ARTO PUURA

# Speeding up the Course of the Neuromuscular Block

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ACADEMIC DISSERTATION

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for public discussion in the small auditorium of Building K,
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# ABBREVIATIONS

| | |
|---|---|
| ACh | Acetylcholine |
| ANOVA | Analysis of Variance |
| ASA | American Society of Anesthesiologists |
| CNS | Central nervous system |
| DBS | Dual burst stimulation |
| ECG | Electrocardiography |
| ED50 | Effective dose of a drug to achieve 50% effect |
| ED95 | Effective dose of a drug to achieve 95% effect |
| EDR | Edrophonium |
| EMG | Electromyography |
| $etCO_2$ | End-tidal carbondioxide |
| i.m. | intramuscular |
| i.v. | intravenous |
| LSD | Least significant difference |
| MMG | Mechanomyography |
| $N_2O$ | Nitrous oxide |
| NMB | Neuromuscular block |
| NMBA | Neuromuscular blocking agent |
| NST | Neostigmine |
| OR | Operation room |
| ORL | Otorhinolaryngological |
| PACU | Postanaesthesia care unit |
| p.os. | per os |
| PTC | Post-tetanic count |
| SD | Standard deviation |
| SEM | Standard error of the mean |
| $SaO_2$ | Oxygen saturation |
| T1 | The first response in the train-of-four sequence |
| TOF | Train-of-four |

# INTRODUCTION

In the past surgeons performed interventions on fully conscious patients. While anaesthesia brought surgery out of the Dark Ages, the use of neuromuscular blocking agents (NMBAs) enables the modern era of surgery. The objective of anaesthesia is to render the patient safely unconscious and pain-free. Many surgical procedures, notably abdominal and thoracic interventions also require a relaxed surgical field. Before NMBAs the necessary muscle relaxation was achieved by administering high concentrations of volatile anaesthetics or by adding large doses of other CNS depressants. Such techniques increased the risk of deep levels of anaesthesia, or even overdose.

The advent of NMBAs eliminated this danger by allowing practitioners to titrate the degree of muscle relaxation separately from the depth of anaesthesia. While a major advance, the application of muscle relaxants to anaesthesia was not an instant and total success. Contrary to expectations, a method to use small doses of tubocurarine allowing spontaneous respiration (Gray and Halton 1946) was associated with six-fold increase in anaesthesia-related deaths (Beecher and Todd 1954). The increased mortality was due to hypoxia caused by ventilatory depression. At the end of the 1950´s, and ever since, when artificial ventilation with nitrous oxide and oxygen was introduced into everyday anaesthesia practice, the use of peripherally-acting muscle relaxants has played an important part in reducing the toxicity of general anaesthetics.

Today, during balanced general anaesthesia specific drugs are used to provide hypnosis, analgesia, amnesia, and neuromuscular block (NMB). NMBAs are used as adjuncts to anaesthesia to provide immobility and skeletal muscle relaxation during surgery and to facilitate endotracheal intubation. The older NMBAs like tubocurarine and succinylcholine have their characteristic adverse effects. The introduction of short- and intermediate-acting non-depolarising NMBAs with minimal side-effects has enhanced the conduct of safer anaesthesia and promoted a prompt to the clinical pattern of the NMB, i.e. onset time, duration time and recovery time from the block.

The present challenge practitioners face is a value-based anaesthesia care, because the new intermediate-acting NMBAs are more expensive than the old long-acting ones or succinylcholine. Anaesthetists are presumed to continue to deliver high-quality patient care while consuming as few resources as possible.

Although the well-being and safety of the patient are far more important than the cost-consciousness of an anaesthetist, the choice of the wrong muscle relaxant or incorrect practice patterns may cause extra expenses. NMBAs should always be administered according to the level of NMB needed. Therefore, it is essential to monitor the NMB and to observe possible movements throughout anaesthesia. A practitioner should also know the main factors that influence neuromuscular transmission and muscle activity during anaesthesia. Some factors may have beneficial effects; others may cause harmful interactions, resulting in unnecessary prolongation of NMB. Therefore, it is of great clinical interest to evaluate the factors that influence neuromuscular transmission and monitoring of NMB in order to minimise waiting times and costs due to anaesthesia.

# REVIEW OF THE LITERATURE

## 1. Neuromuscular anatomy and physiology

### 1.1. Neuromuscular transmission

Skeletal muscles are innervated by large myelinated motor nerves. A motor nerve divides into many non-myelinated filaments, each of which innervates one muscle fibre. The non-myelinated motor nerve terminal communicates with the muscle end plate across a narrow synaptic cleft, which divides the neuromuscular junction into the pre- and postsynaptic areas (Figure 1). The most important neurotransmitter in the neuromuscular junction is acetylcholine (ACh). A small amount of ACh is continuously released spontaneously from the nerve endings even in the absense of nerve impulses. The release of ACh vesicles into the junctional cleft is greatly increased by afferent nerve impulses. The released ACh diffuses across the synaptic cleft and interacts with nicotinic ACh receptors on the postjunctional membrane of the motor end plate. The receptors are located in high density at the crests and shoulders of the postjunctional membrane which is convoluted and exposes a large area to the junctional cleft.

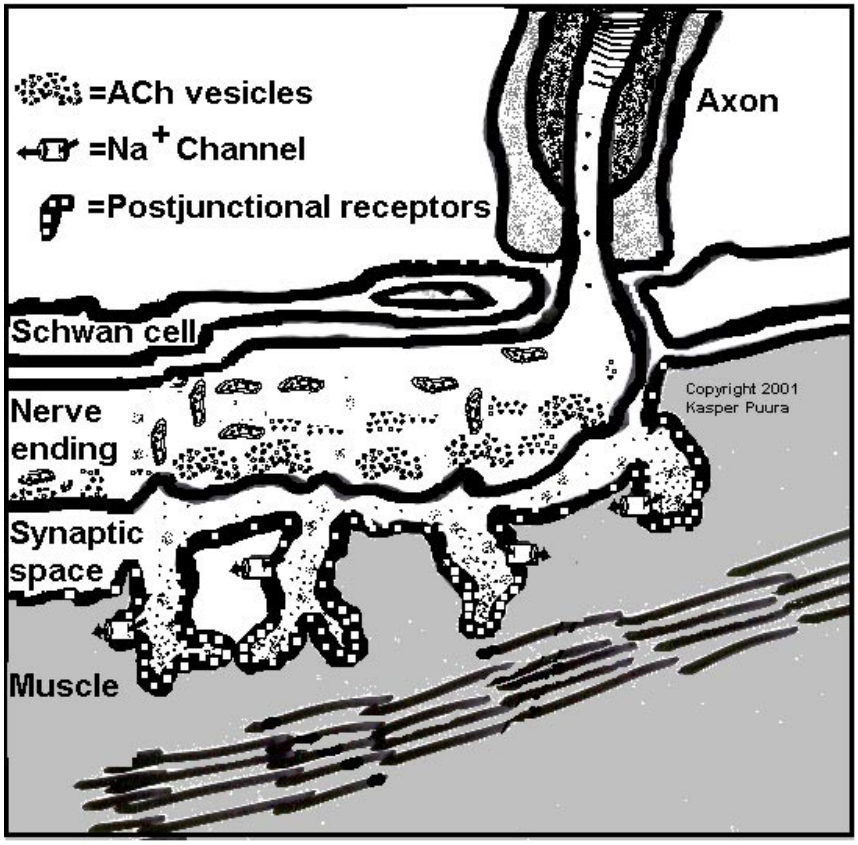


*Figure 1. Neuromuscular junction*

Acetylcholinesterase destroys the released ACh in less than 1 ms (Wessler 1992). The rapid enzyme activity allows each ACh molecule to react no more than once with an ACh receptor and prevents accumulation of ACh in the neuromuscular junction.The perijunctional zone is the area of the muscle between and around the receptive area, which is essential for the function of the neuromuscular junction. The perijunctional zone contains smaller density of Ach receptors, but a high density of sodium-channels. The admixture of these receptors enhances the capacity of the perijunctional zone to respond to the depolarisation and to transduce it into the wave of depolarisation that travels along the muscle fibre and initiates muscle contraction.

### 1.2. Motor nerve ending

The axon of the motor nerve contains all the ion channels, enzymes, other proteins, macromolecules, and membrane components needed by the nerve ending to synthesise, store, and release ACh and other trophic factors. These compounds are synthetised in the cell body and transmitted to the nerve endings by axonal transport. During a nerve action potential, sodium flows across the membrane. The resulting depolarisation voltage opens calcium channels, which allows the entry of calcium ions into the nerve causing the release of ACh. The calcium current persists until the membrane potential returns to normal. If calcium is not present, depolarisation of the nerve does not produce any release of the transmitter. During tetanic stimulation calcium enters the nerve with every stimulus, but it cannot be excreted as quickly as the nerve is stimulated. Thus, after tetanic stimulation the nerve ending contains more than the normal amount of calcium. Consequently, a stimulus applied to the nerve after tetanic stimulation causes the release of more than the normal amount of ACh. Clinically the phenomenon is called post-tetanic potentiation.

### 1.3. Postjunctional acetylcholine (ACh) receptors

Nicotinic ACh receptors are found throughout the body, but the highest quantity is found in the nervous system and in the muscles. The nicotinic ACh receptor is a ligand-gated protein complex, which possesses binding sites for ACh and the ion channel through which the ACh response occurs. Each ACh receptor is about 250,000 dalton of molecular weight and consists of five protein subunits, which are arranged to form a cylinder which spans the muscle cell membrane from side to side (Taylor et al. 1983, Andersen and Koppe 1992). Several different subtypes of nicotinic ACh receptors have been identified in the skeletal muscles, peripheral and central nervous system, and in the autonomic ganglia (Cooper et al. 1991).
Two different types of receptors are synthesised in the muscle cells: junctional and extrajunctional (Dreyer 1982, Bowman 1993). The junctional receptors have two similar subunits, which are known as $\alpha$, and one $\beta$, $\delta$ and $\varepsilon$ unit each (Figure 2). The extrajunctional receptor has a $\gamma$ subunit instead of an $\varepsilon$. The extrajunctional receptors, or immature receptors in neonates and infants, differ in their quantitative response to non-depolarising and

depolarising NMBAs, in their location in the muscle cell, and in the clinical circumstances under which the muscle expresses them. The extrajunctional receptors may be expressed anywhere in the muscle membrane despite the name "extrajunctional receptors".

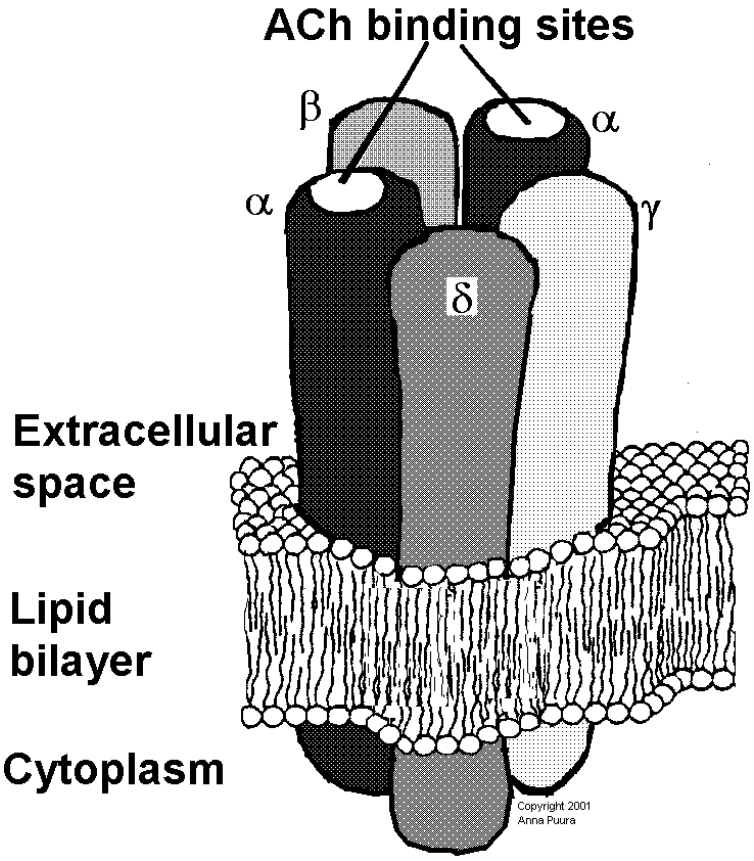


*Figure 2. Postjunctional acetylcholine receptor*

The synthesis of extra-junctional receptors is activated when the neural influence is diminished or abolished (Martyn et al. 2000, Bowman 1993). The extrajunctional receptor is a neonatal type of receptor, which the muscle cells synthetise before innervation and maturation of the neuromuscular junction. They are more sensitive than junctional receptors to agonists, such as ACh and succinylcholine and less sensitive to antagonists, like non-depolarising muscle relaxants (Martyn et al. 2000).

