure, urine output, state of neuromuscular blockade and core temperature. Periods of hypotension (< 80% of the preoperative blood pressure) or haemodynamic instability (requiring inotropic or vasoactive support) were registered. Total blood loss and transfusion (homologous, autologous or cell-saver blood) requirements were measured; volume replacements were derived.

Results: Data are presented as mean (range). There were no morbidity or mortality and no periods of intraoperative hypotension or haemodynamic instability. The operation time averaged 619 (525-780) min. Four donors were extubated in the operating room immediately after surgery; the others were extubated in the intensive care unit, where the mean extubation

time was 16.3 (5-25) h after arrival. The estimated blood loss was 967 (550-1600) mL. No homologous blood was administered; five donors received autologous blood, intraoperatively; three donors received a cell-saver blood transfusion. Intraoperative fluid replacement was with crystalloids, colloids and 4% albumin. Total urine output was 1472 (700-3100) mL. Although intraoperative hypothermia occurred, all subjects were normothermic at the end of operation. The pre- and immediately postoperative haemoglobin concentration averaged 13.6 (9.8-15.6) and 10.5 (6.9-13.0) g dL^{-1}, respectively. On the first postoperative day, the haemoglobin was 11.7 (8.4-15.1) g dL^{-1}. The donors' liver function tests were transiently elevated in the initial postoperative period. The intensive care unit discharge time was 2 (1-3) days. The hospital stay was 13 (7-17) days. There was no morbidity or mortality.

Conclusions: The study demonstrates that right-lobe living-donor surgery was well tolerated, without intraoperative hypotension or haemodynamic instability, without perioperative anaesthetic or surgical complications, and with an excellent general outcome.

Keywords: ANAESTHESIA, general; LIVER, surgery; LIVER, transplantation; TISSUE DONORS, living donors; OUTCOME ASSESSMENT (healthcare).

INTRODUCTION

The worsening, widespread shortage of organs for adult liver transplantation and the increased number of patients awaiting a liver graft have encouraged adult-to-adult living-donor liver transplantation (ALDLTx). Because the safety of the donor is such an essential principle of the procedure, the left lobe of the liver is used most often since more extensive resection (e.g. right or right-extended lobectomies), which increases the operative time and the risk of bleeding, might compromise the intra- and postoperative donor's safety [1,2]. However, ALDLTx with the left lobe is not indicated for large recipients and the small-for-size grafts are correlated with poor survival rates. Consequently, right hepatic lobectomy appears a promising alternative to transplantation of the left lobe or small left lateral segments. Although the size of a right hepatic lobe was favourable for grafting, surgeons still had concerns about the donor's safety [1,2]. The use of a right lobe for ALDLTx was first published in 1994 [3]. However, since 1998, when the first series of right-lobe liver transplantations was published, experience and enthusiasm for the procedure have grown worldwide [4,5]. Our centre started this programme in September 1999, and up until October 2000 eight right hepatic lobectomies for ALDLTx were performed at the Ghent University Hospital [6]. Recently, Beebe and colleagues, and Choudhry and colleagues described their initial experience with anaesthesia during the transplantation of living-related, left lateral liver segments [7,8]. The present paper reviews retrospectively the anaesthetic management and the perioperative course during the more complex right-lobe living liver-donor surgical procedure that is potentially more harmful to the donor than transplantation of the left lobe or small, left lateral segments.

METHODS

Institutional Review Board approval was obtained for the retrospective study. Eight ASA I-II individuals donated the right lobe of their liver to one of their family members. The relationships of the donors to the patients were four sons, three daughters and one wife. All donors were medically fit except for one patient who had thalassaemia minor and another with obesity (BMI = 37.3 kg m^{-2}). Indications for liver transplantation were HCV-related cirrhosis in six patients; combined HCV and HBV cirrhosis in one patient; multifocal hepatocellular carcinoma (HCC) -four lesions, involving both liver lobes- on HCV-related cirrhosis in another patient. An indication for ALDLTx was retained in the latter because of rapid deterioration of the liver disease, rare recipient's blood group and extended, unresectable HCC, as previously noticed. HCV-related cirrhosis, which represents about 50 % of all the indications for transplantation in our institution, was casually the primary indication for ALDLTx in this group*.

The perioperative management of the donors was essentially that of a major abdominal procedure, but an additional concern for the anaesthesiologist was to optimise the condition of the donated hepatic lobe by an appropriate drug and perfusion management. Following a modified donor work-up protocol [9], preoperative investigations included blood tests (full cell count and film, thyroid function tests, pregnancy tests, full virological tests and bacteriological cultures, HLA typing), a chest radiograph, electrocardiography plus Doppler ultrasound of the heart, spirometry, an aminopyrine breath test, and a liver Doppler examination. Finally, magnetic resonance imaging (MRI), angiography and cholangiography were performed, with a volumetric study of the whole liver and the right lobe. Since an adequate initial graft mass and remnant liver volume are essential for safety and success, a graft-recipient body weight ratio of 0.8-1.0 % was required for patient selection. A preoperative psychiatric evaluation was made. We also obtained the informed consent of the donor before the procedure was planned. For every donor, we organized a preoperative collection of 1 unit autologous blood (approximate volume 400 mL).

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*These patients were part of the population described in "*Modulation of portal graft inflow: a necessity in adult living-donor liver transplantation?" R Troisi, G Cammu, G Militerno et al. Ann Surg 2003; 237: 429-36.*

All subjects were premedicated with lorazepam, 2.5 mg, 1 h before induction. After 3 min of preoxygenation, anaesthesia was induced with propofol 300 ml h^{-1} until loss of consciousness and sufentanil 0.3 µg kg^{-1} IV. As soon as the eyelid reflex was absent, assisted lung ventilation by facemask was started with 100% oxygen. After a bolus dose of cisatracurium, 0.15 mg kg^{-1}, tracheal intubation was performed as soon as the first response to the train-of-four (TOF) neuromuscular stimulus (T1) fell to below 10%. Normocapnic ventilation of the lungs was established with an ADU™ ventilator (Datex-Ohmeda, Helsinki, Finland). Anaesthesia was maintained with oxygen 40% in air, isoflurane at inspired concentrations of 1-1.5 MAC and supplemental boluses of sufentanil. Routine monitoring included ECG, pulse oximetry, invasive blood pressure (left radial artery) and central venous pressure (right jugular vein). Temperature was monitored in the oesophagus. A forced air-warming system (Bair Hugger™; Augustine Medical Inc., Eden Prairie, MN, USA) was used over the lower body surface to keep the oesophageal temperature between 35.5 and 37°C. Neuromuscular transmission was monitored on the right arm by the EMG response of the adductor pollicis to TOF stimulation of the ulnar nerve using surface electrodes (M-NMT™ module; Datex-Ohmeda, Helsinki, Finland). After recovery of T1/T0 to 10%, donors were given cisatracurium at an infusion rate of 1.5 µg kg^{-1} min^{-1}. The rate was adjusted to maintain T1/T0 at 10%. At the end of dissection, heparin 50 U kg^{-1} was administered IV to prevent blood clotting in the remaining liver following interruption of the vasculature. The infusion of cisatracurium was discontinued at the beginning of closure, whereas the administration of isoflurane was stopped when the surgeon was closing the skin. The TOF ratio was allowed to recover spontaneously to 0.9. Neostigmine (50 µg kg^{-1}) was only administered when TOF < 0.9 at the end of surgery. When the TOF ratio had recovered to > 0.9, patients were extubated when breathing spontaneously, fully awake and able to follow commands.

