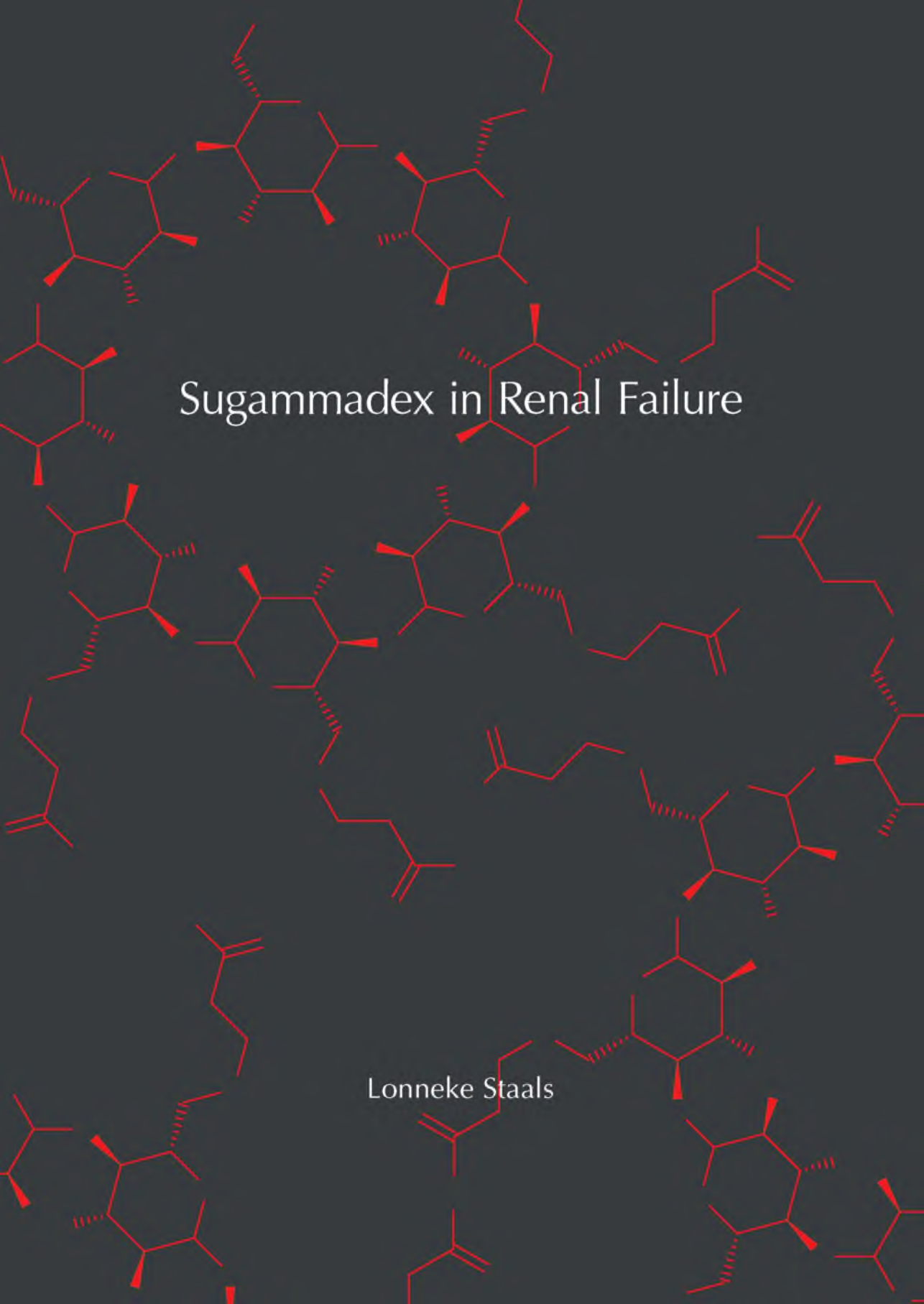

Sugammadex in Renal Failure

Lonneke Staals

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Sugammadex in Renal Failure

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Chapter 1

Introduction

NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents (NMBAs) or muscle relaxants are used in general anaesthesia to provide optimal conditions for endotracheal intubation and to optimize surgical access without hindrance from voluntary or reflex muscle movement. Furthermore, NMBAs facilitate artificial pulmonary ventilation in patients resisting such ventilation.[1]

The NMBAs have been developed gradually over many years from crude curare extracted from South American plants, into modern, completely synthesized and pure drugs. Although NMBAs were initially used in a number of medical disciplines, their application today is limited to anaesthesia and intensive care medicine.

The principal pharmacological effect of NMBAs is to inhibit the transmission of nerve impulses at the neuromuscular junction (NMJ).[2] The clinically used NMBAs can be divided in depolarizing and non-depolarizing relaxants. The depolarizing NMBAs (succinylcholine) act as agonists on the postsynaptic nicotinic acetylcholine receptor in the NMJ. They mimic the effect of acetylcholine by activating the receptor, causing ion channels to open, so ions can move across the muscle membrane and depolarize it. Succinylcholine remains on the receptor and repolarization will not take place. The muscle membrane cannot be depolarized again, which causes blockade of neuromuscular transmission. The non-depolarizing NMBAs act as competitive antagonists of the nicotinic acetylcholine receptor; they prevent acetylcholine from reacting and so prevent the ion channel from opening and no current will flow through it.[2] Recovery from neuromuscular block (NMB) occurs as the NMBA diffuses away from the NMJ and is eliminated.

The effect of all NMBAs is widely variable in intensity and duration. This results in the occurrence of postoperative residual paralysis. Residual paralysis remains a problem in anaesthesia, and is a major risk factor in the development of postoperative pulmonary complications, such as aspiration and hypoxia.[3, 4]

Many factors are responsible for the variability in NMBA effect. Amongst them are age, gender, concurrent diseases, concurrent medication, type and depth of anaesthesia, temperature and acid-base balance.[5-12] One of the most important factors, however, is renal function.[1,13-15]

The non-depolarizing NMBAs used today belong either to the chemical structure group of the benzylisoquinolines (atracurium, cisatracurium, mivacurium) or to the structure group of the aminosteroidal compounds (pancuronium, vecuronium, rocuronium).

The aminosteroidal NMBAs are excreted unchanged in the bile and the urine or metabolised by the liver and then excreted. Where the major excretion takes place differs from substance to substance: pancuronium is excreted mainly in the urine. Rocuronium is mainly excreted in the bile as the unchanged product.[1] The possible metabolites of rocuronium are pharmacologically inactive. Of the three metabolites of vecuronium, 3-desacetyl-vecuronium is the only metabolite with significant neuromuscular blocking

effect. This can cause a prolongation of the duration of the NMB, especially in critically ill patients with renal failure.[13,16] Therefore, aminosteroidal relaxants are organ dependent, which is a main disadvantage.

REVERSAL OF NEUROMUSCULAR BLOCK

To prevent residual paralysis at the end of surgery, the action of the NMBAs is frequently reversed by acetylcholinesterase inhibitors (anticholinesterases), such as edrophonium, neostigmine and pyridostigmine.[1] These drugs inhibit the enzyme acetylcholinesterase, resulting in a greater availability of acetylcholine in the NMJ, increasing neuromuscular transmission.[17] At present, neostigmine is the gold standard for the reversal agents.
Unfortunately, anticholinesterases are unable to reverse a deep NMB (i.e. a block existing immediately after administration of a NMBA, or a block with only two responses to post-tetanic stimulation).[18-20] In addition, they have many unwanted muscarinic side-effects, such as difficulty focusing (blurred vision), salivation, bronchoconstriction, bradycardia and abdominal cramps.[17, 21] Furthermore, blockades resulting from drug interaction with NMBAs, for example aminoglycoside antibiotics, are not always reversible with anticholinesterases.[21]
Sugammadex, a modified γ-cyclodextrin, is a recently introduced selective relaxant binding agent, designed to reverse the neuromuscular blocking effects of rocuronium.[22] Cyclodextrins are cyclic oligosaccharides which can encapsulate a lipophilic guest molecule, such as an aminosteroidal NMBA, to form a host-guest inclusion complex. Sugammadex forms a complex with rocuronium in the plasma, resulting in a rapid decrease in effector site concentration of the unbound muscle relaxant.[22] Due to the concentration gradient of rocuronium molecules between the NMJ and the plasma, the NMBA can diffuse away from the acetylcholine receptor, resulting in rapid recovery of NMB.[23] Sugammadex is free from muscarinic side-effects and also able to reverse deep NMB.[23-25]
Sugammadex is a water-soluble molecule, cleared by the kidneys.[23] Also, the sugammadex-rocuronium complex is cleared by the kidneys. Therefore, administration of sugammadex leads to an altered elimination of rocuronium, which is no longer excreted mainly in the bile but mainly in the urine. This could have implications in patients with renal insufficiency.

AIM OF THE THESIS

The objective of this thesis is to investigate the efficacy, pharmacokinetics and safety of sugammadex in renal failure.

Chapter 2 is an introductory chapter, with an historic overview on the use of curare, synthetic NMBAs, and reversal agents. A number of important issues associated with the administration of NMBAs and reversal agents in patients with renal failure are discussed, based on the existing literature.

To investigate the influence of renal failure on reversal of aminosteroidal NMBA-induced NMB by the reversal agent sugammadex, several studies were conducted.

First, the efficacy of sugammadex was investigated in reversing rocuronium-induced NMB in cats with ligated renal pedicles, as a model for acute renal failure. (**chapter 3**)

Then a comparative clinical study was conducted on the efficacy, safety and pharmacokinetics of rocuronium and sugammadex in patients with severe to end-stage renal failure and patients with normal renal function. (**chapters 4 & 5**)

During these clinical investigations, the primary efficacy variable was time from administration of the reversal agent, sugammadex, to recovery of the acceleromyographic Train of Four (TOF) ratio to 0.9. This TOF ratio is routinely used as the primary parameter of neuromuscular monitoring for the recovery of NMB. A TOF ratio (T4/T1) must exceed 0.9 (or 90%) to exclude clinically important residual NMB.[26] Performing the clinical investigations in our institution, it was observed that in some patients the TOF ratio recovered to 0.9 and even higher, before the first twitch (T1) of the TOF had recovered to 75% of baseline. Because this was unusual, a retrospective study was performed, to describe the relationship of recovery of T1 and the TOF ratio after placebo and different doses of sugammadex. This is described in **chapter 6**.

Because prolonged NMB after long-term administration of vecuronium in critically ill patients with renal failure has been attributed to 3-desacetyl-vecuronium, the ability of sugammadex to reverse NMB induced by 3-desacetyl-vecuronium, the active metabolite of vecuronium, was investigated in rhesus monkeys. (**chapter 7**)

Chapter 8 presents the general discussion and conclusion. Finally, **chapter 9** contains a summary, including a Dutch translation.