Receptor activation by an agonist requires that both recognition sites in the α-units are occupied simultaneously. This produces a conformational change of the protein and opens the ion channel allowing small cations to pass through the ion channel. $Na^+$ and $Ca^{++}$ ions move inwards, and $K^+$ outwards. The channel is selective for small cations (Unwin 1993). The small change of the transmembraneal resting potential generated by quantums of ACh released at the nerve end plate is called the miniature end plate potential. Increased ACh concentration causes an increase in the frequency of channel openings. A discharge of as many as 1-1.5 million ACh molecules takes place when the nerve terminal is activated by the nerve action potential. Several hundred thousand receptors are needed to be opened

simultaneously to produce an end plate potential large enough to trigger an action potential in the muscle fibre. When the end plate becomes depolarised beyond the threshold, an action potential is propagated throughout the muscle fibre. This in turn activates an excitation-contraction coupling mechanism and leads to muscle contraction (Bowman 1993).

The two binding sites for ACh in the α-units are supposed to be nonidentical and to differ functionally since they are in different environments; one is bordered by a β-unit and an ε-unit, the other by a β-unit and a δ-unit (Sine and Taylor 1981). Both agonists and antagonists are attracted to the binding site, which is located near cysteine residues (unique to the α-chain) at amino acid positions 192-193 of the α-subunit (Pedersen and Cohen 1990). The dose-response curve for ACh receptors has a sigmoidal relationship between the end plate response and agonist concentration, which may be a consequence of co-operativity of the binding sites; the binding of one agonist molecule to the receptor increases the affinity of subsequent molecules to the other recognition site (Dreyer 1982, Bowman 1993).

Invidual ion channels, i.e. ACh receptors, are capable of a wide variety of conformations. The channels open and close, they open for a longer or a shorter time than normal, open or close more slowly than usual, they chatter, or pass fewer or more ions per opening than they usually do. Also, the function of the ACh receptors is influenced among others by drugs, changes in the fluidity of the membrane, temperature, and the electrolyte balance in the milieu (Karlin et al. 1987).

### 1.4. Prejunctional ACh receptors

Specific information on the molecular organisation of the neuronal nicotinic ACh receptors on the motoneuron terminal is lacking. Some of the composition of the subunit is similar to that of the postjunctional receptors, but at least ten different gene products (α2-α8 and β2-β4) are thought to contribute to how nicotinic receptors are expressed in the neurons (Galzi and Changeux 1995, Coggan et al. 1997). The neuronal ACh receptors consist only of α-subunits and β-subunits which are different from the corresponding prejunctional subunits (Wessler 1992). These receptors resemble the nicotinic receptors of the autonomic ganglia (Bowman 1980). The prejunctional ACh receptors are assumed to be of both the muscarinic and the nicotinic subtype. They are proposed to act mostly as nicotinic receptors in the positive feedback system (Bowman 1993). However, the linking mechanism between presynaptic receptor activation and the ACh mobilisation is unclear (Bowman 1980, Wessler 1992). Non-depolarising NMBAs sharply decrease the release of transmitter triggered by subsequent nerve pulses in a train. Train-of-four (TOF) fade and tetanic fade are suspected to be a consequence of a prejunctional block (Bowman et al. 1976). The fade effect is thought to be due to inhibition of the process that replenishes releaseable ACh (Bowman et al. 1990).

### 1.5. Somatomotoric reflexes

Most movement responses during general anaesthesia are involuntary reflexes of the laryngeal muscles and the diaphragm, because they are more resistant to NMBAs than the

other peripheral skeletal muscles. The basic reflex arc consists of a sense organ, an afferent neuron, one or more synapses in a central integrating station, an afferent neuron and an effector. Noxious stimuli of surgery are transmitted by A δ and C nerve fibres via the dorsal roots of the spinal nerves or via cranial nerves to the neuraxis in the spinal cord or in the brain. In the spinal cord some impulses pass to the anterior and anterolateral horns to provoke segmental reflex responses via the efferent fibres of the ventral roots. Other impulses are transmitted to higher centres via the spinothalamic and spinoreticular tracts, where they produce suprasegmental and cortical responses. Segmental reflex responses associated with surgery increase skeletal muscle tone and spasm, whereas suprasegmental reflex responses result in increased sympathetic tone and hypothalamic stimulation. The withdrawal reflex is a typical polysynaptic reflex that occurs in response to noxious stimulation. Since the connection between the afferent and efferent neurons is in the central nervous system (CNS), activity of the reflex arc is modified by the multiple inputs converging on the efferent neurons.
The resistance of a skeletal muscle to stretch is referred as to its tone or tonus. The tonus depends on the efferent stimulation to the muscle fibres. If the afferent motor nerve input to the muscle is discontinued like after cutting the nerve or after administration of NMBAs, the muscle becomes flaccid. Descending tracts from a number of areas in the brain regulate the motor neurons of the efferent system to a large degree. Via these descending pathways factors like anxiety and pain increase the tonus of the skeletal muscles. The terms central excitatory state and central inhibitory state have been used to describe prolonged states in which excitatory influences override inhibitory influences and vice versa. Adequate general anaesthesia is a certain form of a central inhibitory state, whereas an NMBA inhibits the reflex arc by blocking the chemical transmission between the afferent nerve and the effector muscle.

## 2. Neuromuscular blocking agents

### 2.1. Classification of NMBAs

The NMBAs are classified as depolarising and non-depolarising agents according to their action at the postjunctional ACh receptors. The only depolarising NMBA in clinical use, succinylcholine, consists of two conjugated ACh molecules. Non-depolarising NMBAs are quaternary ammonium compounds with high water solubility. They are classified into two major classes: steroidals and bentsylisoquinolones. Pancuronium, pipecuronium, rapacuronium, rocuronium and vecuronium have a steroidal chemical structure whereas atracurium, cisatracurium, doxacurium, tubocurarine, metocurine and mivacurium have a benzylisoquinolone structure. The NMBAs are classified into four classes depending on the duration of effect: ultra short acting (succinylcholine), short acting (rapacuronium, mivacurium), intermediate acting (atracurium, cisatracurium, rocuronium, vecuronium) and long acting (alcuronium, doxacurium, tubocurarine, metocurine, pancuronium, pipecuronium).

## 2.2. The action of depolarising NMBAs

The ion channel opens and depolarisation occurs when two succinylcholine molecules or one succinylcholine and one ACh molecule together occupy the two α-subunits. At first, succinylcholine binds to the ACh receptor, generates a nerve action potential and triggers axon reflexes, which leads to the asynchronous repetitive firing of the muscle fibres that can be seen as fasciculations (Staendert and Riker 1967; Bowman and Webb 1976). Only 20 % of the ACh receptors need to be occupied by succinylcholine molecules to establish a 95% NMB (Levy 1967).
Because the metabolism of succinylcholine is slow compared to that of ACh, the depolarisation persists preventing the development of further action potentials resulting in NMB (Gissen and Nastuk 1970). Since the relaxant is not removed from the cleft, the end plate continues to be depolarised. The sodium channels immediately adjacent to the end plate are influenced by the depolarisation of the end plate, and their voltage-dependent gates stay open and consequently their inactivation gates stay closed (Marban et al. 1998). The perijunctional muscle membrane does not depolarise, because sodium cannot flow through the channels. Thus, the perijunctional muscle membrane with it´s sodium channels is a buffer that shields the rest of the muscle from events at the end plate.
In case of prolonged exposure to agonists some receptors may desensitise and the receptors cannot be opened. If the desensitisation occurs after prolonged administration of Succinylcholine, the NMB is called "phase II block", which is characterised by tetanic fade, post-tetanic potentiation and train-of-four fade. After initial depolarisation the membrane potential gradually recovers toward normal, even though the junction is still exposed to the drug, and the ion flux through the channel remains high as long as the depolarising drug is present (Durant and Katz 1982).

## 2.3. The action of non-depolarising NMBAs

The non-depolarising NMBAs do not induce the agonistic conformational change in the ACh receptor as ACh does, although these charged quaternary ammonium compounds mimic the quaternary nitrogen atom of the transmitter ACh. The blocking drug does not remain in contact with the receptor but acts dynamically with the receptor repeatedly, associating with it and dissociating from it (Bowman 1993). Both recognition sites must be occupied by ACh simultaneously for channel opening to occur. Therefore, the binding of a non-depolarising NMBA to either of the α-subunits is sufficient to block the receptor. When 50% NMB is present, 87% of the postsynaptic ACh receptors are occupied. To produce 95% NMB 92% of the receptors should be occupied (Son et al. 1981, Amaki et al. 1985). The amount of NMB produced depends on the extracellular fluid concentration of the relaxant, which depends on the concentration of the free drug in the plasma. Experiments with an isolated arm technique have led to the biophase binding hypothesis (Feldman and Tyrell 1970). The concentrations of the NMBAs in the neuromuscular junction are expected to be equal to concentrations in the plasma only at steady-state conditions. The NMB induced by tubocurarine persists for up to one hour in an isolated arm despite the release of the tourniquet and rapid fall in the plasma concentration of the drug (Feldman and Tyrell

1970). The biophase binding sites serve as a reservoir, causing a continuation of the NMB after the drug is liberated from the sites.
Presynaptic NMB may be one reason for tetanic fade and TOF fade. ACh has been believed to act on the prejunctional receptors to increase transmitter release during high-frequency stimulation (Bowman 1980, Wessler 1992). However, the reports are contradictory. The negative and positive feedback mechanisms in the neuromuscular junction are complex and the contradictory results may be a consequence of different stimulation frequencies (Tian et al. 1994) and different NMBAs (Marshall et al. 1995). TOF fade is more pronounced during spontaneous recovery than during onset of NMB with all non-depolarising NMBAs (Gyermek and Berman 1992). During recovery, tubocurarine produces more fade than atracurium and vecuronium (Gyermek and Berman 1992). The nicotinic receptors mediating the increase of ACh release by tubocurarine may be similar to the ganglionic subtype and are therefore not influenced by vecuronium (Marshall et al. 1995).

### 2.4. Noncompetitive actions of muscle relaxants

Several drugs can interfere with the receptors directly or via their lipid environment to change transmission. Thus drugs may impair transmission without having direct effects via the ACh binding site. Drugs that interfere with the receptor site may cause the channels to be sluggish and open more slowly or to stay open for a longer time (Miller et al. 1991, Raines 1996). These effects have corresponding changes in the flow of the ions and distortions of the end plate potentials. Several anaesthetics may change the opening and closing times of the channels. These interactions do not fit the classical model of transmission and the impaired neuromuscular function cannot be antagonised by cholinesterase inhibitors. Such drug interactions can be classified into two clinically important reactions: the desensitisation block of the receptor molecule and the channel block of the ion channel.

#### 2.4.1. Desensitisation block

The ACh receptor may occur in a number of conformational states (Raines 1996). In addition to the resting and open states the receptor macromolecule has several different conformations. Because these states of the receptors are not sensitive to the channel-opening action of the agonists, the states are termed desensitised. The receptors are in a constant state of transition between resting and desensitisation whether or not agonists are present. The presence of desensitised receptors means that fewer receptor-channels than usual are available to carry transmembrane current. Therefore, the desensitised receptors decrease the efficacy of neuromuscular transmission. When the transmission is impaired the system is more susceptible to block by competitive antagonists such as tubocurarine. Many drugs used by anaesthetists promote the shift of receptors from a normal state to a desensitised state. These drugs include for example volatile anaesthetics, barbiturates, succinylcholine, neostigmine, local anaesthetics including cocaine, alcohols, and some antimicrobics (Gage and Hamill 1981, Miller et al. 1991, Raines 1996).

### 2.4.2. Channel block

Some drugs block the flow of ions in the ACh receptor. The blocking effect is of two major types: closed channel block and open channel block. Certain drugs may obstruct the mouth of a closed ion channel and by their presence prevent the ions of passing through the channel. The open channel block results when a molecule of a drug enters the channel when it is open. Both closed and open channel block impair the ion flow through the channel, resulting in prevention of the depolarisation of the end plate and a weaker or blocked neuromuscular transmission. Different NMBAs have differences in the tendency to bind to the ACh recognition site of the receptor or to occupy the channel. For example, pancuronium preferentially binds to the recognition site, whereas the preferential blocking site of tubocurarine depends on the dose.

## 2.5. Clinical pharmacology of the NMBAs studied

### 2.5.1. Succinylcholine

Succinylcholine consists simply of two molecules of ACh linked through an acetate methyl group. When succinylcholine acts on postjunctional ACh receptors the ion channel opens and the depolarisation is followed by asynchronous repetitive firing of the muscle fibres which can be seen as fasciculations of the skeletal muscles. The extremely brief duration of action of succinylcholine is primarily due to its rapid hydrolysis by the pseudocholinesterase of plasma and the liver. NMB induced by succinylcholine can be prolonged by decreased concentration of normal the enzyme or by the presence of an atypical form of the enzyme.
The intense fasciculations are associated with a rise in intraocular pressure (Craythorne et al. 1960, Cook 1981), intragastric pressure (Andersen 1962, Muravchick et al. 1981) and intracranial pressure (Halldin and Wahlin 1959, Minton et al. 1986). Succinylcholine may induce hyperkalemia, especially in conditions such as burns, degenerative states of the neuromuscular system, trauma and denervation. Succinylcholine may also induce myotonia, malignant hyperthermia, anaphylactic or anaphylactoid reactions and electrocardiography (ECG) changes. Postoperatively the powerful fasciculations induced by succinylcholine may cause myalgia, increased levels of creatinekinase, myoglobinaemia, and myoglobinuria. The most widely used method to prevent the succinylcholine-induced side-effects is precurarisation, in which a small subparalysing dose of a non-depolarising NMBA is administered a few minutes before Succinylcholine. There are differences between the non-depolarising NMBAs in the ability to prevent succinylcholine-induced fasciculations. The stronger TOF fade a small dose of a non-depolarising relaxant exhibits, the greater is the ability of the relaxant to prevent succinycholine-induced fasciculations (Erkola 1988). This supports the theory that the block of the prejunctional ACh receptors is the underlying mechanism of the action of precurarisation.