All vital measures were displayed on an AS/3™ monitor (Datex-Ohmeda, Helsinki, Finland). Intraoperatively, a cell-saver system (Haemonetics™; Braintree, MA, USA) was used. All donors were admitted postoperatively to the ICU. According to the donor's preoperative wishes, analgesia was provided with morphine through a patient-controlled device, or with paracetamol 1g IV combined with piritramide 20 mg IM every 6 h.

The total operation time was recorded. Periods of hypotension (< 80% of the preoperative blood pressure) or haemodynamic instability (requiring inotropic or vasoactive support) were registered. Urine output was recorded, as was the intraoperative oesophageal temperature. Periods of intraoperative hypothermia (oesophageal temperature < 35.5°C) were registered.

Total blood loss was estimated, as well as the amount of homologous, autologous or cell-saver blood transfused. Volume replacements were derived. Haemoglobin and lactate concentrations were recorded before and after operation. Liver tests (alanine A transferase, aspartate A transferase, γ-glutamyl transferase, alkaline phosphatase, bilirubin) were performed and the international normalized ratio (INR) was measured preoperatively and on postoperative days 2, 7, 30 and 90. The volume and weight of the resected right lobe were then computed. The extubation time was derived as well as the time in intensive care and to hospital discharge. Analgesic management was described and perioperative complications noted. The final outcome of the donors was described. Data were presented as the mean (range).

RESULTS

Table 1 shows the physical characteristics of the donors. Table 2 summarizes relevant information about the donors. Total operation time was 619 (525-780) min. No periods of intraoperative hypotension or haemodynamic instability were recorded. The total urine output was 1472 (700-3100) mL. The mean intraoperative temperature was 36.0 (34.8-37.0) °C. Intraoperative hypothermia occurred in four donors, but at the end of surgery all subjects were normothermic. There was no postoperative residual curarization, i.e. all patients had a TOF > 0.9 at the end of surgery. Four donors were extubated in the operating room immediately after surgery. The others were extubated in the ICU, where the mean extubation time was 16.3 (5-25) h after arrival.

Intraoperative fluid replacement was with 5214 (3500-6500) mL of crystalloids (Plasma-Lyte™ A and 5% dextrose; Baxter Healthcare Ltd., Norfolk, U.K.), 1000 (0-2000) mL of colloids (HAES-steril™ 6%, Fresenius AG, Bad Homburg, Germany) and 571 (0-1200) mL 4% albumin (SOPP, CAF-DCF, Brussels, Belgium). The estimated blood loss was 967 (550-1600) mL. Homologous blood was not administered. Five donors received each one unit autologous blood, intraoperatively; three donors received a cell-saver blood transfusion of 700, 750 and 900 mL, respectively. The pre- and immediate postoperative haemoglobin averaged 13.6 (9.8-15.6) and 10.5 (6.9-13.0) g dL^{-1}, respectively; on the first postoperative day, the haemoglobin was 11.7 (8.4-15.1) g dL^{-1}.

The mean volume of the resected right lobe was 943 (780-1351) cm^3; the mean graft weight was 780 (670-1030) g. Table 3 shows the evolution of the donors' liver function tests preoperatively and on postoperative days 2, 7, 30 and 90. The pre- and immediate postoperative lactate concentrations averaged 10.8 (5-16.5) and 29.3 (21.4-43.1) mg dL^{-1}, respectively. On the first postoperative day, lactate was 17.7 (10.6-28.6) mg dL^{-1}. Postoperatively, only two donors received patient-controlled analgesia. The others preferred the combination of paracetamol and piritramide. Although this was a retrospective study and pain score was not recorded, it was observed that the present analgesic management provided adequate pain relief and patient satisfaction. The general discomfort was predominantly related to the physiological postoperative ileus during the first 3-4 days following partial hepatectomy. The ICU discharge time was 2 (1-3) days after surgery. After 4.2 (3-10) days, donors began to eat, while 4.6 (3-10) days after surgery they began to walk. The hospital stay

was 13 (7-17) days. There were no perioperative anaesthetic or surgical complications. During the 11.6 (5-20) months of follow-up, there were no complications in the eight donors.

DISCUSSION

In times of organ shortage, living-donor liver transplantation has gained wide acceptance as an alternative for patients with end-stage liver disease, although considerable ethical consideration is required when subjecting donors to such major, elective surgery when it is not for their direct benefit. The left lateral segment is generally large enough for children, but it does not provide an adequate mass for adults. The right hepatic lobe offers enough volume for adult recipients, but for the donor, right-lobe resection is more difficult technically and has more risks than resection of the left lateral segment [1,2]. However, the first published results of right-lobe living-donor transplants were encouraging and the liver transplantation unit of the Ghent University Hospital began to perform them [6,10].