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Chapter 2

Neuromuscular blocking agents, reversal of neuromuscular block and renal function

A SHORT HISTORY OF CURARE AND ITS DERIVATES

The use of arrow poison by South American Indians was first described by Martyr D'Anghera in 1516 in his book *'De Orbe Novo'*.[1] In 1525 Pigafetta mentioned in his book *'Relazione del primo viaggio intorno al mondo'* the death of a soldier after being struck by a poisoned arrow on the coast of Patagonia.[2] Curare was then described by Raleigh in 1596 in his book *'Discovery of the Large, Rich, and Beautiful Empire of Guiana'*.[3]
Although the muscle relaxant effect of curare was known for a long time, its use in medical care was first suggested by Brodie in 1811, who after conducting experiments with curare, suggested its use in the treatment of tetanus. He also showed that death after administration of curare could be prevented by the use of artificial ventilation.[4,5] Schomburgk (1804-1865) identified the plants from which curare was produced as the *Strychnos* species.[6]
In 1850 Bernard reported on basic studies on the mechanism of action of curare on frogs. He was able to conclude that the effect of curare affected neuromuscular transmission.[7] In 1859 he presented a communication to the Academy of Sciences in Paris from a surgeon, M.L. Vella, on the use of curare for the treatment of a soldier with tetanus.[8] Thereafter only a few physicians used curare for the treatment of tetanus and other spastic muscle conditions.
The first use in anaesthesia was reported in 1912 by the German physician Läwen in Leipzig.[9] However, it was not until Griffith and Johnson had administered curare to their patients in 1942, that it became a popular and routine anaesthetic drug.[10]
The reason for the delayed routine use in anaesthesia was the limited availability and the large variability in effect of the curare which was then still obtained from South American plants. Climate and environment affected the potency of the curare. It wasn't until 1935 when King isolated the active component d-tubocurarine and determined its chemical structure that it was possible to produce a more pure and stable compound.[11]
Until the introduction of d-tubocurarine, muscle relaxation for intra-abdominal and thoracic surgery was provided by the induction of a dangerously deep level of anaesthesia. At that time, patients were not intubated or artificially ventilated. Shortly after its introduction in anaesthesia in 1942 curare was considered a superb anaesthetic adjuvant, as muscle relaxation now could be provided without inducing a potentially harmful deep level of anaesthesia.

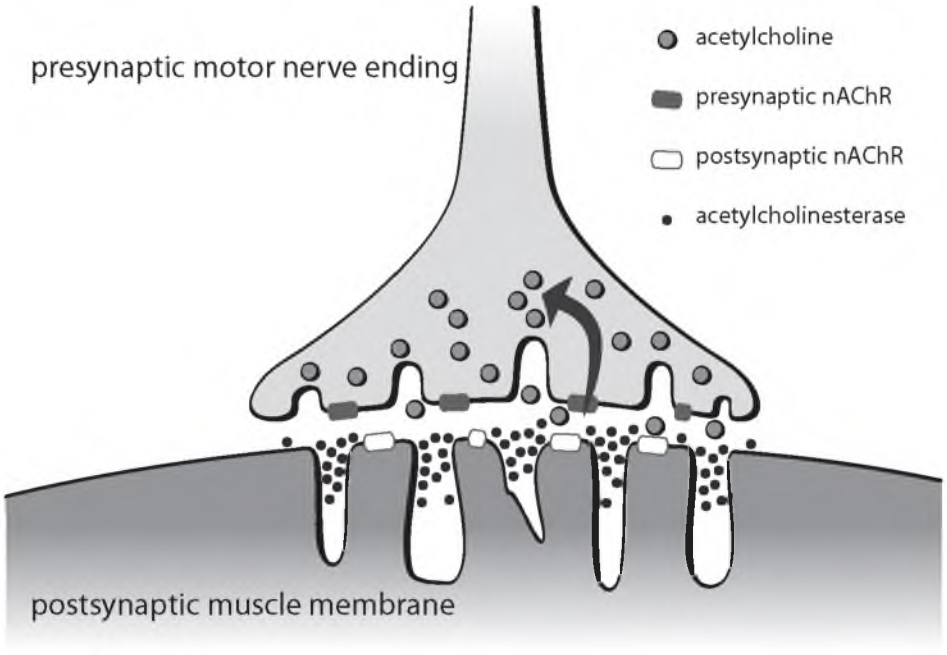
NEUROMUSCULAR BLOCK

The neuromuscular junction

The neuromuscular junction (NMJ) is responsible for the chemical transmission of electrical impulses from nerve to muscle in order to generate an appropriate muscle contrac-

tion. The NMJ consists of a prejunctional motor nerve ending separated from a highly folded postjunctional membrane of the skeletal muscle fibre by a synaptic cleft (Figure 1). The nerve ending contains synaptic vesicles necessary to synthesize and transport the neurotransmitter acetylcholine. The NMJ contains postsynaptic nicotinic acetylcholine receptors (nAChRs) on the skeletal muscle surface and presynaptic nAChRs on the motor nerve ending.[12]

Figure 1: Schematic depiction of the neuromuscular junction. (© E. Crins)



On the arrival of a nerve impulse, a burst of acetylcholine molecules is released from the presynaptic nerve ending. Acetylcholine then stimulates the postsynaptic nAChRs, causing ion channels to open. This allows ions to move across the muscle membrane, which depolarizes the motor end plate, followed by contraction of the muscle fibre. Acetylcholine is then rapidly broken down by the enzyme acetylcholinesterase, which is present in the synaptic cleft.[12;13]

Presynaptic nAChRs are responsible for the increased release of acetylcholine into the synaptic cleft during high frequency stimulation of the presynaptic nerve terminal.[14]

Neuromuscular block (NMB) occurs when nAChRs at the NMJ are occupied by a muscle relaxant, and acetylcholine can no longer bind to the receptor.

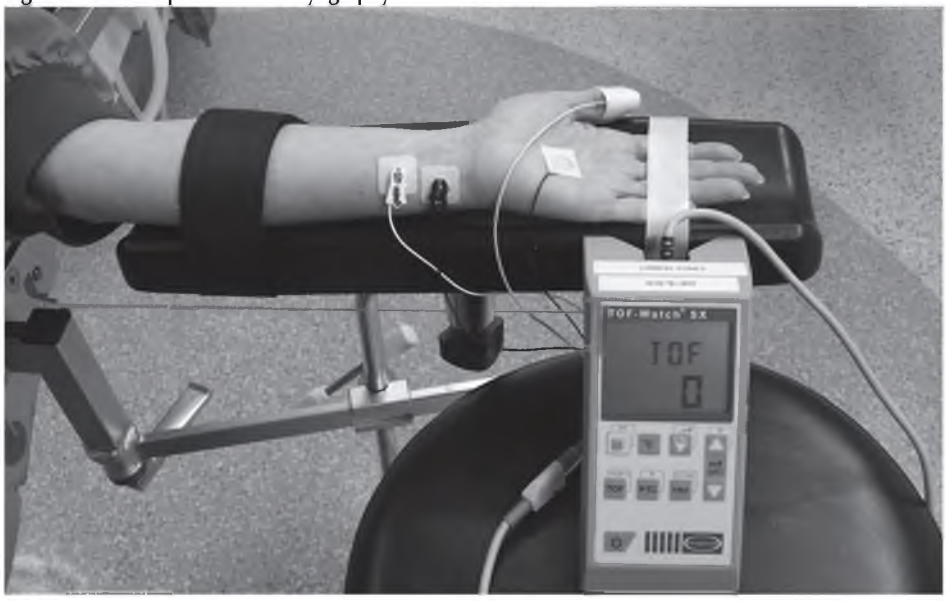
Pharmacodynamics of NMBAs and measurement of muscle contraction

Clinically, a common method for determining the onset and duration of NMB is to observe the skeletal muscle response evoked by a supramaximal electrical stimulus delivered to the nerve by a peripheral nerve stimulator. Most often, the contraction of the adductor pollicis muscle after stimulation of the ulnar nerve is used to assess the effect of neuromuscular blocking agents (NMBAs).

Mechanomyography (MMG) measures the contraction force, and has for many years been considered the gold standard for quantification of NMB. However, the method is somewhat cumbersome and is therefore rarely used in everyday practice.

Acceleromyography (AMG) is replacing this method. The acceleromyographic method of monitoring NMB is based on Newton's second law of motion: force = mass × acceleration. When the mass (the thumb for example) is constant, the acceleration is directly proportional to the force. The acceleration is measured using a small piezo-electric ceramic wafer (Figure 2).[15]

Figure 2: The setup of acceleromyography.



Two electrodes are placed over the ulnar nerve. The response to nerve stimulation is measured using a small piezo-electric wafer, placed on the volar site of the distal phalanx of the thumb. The peripheral skin temperature is measured at the palm of the hand.

Before the 1970s, NMB was measured as either the response to single motor nerve stimuli (single twitch responses) or the response to brief tetanic stimulation.[16] However, it was recognised that even with the complete return of a single twitch response, patients were still not fully recovered from NMB.[16] This was expressed by a phenomenon called fade, a

gradual diminution of the evoked response, after applying tetanic stimulation. Although tetanic fade is a more sensitive method of detecting residual paralysis, tetanic stimulation is painful in conscious patients and patients recovering from anaesthesia.
In the 1970s it was suggested that a brief train of 4 single twitches (the so-called Train of Four (TOF)) at a low frequency (0.2 Hz and 0.1 msec duration) was a more sensitive indicator than the single twitch response. The ratio of the height of the last twitch to the height of the first twitch (T4/T1) in this TOF was proposed as an index for recovery (the TOF ratio).[17] Nowadays, a TOF ratio of at least 0.9 (or 90%) or more is considered full recovery from NMB.[15]

Receptor occlusion during neuromuscular block

A non-depolarizing NMB displays a typical tetanic and TOF fade and a reduction in twitch amplitude, which directly reflects the action of the NMBA at different nAChR subtypes. Inhibition of the presynaptic subtype by non-depolarizing NMBAs creates the TOF fade, whereas reduction in single twitch amplitude is the result of inhibition of the muscle nAChR at the postsynaptic muscle membrane.[14]
Waud and Waud (1975) demonstrated in vitro, using guinea pig lumbrical muscles, that roughly 75-80% of the nAChR pool has to be blocked before the single twitch height begins to fall, and 90-95% of the receptors have to be blocked before the single twitch response is completely abolished.[18] According to the same authors, the TOF requires 25-30 percent free receptors for a normal response.[17] This margin of safety can be affected by disease states causing up- and down-regulation of nAChRs.[19] Therefore, in the clinical use of non-depolarizing NMBAs one should realize that due to the margin of safety of neuromuscular transmission (abundant amount of acetylcholine released, and only some of the available postsynaptic nAChRs are indeed needed for transmission) a large part of the nAChRs are still occupied with muscle relaxants, when the NMB is recovered to a TOF ratio of > 0.9.[17;20] Also, the diaphragm needs fewer free receptors for normal response than other muscles, which means that the diaphragm has a greater margin of safety than peripheral muscles.[21]
It is clear that in order to ensure the safety of the patient after NMB, as low a receptor occupancy as possible is desirable.