### 2.5.2. Vecuronium

Vecuronium is an intermediate-acting steroidal NMBA. Vecuronium is a monoquaternary metabolite of pancuronium, but vecuronium does not have vagolytic or ganglionic blocking properties (Morris et al. 1983, Marshall et al. 1983). The onset time of doses twice the ED95 is 2.2-3.3 min. An onset time of 1-2 min can be achieved by administering vecuronium at higher doses, but this will lead to prolongation of the action (Ginsberg et al. 1989). During nitrous oxide-opioid anaesthesia the infusion requirements of vecuronium to maintain 90-95% NMB are 0.92-1.7 μg/kg/min (Swen et al. 1985, Ali et al. 1988). Although the liver is the principal organ of elimination for vecuronium, the drug also undergoes up to 25% renal excretion (Bencini et al. 1986).

### 2.5.3. Atracurium

Atracurium is a benzylisoquinolone intermediate-acting NMBA. Atracurium is broken down by the non-enzymatic Hoffman elimination, which is a nonspecific ester hydrolysis that is temperature and pH dependent. All ten isomers of atracurium have different pharmacological properties. The onset time and duration of action are similar to those of vecuronium. Doses exceeding 0.5 mg/kg of atracurium speed up onset time, but high doses of atracurium are associated with histamine release and decrease in arterial pressure (Basta et al. 1982). The infusion requirements of atracurium are 5.7-8.5 μg/kg/min to maintain 90% NMB when administered without volatile anaesthetics (O´Hara et al. 1991).

### 2.5.4. Rocuronium

Rocuronium is a steroidal NMBA with intermediate duration of action. The ED95 of rocuronium is 0.3 mg/kg during nitrous oxide opioid anaesthesia (Wierda et al. 1990). Twice the ED95 doses of rocuronium induces complete NMB in approximately 1.5 min (Foldes et al. 1991), but at doses of 0.9-1.2 mg/kg onset times are close to that of succinylcholine (Magorian et al. 1993). The clinical duration of twice the ED95 is comparable to vecuronium and atracurium (Magorian et al. 1993). The infusion requirements of rocuronium for a 95% NMB during nitrous-oxide opioid anaesthesia are approximately 10 μg/kg/min (Olkkola et al. 1994). Rocuronium is eliminated primarily by the liver, with a small 10% fraction eliminated in the urine (Khuenl-Brady et al. 1990).

### 2.5.5. Mivacurium

Mivacurium is a short-acting bisquaternary relaxant that consists of three stereoisomers, which have different pharmacodynamic and pharmacokinetic properties. 95% of mivacurium consists of the cis-trans and the trans-trans isomers, which are rapidly hydrolysed with an elimination half-life of approximately two minutes in the plasma. The cis-cis isomer is 10-15 times less potent than the other isomers, but contributes largely to the long elimination half-life of the mixture (Head-Rapson et al. 1995). The onset time of

2xED95 of mivacurium is 2.5 min during nitrous-oxide opioid anaesthesia and the infusion requirements are 8 µg/kg/min to maintain 95% NMB (Ali et al. 1988). Mivacurium is almost completely metabolised in the plasma through hydrolysis with pseudocholinesterase. In patients heterozygous for the atypical pseudocholinesterase enzyme, mivacurium´s duration of action is lengthened by 30-100 percent, whereas in patients homozygous for the atypical enzyme an ordinary intubation dose of 0.2 mg/kg will last for 3-4 hours (Østergaard et al. 1995).
The relatively short duration of action has raised the question of whether a mivacurium-induced block must be routinely antagonised pharmacologically. Mivacurium-induced NMB can be antagonised from T1 25 level up to TOF ratio 0.7 in 6 minutes, whereas after an equivalent block spontaneous recovery takes 15 minutes (Baurain et al. 1994).

### 2.5.6. Tubocurarine

Tubocurarine is a monoquaternary alkaloid isolated from the South American vine *Chondrodendron tomentosum.* Clinical duration of NMB is over one hour after an average intubation dose of 0.5 mg/kg of tubocurarine. High doses (more than 0.3 mg/kg) of tubocurarine may increase plasma histamine levels as much as 10-fold causing a transient decrease in arterial blood pressure or bronchospasm (Moss et al. 1981). Tubocurarine is not actively metabolised and the major elimination pathway is through the kidneys.

*Table 1. Neuromuscular effects of the NMBAs studied and reviewed in the text.*

| NMBA | Onset time of 2 x ED95 (min) | Duration of 2 x ED95 (min) | Recovery index (min) T1 25-75% | ED95 mg/kg |
|---|---|---|---|---|
| Succinylcholine | 1.0 | 10 | 1-3 | 0.3-0.6 |
| Vecuronium | 2.2-3.3 | 31-41 | 9-20 | 0.05 |
| Atracurium | 1.7-4.0 | 33-45 | 11-14 | 0.2-0.28 |
| Rocuronium | 1.0-1.8 | 30-40 | 10-17 | 0.3 |
| Mivacurium | 2.5-3.3 | 15-20 | 7-9 | 0.06-0.08 |
| Tubocurarine | 3.0-6.0* | 60-90* | 30-50* | 0.5* |

Duration of action = recovery of T1 to 25%.
* = The effect of the usual intubation dose of tubocurarine = 1 x ED95

## 3. Reversal of NMB

Spontaneous recovery from NMB occurs as the drug leaves the neuromuscular junction by redistribution, metabolism, and buffered diffusion. Recovery is accelerated by the anticholinesterase agents neostigmine and edrophonium. Normally, the enzyme acetylcholinesterase destroys ACh and removes it from the competition at the receptor, so that a non-depolarising muscle relaxant has a better chance of inhibiting transmission. If an inhibitor such as neostigmine is added the cholinesterase cannot destroy ACh. The concentration of the agonist in the cleft remains high and this high concentration shifts the

competition between ACh and the muscle relaxant in favor of the former, thus improving the chances of ACh molecules to bind to both receptors; this is the theory ofhow cholinesterase inhibitors overcome the non-depolarising NMB (Martyn et al. 2000).
The hydrolysis of ACh to acetic acid and choline by acetylcholinesterase takes place in milliseconds. Choline is split off from the enzyme-substrate complex. The acetylated enzyme reacts rapidly with water to produce acetic acid and regenerated enzyme (Koelle 1975). Currently the only clinically employed antagonists of non-depolarising NMBAs are neostigmine and edrophonium. Neostigmine is a substrate for acetylcholinesterase and reacts in much the same way as does ACh. However, neostigmine forms a carbamylated rather than an acetylated enzyme as an intermediate product, which reacts with water very slowly with a half-life of regeneration to the normal enzyme of more than 30 minutes (Kitz 1964). Edrophonium combines electrostatically at the anionic site and by hydrogen bonding at the esteratic site of acetylcholinesterase to form an enzyme-inhibitor complex. This reaction is rapidly reversible, with a half-life for dissociation of less than 30 seconds (Wilson 1955). All muscarinic actions of ACh are antagonised by atropine.
Reversal occurs at a rate that depends on the choice of the antagonist and the dose of the drug. The recovery time also correlates inversely with the depth of the block and on the rate of spontaneous recovery. The deeper the block, the longer is the time required for restoration of adequate neuromuscular function. The antagonism should be postponed until some evoked responses are visible and after that the choice and dose of of reversal drugs should be based on the intensity of neuromuscular block (Donati et al. 1989, Beemer et al. 1995) .
A TOF ratio of > 0.70 following nerve stimulation was for a long time regarded as a reliable indicator of acceptable clinical recovery, because it had been shown that clinically detectable muscle weakness was associated with a smaller TOF ratio (Ali et al. 1971). The "golden standard" of TOF ratio over 0.7 is merely an old standard today. There is mounting evidence that acceptable recovery from NMB is no longer a TOF ratio level of 0.7, but in fact greater safety may be achieved at 0.9. In partially paralysed patients ventilatory regulation is impaired during hypoxia (Eriksson et al. 1992). The authors speculated that NMBAs might interfere with signal transmission in carotid bodies.
The clinical importance of residual NMB has not been quantified until recently (Berg et al. 1997), although a high prevalence of residual NMB has been well recognised for 20 years (Viby-Mogensen et al. 1979). The ability of a patient to maintain sustained adequate ventilation and to protect the airway is of main concern when looking at the adequacy of recovery from NMB. The muscles of airway protection are very sensitive to residual NMB (Pavlin et al. 1989), and this predisposes patients to pulmonary aspiration. A residual block following pancuronium was identified as a major risk factor for the development of pulmonary complications in the week following surgery, in particular when combined with prolonged abdominal surgery and old age (Berg et al. 1997). The use of pancuronium and a persistent TOF ratio of 0.7 in the postanaesthesia care unit (PACU) was shown to be associated with a threefold greater occurrence of postoperative pulmonary complications compared to vecuronium or atracurium (Berg et al. 1997). However, neither information about residual NMB nor the shorter duration of action of modern NMBAs have led to the disappearance of residual paralysis. Residual NMB is still common in the PACU (Bevan et al. 1996). Residual paralysis may persist for up to one hour, even after mivacurium-induced

NMB, and such residual muscle weakness is likely to persist for much longer even after intermediate-acting muscle relaxants (Brull 1997).
The effect of muscle relaxants is not identical in different muscle groups. The pharyngeal muscles, which are important for the maintenance of a patent airway, are more sensitive than peripheral muscles to the effects of small doses of pancuronium (Isono et al. 1991 ) or intubating doses of mivacurium (d´Honneur et al. 1996). Upper airway function is impaired even after small doses of vecuronium, as indicated by the greater sensitivity of geniohyoid muscles than the diaphragm to vecuronium (Isono et al. 1992). At TOF ratio of 0.90 or less partial paralysis by vecuronium may cause dysfunction of the pharyngeal muscles and an increased risk for aspiration (Eriksson et al. 1997). A common feature in the above-mentioned studies was that peripheral muscles are less sensitive to the effects of NMBAs than muscles of the pharynx. This means that any muscle weakness detected in peripheral muscles is almost certainly correlated with problems in maintaining a patent airway and difficulties in swallowing. Extubation of the trachea should therefore not be attempted before complete recovery of NMB.

## 4. Monitoring of NMB

Muscle power can be evaluated through tests of voluntary muscle strength in conscious patients, but during anaesthesia and recovery this is not possible. All clinical tests to assess muscle power during anaesthesia are influenced by factors other than NMB. If precise information regarding NMB is needed, the response of a muscle to nerve stimulation should be assessed. The monitoring of NMB by neurostimulation was described to judge the reasons for apnea already in 1958 (Christie and Churchill-Davidson 1958).
When a motor nerve is stimulated with an intense electrical impulse, all muscle fibres supplied by the nerve will react, and the maximum response will be triggered. During NMB the response of the muscle decreases parallel with the number of fibres blocked. The reduction in response reflects the degree of the NMB. The electrical stimulus should be 20 percent above that necessary for a maximal response to ensure truly maximal stimulation throughout the period of monitoring. Therefore, the intensity of the stimulus is called supramaximal. Submaximal stimulation is less painful and it may be used postoperatively when the patients are awake, although the accuracy of the monitoring is unacceptable at low current (Helbo-Hansen et al. 1992). The optimal stimulus to prevent repetitive firing is monophasic, rectangular and of 0.2-0.3 ms duration. Repetitive firing, i.e. burst of action potentials in the nerve, increases the response of the muscle to the stimulation. The specific pattern of the multiple types of peripheral electrical neurostimulation depends on the clinical purpose.

### 4.1. Different patterns of nerve stimulation

During *single-twitch* stimulation supramaximal electrical stimuli are applied to a peripheral motor nerve once every second or once every ten seconds. The evoked response to single twitch stimulation depends on the frequency of the stimuli. At higher than 0.15 Hz the response to stimulation decreases and settles at a lower level (Ali and Savarese 1980).

In *train-of-four* (TOF) stimulation four supramaximal stimuli are given at a frequency of 2 Hz (Ali et al. 1970). Each set of the four stimuli is repeated at intervals of 10 to 20 seconds. The stimulated muscle contracts after every stimulus and the diminution of the responses is the basis of the TOF monitoring. TOF ratio is the amplitude of the fourth response divided by the first response. All four responses are identical when the initial control response is obtained before administration of any NMBAs. During a partial non-depolarising NMB the ratio decreases (fade) and indicates the degree of the block.

*Tetanic stimulation* consists of 30-100 Hz electrical stimuli. The most common pattern of tetanic stimulation has been 50 Hz stimulation given for 5 seconds. During normal neuromuscular transmission the muscle response to 50 Hz stimulation for 5 seconds is sustained. Fade in response to tetanic stimulation is normally considered as a sign of presynaptic action, which is traditionally explained to depend on the rapidly released ACh stores. As the stores become depleted, the rate of ACh-release decreases. When the number of free ACh receptors is reduced by non-depolarising neuromuscular agents, the decrease in release of ACh during tetanic stimulation produces "fade" (Paton et al. 1967). During neuromuscular recovery tetanic stimulation may produce antagonism of the NMB in the stimulated muscle and thereafter the tested site is no longer representative of other muscle groups (Brull and Silverman 1992). Tetanic stimulation is painful and it has very little place in clinical use, except in connection with the technique of post-tetanic count (PTC).