We recorded here the perioperative management of subjects undergoing right-lobe hepatectomy for donation. It seemed important to us to emphasize the effects of anaesthesia on the liver, as it might be significant because of the small residual volume of liver in this kind of surgery. However, unlike other organs, the liver has the ability to regenerate [2,11]. During the induction of anaesthesia, propofol, sufentanil and cisatracurium were administered. Anaesthesia was maintained with isoflurane and additional boluses of sufentanil. Intraoperative muscle relaxation was achieved with a continuous infusion of cisatracurium. None of these drugs is known to affect hepatic function adversely. Single IV boluses of hypnotic agents cause only minimal alterations in plasma indicators of liver function [12]. The pharmacokinetics of single doses of sufentanil and propofol are nearly similar in patients with end-stage liver disease and in normal patients [13,14]. The liver metabolizes only 0.2% isoflurane. Isoflurane dilates the hepatic artery and may protect against renal and splanchnic vasoconstriction. Although total hepatic blood flow decreases, oxygen delivery to the liver is well preserved with isoflurane [15-17]. Sufentanil has a high hepatic extraction ratio, but its clearance in cirrhotic patients was similar to that in controls, as was the elimination half-life [14,18]. Cisatracurium lacks organ-dependent breakdown and has been used safely, even in patients with end-stage liver disease [19,20]. For fluid replacement, Plasma-Lyte™ A was administered as the crystalloid solution lacks lactate. It is probably worth avoiding exogenous lactate in this kind of surgery. Glycaemia was managed with dextrose 5% [21]. HAES-steril™ 6% did not affect coagulation adversely, as <1 g kg^{-1}

body weight was administered. For postoperative analgesia, the IV or IM route was preferred: epidural catheters were banned for fear of spinal or epidural haemorrhages due to (unforeseen) perioperative coagulation disorders. As in other countries, advice was recently issued by the Belgian Society of Anaesthesia and Resuscitation raising concerns over reports of epidural haematomas with concurrent use of heparin and formulating guidelines accordingly [22]. Are we prepared to cancel the whole procedure in case of a bloody puncture in the donor? Moreover, Borromeo and colleagues noticed a postoperative increase in prothrombin time in patients who underwent right-lobe hepatectomy for living donation, irrespective of massive transfusion, and warned for the use of epidural catheters in this context [23].

To diminish intraoperative blood loss on the one hand, and graft oedema formation on the other hand, the central venous pressure was maintained at <5 cm H_2O [24,25] by avoiding excessive fluid administration and by using inhaled anaesthetics in addition to diuresis. If necessary, vasoactive drugs can be used to maintain the systemic blood pressure and improve hepatic perfusion, but this approach was not needed in the present patients. Finally, liver dissection was done by means of the Cusa™ (Cavitron Inc., Stamford, CT, USA), a device that minimizes bleeding on the cutting edge. Dissection was performed without vascular clamping to limit the ischaemic reperfusion lesions in the graft and the remaining liver. The blood loss in the subjects was about one litre: it accounted for the decline in the intra- and postoperative haemoglobin concentrations, but we did not need to transfuse homologous blood, and on the first postoperative day, the haemoglobin began to increase towards preoperative values. There was a similar evolution for lactate: after a transient intraoperative increase, values returned to lower concentrations on the first postoperative day. As was expected from [7,26,27], the donors' liver function tests were elevated in the initial postoperative period in relation to liver injury. However, on the seventh postoperative day, the liver function tests began to normalize, except for γ-glutamyl transferase and alkaline phosphatase, which were still elevated 1 month after living right lobectomy but follow-up showed their evolution to acceptable values after 3 months.

It was demonstrated that donors tolerated right-lobe living-donor surgery well, without intraoperative hypotension or haemodynamic instability, without perioperative anaesthetic or surgical complications, and with an excellent general outcome. The high incidence of postoperative lung ventilation could not be attributed to hypothermia or postoperative residual curarization because no postoperative residual curarization was recorded and all

subjects were normothermic at the end of surgery. However, it was probably related to the learning curve of surgeons and anaesthetists, which was responsible for rather protracted surgery, and to the safety concerns that these donors had to stabilize first on the ICU before being extubated. Therefore, some anaesthetists decided to admit donors to the ICU for postoperative lung ventilation, but once patients are there, it is often ICU policy to keep them sedated for some hours before it is felt they are stable enough and suited to weaning. This choice probably accounts for the rather prolonged postoperative ventilatory period, as no specific perioperative problems or complications had occurred that could have given rise to protracted sedation and ventilation. Moreover, there was no difference in outcome between donors extubated in the operating room and those ventilated postoperatively in the ICU, so it is felt that postoperative ventilation has no substantial advantage in these cases. Comparing the expensive length of stay in the ICU with the interval to the start of eating and walking and with the total hospital stay, it must be considered that the ICU stay was probably too long for this uncomplicated surgical procedure. Consequently, these patients are probably best extubated in the operating room provided that, at the end of surgery, pH, electrolytes and clotting tests are normal, there has been no massive transfusion or overt blood loss, and there are no haemodynamic or respiratory abnormalities.

In summary, the anaesthesia management and perioperative outcome in right-lobe living liver-donor surgery was reviewed and it was demonstrated that there was minimal morbidity in such an extended surgical procedure and that donors had an excellent outcome. These subjects, however, can generally be extubated in the operating room and briefly be observed in the ICU.

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Table 1. Donor characteristics. Values are mean (range).

Age (yr)	31.3 (22-44)
Sex (male / female)	4 / 4
Weight (kg)	73.8 (65-90)
Height (cm)	163.1 (147-184)

Table 2. List of right-lobe living liver-donors with relevant information. AU, autologous blood; CS, cell saver.

No.	estim. blood loss (mL)	blood transfusion need (mL)	operation time (min)	urine output (mL)	ICU stay (days)	hosp.stay (days)
1	750	-	780	1820	3	14
2	1000	400 AU	635	1350	2	8
3	1600	400 AU + 900 CS	565	1350	1	7
4	1000	400 AU + 700 CS	550	700	2	17
5	900	400 AU	680	1150	2	12
6	1000	750 CS	525	3100	2	17
7	550	-	600	835	2	12
8	935	400 AU	620	1470	2	15

Table 3. Donors' liver function tests. Values are mean ± SD. POD, postoperative day. INR, international normalized ratio.

	Preoperative	POD2	POD7	POD30	POD90
Aspartate A transferase (U L^{-1})	18.7 ± 4.3	195 ± 114	67 ± 25	46 ± 18	35 ± 10
Alanine A transferase (U L^{-1})	25 ± 18	265 ± 295	116 ± 30	90 ± 41	39 ± 8
Total Bilirubin (mg dL^{-1})	0.8 ± 0.3	4.0 ± 2.4	1.6 ± 0.8	0.7 ± 0.3	0.6 ± 0.2
Direct Bilirubin (mg dL^{-1})	0.2 ± 0.1	1.8 ± 1.2	0.9 ± 0.5	0.3 ± 0.1	0.3 ± 0.2
γ-Glutamyl transferase (U L^{-1})	20 ± 17	26 ± 17	238 ± 121	161 ± 86	55 ± 15
Alkaline Phosphatase (U L^{-1})	69 ± 23	65 ± 22	183 ± 63	210 ± 195	163 ± 34
INR	1.03 ± 0.09	1.67 ± 0.18	1.10 ± 0.11	1.07 ± 0.06	1.00 ± 0.04

Chapter 9

DISCUSSION AND FUTURE PERSPECTIVES

WHY CONTINUOUS INFUSIONS OF NMBDs ARE NECESSARY AND WHAT EXISTED IN THE LITERATURE ON THIS ISSUE

When surgery is prolonged and continued (constant) muscle relaxation is mandatory, a continuous infusion of a NMBD can be administered: this technique is superior to repeated small bolus doses, because the last of these might cause a too strong fluctuation in the level of block or be too troublesome for the anaesthesiologist. Long-acting agents should be avoided because they might cause an unacceptable degree of PORC. Furthermore, an infusion technique has to be coupled with NMT monitoring because this allows for correct titrating of the dose of drug against effect (constant level of block, e.g. 90%). Not monitoring a NMBD infusion may lead to insufficient block and consequently an unhappy surgeon, or overdosing and unacceptable PORC.