NEUROMUSCULAR BLOCKING AGENTS

In chapter 1, we already described the difference between depolarizing and non-depolarizing NMBAs. The non-depolarizing NMBAs belong either to the chemical structure group of the benzylisoquinolines or to the structure group of the aminosteroidal compounds.

The benzylisoquinolines

D-tubocurarine, the first non-depolarizing NMBA of the benzylisoquinoline group, was introduced in anaesthesia in 1942, as described earlier. Nowadays, the benzylisoquinolines mivacurium, atracurium and cisatracurium are NMBAs widely used in anaesthesia.[13] Atracurium and cisatracurium are degraded spontaneously in the plasma at body temperature and pH (Hofmann elimination). Atracurium is also metabolised by hydrolysis by nonspecific plasma esterases. Mivacurium is hydrolyzed by plasma cholinesterases. The clearance of the benzylisoquinolines is therefore independent of renal or hepatic function.[13] However, the benzylisoquinoline compounds may evoke histamine release, especially d-tubocurarine, but also the newer NMBAs mivacurium and atracurium.

The aminosteroidal muscle relaxants

Guachamacá, a toxin used for hunting, is associated with several members of the plant genus *Malouetia* (Family *Apocynaceae*), which is found in both South America and Africa. Guachamacá was first mentioned by Codazzi in 1841.[22] He indicated that it was the name given in the Apure region of Venezuela to the highly toxic plant also known as *guaricamo*. If its branches happened to be used as a spit, they would cause death to those who eat the meat. Early work on guachamacá led to the isolation of an alkaloidal substance which was given the name guachamacine. Soon after its isolation, guachamacine was shown to have a curare-like action.

Malouetine is pharmacologically certainly the most interesting of the *Malouetia* alkaloids. Quevauviller and Lainé in 1960 described the structure of malouetine after they had isolated it from the plant extract.[23] Malouetine or related drugs could offer alternatives to d-tubocurarine and some compounds were synthesized which appeared indeed to have a neuromuscular blocking effect.[24]Further research led to four aminosteroidal muscle relaxants: pancuronium, vecuronium, rocuronium and rapacuronium. Rapacuronium, however, was withdrawn from the market shortly after its release because of a high incidence of bronchospasm.

The development of pancuronium, vecuronium and rocuronium

Pancuronium consists of a steroidal nucleus with two acetylcholine moieties. The name pancuronium was derived from **p**(iperidino)**an**(drostane)**cur**(arising)-**onium**. In 1966, pancuronium was first given to two patients by Baird.[25] In these two patients a dose of 2 mg produced full NMB without cardiovascular side-effects. Pancuronium appeared to be a potent NMBA with a duration of action comparable to that of d-tubocurarine. In contrast to d-tubocurarine, its ganglion-blocking potency and histamine releasing properties were weak, and hence the side effects of hypotension and bronchospasm associated with d-tubocurarine were absent with pancuronium.

A series of 3 and 17 substituted pancuronium analogs were synthesized. This group of 16 compounds was studied. Vecuronium (Org NC45) was the compound selected for further development. It is a mono-quaternary compound which is only 1.6 times less potent than pancuronium (in cats), shorter acting and without cardiovascular side-effects (in dogs).[26] It was first administered in humans by Crul and Booij in 1980.[27]
Many other aminosteroidal compounds were synthesized and tested in animals and some of them were also tested in humans. Among them a vecuronium analog, Org 9426 (rocuronium), was studied. The results showed that rocuronium had little or no cardiovascular effects and its duration of action seemed similar to that of vecuronium.[28] Rocuronium was further developed and proved to have a fast onset of action in humans.

The pharmacology and pharmacokinetics of vecuronium and rocuronium

Vecuronium
Vecuronium is a monoquaternary aminosteroidal NMBA, with an intermediate duration of effect and without cardiovascular side-effects.[26] In humans its onset of action is about 3 minutes, and its duration of effect is 20-35 minutes when a dose of 0.1 mg kg^{-1} (2 x ED_{95}) is administered. Like all other relaxants, vecuronium is potentiated by inhalational anaesthetics.[29]
Vecuronium is metabolised by de-acetylation in the liver, producing three metabolites: 3-desacetyl-vecuronium, 17-desacetyl-vecuronium, and 3,17-desacetyl-vecuronium.[30] The metabolite 3-desacetyl-vecuronium exerts a strong pharmacological effect equal to 80% that of vecuronium.[31] This 3-desacetyl-vecuronium may contribute to the cumulative effect of repeated doses of vecuronium.[32]
Biliary excretion of vecuronium in animals and humans accounts for 30-50% of the injected dose.[33] Only 10-25% is excreted in the urine.[34] In patients with renal failure, clearance is reduced and terminal elimination half-life is increased.[35]

Rocuronium
Rocuronium is, like vecuronium, a NMBA with a monoquaternary aminosteroidal structure. Rocuronium is however, less potent. It is characterized by a short onset time and an intermediate duration of effect. After a bolus dose of 0.6 mg kg^{-1} (2 x ED_{95}) patients can be intubated within 1-2 minutes, and NMB lasts for about 35 minutes. With a high dose of rocuronium (4 x ED_{95} = 1.2 mg kg^{-1}), the onset time of NMB (mean 55 sec) resembles the onset time of succinylcholine (mean 50 sec).[36] Therefore rocuronium may serve as an alternative for succinylcholine when a rapid sequence induction of anaesthesia is needed. However at this high dose the duration of action resembles the long-acting NMBA pancuronium, in contrast to the duration of action of succinylcholine (3-5 minutes). Ro-

curonium has minimal effect on the heart rate and blood pressure and does not cause histamine release.[37]

The pharmacokinetics of rocuronium resembles those of vecuronium. However, compared to vecuronium, rocuronium lacks an ester group at position 3 of the steroid skeleton. Consequently, de-acetylation, which in the case of vecuronium results in the pharmacologically active 3-desacetyl-vecuronium, cannot occur with rocuronium. So far, active metabolites of rocuronium have not been shown in humans. Rocuronium is mainly taken up by the liver and excreted via the bile, and only 26% of an administered single dose was recovered from urine within 48 hours.[38] Because of this the duration of action may be prolonged in patients with renal or hepatic failure.[35] In patients with severe renal failure, the clearance of rocuronium is reduced by 33-39%, with a 66-84% increase of mean residence time of rocuronium.[39;40]

ANAESTHETIC MORBIDITY WITH NON-DEPOLARIZING MUSCLE RELAXANTS

Nowadays, it is recognized that the use of NMBAs in anaesthesia contributes considerably to its morbidity and mortality. The most important reason for such problems is variability in effect, residual paralysis, histamine release and allergic reactions.

The variability in the effect of NMBAs

Many enthusiastic reports on the clinical use of the early curare preparations appeared in the literature, heralding curare as the drug for muscle relaxation. The clinical anaesthesiologist, however, was entirely dependent on the subjective observations of the surgeon as to whether the patient was sufficiently relaxed. This led to a high incidence of unrecognised residual paralysis at the end of surgery.

The development of clinical quantitative evaluation methods resulted in a more objective measurement of muscle relaxation and the recognition of residual paralysis. Many methods have been developed for objective neuromuscular transmission monitoring, including the methods mentioned earlier, MMG and AMG, which have made it easier to detect the presence of residual paralysis and recognize the variability in the duration of action of the NMBAs.

It was realized that variability in effect might be a factor in the morbidity and mortality of anaesthesia. Many NMBAs have been synthesized and clinically investigated. However, although they provided excellent muscle relaxation, the variability in effect remained. Even the newer NMBAs, belonging to either the benzylisoquinolines or aminosteroidal compounds, display a wide variability in the degree of effect and duration of action.

Numerous factors contribute to such variability. For example inter-individual differences exists in liver and kidney function, body composition[41], age[42], gender[43], concurrent medication[44], concurrent diseases[35;40], haemodynamics, acid-base status, and temperature. There are also differences in the type, the depth, and the duration of the anaesthetic administered.[45] Moreover, different NMBAs have a different pharmacological profile. All these factors have an effect on the pharmacodynamics of the NMBAs. This causes a large variation in their duration of action, leading to the possibility of unwanted residual postoperative paralysis.

Residual paralysis

The second major problem related to the use of NMBAs is the occurrence of residual paralysis, or postoperative residual curarization (PORC). Variability in effect is one of the most important factors causing PORC and postoperative pulmonary complications.

Residual paralysis is still a frequent phenomenon in the post anaesthesia care unit (PACU).[46-49] The incidence of PORC and postoperative pulmonary complications was proven to be higher with NMBAs with a long duration of effect in comparison to those with an intermediate duration of effect.[50] Despite the application of techniques proven to limit the degree of residual paralysis, such as the use of intermediate-acting NMBAs and pharmacological reversal at the end of surgery, up to 33%–64% of patients have evidence of residual paralysis on arrival to the PACU.[51;52] Debaene et al. demonstrated that even after a single intubating dose of a NMBA with an intermediate duration of action, 16% of the patients had a TOF ratio <0.7 and 45% a TOF ratio <0.9.[46]

Residual NMB has been identified as a common aetiological factor in anaesthesia-related mortality and morbidity.[53] In a number of papers it was indicated that PORC resulted in postoperative pulmonary complications, such as upper airway obstruction and hypoxia.[53-58] PORC is also associated with inadequate recovery of pulmonary function, reduced pharyngeal muscle coordination increasing the risk of aspiration and an impaired hypoxic ventilatory response.[59-62]

Residual paralysis was defined in the past as a TOF ratio < 0.7. This was based on the research by Ali et al., who found that at a TOF ratio of 0.7, post tetanic fading was no longer present.[63] Later, it was demonstrated by Eriksson et al. that at a TOF ratio of 0.7, the sensitivity of the peripheral chemoreceptors for hypoxia was still depressed.[59;60;64] Therefore, with residual paralysis severe hypoxemia may occur. Also at a TOF ratio of 0.7 visual disturbances, pharyngeal dysfunction (disturbances in swallowing) and muscle weakness still exist.[61;62] These studies led one to the reconsideration of the value indicating return of complete recovery from NMB. Today, a TOF ratio of ≥ 0.9 is considered full recovery from NMB.[15]

It must be concluded that PORC contributes to the morbidity and mortality of anaesthesia. Therefore neuromuscular transmission must be monitored whenever a NMBA is adminis-

tered and a reversal agent should be administered whenever residual paralysis (TOF ratio < 0.9) is present at the end of surgery.