During partial non-depolarising block tetanic nerve stimulation is followed by a *post-tetanic* increase in twitch tension. This phenomenon is called post-tetanic facilitation of transmission. The main application of the PTC is in evaluating the degree of profound NMB when there is no reaction to single-twitch or TOF stimulation. During PTC-monitoring a 50 Hz tetanic stimulus is applied to a peripheral motor nerve for five seconds and the response to single-twitch stimuli given at 1 Hz are observed starting three seconds after the tetanic stimulation. During very intense NMB there is no response to either tetanic or post-tetanic stimulation. As the very intense NMB dissipates, more and more responses to post-tetanic stimulation appear. For a given NMBA the time until return of the first response to TOF stimulation is related to the PTC (Viby-Mogensen 1984). PTC may also be used when absolute immobility is essential for surgery. To ensure elimination of any bucking NMB of the peripheral muscles must be so intense that PTC is zero (Fernando et al. 1987). On the other hand, the necessary level of block of the adductor pollicis muscle to ensure paralysis of the diaphragm depends on the type of anaesthesia or the level of sedation (Fernando et al. 1987, Werba et al. 1993). Tetanic stimulation should not be given more often than every 6 minutes, because the muscles that are stimulated undergo intermittently antagonism of NMB (Howardy-Hansen and Viby-Mogensen 1984).

*Dual-burst stimulation* (DBS) consists of two short bursts of 50 Hz stimulation separated by 750 ms. The number of 0.2 second square wave impulses in each burst may vary. Initial studies indicated that DBS with three impulses in each of the two bursts (DBS3.3) is suitable for clinical use (Drenck et al. 1989). DBS was developed to allow tactile evaluation of small amounts of residual NMB, because it it easier to feel fade in the response during residual block with DBS than with TOF stimulation (Viby-Mogensen et al. 1985).

Viby-Mogensen et al. (1996) have defined the good clinical research practice methods in pharmacodynamic studies of NMBAs. 0.1 Hz single-twitch and the first response (T1) of the TOF sequence stimulation patterns give sufficient information during onset of NMB. TOF stimulation pattern is adequate during surgical block (T1 = 1-25% of the initial

control) while PTC stimulus mode should be used during period of no-twitch response (Viby-Mogensen et al. 1996). Adequate reversal of NMB should be ensured with DBS or TOF ratio of 0.80 (Viby-Mogensen et al. 1996).

*Table 2. Patterns of neurostimulation in clinical use.*

| | Primary use | Disadvantages |
|---|---|---|
| Single twitch | Induction | No response during intense block |
| TOF | Surgical block<br>Reversal | No response during intense block<br>Antagonism of NMB in the stimulated muscles in too frequent use |
| PTC | Intense block | Antagonism of NMB in the stimulated muscles, long intervals |
| Tetanic stimulation | Reversal | Painful, antagonism of NMB in the stimulated muscles |
| DBS | Reversal | Painful,<br>detects only TOF ratio below 70% |

TOF = Train-of-four, PTC = post-tetanic count, DBS = dual burst stimulation

### 4.2. Recording of evoked responses of the muscles

Stimulating the ulnar nerve and visually observing contraction of the thumb is the most commonly advocated method to monitor neuromuscular transmission clinically. There are three methods available to record the evoked responses: mechanical recording, mechanomyography (MMG), electrical recording, electromyography (EMG) and recording of acceleration of the mechanical response of the muscle.
MMG correlates well with EMG. During MMG isometric contraction is essential. The monitoring is not accurate before a stabilisation period of 10 minutes. Rigid fixation and preload in the monitored muscle are mandatory. MMG may reflect both NMB and muscle contraction. EMG and accelerography devices are easier to set up but they reflect only NMB. The optimal use of EMG necessitates optimal placement of the electrodes and stable temperature. Fixation and preload also influence the EMG-monitoring. Accelerometers are simple devices containing two stimulating electrodes that are placed over the ulnar nerve and an accelerometry probe that is placed on the thumb. The accelerometer is based on Newton´s second law: Force = Mass x Acceleration. When the nerve is stimulated, the device measures the acceleration produced by the thumb. The acceleration is displayed as T1 or TOF ratio, which is the amplitude of the fourth response divided by the first response. Accelerography correlates well with EMG. A free moving thumb and fixation of the fingers are essential to record acceleration of the thumb.

*Table 3. Essentials and problems of different NMB-monitors.*

| | Notes |
|---|---|
| Mechanomyography | Isometric contraction essential |
| | Rigid fixation essential |
| | Preload necessary |
| | 10 min stabilisation period |
| | Reflects both NMB and muscle contraction |
| Electromyography | Optimal placement of all electrodes |
| | Fixation and preload affect EMG response |
| | Direct muscle stimulation possible |
| | Temperature dependent |
| Accelerography | Placement of stimulating electrodes |
| | Free moving thumb |
| | Fixed fingers |
| | Direct muscle stimulation possible |
| | Temperature dependent |

## 5. Methods to speed up onset and recovery from NMB

During the induction of an anaesthesia NMBAs are used to achieve good intubation conditions. The rapid onset of NMB is important in emergency patients, which have to be intubated rapidly to minimise risk of aspiration. There are several methods by which a clinician can speed up the onset of NMB induced by a non-depolarising relaxant.

The most common method to accelerate onset time is the choice of an agent with rapid onset of action (Table 1). Decreased neuromuscular blocking potency seems to be responsible for a more rapid onset of action of NMBAs. The onset times of NMBAs decreased with increasing molar potency both in experimental (Bowman et al. 1988, Min et al. 1992) and clinical studies (Kopman et al. 1999).

Succinylcholine has been used for more than 50 years as the "best" NMBA to facilitate endotracheal intubation despite its many side effects. The introduction of short and intermediate-acting NMBAs has minimised the need for succinylcholine in elective surgery. Because none of the non-depolarising NMBAs is comparable to succinylcholine in respect to onset time, the onset of NMB has been accelerated by priming or timing techniques, by large doses of NMBAs or by use of synergistic mixtures.

In 1984 Francis Foldes introduced a method to accelerate the onset time of non-depolarising NMBAs, the priming principle (Foldes 1984, Schwarz et al. 1985). In the priming method a small subparalysing dose, 20-30% of ED95, of a relaxant is administered followed by the 2xED95% dose 4-6 minutes later. This method produces satisfactory conditions for tracheal intubation more rapidly than the administration of a single 2xED95 dose. The smaller total dose used for facilitation of intubation also results in shortening of the clinical duration of the intubating dose. The priming dose should be large enough to cause moderate inhibition of neuromuscular transmission (70-80% occupancy of end plate receptors), but small enough not to cause unpleasant symptoms. After priming doses of 0.01 mg/kg of vecuronium all patients developed ptosis, several had diplopia or were unable to swallow and in most of the patients $SaO_2$ decreased significantly (Mahajan et al. 1993).

The timing technique entails the administration of a single bolus of the non-depolarising relaxant before the induction agent, which is given at the onset of clinical weakness or at a fixed time interval. The usual clinical endpoints of weakness are ptosis, diplopia or reduction in strength of hand grip (Culling et al. 1989). Rocuronium 0.6 mg/kg given 20 s prior to thiopental provides intubating conditions equivalent to thiopental-succinylcholine for rapid sequence inductions (Nelson et al. 1997), circumventing rocuronium´s longer onset time.
The onset of action of muscle relaxants is faster if the intubation dose is large. However, prolonged duration of NMB in large doses of intermediate acting NMBAs precludes their routine use for short duration surgical cases.
When two different non-depolarising NMBAs are administered simultaneously or in sequence, potentiation of effect or additive effects have been found with different combinations in several studies (Mirakhur et al. 1985, Rautoma et al. 1995a, Rautoma et al. 1995b). The combination of two NMBAs exhibits potentiation of effect if the response is greater than the additive sum of maximum effects expected from each drug alone. In addition, the onset of NMB can be accelerated by some combinations.
The clinical use of mixtures of NMBAs is rare. Near the completion of surgery a clinician may prefer to use a short-acting agent to continue NMB induced by a long-acting agent. However, the NMBA given first tends to play a dominant role and exerts a determining influence on the effect of the NMBA subsequently given (Goudsouzian et al. 1994, Naguib et al. 1994, Rautoma et al. 1995b).
The choice of succinylcholine ensures rapid onset of NMB. However, the use of succinylcholine before non-depolarising relaxants may influence the neuromuscular blocking characteristics of the latter. The effect of prior administration of succinylcholine on atracurium-induced block depends on the state of recovery from succinylcholine at the moment atracurium is given and concerns atracuriums potency, onset and duration characteristics (Roed et al. 1997), whereas prior administration of succinylcholine seems not to influence the potency of mivacurium (Naguib et al. 1994, Erkola et al. 1995). After succinylcholine the onset time of atracurium is shorter, max T1 depression is greater and duration 25% increases the more recovery from succinylcholine progresses (Roed et al. 1997).

## 6. Nicotine and NMB

### 6.1. Pharmacology of nicotine and nicotine patch

Smoking a single cigarette results in plasma nicotine concentrations of up to 55 µg/l (Benowitz et al. 1982), which decreases during the following 10 h of abstinence to 2.1 - 4.5 µg/l in chronic smokers (Dubois et al. 1989). At low plasma concentrations, i.e. below 100 µg/l, nicotine mimics agonistic cholinergic activity (Taylor et al. 1983). The half-life of nicotine in the blood is approximately one hour (Rosenberg et al. 1980). Application of a transdermal nicotine system releasing 21 mg/day of nicotine results in plasma concentrations of 8-16 µg/l (Caspary et al. 1991). Steady state of the plasma concentrations of nicotine is achieved 3-6 h after sticking the patch on to the skin (Caspary et al. 1991).

Chronic smokers adapt to the effects of nicotine and therefore abstinence from smoking results in a withdrawal syndrome.

### 6.2. The effect of nicotine on NMB

Some authors have stated that smokers need larger than average doses of muscle relaxants (Nigrovic et al. 1994). Smoking was found to increase the dose requirements for vecuronium (Teiriä et al. 1996) and rocuronium (Rautoma and Svartling. 1998b). On the other hand, smoking has been reported to have no effect (Latorre et al. 1997, Puhringer et al. 2000) on consumption of rocuronium. The effects of acute smoking, chronic smoking, and abstinence from smoking on NMB are unclear.

*Table 4. Studies concerning smoking and neuromuscular block.*

| | Agent | n | Effect of smoking on NMB | Monitoring of NMB | Anaesthesia |
|---|---|---|---|---|---|
| Teiriä et al. 1996 | Vec | 24 | Maintenance dose↑ | EMG, TOF | Propofol-alfentanil-N2O |
| Latorre et al. 1997 | Roc | 40 | None | EMG, single twitch | Tiopental-fentanyl-enflurane-N2O |
| Rautoma et al. 1998b | Roc | 40 | Maintenance dose↑ | EMG, TOF | Propofol-alfentanil-N2O |
| Puhringer et al . 2000 | Roc | 74 | None | MMG, single twitch | Propofol-fentanyl-N2O |

## 7. Costs due to waiting time

Anaesthesia costs are a small portion of the overall costs associated with a surgical patient´s hospital stay. The largest hospital cost category is the operating room (33%), while anaesthesia comprises only 5.6% of perioperative costs (Macario et al. 1995). Anaesthetic drug expenditures have been a focus of cost-containment efforts. It has been shown that concerted educational efforts can decrease the per-case expenditures for both volatile anaesthetic drugs and NMBAs (Szocik and Learned 1994, Freund et al. 1997). Because the acquisition costs of the intermediate-acting relaxants are considerably greater than those of long-acting drugs like pancuronium (Table 5), there has been pressure to reduce health-care costs by reverting to a more widespread use of long-acting relaxants (Durfee 1995, Gora-Harper et al. 1995).
However, of the overall operation room costs, over 70% arise during working hours even if there is no patient in the OR. A patient being kept in the OR to recover from anaesthesia and muscle relaxation delays the operation of the next patient. Greater cost savings may be achieved by improving operating team efficiency as well as those processes of care that reduce the length of operating room stay. The choice of the "right" muscle relaxant attempts

to minimise or at least to reliably predict the time patients spend between the end of surgery and their transfer to a ward or step-down unit. This may be more important than restriction of anaesthetic agents and supplies. On the other hand, when trying to decrease costs by improving efficiency, the time saved has to be long enough to enable the performance of at least one additional procedure during the same shift. Dexter et al. (1995) stated that anaesthesia time would have to be decreased by more than 100% to permit one additional short operation, each lasting more than 45 min, to be performed in an OR during an 8 hour day.

Furthermore, the use of old-fashioned, inexpensive, long-acting paralyzing drugs has been found to be associated with prolonged postoperative recovery (Ballantyne and Chane 1997). The most significant outcome difference between intermediate-acting and long-acting drugs is the relative incidence of residual NMB in the postoperative period. The incidence of residual NMB in the recovery room declined significantly when intermediate-acting NMBAs became more popular (Bevan et al. 1986). The incidence of residual NMB in the recovery room is greater with long-acting relaxants, because reversal of their neuromuscular blocking effects takes longer than that of intermediate-acting drugs (Kopman 1986). As a result of the adverse effects of residual NMB, the use of long-acting versus intermediate-acting relaxants can predispose patients to a greater risk of postoperative pulmonary complications. These complications constitute the greatest potential for added expenses.