Computer-controlled closed loop systems have been used for the continuous administration of NMBDs [1, 2].With such a system a preset degree of neuromuscular blockade can be maintained and the rate of infusion is determined by measurement of the degree of blockade. Systems for closed-loop administration of atracurium, mivacurium and vecuronium have been developed[3]. Rocuronium as well has been administered by continuous infusion in a closed-loop feedback control system [4, 5].

Most of the literature on continuous infusions of NMBDs describes dose-finding studies, often performed by the manufacturers themselves, in healthy subjects undergoing basic surgery. Very little material exists on how the dose requirements of continuous infusions of NMBDs evolve with time and how PORC can be avoided when NMBD infusions are administered during protracted surgery and/or in organ failure.

There are some data available on the pharmacokinetics of NMBDs in ICU patients [6-11]. One of the limitations in such studies is the variability in diseases and drugs co-administered in such patients; this variability will disturb the results. Moreover, it is important to remember that critical illness neuropathy is a syndrome different from relaxant-induced neuromyopathy, but it may be enhanced by NMBD administration.

Table 1. Continuous infusion of NMBDs

INFUSION OF SUXAMETHONIUM

Infusion rate	Remarks
70–80 µg/kg/min	Large variability (Delisle, 1982) Tachyphylaxis and phase II block (non-depolarising characteristics) (Ramsey, 1980)

INFUSION OF NON-DEPOLARISING NMBDs

Infusion rate	Remarks
Atracurium: 7–8 µg/kg/min	High PORC rate (Fawcett, 1995)
Cisatracurium: 1.4 µg/kg/min	
Mivacurium: 5–10 µg/kg/min	Decreased infusion rate after 30 min (Dahaba AA, 1996)
Pancuronium: 0.06–0.1 mg/kg/h	
Vecuronium: 1–2 µg/kg/min	High PORC rate (Fawcett, 1995) Neonates: 0.9 µg/kg/min Older children: 1.6 µg/kg/min (Hodges, 1996)
Rocuronium: 6–10 µg/kg/min	Pharmacokinetics upon infusion similar to bolus pharmacokinetics (Shanks, 1993; McCoy, 1996)

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METHODS AND RESTRICTIONS IN THE VARIOUS STUDIES IN THIS THESIS

Either repeated boluses or a continuous infusion of NMBDs can satisfactorily maintain muscle relaxation, but the margin of safety is slim because blockade occurs over a narrow range of receptor occupancy. The percentage of cholinoceptors that have to be occupied (blocked) by a NMBD before the first clinical signs of neuromuscular block are visible, differs from one muscle to the other and from one NMBD to the other. It varies between 70 and 80%. Alternatively, it should be realised that at a recovery to 100% of baseline values as measured by single twitch stimulation it can still be that up to 70% of the receptors at the post-junctional membrane are occupied by NMBD molecules. Moreover, there is considerable interindividual variability in response to the same dose of NMBD. During protracted administration and/or where organs of elimination are impaired (liver and to some extent the kidneys), accumulation of the effect of these drugs is to be expected. Variability in dose requirements during the course of NMBD infusion has been reported. Pharmacokinetic and pharmacodynamic variability between patients can pose a clinical challenge when titrating drug requirements to the desired level of clinical effect. Volumes of drug distribution, rate constants and elimination half-lives vary in a physiological manner, while pathological processes and drug interactions may further alter the requirements. Moreover, it is now widely appreciated that the value of the elimination half-life in predicting duration of effect for anaesthetic drugs is rather limited, as most drugs are rarely given for long enough to achieve a steady state [12]. Plasma concentrations have been measured for all the non-depolarising NMBDs used clinically. The pharmacokinetic variables derived from these experiments depend on the dose given, the sampling schedule used, the accuracy of the assay, and the model chosen [13]. Thus it is better to rely on the shape of the plasma concentration–time curve and to relate duration of action to the concentration required for the desired effect, rather than to base decisions only on pharmacokinetic variables such as the elimination half-life.

A standard approach to manual infusion is to administer a loading dose followed by a continuous infusion. In general, the administration of an appropriate bolus at the start of an infusion permits a gradual increase in plasma concentration from the infusion to be matched by exponentially declining drug concentrations from the bolus. This process will result in an early, but not immediate, plateau. Generally speaking, the longer the interval between the loading dose and the start of the infusion, the greater the dose of additional relaxant required

to ‘catch up’. In the present studies, infusion was not begun immediately, as the standard loading dose (equivalent to 2–3 × ED_{95}) needed to facilitate tracheal intubation resulted in complete paralysis for approximately 0.5 h in all groups studied. Our approach permitted the return of neuromuscular function to a detectable level in the most rapid manner possible, at which point the infusion was begun. The rationale was to mimic a standard approach to the infusion of cisatracurium and/or rocuronium, whereby their infusion was begun upon return of a single twitch of about 10% [12].

WHAT THIS THESIS ADDS TO CURRENT KNOWLEDGE

This thesis has described studies on the optimisation of continuous infusions of the newer NMBDs, cisatracurium and rocuronium. Optimising the dose in relation to the duration, by means of NMT monitoring, improved the total anaesthesiological management of the patient, especially when pathology or type of surgery unpredictably disturb the dose–effect relation as, for example, in anaesthesia for liver and cardiac surgery, where those two factors are very important.