Histamine release

Part of the morbidity related to NMBAs is due to histamine release, a characteristic especially associated with the benzylisoquinoline derivatives and also succinylcholine.[13] Histamine release not only leads to facial erythema, hypotension and tachycardia, but also to bronchospasm and hypoxia, and is therefore potentially harmful.

Histamine release associated with the administration of d-tubocurarine was described as early as 1939.[65] The histamine release associated with benzylisoquinolines, including the newer benzylisoquinolines atracurium and mivacurium, has been confirmed by many authors.[66] The mechanism is due to the non-immunologic degranulation of mast-cells. Such effects have not been described for the aminosteroidal NMBAs.

Allergic reactions

Immediate hypersensitivity reactions, such as allergic or anaphylactic reactions, occur in one of every 5000 to 10.000 anaesthetics. NMBAs represent the most frequently incriminated substances and are responsible for 50-70% of the cases.[67] Hypersensitivity reactions to NMBAs are mainly acute immunoglobulin E (IgE)-dependent allergic reactions. In sensitized individuals these IgE antibodies bind to receptors in mast cells and blood basophils, and stimulate cells to release inflammatory mediators, such as histamine, tryptase and several cytokines. The involved target organs include the skin, mucous membranes, cardiovascular and respiratory systems and the gastrointestinal tract, causing erythema, urticaria, hypotension, tachycardia or bronchospasm. Clinical manifestations show variations, ranging from mild hypersensitivity reactions to severe anaphylactic shock and death.[67;68]

In most reports succinylcholine seems to be more frequently involved. Pancuronium and cisatracurium are the NMBAs associated with the lowest incidence of anaphylaxis during anaesthesia. Some controversy has arisen concerning a potential increased prevalence of allergic reactions to rocuronium.[67] The quaternary ammonium ions are suggested to be the allergenic determinants in NMBAs.[68]

In 15-50% of cases, the reactions are reported at the first known contact with a NMBA. This suggests a possible cross-reaction with IgE-antibodies generated by previous contact with apparently unrelated chemicals. An example is the report that an exposure to a cough mixture containing pholcodine may be responsible for the significant increase in specific IgEs to NMBAs, leading to an increased risk of allergic reactions to NMBAs.[67;69]

THE USE OF NEUROMUSCULAR BLOCKING DRUGS IN RENAL FAILURE

Prolonged NMB has been reported in patients with renal failure after administration of older non-depolarizing NMBAs (such as gallamine, d-tubocurarine and pancuronium), all of which are excreted, in part, by the kidney.[13] This has also been described for the newer NMBA rocuronium: the mean time to spontaneous recovery to a TOF ratio of 0.7 from rocuronium-induced NMB was significantly prolonged in patients with end-stage renal failure compared with patients with normal renal function.[40] This has been confirmed in several other clinical studies, although not consistently so.[39;70] Also, inter-individual variability is increased in renal failure patients, resulting in a less predictable duration of action.[35]
The prolonged duration of action of NMB in renal patients may be due to the reduced clearance of rocuronium, but also due to the disease state itself (causing a different volume of distribution, for example) and the possible interactions with additional medication often taken by these patients. Therefore, patients with renal insufficiency have an increased risk of PORC and postoperative respiratory complications.
Vecuronium has no prolonged duration of action in patients with renal failure. However, residual paralysis has been described after long-term administration of vecuronium in critically ill patients with renal failure.[71] Vecuronium undergoes hydrolysis to three pharmacologically active metabolites, of which 3-desacetyl-vecuronium is the most potent.[30,31] This 3-desacetyl-vecuronium, which has 80% of the potency of the parent compound vecuronium, is probably responsible for the reported episodes of prolonged NMB in critically ill patients with renal insufficiency.[71;72]

THE REVERSAL OF NEUROMUSCULAR BLOCK

Reversal of NMB is important not only for the prevention and treatment of residual paralysis at the end of an operation, but also as an escape route in situations where, after administration of a NMBA, it is impossible to intubate the trachea and to ventilate the patient by mask (*cannot intubate cannot ventilate*). Reversal of NMB can be achieved by administration of acetylcholinesterase inhibitors.

Short history of the use of acetylcholinesterase inhibitors in anaesthesia

The curare reversal effect of neostigmine was described in 1931 by Aeschlimann and Reinert.[73] The muscarinic side effects, such as bradycardia, bronchoconstriction, hypersalivation, abdominal cramps, and nausea and vomiting,[74] made anaesthetists reluctant to use reversal agents in anaesthesia. Hunter in 1953 demonstrated that neostigmine could cause considerable cardio-depression.[75] He advocated the simultaneous administration of 1.3 mg atropine with 2.5 mg of neostigmine. However, atropine also has side effects, such

as blurred vision, dry mouth and tachycardia. Nevertheless neostigmine is still used today and is considered the gold standard for reversal of NMB.

After Gray had introduced the 'Liverpool anaesthetic technique' with administration of high dose curare, the administration of neostigmine at the end of surgery became more or less routine in the United Kingdom.[76] In continental Europe, however, administration of neostigmine was not considered 'a must', and was even believed indicative of the poor capabilities of the anaesthetist, not being able to appropriately dose the various drugs according to the need of the individual patient. Only when monitoring of the neuromuscular transmission became more frequently applied, the need to reverse NMB became clear. Variability of effect and PORC nowadays underline the need for adequate reversal of NMB.

Reversal of neuromuscular block with acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors (anticholinesterases) inactivate the enzyme acetylcholinesterase at the NMJ, inhibiting the breakdown of the neurotransmitter acetylcholine, leading to an increase of the concentration of acetylcholine available for the nAChR.[77] However, once the enzyme is completely inactivated, additional administration of anticholinesterase produces no further increase in the availability of acetylcholine. Therefore, a dose exceeding 0.07 mg kg^{-1} neostigmine is unlikely to achieve additional effect.[78] Administration of an anticholinesterase has no effect on the NMBA itself and therefore no effect on the concentration of the NMBA at the NMJ.

Until recently the administration of anticholinesterases was the common method of reversing a NMB. As with NMBAs, there is a large inter-individual variability in the effect of these compounds. Furthermore, specific antibiotics may augment the NMB and some of these combined blocks may be not reversed by neostigmine.[79]

The most important factor in the ease of reversal is the degree of NMB.[80] More time and larger doses are required for the reversal of a profound NMB compared to more shallow depths of block.[81;82] The administration of anticholinesterases results in an increased concentration of acetylcholine which then competes with the NMBA to cause reversal of NMB. All the anticholinesterases have a ceiling effect when all the acetylcholinesterase is blocked and further administration of the inhibitor no longer increases the concentration of acetylcholine. Anticholinesterases fail to fully reverse a NMB when relaxant concentrations are high, making the rapid reversal from a deep NMB impossible.[78]

The anticholinesterases also have muscarinic side effects, described above, which contribute to morbidity and mortality. In patients with asthma the administration of anticholinesterases may provoke an asthma exacerbation, as neostigmine causes significant bronchoconstriction.[83] Anticholinesterases increase the motility of the gastro-intestinal tract. Postoperatively, increased intestinal motility can lead to disruption of intestinal anastomoses.[84]

Further developments in reversal of neuromuscular block

It was necessary to search for an alternative reversal agent with a better pharmacological profile. Other existing anticholinesterases were tested for their NMB reversing ability. New anticholinesterases were developed, with the aim of specifically inhibiting the acetylcholinesterase at the NMJ, thus avoiding the unwanted muscarinic side effects. However, this proved to be impossible.

Gaddum in 1957 mentioned antagonism by neutralisation: two drugs combining with one another to form an inactive compound.[85] Removal of NMBA from the receptor was mentioned as a possibility to reverse paralysis in 1961 by Linssen in his PhD thesis at the Radboud University in Nijmegen.[86] He described *in vitro* and *in vivo* studies with *germanine*, antagonizing gallamine, d-tubocurarine and succinylcholine. He wrote:

'By chemical antagonism or antagonism by neutralisation is an antagonism meant in which a pharmacological active substance is removed from the (receptor) environment via another, possible pharmacological inactive, substance. The effective concentration of the pharmacological active substance in the biophase is thereby decreased.'

And further: *'In case of chemical antagonism is the activity of the antagonist not determined by its affinity for certain specific receptors, but by the affinity between the pharmacological active substance, the agonist, and the antagonist.'*

Following to this principle of drug binding, studies started on the potential reversal of NMBAs by chemical chelation with anionic cyclophanes (Organon Laboratories in Newhouse, Scotland).[87] This was based on the knowledge that both quaternary ammonium and steroidal groups form complexes with the hosting cyclophanes. The compounds proved *in vitro* to be less potent in their reversal activity than the traditionally used neostigmine. However, one of the compounds when used in a high concentration almost caused complete reversal of the NMB. Unfortunately, the cavity of such small host-molecules varied considerably and their water solubility was relatively low. It was anticipated that this might cause problems for reliability and safety of reversal.

In 1996 Bom at the Organon Laboratories searched for a new solvent for rocuronium. He observed that rocuronium was less potent when dissolved in cyclodextrin than when dissolved in the original buffer solution.[88] He made the mental connection of the retention of rocuronium by the cyclodextrin. He also realised that cyclodextrins have a better defined lipophilic cavity and were more soluble in water than the cyclophanes which were tested previously. With this serendipity, the idea of encapsulation as a method for reversal of NMB was born.