*Table 5. Cost of neuromuscular blocking agents available in Finland in Finnish marks (FIM) ( 1 EURO = 5.95 FIM).*

| Agent, ampoule size and price FIM/mg | Intubation dose, 2xED95, FIM | Waste FIM | Minimum costs | Maintenance FIM/h, first / next hours | Total FIM in 0.5 / 1 / 3 / 6 hours |
|---|---|---|---|---|---|
| Succinylcholine | | | | | |
| 500mg = 0.1 FIM/mg | 7 | (43) | 7 or (50) | (- / - ) | (50) / (-) / (-) / (-) |
| Mivacurium | | | | | |
| 10mg = 2.02 FIM/mg | 21 | 19 | 40 | 54 / 68 | 61 / 81 / 211 / 415 |
| 20mg = 1.65 FIM/mg | 17 | 16 | 33 | 44 / 55 | 66 / 66 / 171 / 336 |
| Atracurium | | | | | |
| 25mg = 0.86 FIM/mg | 30 | 13 | 51 | 11 / 25 | (51) / 51 / 99 / 174 |
| 50mg = 0.76 FIM/mg | 27 | 12 | 47 | 10 / 22 | (46) / 46 / 89 / 155 |
| Cis-atracurium | | | | | |
| 5mg = 2.40 FIM/mg | 17 | 7 | 32 | 8 / 14 | (-) / 44 / 61 / 103 |
| 10mg = 2.29 FIM/mg | 16 | 7 | 31 | 7 / 13 | (-) / 54 / 57 / 96 |
| 20mg = 2.19 FIM /mg | 15 | 28 | 51 | 7 / 13 | (-) / 52 / 56 / 95 |
| Vecuronium | | | | | |
| 4mg = 4.42 FIM/mg | 31 | 4 | 43 | 10 / 24 | (43) / 61 / 97 / 169 |
| 10mg = 3.83 FIM/mg | 27 | 11 | 46 | 9 / 21 | (46) / 46 / 86 / 149 |
| Rocuronium | | | | | |
| 50mg = 0.68 FIM/mg | 29 | 5 | 42 | 12 / 29 | (42) / 76 / 107 / 194 |
| 100mg = 0.68 FIM/mg | 29 | 39 | 76 | 12 / 29 | (76) / 76 / 107 / 194 |
| Pancuronium | | | | | |
| 10x4mg = 3.97 FIM/mg | 28 | 4 | 40 | 1 / 8 | (-) / 40 / 53 / 77 |
| 50x4mg = 2.21 FIM/mg | 15 | 2 | 25 | 1 / 4 | (-) / 26 / 33 / 46 |

The costs are based on the *Farmaca Fennica*® (Pharmaceutical Information Centre Ltd 2000), in which wholesale prices without value added tax are listed annually. In the calculations the intubation dose is for a 70 kg patient and excess drug remaining in the syringe after intubation is waste. Total sum at 0.5 and 1 h is based on the ampoule price multiplied by the number of the opened ampoules. Maintenance costs have been calculated using an infusion to sustain 95% block assuming that the infusion started 30% before end of the average duration time of the intubation dose. In the total costs of 3 and 6 hours remaining drug in the infusion bag, i.e. waste, is excluded. The minimum costs and total costs includes mean price (8 FIM) of the antagonists with all drugs except succinylcholine and mivacurium. Parentheses indicate inappropriate use of NMBAs.

# THE PURPOSE OF THE STUDY

The aims of the present study were:

1. To define the interactions of priming combinations of tubocurarine and vecuronium (III).

2. To evaluate the usefulness of post-tetanic-count in preventing airway pressure alarms and movements during profound NMB (V).

3. To compare the antagonistic effect of edrophonium and neostigmine on residual vecuronium-induced NMB (I).

4. To evaluate the influence of smoking and transdermal nicotine patch on atracurium-induced neuromuscular block (II).

5. To evaluate the clinical course of the NMB (I-V) and costs (IV) due to residual NMB.

# PATIENTS AND METHODS

## 1. Patients and study designs

After the approval of the local ethics committee and written informed consent from the patients, a total of 291 patients participated in these studies. Studies I and III were carried out simultaneously, hence the 50 patients are included in both studies. Also, all patients in Studies IV and V are same. All studies were performed in a prospective, randomised and double blind manner. Patient characteristics are shown in Table 6. Patients were of ASA physical status 1-2 in Studies I-III and V and of 1-3 in Studies IV and V. The patients did not have any medication or disease known to alter neuromuscular transmission. The patients did not have any significant renal, hepatic, cardiovascular, pulmonary or diabetic disease, nor had they any history of hypersensitivity to any drugs used in these studies. Body mass index was below 30 with every patient. All patients were hospitalised for elective surgery requiring general anaesthesia and muscle relaxation.

## 2. Anaesthesia methods

The patients were premedicated with oral diazepam 5-10 mg (II, IV and V) or with intramuscular promethacin 1 mg/kg (I and III). Anaesthesia was induced with thiopental 3-5 mg/kg (I-III) or propofol 1-2 mg/kg (IV and V). The cardiovascular response to intubation was attenuated with fentanyl 2 μg/kg or alfentanil 20 μg/kg . The intubation doses of NMBAs averaged 2xED95 in all studies, except when usual clinical intubation doses of succinylcholine (1 mg/kg) and TC (0.5 mg/kg) were used. General anaesthesia was maintained with nitrous oxide ($N_2O$) in oxygen 2:1 in Studies I-III, whereas 30-100% oxygen in air was used during jet ventilation in Studies IV and V. In Studies I and III the anaesthesia was supplemented with fentanyl and low concentrations of halothane (less than 0.5 vol%), when needed. In Study II the maintenance period of the anaesthesia was supplemented with fentanyl and constant 0.7% isoflurane. In Studies IV and V the hypnotic component of anaesthesia was ensured with an infusion of propofol. Additional doses of 5 μg/kg of alfentanil were given when indicataed by the haemodynamic response. Ventilation was controlled to maintain end-tidal $CO_2$ ($etCO_2$) 4.5-5.5 % in Studies I-III, but during jet ventilation in Studies IV-V the aim was to keep the $etCO_2$ constant at each patients starting level during the procedure. Monitoring during anaesthesia included ECG, noninvasive blood pressure, pulse oximetry and end-tidal $CO_2$. In Studies I and III the residual NMB was antagonised with edrophonium 0.5 mg/kg + atropine 7 μg/kg or neostigmine 40 μg/kg + glycopyrrolate 8 μg/kg, whereas in the other Studies (II, IV, V) 2.5 mg of neostigmine combined with 0.5 mg of glycopyrrolate was used to antagonise the NMB.

## 3. Monitoring of neuromuscular function

The examined hand was immobilised to ensure a stable recording. In Studies I-III NMB was monitored with a Relaxograph® (Datex, Helsinki, Finland). Stimulating surface electrodes were attached over the ulnar nerve at the wrist. In Studies I and III the recording electrodes were placed on the base of the index finger and over the adductor pollicis muscle, whereas in Study II the compound EMG was recorded on the first dorsal interosseus muscle. A neutral electrode was placed between the stimulating and recording electrodes. The Relaxograph® automatically seeks the supramaximal stimulus current. It uses supramaximal square wave impulses of 0.2 ms duration at a frequency of 2 Hz as TOF every 20 s. The same device also records the summative EMG. In Studies I and III the nerve was stimulated 2 minutes before the priming dose to stabilise the EMG signal. After the stabilisation period the summative EMG response was considered to be an initial control value (100%). Thus all T1 values during anaesthesia were percentages compared to the initial T1 control value, whereas the TOF ratio was calculated at each time point as T4/T1. In Studies II, IV and V a stabilisation period of the EMG was not used.
In Studies IV and V we used two identical devices for monitoring the single twitch and the PTC (Myotest®, Biometer, Copenhagen, Denmark).

*Table 6. Patient characteristics, mean (SD).*

| Study | Subgroups | n | Age | Weight | Height |
|---|---|---|---|---|---|
| I | EDR | 34 | 48 (8) | 73 (10) | 166 (6) |
| | NST | 30 | 46 (9) | 74 (11) | 169(6) |
| II | NON-SMOK | 20 | 46 (10) | 76 (8) | 171(8) |
| | TD-NICO | 30 | 42 (11) | 77 (11) | 173 (9) |
| | SMOK | 20 | 43 (9) | 80 (10) | 175 (7) |
| | ABST | 30 | 46 (13) | 79 (16) | 172 (8) |
| III | vec/VEC0.1 | 16 | 42 (15) | 68 (13) | 168 (8) |
| | vec/VEC0.15 | 16 | 47 (16) | 70 (13) | 166 (9) |
| | vec/VEC0.2 | 18 | 52 (15) | 67 (13) | 166 (7) |
| | tc/VEC0.1 | 16 | 44 (16) | 71 (12) | 167 (7) |
| | tc/VEC0.15 | 15 | 43 (20) | 69 (16) | 167 (10) |
| | tc/VEC0.2 | 12 | 62 (9)* | 77 (12) | 172 (10) |
| | tc/TC | 9 | 46 (17) | 70 (10) | 174 (7) |
| | vec/TC | 10 | 38 (10 | 69 (12) | 172 (7) |
| | pla/SUCC | 15 | 47 (17) | 70 (15) | 167 (10) |
| IV | ATR | 10 | 47 (9) | 79 (13) | 173 (13) |
| | MIV | 10 | 44 (13) | 76 (12) | 175 (10) |
| | ROC | 10 | 48 (11) | 73 (13) | 175 (9) |
| | VEC | 10 | 39 (9) | 70 (12) | 172 (9) |
| | SUCC | 10 | 49 (14) | 77 (13) | 176 (6) |
| V | As in Study IV | | | | |

* Group older than other subgroups, $P<0.05$

*Table 7. Patients and methods.*

| Study | I | II | III | IV | V |
|---|---|---|---|---|---|
| Study objective | Antagonism of residual NMB | Smoking and NMB | Priming combinations of TC and VEC | Waiting times and costs due to NMB | PTC during jet-ventilation |
| Study design | Prospective, randomised, double-blind, clinical | Prospective, randomised, placebo-controlled, double-blind, clinical | Prospective, randomised, double-blind, clinical | Prospective, randomised, double-blind, clinical | Prospective, randomised, double-blind, clinical |
| Procedures | Otorhino-laryngological surgery | General surgery | Otorhino-laryngological surgery | Laryngo-microscopy | Laryngo-microscopy |
| n | 64 | 100 | 127# | 50 | 50* |
| Compared subgroups | EDR and NST | Non-smokers, abstinent smokers, acute smokers and transdermal nicotine | VEC+VEC, TC+VEC, VEC+TC and TC+TC | ATR, MIV, ROC, VEC and SCh | ATR, MIV, ROC, VEC and SCh |
| Statistics | ANOVA, post hoc t-test, Chi square | ANOVA, post hoc LSD test, Chi square | ANOVA, post hoc t-test, Chi square | ANOVA, post hoc LSD test, Chi square | ANOVA, post hoc LSD-test or Bonferroni correction, Chi square |

# 50 of the patients are the same as in Study I.
* Same patients as in Study IV .

The ulnar nerve was stimulated at the wrist with supramaximal current. Single-twitch stimulation was started immediately once the patients were unconscious. Monitoring of PTC was started one minute after disappearance of the single twitch. PTC was monitored from both hands in turn at three-minute intervals. For PTC, the Myotest® delivers 1 Hz single-twitch stimulation, which begins 3 s after a 50 Hz tetanic stimulation of 5 s duration. The PTC and DBS responses were evaluated tactilely from the thumb of the patient.
The examined hand and the whole patient, except for the operation area, were covered with thermal blankets to reduce temperature loss-caused zero shift of the EMG. The intravenous fluids were also warm. Temperature was not monitored in all patients in Studies I and III. In Studies IV and V only axillary temperature was monitored, whereas in Study II temperature was recorded from the tympanic membrane and the skin of the hand used for monitoring of NMB.

## 4. Monitoring of airway pressure during jet ventilation

In Study IV different signs of recovery of NMB were recorded: alarms of the airway pressure monitor, movements of the vocal cords on the video monitor of the operating microscope and movements of the abdomen. The movement responses were recorded as negative or positive, without aiming to classify the intensity of the responses. The tracheal pressure signal was monitored below the vocal cords using the second lumen of the double lumen jet catheter. The same line was used for end tidal gas monitoring during expiration (Baer 1985). A specially designed airway pressure curve monitor was used (Baer 1985). The airway pressure curve monitor was adjusted to rise an alarm if deviation of the slope during inspiration occurred for more than 30%. During every inspiration the slope was compared to the mean slope of six preceding consecutive cycles.

## 5. Costs incurred by waiting time

In Study IV the costs of waiting time caused by the NMB included both the onset time and the total recovery time. Total recovery time includes both the spontaneous recovery time and the neostigmine-induced reversal time. Waiting time-related costs were calculated based on the average operation room (OR) costs (FIM 2400 ~ $ 480) per hour in the otorhinolaryngological (ORL) department of Tamper University Hospital in 1997 (Baer 2001). OR costs includes all equipment, labour, supplies and fixed costs such as depreciation of the devices in the OR. The minor expenses of each drug were ignored in Study IV, but the prices of each muscle relaxant available in Finland are presented in the present dissertation (Table 5).