We first studied the effects of the continuous administration of cisatracurium and rocuronium and the need for NMT monitoring during protracted, major surgery without routine pharmacological reversal in patients not suffering from organ failure. Although there was a rational intraoperative dosage regimen for cisatracurium or rocuronium infusions, we found dramatic results for PORC: at the end of surgery, only one patient in the rocuronium group and four in the cisatracurium group had recovered spontaneously to a TOF ratio of 0.9. In the other patients in both groups, we observed significant intervals between the end of surgery and recovery to a TOF ratio of 0.9. Achieving spontaneous recovery of neuromuscular function took so long that six patients in the cisatracurium group and seven in the rocuronium group required pharmacological reversal, meaning that they had begun to wake while their TOF ratio was < 0.9. If partial curarisation had not been recognised by monitoring, or if pharmacological reversal had not been attempted, there would have been a risk of full awakening with partial paralysis in these patients, and to a much more serious extent for rocuronium than for cisatracurium. If overdosing had occurred, the recovery results would probably have been worse. We found some variable correspondence between the various clinical/neuromuscular tests and a TOF ratio of 0.9 in the operating room as well as in the PCU. When comparing the recovery characteristics of cisatracurium and rocuronium we found no significant difference in TOF at the end of surgery, but the difference in time

interval between the end of surgery and a TOF ratio of 0.9 was obvious though not statistically significant. Of importance to us was the significant difference in TOF in those patients who received neostigmine: when patients began to wake, those in the cisatracurium group had a TOF ratio of nearly 0.7 whereas those in the rocuronium group had a TOF ratio of only 0.4, a value that is associated with a much more dangerous degree of neuromuscular block. So, in this study, optimisation of the dose of continuous infusions of NMBDs alone did not prevent PORC. Selective antagonisation was obligatory even in these 'healthy' patients. Therefore, NMT monitoring was essential to avoid the complications by PORC and/or the inappropriate administration of reversal agents.

Consecutively, we studied patients with organ failure and/or undergoing special surgical techniques. We compared continuous with bolus dosing of NMBDs: we investigated whether a high bolus dose of cisatracurium ($8 \times ED_{95}$), given at induction, can provide muscle relaxation for the main part of a cardiac procedure, avoid significant PORC and, simultaneously, cause no waste of product. Six out of 10 patients in the bolus group required additional boluses of cisatracurium intraoperatively because of inadvertent movement. Four of these six had received an additional bolus near the end of surgery and had a TOF ratio of 0 at the end of the procedure. The other four patients in this group had a final TOF ratio > 0.9. In the infusion group, only two patients had a TOF ratio > 0.9 at the end of surgery; no patient had moved and, obviously, none received additional boluses. The total amount of cisatracurium used in the bolus and infusion groups was 34.5 ± 7.8 mg and 21.3 ± 5.7 mg, respectively ($P = 0.0004$). It appears that the continuous administration of cisatracurium during this type of surgery should be advocated. A high bolus dose of cisatracurium was, although safely used, not an option, as its neuromuscular blockade did not cover the intraoperative period and there was a high incidence of movement. In the patients who received a high bolus dose of cisatracurium, significant PORC appeared after additional boluses had been given and the consumption of cisatracurium was significantly greater by high bolus than continuous infusion. Conclusively, for certain surgical interventions, some form of continued muscle relaxation is absolutely necessary, as shown in this study.

We then studied, by means of NMT monitoring, the dose requirements for continuous infusions of cisatracurium and rocuronium in cardiac surgery with hypothermic CPB. During hypothermic CPB, complex changes in drug pharmacokinetics occur, prolonging the duration of action of many non-depolarising NMBDs [14-17]. The half-life of cisatracurium is presumably prolonged during hypothermic CPB, as its breakdown is even more dependent on temperature

and pH than that of atracurium, for which a reduced dose requirement has been observed during CPB [18]. The pharmacokinetics of rocuronium resemble those of vecuronium, except that rocuronium has a smaller volume of distribution [19]. The termination of the effect of rocuronium is similar to that of vecuronium, and is mainly dependent on redistribution, by hepatic uptake, followed by biliary elimination. A smaller proportion (< 20%) is excreted renally [20]. Smeulers and colleagues found that hypothermic CPB prolonged the duration of action of maintenance doses of rocuronium [21]. In our study, we found that a cisatracurium infusion rate of 0.75 µg/kg per min was appropriate during CPB. Moreover, we found that the first response to a TOF stimulus, T1/T0, of 15% could be achieved before CPB with a dose < 1.5 µg/kg per min. Even after the bypass, infusion rates for cisatracurium were lower than those before bypass, probably because of a further fall in body temperature, a tendency described in previous reports for other NMBDs [18]. Less rocuronium was required during and, to a lesser extent, after CPB than before CPB, but the differences in infusion rates were not statistically significant. Optimisation via NMT monitoring of the infusion dose requirements for these NMBDs during cardiac surgery with hypothermic CPB revealed a reduction in the consumption of muscle relaxant, most importantly for cisatracurium.

Finally, NMT monitoring is an absolute necessity in patients undergoing off-pump CABG when it is planned to extubate them at the end of the procedure. We found a high incidence of residual curarisation (i.e., TOF ratio < 0.9) at the end of off-pump surgery after a rocuronium block in our two study groups; the need to reverse the neuromuscular block was obvious. The extubation rate in the group not monitored blind did not differ from that in the group whose neuromuscular monitoring had been blinded. So, at first glance, we could find no additional benefit for using NMT monitoring in off-pump CABG patients who were to undergo planned extubation in the operating room. Nevertheless, it appeared unsafe not to perform this monitoring, as clinical criteria for extubation were found to be misleading and one patient was extubated at a dramatic TOF ratio. In this study, 50% of the patients who reached the intraoperative criteria were extubated in the operating room, where the time to extubation was about 20 min. Although the immediate postoperative extubation of such patients is feasible, the results of this study make it debatable whether this practice should become routine. Previous reports had suggested that, although it is possible to extubate on the operating table some patients who have undergone coronary surgery, the early risks of hypothermia, bleeding and cardiorespiratory instability probably outweigh the potential benefits [22]. Moreover, the practice of operating-room extubation has not been associated with a significant reduction in the length of stay on the ICU or in hospital [23]. We draw the same conclusion from our study.

So, again it was demonstrated that, although the dose of muscle relaxant had been optimised, a high incidence of PORC was encountered when continuous infusions were used: the advantage of NMT monitoring lays in its ability to guide selective antagonisation whereas routine reversal is required in its absence.