SUGAMMADEX

The idea of Bom started the search for more specific binding of rocuronium to cyclodextrins to produce host-guest complexes. Only the β- and γ-cyclodextrin cavities were large enough to hold the steroid nucleus of rocuronium. Initially, a series of γ-cyclodextrins with an increased binding ability for rocuronium was synthesized. Unfortunately the whole steroid nucleus of rocuronium was still unable to fit into the cavity. Extending the cavity height by adding side chains was indicated. Theoretically, by giving these side chains on the γ-cyclodextrin molecule a negative charge electrostatic binding with the positively charged ammonium group of the rocuronium molecule would occur. Anionic carboxylic functions were added to the γ-cyclodextrin at the glucose monomers 6 position. This served to increase the electrostatic affinity for rocuronium, as well as increasing the height and the width of the cavity.[89]

Nine members of this modulated series of γ-cyclodextrin derivatives were studied in animals. Compound Org 25969 (per-6-(2-carboxyethylthio)-per-6-deoxy-γ cyclodextrin sodium salt) was selected because of its high affinity for rocuronium compared with the other compounds.[90] Finally, this led to the compound sugammadex, a modified γ-cyclodextrin which encapsulates aminosteroidal NMBAs.[91]

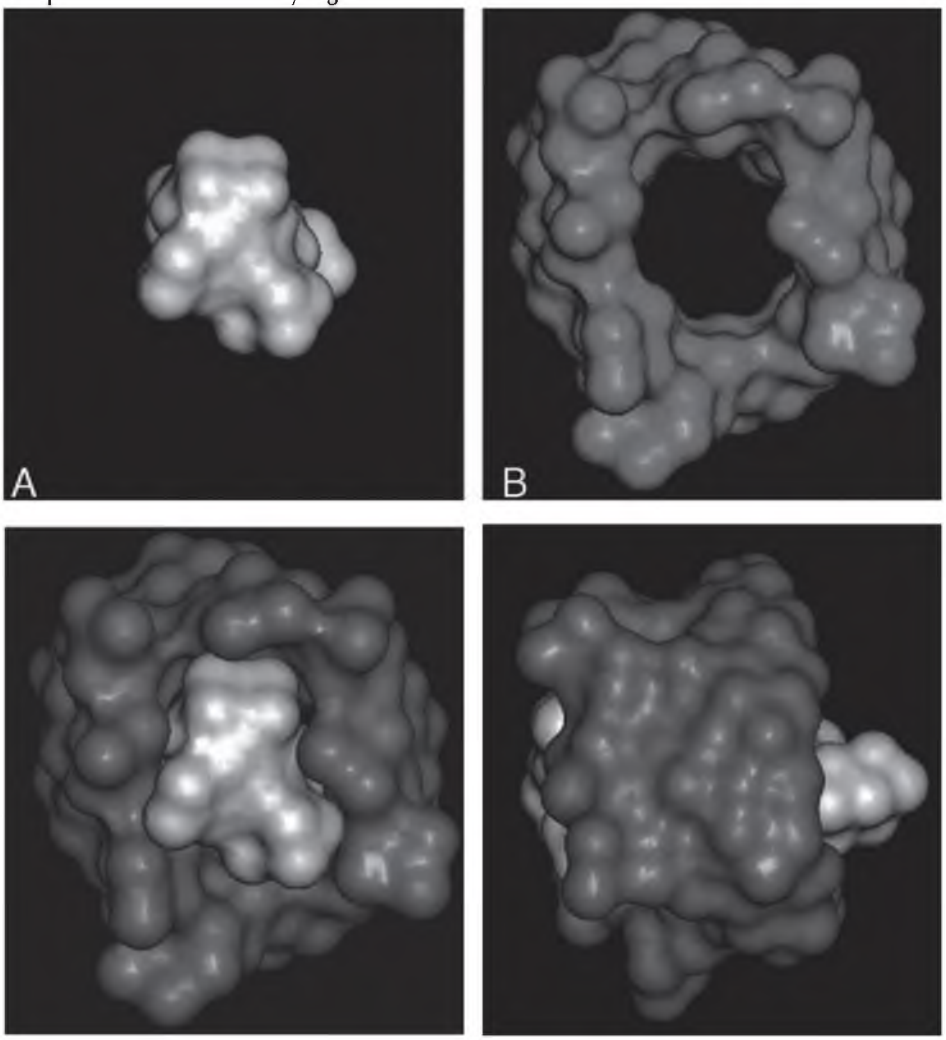
The mechanism of action of sugammadex

Sugammadex is the first selective relaxant binding agent designed to reverse the NMB induced by aminosteroidal NMBAs. Sugammadex does not interfere with acetylcholinesterase or the nAChR, but binds the NMBA molecule itself (Figure 3). Each molecule of sugammadex encapsulates one molecule of rocuronium or vecuronium, which leads to a rapid decrease of the concentration of free NMBA molecules in the plasma. As a result of the concentration gradient of free molecules between plasma and NMJ, steroidal NMBA molecules diffuse away from the NMJ (and the nAChR) into the plasma. This leads to a rapid dissociation of the NMBA from the nAChR and a rapid recovery from NMB. Acetylcholine receptor occupation can then recur and muscle contraction becomes possible.[91;92]

The binding of the steroidal molecules by sugammadex is very strong. This is due to the intermolecular (van der Waals) forces, hydrogen bonds and hydrophobic interactions. The complex of the steroidal NMBA with sugammadex exists in equilibrium, with a high association rate and a low dissociation rate, which favours the complex formation. The association constants of sugammadex for vecuronium and rocuronium are 10×10^6 mol^{-1} and 25×10^6 mol^{-1}, respectively.[94]

Due to its mechanism of action sugammadex has no effect on the acetylcholine concentration in the nicotinic or muscarinic synapses. Therefore, sugammadex is free from muscarinic effects such as bradycardia, vomiting, and bronchoconstriction. Also, sugam-

Figure 3: X-ray crystal structures of a rocuronium molecule (A) and a sugammadex molecule (B). Encapsulation of rocuronium by sugammadex at 1:1 ratio.



Gijsenbergh et al. *Anesthesiology* 2005; 103: 695-703,[93] with permission from MSD.

madex does not interfere with any receptor, which also makes the occurrence of unwanted effects very unlikely.

In vitro and in vivo animal studies with sugammadex

Studies in mouse nerve-hemidiaphragm indicated that rocuronium-induced NMB is more effectively reversed by sugammadex than vecuronium-induced NMB.[94] Studies were also performed using atracurium and mivacurium, neither of which were reversed by sugammadex.[95] Sugammadex proved to be specific for aminosteroidal NMBAs.

In a study in guinea pigs it was demonstrated that after administration of sugammadex the total plasma concentration of rocuronium increased.[92] Later, this was confirmed in studies in humans.[93;96;97] This increase of rocuronium is explained by rapid formation of the rocuronium-sugammadex complex in the plasma. After sugammadex administration, free rocuronium molecules in the plasma are rapidly bound to sugammadex. This creates a concentration gradient of free rocuronium molecules between the NMJ and the central compartment (the plasma). As they enter the plasma, more free rocuronium molecules are encapsulated by abundant sugammadex. As the assay method cannot differentiate between free and encapsulated rocuronium, the encapsulation of rocuronium appears as an increase in total plasma rocuronium concentration.

This confirmed the concept that sugammadex binds rocuronium, resulting its removal from the effect compartment (the NMJ) and the diffusion of rocuronium to the plasma, thus resulting in recovery from NMB.

In some relatively rare situations, is it necessary to re-establish NMB after reversal by sugammadex of a previous NMB. In these circumstances some free sugammadex may still be present and will encapsulate newly administered NMBAs, decreasing the neuromuscular blocking effect. The duration of action of sugammadex was therefore studied in anaesthetized rhesus monkeys.[98] The effect of the second dose of rocuronium, after reversal by sugammadex, increased with the time delay after the sugammadex administration and almost reached the original effect after a delay of 60 min. This experiment indicates that after reversal of NMB with sugammadex, it is possible to reinstate NMB with rocuronium, although, depending on the elapsed time, a higher dose of rocuronium will be required.[99] Since non-steroidal NMBAs (succinylcholine and benzylisoquinolines) are not reversed by sugammadex, it is also possible to re-establish NMB with these NMBAs.

The conclusion from these animal studies is that sugammadex proved to be a safe, rapid, and effective reversal agent for shallow and profound NMB induced by steroidal NMBAs, and in particular rocuronium.

Clinical studies with sugammadex

In the first study in volunteers it was demonstrated that dosages of 4-8 mg kg^{-1} of sugammadex resulted in an adequate and rapid reversal (within 2-3 minutes) of a rocuronium-induced NMB, even when sugammadex was administered within 3 minutes after the rocuronium administration.[93] Sugammadex not only is effective in reversing rocuronium-induced NMB, but also in reversing vecuronium-induced NMB and with a higher dose, pancuronium-induced NMB.[100-102]

The longer the time interval between the administration of rocuronium and that of sugammadex, the faster complete recovery of NMB after sugammadex administration is achieved.[96] However, sugammadex in a high dose was also effective in reversing a pro-

found NMB induced by a high dose of rocuronium (1.2 mg kg^{-1}), even when sugammadex was administered only 3 minutes after induction of NMB. [103]

Inhalational agents potentiate the effect of NMBAs.[45] The effect of sugammadex, however, does not differ between inhalational and intravenous anaesthesia.[104] The time of reversal of NMB by sugammadex is similar in all the age groups at a dose of 2 mg kg^{-1} for reversal of shallow NMB (after reappearance of the second twitch of the TOF).[105]

Sugammadex was administered in patients with pulmonary and cardiovascular diseases.[106;107] Unwanted effects were not observed, and the effect of sugammadex was not affected by the diseases. A study in volunteers demonstrated that sugammadex has no effect on QT-time.[108]

Sugammadex is biologically inactive, and appeared to be safe and well-tolerated in the clinical studies described. In some clinical trials dysgeusia (a metallic or bitter taste) was reported, which was mainly seen after sugammadex dosages > 32 mg kg^{-1}.[109] A few cases of allergy-like reactions (flushing, erythematous rash) were reported.[110]

Comparison with neostigmine

The reversal of rocuronium-induced NMB is faster with sugammadex than either with neostigmine or edrophonium.[111;112] In another study it has been proven that rocuronium reversed with sugammadex has a faster recovery than cisatracurium reversed with neostigmine.[113] Furthermore, neostigmine is unable to reverse deep NMB whereas sugammadex 16 mg kg^{-1} is able to reverse the effects of high-dose rocuronium even 3 minutes after induction of the NMB.[103;114]

Pharmacokinetics of sugammadex

After intravenous administration, sugammadex demonstrates linear pharmacokinetic properties over the dose range of 1–16 mg kg^{-1}. Sugammadex and the sugammadex-rocuronium complex do not bind to plasma proteins or erythrocytes. Sugammadex does not appear to undergo metabolism and is primarily excreted in the urine as the unchanged drug; the elimination half-life is approximately 1.7 hours. The plasma clearance is estimated to be 85-120 ml min^{-1}, which is similar to the glomerular filtration rate. In healthy volunteers, a mean percentage of 59-80% was excreted in the urine up to 24 hours after sugammadex administration.[93]

When sugammadex is administered after a dose of rocuronium, urinary excretion of rocuronium increases, with increasing doses of sugammadex. In patients receiving rocuronium alone, 19% of the rocuronium dose is recovered in the urine until 16 hours after administration. After administration of sugammadex, the proportion of the rocuronium dose excreted in the urine is increased to 53% until 16 hours after administration.[97] The percentage urinary excretion of a dose of rocuronium increases up to a maximum of 68% over 24 hours. After encapsulation by sugammadex, rocuronium is confined in the space

in which sugammadex resides and the plasma clearance of rocuronium assimilates into the plasma clearance of sugammadex.[93]

The molecule has a very limited trans-placental transfer and passage of the blood-brain barrier. Unlike rocuronium, the sugammadex-rocuronium complex is not eliminated via the biliary route.