## 6. Specific study plans

In Study I the patients were randomised into two antagonist groups to receive either edrophonium 0.5 mg/kg + atropine 7 μg/kg or neostigmine 40 μg/kg + glycopyrrolate 8 μg/kg. Spontaneous recovery of muscular function was allowed to proceed before antagonising the NMB. The mixtures were introduced into a freely flowing intravenous (i.v.) line. The TOF recordings before injection of the antagonists and 1,2,3,4,5,7 and 9 min thereafter were selected for statistical analysis.

In Study II eighty smokers were compared to 20 non-smokers (group NON-SMOK). The smokers were randomised into three groups. The first abstinent group (group TD-NICO) received a transdermal nicotine system releasing 21 mg/day of nicotine (Nicotinell®, Novartis) on their back at least 10 hours before induction of anaesthesia. The other abstinent group (group ABST) received a placebo transdermal system and the patients of the third group (group SMOK) were allowed to smoke until premedication with oral diazepam. The abstinent groups refrained from smoking for at least 10 hours before anaesthesia. The transdermal systems were attached and covered with an adhesive tape by a nurse who did not otherwise participate in the Study. Neither the patient nor the anaesthesist knew whether the transdermal system was active or placebo.

*Table 8. Anaesthesia methods.*

| Study | I | II | III | IV | V |
|---|---|---|---|---|---|
| Premedication | Promethacin 1 mg/kg i.m. | Diazepam 5-10 mg p.os. | Promethacin 1 mg/ kg i.m. | Diazepam 5-10 mg p.os. | Diazepam 5-10 mg p.os. |
| Induction of sleep | Thiopental 3-5 mg/kg | Thiopental 5 mg/kg | Thiopental 3-5 mg/kg | Propofol 1-2 mg/kg | Propofol 1-2 mg/kg |
| Maintenance of anaesthesia | N2O, fentanyl halothane ≤ 0.5% | N2O, fentanyl, isoflurane 0.7% | N2O, fentanyl, halothane ≤ 0.5% | Propofol infusion, alfentanil bolus | Propofol infusion, alfentanil bolus |
| Priming time | 6 min | No | 6 min | No | No |
| Initiation of NMB | VEC 0.1-0.2 mg/kg | ATR 0.5 mg/kg | VEC 0.1-0.2 mg/kg or TC 0.6 mg/kg | 2xED95, SCh 1mg/kg | 2xED95, SCh 1mg/kg |
| Maintenance of NMB | VEC 0.03 mg/kg bolus | ATR 0.1 mg/kg bolus | VEC 0.03 mg/kg bolus | 0.5xED95 of ATR,VEC and ROC, ED95 of MIV, SCh infusion | 0.5xED95 of ATR,VEC and ROC, ED95 of MIV, SCh infusion |
| NMB target | T1 0-25% | T1 0-25% | T1 0-25% | PTC≤2 | PTC≤2 |
| NMB before antagonism | T1 40% | T1 > 15% | T1 40% | PTC 10 | PTC 10 |
| Reversal procedure | EDR 0.5mg/kg + ATR 7µg/kg or NST 40µg/kg + GLY 8µg/kg | NST 2.5 mg + GLY 0.5 mg | EDR 0.5mg/kg + ATR 7µg/kg or NST 40µg/kg + GLY 8µg/kg | NST 40 µg/kg + GLY 8 µg/kg | NST 40 µg/kg + GLY 8 µg/kg |

EDR=edrophonium, NST = neostigmine, GLY = glycopyrrolate, ATR = atropine

*Table 9. Monitoring methods*

| Study | I | II | III | IV | V |
|---|---|---|---|---|---|
| Monitoring of NMB | Relaxograph® | Relaxograph® | Relaxograph® | Twitches of the thumb, tactile | Twitches of the thumb, tactile |
| Pattern of the stimulus | TOF | TOF | TOF | Single-twitch, PTC, DBS | Single-twitch, PTC, DBS |
| Monitored muscles | Hypothenar | 1st dorsal interosseal muscle | Hypothenar | Adductor pollicis | Adductor pollicis |
| Stabilisation of the stimulus | 2 min | No | 2 min | No | No |
| NMB target | T1 0-25% | T1 0-25% | T1 0-25% | PTC≤2 | PTC≤2 |
| Accepted sign of recovery | TOF ratio 0.7 | TOF ratio 0.7 | TOF ratio 0.7 | No fade in DBS | No fade in DBS |
| CO2-monitoring | Cardiocap® | Cardiocap® | Cardiocap® | Cardiocap® | Cardiocap® |
| Monitoring of temperature | Esofageal / rectal / none | Tympanic membrane and skin of the hand | Oesofageal / rectal / none | Axillary | Axillary |

In Study III patients receiving different primers and different intubation agents were randomised into 9 groups. The priming doses were either 0.015 mg/kg of vecuronium or 0.15 mg/kg of tubocurarine. The intubation doses were 0.1, 0.15 or 0.2 mg/kg of vecuronium or 0.6 mg mg/kg of tubocurarine. In the control group placebo priming was followed by 1 mg/kg of succinylcholine. The priming time, i.e. the time between the priming dose and the intubation dose of a muscle relaxant, was six minutes. In the names of the groups the priming agent is written with small letters and the intubation agent with capitals. Comparisons were made between groups involving the same intubation agent and

dose but different priming agents: vecVEC0.1-tcVEC0.1, vecVEC0.15-tcVEC0.15, vecVEC0.2-tcVEC0.2 and vecTC-tcTC. The succinylcholine group was compared to all other groups.
In Study IV the patients were randomised into five groups: atracurium, mivacurium, rocuronium, vecuronium, and succinylcholine. After the initial 2 x ED95 dose of the non depolarising NMBAs, additional doses were 25% of the initial dose of atracurium, rocuronium and vecuronium, but 50% of the initial dose for mivacurium at three minute intervals until PTC = 2 was reached. The first additional doses were given four minutes after the initial dose of the muscle relaxant, when needed. The initial bolus 1 mg/kg of succinylcholine was followed by succinylcholine infusion, which was adjusted to keep PTC = 2. The onset time between administration of an NMBA and the time to reach intense NMB (PTC = 2) was recorded. Total recovery time included both the spontaneous recovery time from completion of the endolaryngeal procedure until administration of the antagonists at PTC 10, and the neostigmine-induced reversal time from the administration of the antagonists until no fade was detected in DBS. The waiting time caused by the NMB included both the onset time and the total recovery time.
In Study V the same randomised groups as in Study IV were compared during intense NMB controlled by PTC. During intense NMB the incidence of alarms of airway pressure were compared to the incidence of movements of the vocal cords and the diaphragm.

## 7. Data analysis

In Studies I-III the onset time , i.e. the duration of the onset of NMB was measured from the administration of the NMBA to the initial depression of T1 to 10% of the pre-relaxant control. The duration of the surgical NMB was measured from the administration of the intubation dose to the spontaneous recovery of the T1 to 25% of the initial control. In all calculations T1 values were determined comparing T1 to the initial control value, but TOF ratio was determined at each time point as T4/T1. In Study I the reversal time was measured from administration of the antagonists to the recovery of TOF ratio to 70% level.
In Study II the maintenance dose of atracurium was calculated using the duration time of action of additional consecutive bolus doses of atracurium which were administered at T1 25% level.
In Studies IV and V the onset time between administration of a muscle relaxant and the time to intense NMB (PTC = 2) was recorded. In Study IV total recovery time included both the spontaneous recovery time from completion of the procedure until administration of the antagonists, and the neostigmine-induced reversal time from the administration of the antagonists until no fade was detected in DBS. The waiting time caused by the relaxant included both the onset time and the total recovery time.

## 8. Statistics

In Studies I and III all statistical analyses of the continuous variables were performed with the Statpac Gold® 2.0 statistical program using analysis of variance (ANOVA) for repeated measurements. Further comparisons between the groups, for which ANOVA had shown

statistical significance were performed by Student´s unpaired two-tailed *t*-test. In study III comparisons were made between groups involving the same intubation agent and dose but different priming agents: vecVEC0.1-tcVEC0.1, vecVEC0.15-tcVEC0.15, vecVEC0.2-tcVEC0.2 and vecTC-tcTC. The succinylcholine group was compared to all other groups.
In Studies II, IV and V the computation was accomlished on Statistica/Win (Version ´98) software. The statistical analyses were also based on ANOVA, and *post-hoc* comparisons were based on the LSD method (least significant difference). The Chi square test was used for discrete variables in all studies. In Study V the number of movements and pressure alarms were compared using ANOVA. The *post-hoc* tests were based on the Bonferroni correction.
The results are given as mean followed by SD or 95% confidence intervals. The power analyses were carried out *ex post facto*. In the power analyses probability of type I error was 0.05 in Studies I-IV but 0.1 in Study V. The sample sizes needed to detect a true difference in population means with 0.80 power are presented in Table 10. When dichotomous variables were analysed, power was calculated for uncorrected chi-square test.

## 9. Ethical considerations

In Study II several patients in the SMOK-group refused to participate after being adviced that smoking is actually not advisable before anaesthesia. Smoking before anaesthesia may be harmful due to carboxyhaemoglobinaemia. Therefore, only healthy ASA 1-2 patients were included in the Study and no serious adverse effects were recorded before, during or after anaesthesia. One patient in the TD-NICO group removed the nicotine patch due to irritation and pain on the skin. This patient was replaced with a new one while the randomisation was opened. The whole data were analysed only after 100 patients.
During the Study we found that increase in arterial pressures or heart rate after intubation was common among all groups of smokers. All adverse arterial blood pressures normalized in 5 min, whereas high heart rate lasted longer.
Also in Study III we also opened the randomisation after 90 patients, because unnecessarily prolonged anaesthesia may be harmful to a patient. We stopped collecting data in groups tc/VEC0.2, tc/TC and vec/TC, because the intubation dose of tubocurarine caused prolonged recovery in many cases.

# RESULTS

## 1. Priming combinations of tubocurarine and vecuronium (III)

Priming with vecuronium before tubocurarine resulted in rapid NMB, whereas priming with tubocurarine did not enhance the onset time of vecuronium nor tubocurarine compared to priming with vecuronium. The mean TOF ratio decreased to 87 (76-97)% of initial control during vecuronium priming, which was significantly higher than after tubocurarine priming 67(56-78)% ($P<0.001$). The onset time in group vec/TC, 64 (47-81) s, was significantly shorter than in group tc/TC: 113 (84-142) s ($P=0.0018$). The onset time of succinylcholine, 41 (34-47) s, was significantly shorter than in groups vec/VEC0.1, tc/VEC0.1, tc/VEC0.15 and tc/TC ($P<0.05$ in all pairwise comparisons).
When tubocurarine was used as a primer before intubation doses of vecuronium, the duration of clinical NMB was significantly longer in all pairwise comparisons, than after priming with vecuronium ($P<0.001$). The prolongation of NMB was most marked when the highest intubation doses (0.2 mg/kg) of vecuronium were used. Changing the priming relaxant from vecuronium to tubocurarine increased duration of NMB from 60 (50-70) minutes in group vec/VEC0.2 up to 143 (110-175) minutes in group tc/VEC0.2 ($P<0.0001$).

## 2. Control of profound NMB with post-tetanic count (V)

Visually detectable movements of the vocal cords and abdomen were earlier signs of recovery of NMB than the alarms of our airway pressure monitor. We also noticed that movements of the larynx or diaphragm may be observed during alfentanil-propofol anaesthesia at PTC 0-2 regardless which relaxant had been chosen. At PTC level zero movements were recorded twelve times in ten patients. During intense NMB controlled by PTC, movements of the vocal cords and the abdomen were most often the first signs of neuromuscular recovery while airway pressure curve alarms were rare. In 95 % confidence interval analysis, the proportion of airway pressure alarms was 7 % (1-23) while the proportion of movements was 93% (77-99).

## 3. Antagonism of residual block with edrophonium or neostigmine (I)

Edrophonium after vecuronium is a faster antagonist of NMB than neostigmine, if the level of T1 at which antagonism is started is 25-75% of initial control. The T1 response to TOF stimulation was significantly higher at 1 and 2 min after administration of the antagonists in the edrophonium group than in the neostigmine group (1 min $P<0.01$, 2 min $P<0.05$). TOF ratio was also higher at 1 and 2 minutes in the edrophonium group than in neostigmine group (1 min $P<0.01$, 2 min $P<0.05$). More patients reached the endpoint of recovery (TOF ratio>0.70) in the edrophonium group at 2 and 3 min after antagonism than in the neostigmine group (2 min $P=0.05$, 3 min $P=0.007$).

## 4. Effect of smoking and nicotine patch on NMB (II)

Neither smoking nor transdermal nicotine had any significant effect on onset of NMB. However, the duration of NMB in abstinent smokers was 48.2 (10.1) min, which was significantly longer than in patients with transdermal nicotine system, recent smokers, and non-smokers (42.7(7.1), 41.4(10.4), and 42.8 (7.3) min; P=0.02, P=0.01, and P=0.04 respectively). The maintenance dose of the abstinent smokers (0.23(0.03) mg/kg/h) was lower than in patients with transdermal nicotine system, recent smokers and non-smokers (0.30 (0.07), 0.32 (0.06) and 0.32 (0.05) mg/kg/h; $P<0.001$ for all pairwise comparisons).