We then sought to draw parallels with liver surgery, where we investigated the dose requirements for an infusion of cisatracurium, the preferred NMBD in liver surgery, during liver transplantation. The liver plays an important part in the pharmacokinetics of NMBDs with regard to offsetting the block. Studies of these drugs in patients with liver disease show that their duration of action is often prolonged. Atracurium and cisatracurium seem to be favourable exceptions because of their unique mechanism of breakdown. In our investigation, the dose requirements for a cisatracurium infusion during liver transplantation tended to be higher than the previously reported infusion rates for cisatracurium in healthy individuals. The higher dose requirement can perhaps be explained by an increased volume of distribution for cisatracurium in patients with liver disease, assuming this explanation can be extrapolated from single-bolus data [24]. We also found a significant difference between the pre-anhepatic infusion rate for cisatracurium and the dose requirement once the new liver had been reperfused. The increased infusion rate after reperfusion may reflect the [albeit small (7%)] contribution of the liver to the breakdown of cisatracurium [25]. On looking at the pharmacodynamics of spontaneous recovery after a cisatracurium infusion during liver transplantation, we found that recovery was longer than previously reported in healthy patients. In seeking explanations for these findings, one must realise that it is not liver failure alone that makes liver-transplant patients different from ‘healthy’ patients: ascites, serum albumin disorders, diuretic and/or β-blocker therapy, intraoperative fluid shifts, secondary hyperaldosteronism, and portopulmonary hypertension are common in the liver-transplant patient and are all likely to influence the pharmacokinetics and pharmacodynamics of drugs. Finally, temperature and pH may be very deranged in the anhepatic (low pH) and post-reperfusion (low temperature) phases of liver transplantation. The potential effects of temperature or pH change on the recovery profile of cisatracurium were not, however, found to be of relevance in our study, as changes were minimal in this population. On the other hand, it is perhaps reasonable to consider the importance of non-Hofmann elimination in the clearance of cisatracurium in seeking to explain delayed recovery from a cistatracurium infusion administered during liver transplantation. The ‘fixed-dose rule’ was again found incorrect and NMT monitoring was clearly necessary in this kind of surgery in order to steer

continuous muscle paralysis: moreover, even with an optimised dose of NMBD infusion, we encountered prolonged recovery after NMBD infusion.

Finally, by relying on NMT monitoring, we could optimise anaesthetic management and control the continuous infusion of cisatracurium in right-lobe living-donor liver surgery. We recorded the perioperative management of individuals undergoing right-lobe hepatectomy for donation. It seemed important to us to emphasize the effects of anaesthesia on the liver, as this might be significant because of the small residual volume of liver in this kind of operation. In this study, intraoperative muscle relaxation was achieved with a continuous infusion of cisatracurium, which is not known to affect hepatic function adversely and lacks organ-dependent breakdown, and which has been used safely, even in patients with endstage liver disease [24, 25]. We demonstrated that donors tolerated right-lobe living-donor surgery well, without intraoperative hypotension or haemodynamic instability, or perioperative anaesthetic or surgical complications, and with an excellent general outcome. Liver enzymes and hepatic function were normalised after some weeks. Postoperative ventilation was frequently required in this study population; this need could not be attributed to hypothermia or PORC (no PORC was recorded and all patients were normothermic at the end of surgery). Why, in these cases, no PORC was seen after a continuous infusion of cisatracurium can perhaps be explained by the remnant liver adequately metabolising the non-Hofmann eliminated part. Moreover, the population was young and it is known that the rate of plasma clearance of, for example, rocuronium declines dramatically with age. The pharmacokinetic profile of cisatracurium, though, is essentially unaffected by increasing age [26, 27]. So, younger age may not be an explanation for a higher metabolic rate in the case of cisatracurium. The high incidence of postoperative ventilation was probably related to the surgeons' and anaesthetists' position on the 'learning curve', which was responsible for rather protracted surgery, and to safety concerns, which meant that these donors had first to be stabilised on the ICU before being extubated.

NMT MONITORING: AN ABSOLUTE NECESSITY IN ANAESTHESIA PRACTICE

When administering NMBDs, certain issues need to be considered: there is the individual patient response, accentuated in certain disease states or conditions (such as hypothermia); the pharmacokinetic parameters of NMBDs are altered in the elderly and those with elimination organ impairment; and, finally, interactions between NMBDs and other drugs can influence the response to NMBDs and reversal agents. The great fear when administering muscle

relaxants is of encountering PORC: with long-acting NMBDs, PORC is found in > 40% of patients [28, 29]. With the newer NMBDs, the incidence of PORC is still about 20% [30, 31]. Even with mivacurium, PORC has been detected [32]. As might be expected, the use of continuous infusions of NMBDs brought about a huge incidence of PORC [33, 34]. Even in a population among which PORC is by definition detrimental – day-stay surgical patients – a significant incidence of PORC has been found; the medium-duration, non-depolarizing NMBDs performed similarly, while the short-duration mivacurium was associated with a lower incidence in line with its profile, but even so PORC was not excluded [35].

One of the annoying problems with PORC is the lack of outcome measures; only two studies have been published on this issue. Lunn found that PORC was an important predisposing factor for death under anaesthesia [36] and Berg cites PORC as a significant risk factor for the development of postoperative pulmonary complications [37]. A recent study showed that impaired inspiratory flow and upper airway obstruction occur frequently during minimal neuromuscular blockade (TOF about 80%) and that extubation may put the patient at risk [38]. Another recent study has shown that PACU recovery times are prolonged after using long-acting NMBDs in surgical patients [39].

Despite the limited amount of published data, every clinician knows that PORC is detrimental to our patients, and must either be avoided or treated properly when detected. How can PORC be avoided ? Obviously, the most pragmatic way is not to use NMBDs, but that is not always reasonable nor feasible clinically [40]. An evidence-based suggestion is that long-acting NMBDs should no longer be used in clinical practice. Moreover, hypothermia, which delays recovery, should be prevented. One can use clinical criteria **(Table 2)** to evaluate neuromuscular function before extubating a patient; however, it is impossible clinically to monitor airway protection and patency. Clinical tests are influenced by the effect of premedication, general anaesthetics, the degree of consciousness, the level of cooperation and postoperative pain. There are contradictory findings concerning the correlation between clinically sufficient recovery and NMT monitoring. Another possibility is to reverse any block with adequate doses of the appropriate anticholinesterase reversal agent; however, routine reversal may have complications: the occurrence of arrhythmias [41], PONV [42] and a long onset time of reversal agents [43]. Therefore, objective monitoring of neuromuscular block (and reversing any TOF ratio < 0.9) is the only approach for good clinical practice.

Table 2. Clinical tests of postoperative neuromuscular recovery [Adapted from Viby-Mogensen J. Postoperative residual curarization and evidence-based anaesthesia. Br J Anaesth 2000; 84: 301-303]

Sustained head lift for 5 s
Sustained leg lift for 5 s
Sustained hand grip for 5 s
Sustained tongue depressor test
Maximum inspiratory pressure > -50 cm H_2O

How can we avoid PORC when using infusions of NMBDs? The possible answers are the subject of this thesis. First, one should optimise the dose requirements over time, as a fixed dose regimen implies a high PORC rate ***(Chapters 4 and 6)***. Routine antagonisation is another possibility, but, still there remains PORC ***(Chapter 6)***. So, with continuous infusions of NMBDs, the greater risk for PORC than with a single bolus can only be tackled by measuring the effect by NMT monitoring (and selectively antagonising the block) ***(Chapters 3, 4, 5, 6, 7 and 8)***.