Interaction of sugammadex with other drugs

Theoretically, sugammadex is able to bind other drugs. Such interactions were studied *in vitro* for two reasons. First, because these drugs may displace rocuronium, which can result in recurrence of NMB. Second, the effect of the other drugs may be decreased when they are encapsulated by sugammadex. Many relevant compounds (>300) have been studied and it was found that sugammadex also binds toremifene (a substituent of the anticancer drug taxol), flucloxacillin (an antibiotic), and fusidic acid (a bacteriostatic agent).[115]

The ability of sugammadex to form complexes with other steroidal and non-steroidal compounds such as cortisone, atropine, hormonal contraceptives, remifentanil, verapamil, fusidic acid, and flucloxacillin is insignificant and approximately 120–700 times less than the affinity for rocuronium.[115] However, it is recommended that flucloxacillin should be avoided until 6 h after sugammadex and a missed dose advice should be followed in patients taking oral contraceptives when given sugammadex.[110]

In none of the clinical studies performed so far any sign of drug interactions was noticed.

Conclusion

Sugammadex is an effective selective relaxant binding agent that rapidly reverses shallow, moderate and profound levels of NMB induced by aminosteroidal NMBAs. Its effect is not influenced by either inhalational or intravenous anaesthesia. It is free from muscarinic side effects and can modify the time course of action of the steroidal NMBAs to the individual need of the case. With sugammadex available sufficient NMB can be maintained until the end of surgery without concern about residual paralysis, easing the work of the surgeon. The duration of action of rocuronium can be changed from intermediate to short because its effects can be rapidly reversed by sugammadex even just 3–5 min after a large dose of rocuronium. Rapid reversal of rocuronium can be achieved if there is difficulty with airway management and tracheal intubation (*cannot intubate cannot ventilate*), and may enable rapid return of spontaneous respiration, so called 'rescue' reversal.

Most importantly, sugammadex may improve patient safety, as it prevents PORC after the use of aminosteroidal NMBAs. Reduction of the incidence of PORC may also decrease the incidence of postoperative pulmonary complications, which may have an effect on anaesthesia-related morbidity.

THE USE OF SUGAMMADEX IN RENAL FAILURE

As described before, patients with renal failure are especially vulnerable to the effects of NMBAs. They may have a longer duration of action of rocuronium and are therefore at risk of developing residual paralysis. This patient group would benefit from a selective relaxant binding agent, such as sugammadex, with few side effects.

However, sugammadex and the sugammadex-rocuronium complex are eliminated by the kidneys.[93] Also, administration of sugammadex leads to altered elimination of rocuronium, as it promotes the renal excretion of rocuronium, and the extrarenal route of elimination is expected to be unavailable for encapsulated rocuronium.[96]

Patients with renal failure will retain the sugammadex-rocuronium complex for a longer period of time. This raises concerns regarding the safety of the drug in this patient group: when the elimination pathway of rocuronium is diverted from hepatic clearance to renal clearance after administration of sugammadex, what will happen to the complex when renal clearance is decreased? Will the reversal of rocuronium-induced NMB by sugammadex be effective? And if the complex is not cleared renally, will patients with severe renal failure have more side effects from the drug? Is there a possible risk, when rocuronium is not cleared from the body, that paralysis will recur?

The aim of the studies described in this thesis is to investigate the efficacy of sugammadex in reversing NMB in renal failure, both in animals (the cat) and in humans; to describe the pharmacokinetics and the safety profile of sugammadex and rocuronium in renal failure patients compared to healthy controls; and to investigate the efficacy of sugammadex in reversing NMB induced by 3-desacetyl-vecuronium, a metabolite of vecuronium, possibly leading to residual paralysis in critically ill patients with renal failure.

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Chapter 3

Reversal of rocuronium-induced neuromuscular block by sugammadex is independent of renal perfusion in anesthetized cats

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ABSTRACT

Purpose

Sugammadex is a selective relaxant binding agent designed to encapsulate the aminosteroidal neuromuscular blocking agent rocuronium, thereby reversing its effect. Both sugammadex and the sugammadex-rocuronium complex are eliminated by the kidneys. This study investigated the effect of sugammadex on recovery of rocuronium-induced neuromuscular block in cats with clamped renal pedicles, as a model for acute renal failure.

Methods

Twelve male cats were divided into two groups and anesthetized with medetomidine, ketamine and alpha-chloralose. The cats were intubated and ventilated with a mixture of oxygen and air. Neuromuscular monitoring was performed by single twitch monitoring. Rocuronium 0.5 mg kg^{-1} i.v. was administered. After spontaneous recovery from neuromuscular block, both renal pedicles were ligated. A second dose of rocuronium 0.5 mg kg^{-1} i.v. was given. One minute after disappearance of the twitches, in Group 1 placebo (0.9% saline) and in Group 2 sugammadex 5.0 mg kg^{-1} i.v. was administered. Onset time, duration of neuromuscular block and time to recovery to 25, 50, 75 and 90% were determined.

Results

After renal pedicle ligation, sugammadex reversed rocuronium-induced neuromuscular block significantly faster than spontaneous recovery. Mean time (SEM) to 90% recovery of the twitch response was 4.7 (0.25) minutes (Group 2) versus 31.1 (5.0) minutes (Group 1) ($p<0.0001$). No signs of recurrence of neuromuscular block were observed for 90 minutes after complete twitch restoration. Sugammadex caused no significant cardiovascular effects.

Conclusion

Sugammadex rapidly and effectively reversed rocuronium-induced neuromuscular block in anesthetized cats, even when both renal pedicles were ligated and renal elimination of the drugs was no longer possible.

INTRODUCTION

Rocuronium is a non-depolarizing aminosteroidal neuromuscular blocking agent, widely used in anesthesia.[1] Recovery from neuromuscular block occurs spontaneously as the muscle relaxant diffuses away from the neuromuscular junction and is eliminated. However, postoperative residual curarization is a potential problem after administration of neuromuscular blocking agents, as it is a risk factor for postoperative pulmonary complications, for example aspiration and hypoxia.[2] Reversal of neuromuscular blocking agents has traditionally been achieved by administration of acetylcholinesterase inhibitors (anticholinesterases). However, anticholinesterases are only effective in reversing neuromuscular block if recovery has already started.[3] Also, anticholinesterases have muscarinic side-effects (nausea, vomiting, bradycardia, bronchoconstriction), which require the concomitant administration of atropine.[3]

Sugammadex, a modified γ-cyclodextrin, is the first selective relaxant binding agent designed to encapsulate and inactivate rocuronium, thereby rapidly reversing its effect.[4] The high affinity of sugammadex for rocuronium (association constant K_a of the sugammadex-rocuronium complex is 25×10^6 M^{-1}) results in complex formation (1:1).[4,5] Sugammadex encapsulates a large fraction of the rocuronium molecules in plasma, which results in a rapid decrease in the concentration of free (unbound) rocuronium in plasma. This creates a concentration gradient of free rocuronium molecules between the effect compartment, the neuromuscular junction, and the plasma. Rocuronium molecules return to the plasma, where they are encapsulated by more sugammadex molecules.[4,6] Second, because of the high concentration of uncomplexed sugammadex in plasma, sugammadex molecules will rapidly distribute from plasma towards the extracellular compartment, because of the concentration gradient.[5] As a result of these concentration gradients, complexation will occur rapidly and the neuromuscular block will decrease.

Because sugammadex does not interfere with acetylcholinesterase, it lacks muscarinic side-effects. Also, it has been proved to reverse profound neuromuscular block directly after a high dose of rocuronium had been administered.[7] Sugammadex is a water-soluble molecule, which is excreted in the urine in its unchanged form.[8]

In patients receiving rocuronium, the drug is mainly taken up by the liver and excreted into the bile.[1] The mean percentage of rocuronium recovered from the urine within 48 hours after administration is 26% of the administered dose.[9] After complex formation by rocuronium and sugammadex, the pathway of hepatic uptake and biliary excretion of encapsulated rocuronium is no longer possible and the complex can only be excreted by the kidneys. Therefore, administration of sugammadex promotes the renal elimination of rocuronium, dose-dependently, up to 74% after administration of high doses of sugammadex (8 mg kg^{-1}). [8,10]

Because of the changed distribution and elimination of rocuronium (from hepatic to renal elimination) after its encapsulation by sugammadex, the efficacy and persistence of reversal of neuromuscular block could be related to the renal excretion of the rocuronium-sugammadex complex. Because excretion of the complex by the kidneys is no longer possible in renal failure, there are concerns regarding the safety of the drug, and the possibility of recurrence of neuromuscular block. The objective of this study was to determine whether the sugammadex-induced reversal of rocuronium-induced neuromuscular block was modified by occlusion of both renal arteries in anesthetized cats.

METHODS

In-vivo experiments were performed in the Animal Laboratories for Experimental Anesthesia, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands. The experiments were approved by the regional ethics committee on animal experiments.
Twelve experiments were performed on 12 different male cats, weighing between 3.3 and 5.5 kg (mean weight 4.65 kg). The cats were deeply anesthetized with medetomidine (Dormitor®, Norden Labs) 80 μg kg^{-1} and ketamine (Ketaset®, Willows Francis) 5 mg kg^{-1}, intramuscularly. Alpha chloralose (BHD) 90 mg kg^{-1} was administered intraperitoneally, followed by intravenous administration of 10 mg kg^{-1} as required, for maintenance of anesthesia. Two intravenous lines were placed; one for anesthetic administration, including rocuronium, the other for test drug administration.
After anesthesia induction, the cats were intubated endotracheally and the lungs were ventilated with a mixture of oxygen and air in a volume ratio of 1:3. Heart rate, oxygen saturation, blood pressure and temperature were monitored and recorded every 10 s. Heart rate and peripheral oxygen saturation were determined at the ear with a pulse-oximeter (Biox; Ohmeda, Madison, WI, USA); also a blood gas analyzer (Rapidlab 248, Bayer) was used for arterial oxygen saturation measurement. Blood pressure was determined using an arterial line placed into the right femoral artery. Temperature was recorded with a rectal probe and was kept at 37-38 ^{0}C.
A laparotomy was performed to place a ligature at both renal pedicles, so both renal arteries and veins could be occluded later during the experiment.
For monitoring purposes the sciatic nerve of the right leg was stimulated supramaximally using clamp electrodes and a force displacement transducer for mechanomyography was connected to the tibialis muscle. Stimulation was performed with 2 ms square wave pulses in a single twitch sequence of 0.1 Hz by a Grass S88 Stimulator (Grass Medical Instruments, Quincy, MA, USA).
When the animal was in a hemodynamic stable situation and neuromuscular monitoring was stable, rocuronium bromide was administered as an intravenous bolus injection in a

dose of 2 x ED_{90} (0.5 mg kg^{-1}). The ED_{90} was defined as the dose of rocuronium which produced a mean maximum neuromuscular block of 90% in the cat population. The animals were left to recover from neuromuscular block (100% recovery of the twitch response) spontaneously. Ninety minutes after recovery of the twitch responses both renal pedicles were ligated. Thirty minutes after the renal pedicle ligation, a second dose of rocuronium bromide 0.5 mg kg^{-1} was administered.