## 5. Costs of intense NMB due to waiting time (IV).

Succinylcholine is economically superior to all the other NMBAs for use during short operations when intense NMB is mandatory. Of the non-depolarising muscle relaxants, mivacurium is the most economic alternative. The onset time to achieve intense NMB (PTC = 2) was shorter after succinylcholine than after all other muscle relaxants (P = 0.02 - 0.0002 in pairwise comparisons). The mean onset times to PTC = 2 after atracurium, rocuronium and vecuronium were 6.6-8.2 min with no significant differences
between the drugs. After mivacurium the onset time to PTC = 2 was 9.0 (2.2) min, which was significantly longer than in groups succinylcholine (4.6 (2.0) min, P=0.0002) and vecuronium (6.6 (0.3) min, P=0.003).
The total recovery times in groups mivacurium and succinylcholine were 7.6(2.8) minutes and 7.9(4.1) minutes, respectively, which were significantly shorter than the recovery times of atracurium, rocuronium and vecuronium (26.0(8.2), 18.6(6.9) and 17.2(5.3) minutes respectively, $P<0.001$ in all pairwise comparisons). In group atracurium the total recovery lasted longer (26.0 (8.2) min) than in any other group.
The total waiting time due to intense NMB varied from 12.4(6.1) in the succinylcholine group to 34.2(11.3) minutes in the atracurium group. The longest difference between the group means (21.8 min) in relaxation waiting time caused extra operation room costs of FIM 800 (~EUR 150) per patient in our hospital.
The achieved statistical power of the strategic variables using actual differences between the group means, actual SDs, and actual sample sizes are displayed in Table 10. With dichotomous variables achieved power was calculated for uncorrected chi-square test.

*Table 10. Power of the results.*

| Study | I | II | III | IV | V |
|---|---|---|---|---|---|
| Compared subgroups | EDR / NST | ABST / NON-SMOK +SMOK + TD-NICO | VecTC / tcTC | Succinyl-choline / atracurium | Airway pressure alarms/ Movements |
| Variable | Percentage of adequate recoveries 2 min after antagonists | Duration time | Onset time | Total waiting | Percentages of airway pressure alarms and movements |
| Type of variable | Dichotomous | Continuous | Continuous | Continuous | Dichotomous |
| Study design | Independent | Independent | Independent | Independent | Independent |
| $\alpha$ | 0.05 | 0.05 | 0.05 | 0.05 | 0.1 |
| Expected $\Delta$ or P0/P1 | 15%/50% | 8 min | 15 sec | 10 min | 20%/80% |
| Expected SD | - | 10 | 15 | 7 | - |
| n | 27 | 26 | 17 | 9 | 7 |
| Actual $\Delta$ or P0/P1 | 23%/56% | 5.4 min | 49 sec | 21.8 min | 7%/93% |
| Actual SD | - | 8.7 | 16 | 8.5 | - |
| Actual n | 34/30 | 30/70 | 10/9 | 10/10 | 10/10 |
| Achieved power | 0.80 | 0.80 | 0.99 | 0.99 | 0.99 |

$\alpha$ = Probability of type I error.
$\Delta$ = The difference in the group means.
P0 and P1 = Probability of the event in the controls and in the experimental patients.
SD = The intra-group standard deviation for independent design and continuous variable.
n = The sample size needed to detect a true difference ($\Delta$) in population means with $\alpha$, 0.80 power and SD defined in the same column. When dichotomous variables were analysed, n = case sample size for uncorrected chi-square test.
Achieved power = The achieved statistical power of the *post hoc* test using actual statistical variables and actual sample sizes. When dichotomous variables were analysed, achieved power was calculated for uncorrected chi-square test.

# DISCUSSION

The general aim of this thesis was to study some clinically interesting factors influencing the course of action of NMBAs and the costs of residual NMB. Although we found statistically significant differences in every study, the methods, the results, and before all, the clinical implications merit discussion.

## 1. Methodological considerations

We used EMG instead of MMG in Studies I-III, because the latter entails problems with transducer fixation and overload and immobilisation of the arm (Carter et al. 1986). In Studies IV and V PTC was used, because it is a reliable method to monitor intense NMB when no response is seen in TOF monitoring (Viby-Mogensen et al. 1981, Howardy-Hansen and Viby-Mogensen 1984). The PTC was monitored by tactile evaluation of the movements of the thumb. Quantitative monitoring might yield more accurate results of the level of NMB. However, not every clinician has an access to new devices with the capability to monitor PTC or NMB quantitatively. Our method of monitoring PTC gives valuable information for an anaesthetist, who has only a simple device to monitor NMB.

Our method of monitoring PTC during a NMB induced by a depolarising agent, like succinylcholine, is not commonly accepted. We elected to compare succinylcholine to non-depolarising NMBAs in Studies IV and V, because succinylcholine is the golden standard of NMB with rapid onset and recovery times. In the succinylcholine group single twitch responses were recorded after a 50 Hz tetanic stimulation like in all other groups, although we were not counting on post-tetanic facilitation. Therefore, the target level of NMB, as well as the type of the NMB, was not comparable between the groups. Post-tetanic facilitation is one of the characteristics of non-depolarising NMBA-induced block or "phase 2" block during succinylcholine infusion. Some of the patients in the succinylcholine group may have been in the transition state from "phase 1" block to the "phase 2" block, since slight post-tetanic facilitation was seen, although our cumulative doses of succinylcholine were not high enough to cause "phase 2" block. The cumulative dose requirement of succinylcholine to cause "phase 2" block is over 6 mg/kg (Lee and Katz 1980), while in our Study none of the cumulative doses of succinylcholine exceeded 4 mg/kg. However, clinical characteristics of "phase 2" block with slow recovery were not detected.

The compound EMG response decreases both in latency and in amplitude after induction of anaesthesia (Edmonds et al. 1988). This phenomenon is correlated to preload and increase of peripheral temperature (Kopman et al. 1995). However, stabilisation of the twitch response takes too long for many studies of neuromuscular function in the clinical research setting (van Santen et al. 1998). We used a 2 min stabilisation period in Studies I and III, whereas no stabilisation was anticipated in Study II. Naturally, no stabilisation period was used in Studies IV and V, because tactile evaluation of the NMB was used.

Hypothermia during surgery is a common feature. Hypothermia may have caused baseline error in the EMG signal in some patients in Studies I and III, because core temperature was not recorded in all patients. In these studies the whole patient, except the head, was covered

with thermal blankets and the temperature loss was minimal because of small operation areas (ear, nose or neck). The warm intravenous fluids and drugs were introduced into a vein of the opposite forearm. Our efforts to maintain normothermia seemed successful, but we could not include core temperature in the statistical analysis. The drift in EMG signal may have increased the interindividual variability of the EMG responses, because twitch tension decreases by a mean of 19% for each $^{o}$C reduction in core temperature (Heier et al. 1994) and hypothermia prolongs the effect of NMBAs (Heier et al. 1991). However, all our groups were treated under similar conditions. Therefore we assume that the differences between the groups were not affected by the poor temperature monitoring. The drift of EMG due to hypothermia does not affect TOF ratios significantly, because both T4 and T1 in the equation do change (Hopf and Maurer 1990). Despite the variability in temperature the differences were big enough to be significant in the statistical analysis.

In Studies IV and V axillary temperature did not change significantly. There were no differences in this respect between the study subgroups. In Study II temperature was recorded properly and there were no significant changes in the temperature of the tympanic membrane and the skin of the hand used for monitoring of NMB. The good clinical research practice in pharmacodynamic studies of NMBAs includes monitoring of both central and skin temperature of the monitored muscle (Viby-Mogensen et al. 1996).

Interaction between volatile anaesthetics and NMBAs may have influenced the results of Studies I-III. The degree of potentiation of NMBAs by volatile anaesthetics depends both on the inhaled anaesthetic and the NMBA. A low concentration of halothane was chosen in Studies I and III, because halothane appears to be less potent in augmenting the neuromuscular action of NMBAs than other volatile anaesthetics (O´Hara et al. 1991, Taivainen and Meretoja 1995).

Hypoventilation enhances the potency and duration of the action of NMBAs, whereas hyperventilation has opposite effects (Aziz et al. 1994). In Studies I-III ventilation was controlled to maintain et$CO_2$ at 4.5-5.5. in all patients. During jet ventilation in Studies IV and V et$CO_2$ was lower than normal, because the end tidal sample is a mixture of inhaled and exhaled gas due to jet mixing. Therefore ventilation was adjusted to keep et$CO_2$ at each patient´s starting level. Et$CO_2$ averaged 3.8(0.9) kPa at the start and 3.7(1.2) kPa at the end of the anaesthesia.

All parametric data were analysed with standard methods: analysis of variance followed by *post hoc* tests. A P-value less than 0.05 was considered statistically significant in all studies except Study V. In Study V the inference was based on the 90 % confidence intervals ($P<0.1$) when analysing the observed proportions of these early signs of recovery of NMB, because our sample size was small.

In Study II some patients declined to participate in the Study when they were randomised to the smokers´ group. Our attempt to re-randomise the patients leaves us with the potential for selection bias in the smokers group, because patients who remained in that group were possibly more determined smokers or less concerned about health issues in general.

## 2. Priming

Priming with vecuronium before tubocurarine results in rapid NMB, whereas priming with predominantly pre-synaptic muscle relaxant, like tubocurarine, does not enhance the onset

time of vecuronium nor tubocurarine compared to priming with vecuronium. Therefore, we assume that the potentiation of NMB after combination of vecuronium and tubocurarine seems not to be dependent on "fade" receptors. We found moreover, that priming with tubocurarine changes vecuronium from intermediate acting muscle relaxant to a long-acting agent.

Four minutes is the optimum priming interval to shorten the onset time of vecuronium, if vecuronium is used as a primer (Taboada et al. 1986). It takes five minutes to onset of maximum block of tubocurarine (Mirakhur et al. 1984), while the onset time of vecuronium is only 1.5-3 minutes (Casson and Jones 1986). In the present study we used 6 min priming time as a compromise, because the optimal priming period of tubocurarine has not been studied and these two agents may have different optimal priming times.

Although priming accelerates the onset of NMB it is no longer popular, because large priming doses are unsafe in clinical practice in patients with risk of aspiration (Musich and Walts 1986). The optimal priming dose that produces the most rapid onset of NMB is associated with significant incidence of unpleasant feelings of weakness in conscious patients (Glass et al. 1989). Furthermore, it is no longer necessary to use the priming principle because new non-depolarising NMBAs with rapid onset time, like rapacuronium and rocuronium, are available.

## 3. Combining NMBAs

Administration of combinations of muscle relaxants makes sense only if they potentiate each other, if the combination results in fewer side-effects or if the pharmacodynamic result is advantageous. In general, a beneficial difference in pharmacodynamics would be a shorter onset and shorter duration of action. The effects of combinations of NMBAs may be synergistic or additive. For example, the interaction between cisatracurium and mivacurium, vecuronium or rocuronium was found to be synergistic, but the interaction between cisatracurium and atracurium was found to be additive (Kim et al. 1998). In our Study III priming with vecuronium before tubocurarine resulted in rapid NMB, whereas priming with predominantly pre-synaptic muscle relaxant, tubocurarine, did not enhance the onset time of vecuronium nor tubocurarine when compared to priming with vecuronium. Therefore, it seems that the potentiation of the combination of vecuronium and tubocurarine does not depended on "fade" receptors. We also found that priming with tubocurarine changes vecuronium from an intermediate-acting muscle relaxant to a long-acting agent.

It is often necessary to give an additional dose of an NMBA towards the end of surgery, for a short-acting relaxant after a long-acting one. However, the administration of short-acting muscle relaxants after long-acting agents results in unexpected effects. Mivacurium becomes a long acting agent if it is administered during recovery from pancuronium-induced NMB (Erkola et al. 1996) or intermediate-acting if administered after atracurium (Goudsouzian et al. 1994). The effect of succinylcholine is not predictable during recovery from NMB induced by non-depolarising NMBAs (Scott and Norman 1988). Small doses of succinylcholine produce antagonism or enhancement of the atracurium-induced block or a combination showing a biphasic response (Scott 1988). A dose of 3 mg/kg of succinylcholine was needed to produce consistently 100% block of the twitch. The subsequent recovery rate for T1 was as fast as that seen normally after succinylcholine and

was not enhanced by neostigmine (Scott 1988). Pretreatment with mivacurium had a marked antagonistic effect on the development of a subsequent depolarising block produced by succinylcholine (Naguib et al. 1994). Isobolographic analyses of the succinylcholine-mivacurium and succinylcholine-atracurium combinations also demonstrated antagonistic interactions (Kim et al. 1996).