That the use of NMT monitoring is a necessary part of evidence-based practice was only relatively recently advanced in two critical editorials from Viby-Mogensen and Lars Eriksson, respectively [44, 45]; they demonstrated the absolute necessity of NMT monitoring, ideally quantitative monitoring, as tactile and visual evaluation of the TOF ratio only allows the detecting of ratios of 0.3-0.4. DBS seems superior when tactile evaluation is performed, but yet quantitative TOF values are much more preferable [46, 47, 48]. When a TOF value is applied, an adductor pollicis TOF < 0.9 is accompanied by pharyngeal dysfunction and aspiration in non-anaesthetized volunteers [49]; hypoxic ventilatory control is impaired in PORC [50]. In conclusion, one cannot do better than to cite Lars Eriksson: “the only way we can reliably assess a neuromuscular block is by objective monitoring methods, such as acceleromyography or EMG. Based on the current literature, it is time to replace old subjective methods with new objective measurements” [45].

WHAT WILL THE FUTURE BRING?

In my personal opinion, three 'scientific territories' are still wide open and suitable for exploration. First, the PORC phenomenon has to be investigated further: ideally, the true impact of PORC as a separate risk factor for postoperative morbidity should be studied. Unfortunately, extremely large series of patients are necessary in order to deliver enough power to draw conclusions from such work.

Second, additional investigtions are needed to demonstrate the prevalence and dangers of PORC in order to convince clinical anaesthesiologists that they should use NMT monitoring in daily practice. We have now performed a study on 700 subjects, focusing on the incidence of PORC on the recovery ward when single, repetitive boluses and/or continuous infusions of NMBDs are administered during all kinds of surgical interventions, including ambulatory surgery. Also, the daily use of a NMT monitor and the practice of (routine) pharmacological reversal of an induced block have been investigated. Ambulatory patients are by far those in whom we can least afford to have residual paralysis, as they leave hospital very soon after their surgical procedure. So, in this population, possible PORC lies very close to a risk of adverse outcome.

Third, when we have convinced the anaesthetist of the high incidence of PORC and the need to apply NMT monitoring more intensely and rigorously, we will be able to predict PORC in every case and think about its treatment. Selective antagonisation with classical reversal agents will be required, but more hopefully soon with safe, selective antagonists of an induced neuromuscular block. Our group is involved in studies on the clinical use and safety of a newly developed, selective antagonist of rocuronium block. The compound ORG25969 (cyclodextrin) encapsulates rocuronium and decreases its effective plasma concentration to zero. In theory, even profound degrees of block can be reversed. Neuromuscular recovery will occur rapidly and completely as the relaxant diffuses from the neuromuscular junction back into the plasma. Because cyclodextrins do not work through cholinesterase inhibition, they are free of muscarinic effects [51]. If this drug indeed appears safe, then an extraordinary tool will have been delivered to overcome every case of PORC with this particular NMBD.

Finally, the continuing search for a succinylcholine replacement has brought about a new curare (GW280430A), which has now passed some stages of clinical investigation, and its

rapid onset and short duration of action will be of interest. Nevertheless, histamine release already appears to be an unfortunate capacity of this drug [52, 53, 54].

Also, in the field of monitoring devices, there is an evolving interest in phonomyography, the recording of low-frequency sounds created during muscle contraction. Although the standard for NMT monitoring is the measurement of the force of contraction (mechanomyography), phonomyography is easier to apply, does not require a special monitoring board, and could prove to be a reliable way of routinely determining neuromuscular block [55].

… He has half the deed done, who has made a beginning (Horace).

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Chapter 10

SUMMARY

SAMENVATTING

De continue toediening van spierrelaxantia is aangeraden tijdens bepaalde chirurgische ingrepen. Zelfs een eenmalige, grote cisatracurium bolus (aan het begin van de ingreep) is – ofschoon veilig in gebruik- geen alternatief voor het onderhouden van de spierverslapping: het aldus verkregen blok is immers van kortere duur dan de ingreep zelf en er waren veel ongewenste patiënt-bewegingen tijdens de operatie. Bij gezonde patiënten evenwel, zijn cisatracurium en rocuronium niet geschikt voor aanhoudende spierverslapping tijdens buik- en thoraxchirurgie waarbij verslapping nodig is tot het begin van het chirurgisch sluiten en waarbij de patiënt op het einde van de ingreep dient geëxtubeerd te worden. De enige objectieve en betrouwbare gids om een blok selectief te antagoniseren, is de neuromusculaire transmissie monitor. Bij continue infusen van cisatracurium en rocuronium tijdens hartchirurgie, vonden we bij cisatracurium een belangrijke halvering van de begindosis tijdens het kunsthart; voor rocuronium vonden we een globaal lagere dosering dan bij vorige studies, maar geen extra reductie tijdens het kunsthart. Tenslotte vonden we geen strikte voordelen van het gebruik van neuromusculaire transmissie monitoring bij patiënten die coronaire chirurgie zonder kunsthart ondergaan, maar gepland zijn om op de operatietafel geëxtubeerd te worden; nochtans bleek het een absolute noodzaak te zijn om veiligheidsredenen. Bovendien bleek selectieve farmakologische antagonistatie noodzakelijk, wegens de hoge incidentie aan postoperatieve restcurarisatie.

Wanneer cisatracurium wordt toegediend tijdens een levertransplantatie, is het essentieel deze spierverslapper te titreren naar effect om onder- of overdosering en postoperatieve restcurarisatie te vermijden. Dit betekent dat het gebruik van neuromusculaire transmissie monitoring, ook in deze gevallen, uitermate noodzakelijk is: tijdens levertransplantatie zijn farmakokinetiek en -dynamiek immers onvoorspelbaar. Tijdens levende donatie van de rechter leverkwab vonden we geen restcurarisatie na een monitor-gestuurd cisatracurium infuus. Bovendien was er een minimale morbiditeit na een dergelijk uitgebreide ingreep en hadden de donoren een uitstekende prognose.