Twelve cats were studied and were divided into two groups. In Group 1 (control, n=5), placebo (0.9% saline) was administered 1 minute after complete neuromuscular block was induced by the second dose of rocuronium. In Group 2 (n=7), 5.0 mg kg^{-1} sugammadex was administered, 1 minute after induction of neuromuscular block by the second dose of rocuronium.

Onset time of neuromuscular block, duration of neuromuscular block, time to recovery of the twitch response to 25, 50 and 90% and the recovery index (time from 25% recovery to 75% recovery) were determined for each rocuronium administration. Onset of neuromuscular block was defined as the time (min) from administration of rocuronium until disappearance of single twitch response. Duration of neuromuscular block was defined as the time (min) from disappearance of twitch response until the first visible twitch response. Time to 25, 50, 75 and 90% recovery was defined as the time (min) from administration of rocuronium until recovery of the twitch response to 25, 50, 75 and 90% of twitch height relative to baseline values. Residual block and recurrence of neuromuscular block were assessed by continuing neuromuscular monitoring for another 90 minutes after complete twitch restoration.

Blood pressure and heart rate were recorded for analysis at four time points: before injection of rocuronium (both groups), 1 minute after rocuronium (both groups), before sugammadex (Group 2) and 1 minute after sugammadex (Group 2). The changes were expressed as percentages of the values before either rocuronium or sugammadex injection.

At the end of the experiment, intravenous administration of methylene blue confirmed successful renal pedicle clamping in all cats. After completion of the experiment, the animals were killed.

Statistics

During the experiments all variables were automatically collected, in real time intervals of 10 s, and assembled in a data file, which was imported into EXCEL to perform all calculations. The data were statistically analyzed with the SAS (v 8.02) procedures (SAS, Cary, NJ, USA). Data are presented as mean values with SEM in parentheses. All measurements obtained from first and second administration of rocuronium were treated as paired observation (difference). To reduce inter-individual variability, onset and duration times of neuromuscular block were treated as relative paired observation (difference between two observations normalized to the first). Changes in blood pressure and heart rate as a

result of rocuronium or sugammadex were also analyzed as relative paired observations (difference/value before) within the groups. Student's t test was performed. The level of significance used was $p < 0.05$.

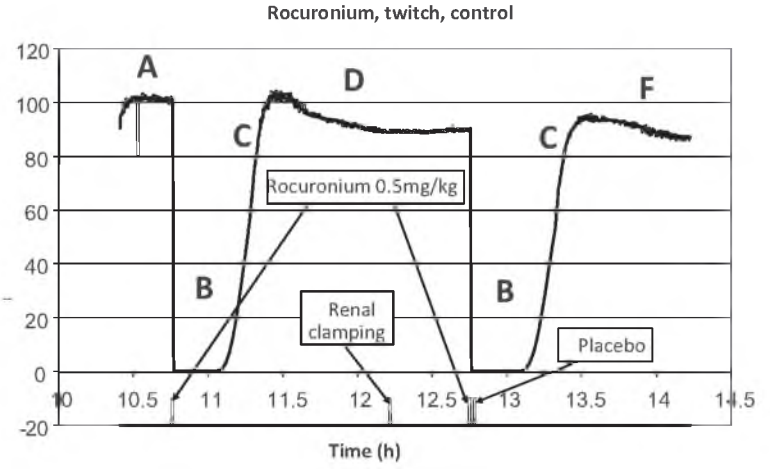
RESULTS

Neuromuscular Block

The experimental time course with spontaneous recovery is illustrated in the tracing of an experiment of Group 1 (control) and presented in Figure 1. Figure 2 is an experiment of Group 2, showing recovery after sugammadex administration. Various periods can be recognized: equilibration (A), constant neuromuscular block 100% (B), spontaneous recovery (C), period of renal pedicle clamping at 100% twitch height (D), recovery in presence of sugammadex (E), and period for evaluation of any recurrence of neuromuscular block (F). The effect of sugammadex on recovery times from rocuronium-induced neuromuscular block before and after bilateral renal pedicle ligation is shown in Table 1.

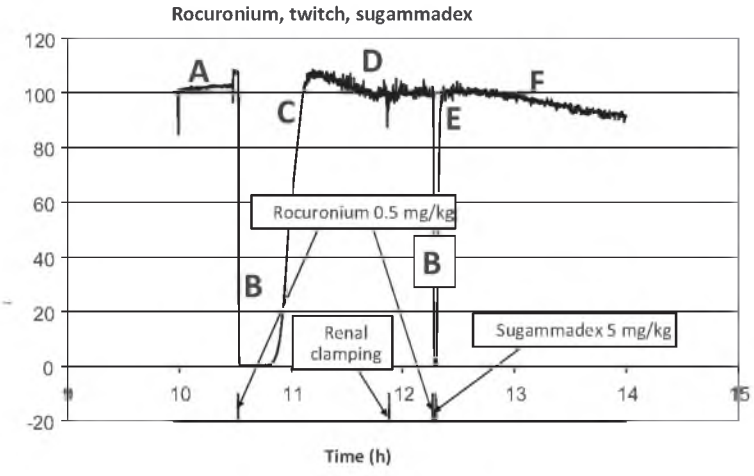
Onset time and duration of rocuronium-induced neuromuscular block after the first administration of rocuronium 0.5 mg kg^{-1} was not significantly different between the two groups. Neither was the onset time after the second administration. Spontaneous recovery times of neuromuscular block after administration of rocuronium 0.5 mg kg^{-1}, before or

Figure 1: Experimental time course in Group 1 (controls).



Twitch response after administration of rocuronium 0.5 mg kg^{-1}. After spontaneous recovery, renal arteries were clamped. Thirty minutes after renal clamping, a second dose of rocuronium 0.5 mg kg^{-1} was administered. One minute after disappearance of the twitches, placebo (0.9% saline) was administered. A: equilibration; B: constant neuromuscular block 100%; C: spontaneous recovery; D: period of renal clamping at 100% twitch height; F; period of evaluation of recurrence of neuromuscular block.

Figure 2: Experimental time course in Group 2 (sugammadex).



Twitch response after administration of rocuronium 0.5 mg kg^{-1}. After spontaneous recovery, renal arteries were clamped. Thirty minutes after renal clamping, a second dose of rocuronium 0.5 mg kg^{-1} was administered. One minute after disappearance of the twitches, sugammadex 5.0 mg kg^{-1} was administered. A: equilibration; B: constant neuromuscular block 100%; C: spontaneous recovery; D: period of renal clamping at 100% twitch height; E: recovery after administration of sugammadex; F: period of evaluation of recurrence of neuromuscular block.

Table 1: Effect of sugammadex on recovery times from rocuronium-induced neuromuscular block before and after bilateral renal pedicle ligation.

In Group 1, after the second administration of rocuronium, placebo (0.9% saline) was administered 1 minute after complete neuromuscular block. In Group 2 sugammadex 5.0 mg kg^{-1} was administered 1 minute after complete neuromuscular block after the second administration of rocuronium.
Data are presented as the mean time (SEM) in minutes after administration of an i.v. bolus dose of rocuronium 0.5 mg kg^{-1}. Statistics: In Group 2, onset time, duration times and recovery times are treated as relative paired observation (difference between two observations relative to the first).
Level of significance: $p<0.05$. ns= not significant.

	Group 1 (*N*=5) (controls)		Group 2 (*N*=7) (sugammadex-induced recovery)		Comparing variables in Group 2 in the two administrations
Rocuronium	First Admin.	Second Admin.	First Admin.	Second Admin.	Significance (Paired relative)
Renal blood flow	Intact	Interrupted	Intact	Interrupted	
Onset time (min)	1.0 (0.17)	0.9 (0.17)	0.7 (0.03)	0.8 (0.05)	ns
Duration (min)	13.8 (2.7)	16.8 (3.2)	17.6 (2.0)	2.5 (0.07)	<0.0001
Recovery of the single twitch response to					
25% (min)	18.5 (2.7)	21.8 (3.4)	23.3 (2.9)	3.0 (0.12)	<0.0001
50% (min)	21.2 (3.0)	25.1 (3.9)	26.2 (3.3)	3.5 (0.15)	<0.0001
90% (min)	26.4 (3.3)	31.1 (5.0)	30.6 (3.8)	4.7 (0.25)	<0.0001
Index 25-75 (min)	5.2 (0.8)	6.7 (1.8)	5.9 (1.0)	1.0 (0.09)	<0.0001

after renal clamping, were also not significantly different (limited to the control group). (Table 1)

In Group 2, 30 minutes after renal clamping, sugammadex 5.0 mg kg^{-1} was administered 1 min after disappearance of the twitches after the second dose of rocuronium 0.5 mg kg^{-1}. After renal pedicle ligation, time to complete recovery of rocuronium-induced neuromuscular block was significantly shorter after the administration of sugammadex 5.0 mg kg^{-1}. Mean time (SEM) to recovery to 90% of the twitch height was 4.7 (0.25) min in de sugammadex-induced recovery group (Group 2), compared with 31.1 (5.0) min in the control group (Group 1), both after interruption of renal blood flow. In Group 2, the second recovery to 90%, after renal pedicle ligation and sugammadex-induced recovery (4.7 min), was also significantly shorter (p <0.0001) than spontaneous recovery to 90% after the first administration of rocuronium (30.6 (3.8) min) and normal renal function.

After administration of sugammadex 5.0 mg kg^{-1} all recovery times were significantly faster than spontaneous recovery times of rocuronium 0.5 mg kg^{-1}, although renal blood flow was interrupted and renal excretion of sugammadex and rocuronium was no longer possible.

During neuromuscular monitoring for 90 minutes after complete twitch restoration after sugammadex no signs of residual paralysis or recurrence of neuromuscular block were observed in any of the cats. Also, during recovery from neuromuscular block, the stable T1 response was within 80 – 120% of the control (baseline) value, as should be the case according to the guidelines on good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents. [11]

Hemodynamics

Because of technical problems, two cats in Group 2 did not provide usable recordings of blood pressure. A small (3%) but significant increase in heart rate (p=0.035 and 0.037 in Group 1 (n=5) and Group 2 (n=5) respectively and p=0.0012 for the two groups together) was observed in both groups after all administrations of rocuronium. After sugammadex injection in Group 2, there were no significant changes, although there was a tendency towards a decrease of heart rate (2.6 %, SEM = 1.1) (p=0.075). Inspecting the heart rate tracings suggests that sugammadex immediately reverses the small increase in heart rate observed after rocuronium administration.

There were no significant changes in mean arterial pressure after either drug.

DISCUSSION

This study investigated the efficacy of sugammadex in reversing rocuronium-induced neuromuscular block in an animal model of acute renal failure. After complete interruption

of renal perfusion, sugammadex rapidly and effectively reversed the effect of rocuronium, even when renal elimination of both drugs was no longer possible. Sugammadex still reversed rocuronium-induced neuromuscular block completely in a time significantly faster than spontaneous recovery. Recurrence of neuromuscular block was not observed for 90 minutes after twitch restoration.