## 4. Control of movements with PTC

Movements during anaesthesia are considered a sign of too "light" anaesthesia. The site at which anaesthetics act to produce surgical immobility has been believed to be in the rostral central nervous system - most likely the cerebral cortex. However, the EEG, an indicator of cerebral activity, is at best a poor predictor of movement in response to pain. Even subjects with anaesthetic-induced burst suppression are capable of complex purposeful movements. All inhaled anaesthetics appear to depress the excitability of spinal motor neurons (Rampil and King 1996). This effect may contribute to surgical immobility, and its magnitude is comparable at equipotent concentrations of agents.
We should actually differentiate between hypnosis (cortical component) and analgesia and muscle relaxation (subcortical components).
Tracheal intubation can be performed before onset of complete block at the adductor pollicis, because both non-depolarising and depolarising NMBAs act more rapidly in the larynx and the diaphragm than in the peripheral muscles of the hand (Donati et al. 1991, Pansard et al. 1987). NMB develops faster and lasts a shorter time in the respiratory muscles. The use of the relatively sensitive adductor pollicis muscle of the hand to assess NMB has both disadvantages and advantages. During surgery not even total elimination of the response to TOF stimulation excludes the possibility of hickuping or coughing. On the positive side the possibility of overdosing NMBAs decreases when a relatively sensitive muscle is used for monitoring of NMB.
Repeated PTC monitoring has not been in routine clinical use. PTC has been used only during profound NMB when no response to TOF stimulation can be detected. PTC is also an easy way to check that electrodes, leads, and monitoring devices are intact, if the time with no response to TOF stimulation is longer than expected.
Despite the use of PTC-monitoring, a clinician may perceive additional information of the early recovery of NMB by observing the minor movements of the vocal cords and the abdomen.
Although twitch height and tetanic fade after tetanic stimulation may be repeated at intervals of 2 or 5 min (Silverman and Brull 1993), we used 6 min intervals between stimulations, because intervals shorter than six minutes between PTC may produce antagonism of NMB in the stimulated muscles (Howardy-Hansen and Viby-Mogensen 1984).
There were more movements in the mivacurium group than in the other groups. The long interval between PTC recordings may have influenced the results, because neuromuscular transmission recovers more rapidly after mivacurium than after other non-depolarising agents. We used double bolus doses of mivacurium during maintenance of NMB to keep the level of NMB at target level. Therefore, there was no difference between the NMBAs in the

mean PTC level during the anaesthesias. However, only an infusion of a short-acting NMBA guarantees a steady level of NMB.
According to our findings, the NMB should be even deeper than indicated by PTC to prevent all visual muscle activity. The findings indicate that NMB is not the only determinant of anaesthetic adequacy in endolaryngeal procedures; prevention of nociception and reflex movements is as important as NMB.
Although in Study V we could not control all movements with PTC, the use of NMBAs prevents intense muscle activity. In patients with severe head injury the changes in the intracranial pressure during endotracheal suctioning were significantly smaller in subjects who received NMBA plus opiates than patients who received only opiates (Kerr et al. 1998). Even more profound levels of NMB may be evaluated with post-tetanic burst-count (Saitoh et al. 1995) or with PTC following 100 Hz stimulation (Fernandes et al. 1997).
Because different muscle groups have different sensitivities to NMBAs (Johansen et al. 1964), results concerning one muscle cannot be extrapolated to other muscles. The diaphragm is most resistant to both depolarising (Smith et al. 1988) and non-depolarising (Donati et al. 1986) NMBAs. The diaphragm requires 1.4-2 times as much muscle relaxant as the adductor pollicis muscle for an identical degree of block (Donati et al. 1986). Our study agrees with these earlier results because low PTC of the adductor pollicis did not prevent all movements of the vocal cords and the diaphragm.
More sensitive to muscle relaxants than the adductor pollicis muscle are adductor muscles of the larynx and the orbicularis oculi muscles (Donati 1991 et al., Urgureanu et al. 1993). The upper airway muscles are the most sensitive (Eriksson et al. 1997).

## 5. Reversal of NMB

Recovery from a moderate block is achieved more rapidly after the administration of edrophonium (I), but neostigmine is more effective in reversing an intense NMB, as reviewed recently by David Bevan (2000). Suggested doses for the reversal of intermediate and long-acting NMBAs are 0.04-0.07 mg/kg of neostigmine, when 1-3 visible twitches can be detected, but edrophonium 0.25-0.5 mg/kg is preferable if 4 twitches with only a slight fade are visible (Bevan 2000).
Postoperative residual neuromuscular block is frequent, dangerous, and difficult to recognise clinically (Viby-Mogensen et al. 1979, Drenck et al. 1989, Berg et al. 1997). Thus, the action of neuromuscular blocking agents should always be reversed unless there is unequivocal evidence of adequate function. Several studies have shown that a clinician should be concerned about residual NMB corresponding to TOF ratios even higher than 0.7. Small degrees of NMB may be associated with abnormalities in response to hypoxemia (Eriksson et al. 1992) and increased risk of aspiration (Eriksson et al. 1997). Despite the rapid mean recovery time in both our sub-groups, the longest recovery times were 16 min after both antagonists, which reminds us of the importance of an adequate monitoring of recovery.
Today, after the studies of Eriksson et al. (1992, 1997), the standard for acceptable recovery is TOF ratio 0.9. Traditionally anaesthetists have accepted a TOF ratio of at least 0.7 as the standard that equates with recovery of ventilatory function (Ali et al. 1975). However, detecting this unsatisfactory level of recovery with clinical TOF-monitors is not possible.

Fewer than half of the clinicians are able to feel a fade in response when the TOF ratio is above 0.6 (Drenck et al. 1989). Anaesthetists can clinically detect a fade in the TOF response when the TOF ratio is <0.5. Fade to DBS is easier to detect than that to TOF stimulation, but, as the block recovers, the anaesthesist's ability to detect fade decreases.
The clinical monitoring of residual NMB is inaccurate (Kopman et al. 1997). The ability to sustain head lift or leg lift for 5 s corresponds to a TOF ratio of about 0.6. Grip strength is a poor means of assessing the intensity of NMB. The most sensitive test is the ability to hold a wooden spatula in the jaws by clamping the jaws tight, this corresponds to a TOF ratio of about 0.86 (Kopman et al. 1997). All patients experience some degree of visual disturbance until the TOF ratio recovers to at least 0.9 (Kopman et al. 1997).
Because residual NMB is a major risk factor for the development of pulmonary complications, pharmacological reversal of NMB should be based on the findings of neuromuscular monitoring and considered whenever necessary, even after the use of a short-acting drug, like mivacurium (Bevan 1996). Because NMB may persist for as long as four hours after a single bolus dose of vecuronium 0.1 mg/kg (Caldwell 1995), even the intermediate duration drugs should always be reversed.
At the end of a general anaesthesia the monitoring of NMB enables the anaesthesist to assess neuromuscular transmission reliably while the patient is still asleep. The antagonists should not be administered before the first twich of TOF is detectable. Patent airway, hypnosis, and amnesia have to be adequate until full recovery from NMB is achieved. The hypnosis can be sustained during recovery from NMB by appropriate concentrations of inhalational anaesthetics. However, in order to facilitate recovery of NMB high concentrations of anaesthetic vapors should be avoided at the end of anaesthesia (Baurain et al. 1991).
The usual surgical level of NMB needed during surgery is T1 0-25% of the initial control values. We found (V), that at this level of NMB slight movements of the diaphragm may occur, if the anaesthesia is insufficient. Bucking or tension of muscles may be harmful or even hazardous in operations in which absolute immobility is mandatory like in opthalmic and neurosurgery.

## 6. Interaction between smoking, transdermal nicotine, and NMB

It seems that smoking *per se* does not significantly affect the NMB induced by NMBAs. However, it seems that chronic presence of agonistic nicotine in the neuromuscular junction makes abstinent smokers more sensitive to NMBAs. The contradictory results about interaction between smoking and NMB may be due to methodological differences in earlier studies. According to our results it seems that the unstandardised abstinence time may have influenced the results of earlier studies (Teiriä et al. 1996, Rautoma and Svartling 1998b, Latorre et al. 1997, Puhringer et al. 2000).
A more important effect of nicotine may be effect on the depth of anaesthesia and cardiovascular response to intubation. After intubation both nicotine patch and acute smoking increased heart rate significantly compared to abstinent smokers. Furthermore movements were significantly more common among recent smokers than among abstinent smokers.

## 7. NMB and costs due to waiting times

The duration of the action of NMBAs ranges from ultrashort to long-acting. It is obvious, that the choice of a muscle relaxant depends on the estimated duration of the surgical procedure. If the duration of surgery is uncertain, preference should be given to NMBAs with a short or intermediate duration of action because they can more easily be adapted to a varying duration of surgery.

Rapid onset of the action of the NMBAs has no important impact on waiting times and costs. According to our results (IV) ease and speed of the reversal of the NMB is far more important with respect to costs. The time from injection of NMBAs to their maximum effect is in the order of less than one minute (succinylcholine) to up to three minutes (atracurium). This implies that even when the choice of the NMBA is based on a rapid onset of action, the time saved is minimal. Furthermore, a practitioner need not wait for complete NMB in the peripheral muscles of the hand, because the time course of NMB is faster in the laryngeal muscles than in the adductor pollicis muscles (Plaud et al. 1995 and 1996).

At a time of cost reduction in medical care efforts to manage the ever-increasing costs of new drugs become increasingly important. The present challenge facing an anaesthetist is to continue delivering the same high-quality patient care while consuming fewer resources. It has been suggested that a new drug should not replace an existing drug unless it has been shown to be more effective, associated with fewer side-effects or is less expensive. Many operation theatre managers and administrators may tend to adopt a simplistic view that the drug with the lowest acquisition price is the preferred drug, and that there are no cost consequences associated with differences in the duration of action or side effects of the drugs in the same class. Older, long-acting relaxants such as pancuronium and tubocurarine are cheaper but they are associated with a more frequent incidence of residual NMB in the postoperative period (Bevan et al. 1988) ensuing morbidity related to the inadequate return of airway reflexes (Berg et al. 1997). Longer recovery time associated with the use of long acting drugs results in recovery room charges, which exceed the larger acquisition costs of the newer drugs (Ballantyne and Chang 1997). The potential costs of reintubation or anaesthetic supervision which may delay the operation theatre schedule should also be factored in. New short-acting drugs are desirable, because the risk of aspiration and hypoxemia can be reduced. They also have a lower propensity for inadequate reversal because of their rapid and predictable recovery profile. If antagonism of NMB is not required, both their associated side-effects can be prevented and the costs of reversal drugs are saved. Antagonism after mivacurium-induced block shortens the waiting time only less than ten minutes (Baurain et al. 1994).

The new NMBAs appeal to anaesthetists, especially in ambulatory surgery, where early return to street fitness reduces the length of hospital stay. The use of short-acting NMBAs may make it possible to increase the number of procedures performed on a same-day discharge basis thereby reducing the spiraling costs of surgical care in ambulatory surgery.

To re-introduce older, long-acting drugs that most anaesthetists have stopped using in their clinical practice, would reduce the total hospitalisation cost by less than 3 % (Macario et al. 1995) yet may lead to more adverse sequela. The cost-versus-quality debate must continue to rage as physician autonomy in drug selection becomes subsumed by fiscal tightening measures. Succinylcholine is still the "golden standard" for facilitating rapid airway control

and it is the only approved drug with both an ultra-rapid onset time and short duration of action. However, its plethora of well known adverse effects (myalgia, increased intraocular and intracranial pressures, dysrhytmias, hyperkalemia, prolonged block in pseudocholinesterase-deficiency states, masseter spasm, and malignant hyperthermia) may make its use due to low acquisition costs unwise. One of the most important "costs", or consequences, are possible patient distress and discomfort. However, the side-effects are rare. We did not observe any adverse effects with succinylcholine nor with other muscle relaxants.

Because personnel costs are a major proportion of costs in the operating and recovery room suites, anaesthetic techniques associated with a greater need for nursing services may be more expensive (Lubarski et al. 1997). In a post anaesthesia care unit (PACU) the personnel costs account for as much as 98% of the total costs (Dexter et al. 1995). Decisions made solely on the acquisition costs of drugs without considering personnel costs may fail to achieve the desired financial savings.

However, there is no linear relationship between labour costs and the time spent in providing a clinical service. If a patient spends an additional 15-30 min in the PACU, institutional costs may not be affected unless overtime costs are incurred, increased patient throughput is achieved with the same shift or staff, or the PACU can be closed earlier after the discharge of the last patient (Dexter et al. 1995).

Furthermore, rapid recovery in the operating theatre is not always translated into earlier discharge readiness if the patient needs more antiemetics, analgesics or sedation in the PACU. It is also important to remember that late arrivals or scheduling errors by surgeons or a failure of operating room staff to prepare the patient in a timely manner can increase wasted time and thus negate any savings related to the choice of NMBAs.

# SUMMARY AND CONCLUSIONS

The correct methods to use NMBAs and antagonists combined to proper monitoring influences the course of NMB and the costs due to residual NMB considerably.

On the basis of the present studies, the following conclusions can be drawn.

1. The use of a priming dose of vecuronium accelerates the onset of NMB more than a priming dose of tubocurarine regardless which one is used as the main NMBA. Priming with tubocurarine changes vecuronium from an intermediate-acting muscle relaxant to a long-acting agent.

2. It is not possible to prevent all movements of the vocal cords and the diaphragm by the post-tetanic count information. Post-tetanic count helps to avoid unnecessary doses of NMBAs, although the long interval between stimulations makes the method doubtful.

3. Edrophonium is a faster antagonist than neostigmine to reverse vecuronium-induced residual NMB.

4. Abstinent smokers have a longer duration of NMB and lower maintenance requirements when compared to non-smokers, recent smokers, and smokers using a nicotine patch.

5. The results above do all have impact on clinical course of NMB.
When profound NMB with rapid recovery is essential the choice of an intermediate-acting NMBA instead of a short acting drug results in 20-30 min longer waiting times and considerable extra costs due to residual NMB. The waiting times are shortest after succinylcholine. The best non-depolarising agent until now to shorten waiting times is mivacurium.

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