Tot slot moet men in de tijd altijd de dosis aanpassen van een continu infuus spierverslappers (cisatracurium en rocuronium). Daarom is neuromusculaire transmissie monitoring onmisbaar. Ondanks deze monitoring techniek vonden we toch een hoge incidentie aan postoperatieve residuele curarisatie bij gezonde patiënten en bij deze die lever- en hart-

chirurgie ondergaan. Daarom moet neuromusculaire transmissie monitoring gezien worden als een hulpmiddel om een neuromusculair blok selectief te antagoneren. Routinematig antagoneren is –zeker in de bestudeerde populaties- niet aan te raden en er moet daarom gewacht worden op de komst van veilige en selectieve antagonisten van het neuromusculaire blok.

SUMMARY

We advocate the continuous administration of neuromuscular blocking drugs (NMBDs) during certain types of surgery. Even a large bolus dose of cisatracurium is, although safely used, not an alternative for producing continuous muscle relaxation, as its neuromuscular blockade does not cover the intraoperative period and there is a high incidence of movement. However, in healthy patients, both cisatracurium and rocuronium are unsuitable for continuous relaxation in abdominal/thoracic surgery where paralysis is essential until the closing of the abdomen/thorax begins and the patient has to be extubated at the end of surgery – unless selective reversal is attempted. The only objective and reliable guide to facilitating the decision for selective antagonisation is the neuromuscular transmission monitor. When looking at continuous infusions of cisatracurium and rocuronium during cardiac surgery, we found that a considerable reduction (to half of the initial infusion rate) was appropriate for cisatracurium during cardiopulmonary bypass (CPB). For rocuronium, a lower infusion rate was used in our study than in previous reports, but a further reduction during CPB was not found necessary. Finally, although we found no benefits of using NMT monitoring in off-pump coronary artery bypass surgery where it was planned to extubate the patient in the operating room, it appeared to be an absolute necessity to use NMT monitoring for reasons of safety when practising this extubation strategy. Moreover, due to the high incidence of residual curarisation, selective pharmacological reversal was mandatory if extubation on the table was to be performed in these procedures.

When administering cisatracurium during liver transplantation, it is essential to titrate this drug against effect to avoid under- or overdosing and postoperative residual curarisation (PORC), so neuromuscular transmission (NMT) monitoring is of extreme importance in this setting also. Multiple conditions, however, make pharmacokinetics and pharmacodynamics unpredictable during liver transplantation. During right-lobe living liver-donor surgery, we found no PORC following a NMT-monitored infusion of cistatracurium. Moreover, we demonstrated that there was minimal morbidity in such an extended surgical procedure and that donors had an excellent outcome.

To conclude, when administering continuous infusions of the newer neuromuscular blocking drugs, cisatracurium and rocuronium, one should always optimise the dose requirements over time; therefore, NMT monitoring is of extreme importance. Even with NMT monitoring, a

high incidence of PORC is found in healthy patients, and in those undergoing liver and cardiac surgery. Therefore NMT monitoring should help the clinician to antagonise selectively the neuromuscular block at the end of surgery. One should probably avoid routine antagonisation, certainly in these subpopulations of patients, until a selective and safe reversal agent is available.

RESUME

L'administration continue de drogues paralysantes pour certains types de chirurgie devrait être encouragée. Même si une dose élevée de cisatracurium administrée en bolus est parfaitement acceptable et sûre, elle ne représente pas une alternative à une infusion continue pour assurer une relaxation musculaire optimale et constante, si la paralysie musculaire qu'elle entraîne ne couvre pas la période peropératoire et qu'une incidence élevée de mouvements survient. Il faut savoir cependant que chez les sujets sains, le cisatracurium ainsi que le rocuronium par ailleurs ne sont pas recommandés pour assurer une relaxation constante en chirurgie thoracique/abdominale lorsqu'une paralysie musculaire complète est exigée jusqu'à la fermeture totale de l'abdomen ou du thorax et que le patient doit être détubé en fin d'intervention chirurgicale, à moins qu'une décurarisation sélective ne soit tentée. Pour prendre la décision d'antagoniser sélectivement, le seul moyen objectif et fiable est le monitoring de la fonction neuromusculaire. Lors de l'administration d'une infusion continue de cisatracurium ou de rocuronium en chirurgie cardiaque, nous avons constaté qu'une réduction significative allant jusqu'à la moitié de la vitesse d'infusion initiale était de mise durant la circulation extracorporelle et ceci pour le cisatracurium. Pour le rocuronium, dans notre étude, une vitesse d'infusion plus lente que celles décrites dans la littérature a été utilisée, sans qu'il ne soit nécessaire de la réduire plus durant la circulation extracorporelle. Finalement, bien que nous n'ayons vu aucun avantage à utiliser le monitoring de la transmission neuromusculaire dans la chirugie coronaire à coeur battant, où il était prévu de détuber le patient en salle d'opération, il est cependant indispensable et primordial d'utiliser ce monitoring pour des raisons de sécurité lorsque l'on désire pratiquer cette stratégie pour la détubation du patient. De plus l'incidence élevée de curarisation résiduelle exige une antagonisation pharmacologique sélective si l'on décide de détuber le patient sur la table d'opération dans ce type d' interventions.

Lorsqu'on administre du cisatracurium durant une transplantation hépatique, il est essentiel de la titrer en fonction de ses effects afin d'éviter tout sous- ou surdosage et de courir le risque d'une curarisation résiduelle postopératoire. Cela signifie que le monitoring de la fonction neuromusculaire est d'une extrême importance, également dans ce type de chirurgie. De nombreux paramètres rendent cependant la pharmacocinétique et la pharmacodynamique imprévisibles durant les transplantations hépatiques. Durant la chirurgie de prélèvement du lobe droit du foie sur donneur vivant nous n'avons constaté aucune curarisation résiduelle postopératoire après une infusion continue de cisatracurium avec monitorage de la fonction

neuromusculaire. De plus, nous avons pu démontrer que la morbidité dans ce type de chirurgie lourde était minime et que les donneurs avaient un excellent pronostic.

En conclusion, lors de l'administration d'une infusion continue d'une des nouvelles drogues paralysantes, cisatracurium et rocuronium, on devra toujours veiller à optimaliser les doses requises en fonction de la durée d'administration. De ce fait il est évident que le monitoring de la transmission neuromusculaire revêt une importance primordiale. Malgré ce monitoring, on retrouve une incidence élevée de curarisation postopératoire résiduelle chez les sujets en bonne santé ainsi que chez ceux soumis à une intervention hépatique ou cardiaque. Le monitoring de la transmission neuromusculaire sera donc une aide précieuse pour le clinicien pour antagoniser sélectivement le bloc neuromusculaire en fin d'intervention. Une antagonisation de routine devrait être évitée, en tout cas dans les subpopulations de patients que nous venons d'étudier, aussi longtemps qu'un agent antagonisant sélectif et fiable n'est disponible.