This demonstrates that reversal of neuromuscular block and the speed of reversal are not dependent on the renal elimination of the sugammadex-rocuronium complex. It is the formation of the complex between rocuronium and sugammadex and the redistribution of rocuronium molecules that prevents their action at the neuromuscular junction. Because of the strong complex formation (K_A=25,000,000 M^{-1}), a large fraction of the rocuronium molecules is always encapsulated by sugammadex, although the compounds cannot be excreted in renal failure.

In one study in humans with end-stage renal failure, sugammadex effectively and rapidly reversed rocuronium-induced neuromuscular block. Recovery times after sugammadex 2.0 mg kg^{-1} to reverse the neuromuscular blocking effect of rocuronium 0.6 mg kg^{-1} were not statistically different in renal patients compared with healthy controls.[12] Sugammadex was safe and well-tolerated in end-stage renal failure patients and no patients showed signs of recurrence of neuromuscular block.[12] However, the number of patients studied was small.

This does raise questions regarding the long-term safety of sugammadex in renal failure. What happens with the sugammadex-rocuronium complex which normally is excreted via the kidneys and which cannot be metabolized by humans?

Therefore, more animal and human studies are needed to determine the long-term safety aspects and the disposition of sugammadex in renal failure, because the clearance of both rocuronium and sugammadex is much reduced.[13] However, it is to be expected that, as long as the biliary route is open for the free rocuronium molecules, it is most likely that rocuronium plasma concentration will decrease faster than that of sugammadex.

Sugammadex is a γ-cyclodextrin, an oligosaccharide forming a cylindrical capsule with a lipophilic internal cavity and a hydrophilic exterior.[4] Cyclodextrins are highly water-soluble and do not have intrinsic biological activity; it is therefore unlikely that side effects will occur.[4] This has also been demonstrated in other animal studies and in various clinical trials in humans.[6,7,8,10,14] In our study there was a tendency towards a decrease in heart rate after administration of sugammadex, which could be interpreted as a restoration of the increase in heart rate caused by the preceding injection of rocuronium.

The results of this study also show that occlusion of both renal pedicles in anesthetized cats does not significantly prolong the neuromuscular blocking effect of rocuronium and the subsequent spontaneous recovery of neuromuscular function, as recovery times before and after renal clamping in Group 1 are not significantly altered.

In patients with normal renal function receiving rocuronium intravenously, 26 % of the administered dose of rocuronium was recovered from the urine in 48 h.[9] In cats a mean percentage of 8.7% of an injected dose of rocuronium is excreted into the urine in 6 h.[15] Rocuronium is not dependent on renal blood flow for its major route of excretion, but is taken up by the liver and excreted into the bile in high concentrations.[9] Although hepatic uptake and biliary elimination are thought to be the main routes of elimination for rocuronium, it seems that renal failure can have a marked effect on rocuronium pharmacokinetics and pharmacodynamics, although not consistently so.[16,17,18] In patients with no or minimum renal function, the clinical duration and recovery time of rocuronium 0.6 mg kg^{-1} increased significantly.[16,17,18] The only explanation that can be given is a change in the volume of distribution of rocuronium in renal failure patients. It is probably redistribution rather than excretion that is responsible for the duration of action of rocuronium. In our study, we clamped the renal pedicles of the cats 30 min before administering the second dose of rocuronium, which is a different situation from chronic end-stage renal failure. This probably explains why we did not find any differences in onset and duration of action, after renal pedicle ligation. Acute renal failure very likely has no effect on the duration of action of rocuronium. We therefore conclude that in this experiment recovery times before and after renal clamping are comparable.

In conclusion, this study shows that after complete interruption of renal perfusion, sugammadex still causes rapid and complete reversal of rocuronium-induced neuromuscular block, without signs of recurrence of neuromuscular block and without significant cardiovascular effects. Reversal of neuromuscular block and the speed of reversal are not dependent on the renal excretion of the sugammadex-rocuronium complex.

Further studies in humans are required, because this animal model of acute renal failure is not fully comparable with humans with chronic end-stage renal failure and more information is needed regarding the long-term safety aspects of sugammadex in renal failure.

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Chapter 4

Multicentre, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function

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ABSTRACT

Background

Sugammadex, a modified γ-cyclodextrin, is the first selective relaxant binding agent that specifically encapsulates the steroidal neuromuscular blocking agent, rocuronium. The action of rocuronium is prolonged in patients with renal failure. As sugammadex is primarily cleared renally, this phase III trial investigated the efficacy and safety of sugammadex for reversal of rocuronium-induced neuromuscular block (NMB) in patients with end-stage renal failure.

Methods

Thirty adult patients were studied: 15 renally-impaired (creatinine clearance (CL_{CR}) <30 ml min^{-1}) and 15 controls (CL_{CR} ≥80 ml min^{-1}). Anaesthesia was induced and maintained using i.v. opiates and propofol. Neuromuscular monitoring was performed by acceleromyography and train-of-four (TOF) nerve stimulation. Rocuronium 0.6 mg kg^{-1} was given, followed by a single i.v. dose of sugammadex 2.0 mg kg^{-1} at reappearance of the second twitch of the TOF. The primary efficacy variable was time from administration of sugammadex to recovery of the TOF ratio to 0.9. Safety variables included clinical evidence of reoccurrence of NMB.

Results

After sugammadex administration, the mean (SD) time to recovery of the TOF ratio to 0.9 was 2.0 (0.72) min in renal patients and 1.65 (0.63) min in controls (NS). Recurrence of NMB was not observed in any patient. No sugammadex-related serious adverse events were reported.

Conclusions

Sugammadex administered at reappearance of T2 rapidly and effectively reverses NMB induced by rocuronium in renal failure and healthy patients. Sugammadex was well tolerated by all patients. Further safety studies on sugammadex in patients with severe renal impairment are warranted.

INTRODUCTION

Rocuronium is a non-depolarizing aminosteroidal neuromuscular blocking agent (NMBA), with a rapid to intermediate onset of action and an intermediate duration of effect.[1] Recovery from neuromuscular block (NMB) occurs as the NMBA diffuses away from the neuromuscular junction (NMJ) and is eliminated. Use of an acetylcholinesterase inhibitor, such as neostigmine or edrophonium, enhances recovery and reduces the risk of residual block after operation.[2] However, residual NMB remains a potential problem in anaesthesia, as it is a risk factor for postoperative pulmonary complications and antagonists are not always administered.[3] In addition, acetylcholinesterase inhibitors do not effectively reverse profound NMB, particularly in the presence of volatile anaesthetics, and are ineffective when reversal is attempted before spontaneous recovery.[4,5,6]

Sugammadex is a modified γ-cyclodextrin, designed to selectively reverse the effects of rocuronium. It is also the first selective relaxant binding agent (SRBA). Cyclodextrins are cyclic oligosaccharides which can encapsulate a lipophilic guest molecule, such as an aminosteroidal NMBA, to form a stable host-guest inclusion complex.[7] Sugammadex forms a stable complex with rocuronium in the plasma, resulting in a rapid decrease in effector site concentration of the unbound relaxant.[7] Owing to the concentration gradient of rocuronium molecules between the NMJ and the plasma, the drug can diffuse away from the nicotinic receptor, giving rapid recovery from NMB.[8,9]

Prolonged NMB has been reported in patients with renal failure after administration of older non-depolarizing NMBAs (gallamine, tubocurarine, pancuronium), all of which are excreted, in part, by the kidney.[1] In addition, the mean time to spontaneous recovery (train-of-four (TOF) ratio of 0.7) from rocuronium- induced NMB has been shown to be significantly prolonged in patients with end-stage renal failure in comparison with patients with normal renal function.[10] As sugammadex and the sugammadex–rocuronium complex are cleared by the kidneys,[11] this Phase III investigation compared the efficacy and safety of sugammadex for the reversal of rocuronium-induced NMB in patients with normal or severely impaired renal function.

METHODS

The study was approved by the Independent Ethics Committee of each trial centre and was conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, Good Clinical Practice and current regulatory guidelines. All patients provided written informed consent. Thirty patients aged ≥18 years were included in the trial: 15 ASA class II–III patients with end-stage renal failure (creatinine clearance (CL_{CR}) <30 ml min^{-1}) and 15 ASA class I–II control

patients (CL_{CR} ≥80 ml min^{-1}). CL_{CR} was calculated using the serum creatinine value and the Cockroft & Gault formula.[12]

Patients were undergoing elective surgical procedures in the supine position under general anaesthesia where it was anticipated that only one dose of rocuronium given before tracheal intubation would be required. Pregnant and breast-feeding women, patients with known or suspected neuromuscular disorders, a history of malignant hyperthermia, or allergy to narcotics, NMBAs or other medication used during general anaesthesia were excluded, as were patients receiving medication known to interfere with the action of rocuronium, for example, aminoglycoside antibiotics, anticonvulsants or Mg^{2+}.

Anaesthesia was induced and maintained using i.v. infusions of propofol and opiates. Blood pressure, heart rate, ECG, oxygen saturation, central core temperature (measured by nasopharyngeal or rectal probe), and end-tidal CO_2 were recorded throughout.

After induction of anaesthesia, neuromuscular function was monitored continuously by acceleromyography (AMG) at the adductor pollicis muscle using the TOF-Watch® SX (Organon Ireland Ltd, a part of Schering-Plough Corporation, Dublin, Ireland). Surface paediatric ECG-electrodes (Neotrode®, Conmed, Utica, NY, USA) were placed over the ulnar nerve, near the wrist. A temperature sensor was attached to the ball of the thumb: peripheral temperature was maintained above 32°C.[13] Central core temperature was maintained above 35 °C. The AMG transducer was attached to the distal phalanx of the thumb, perpendicular to its movement. The arm and other fingers were immobilized on an arm board. After induction of anaesthesia, a 5 s of 50 Hz tetanic stimulation was performed to reduce the time required to stabilize the response to subsequent TOF stimulation. This was followed by 2–5 min of TOF pulses at 2 Hz, repeated every 15 seconds, until the twitch response stabilized. The TOF-Watch® SX device was then calibrated. After stabilization of the TOF signal and calibration, repetitive TOF stimulation was performed every 15 s using supramaximal stimuli of 0.2 ms.

A single i.v. dose of rocuronium (0.6 mg kg^{-1}) was administered. After maximal NMB was obtained, tracheal intubation was performed followed by mechanical ventilation with a mixture of oxygen and air. End-tidal CO_2 was maintained within a range of 4.0 – 5.3 kPa. At reappearance of the second twitch response (T2), a single i.v. dose of sugammadex (2.0 mg kg^{-1}) was given. Anaesthesia and neuromuscular monitoring were continued until recovery of the TOF ratio to 0.9, and for a minimum of 30 min after the administration of sugammadex.

The primary efficacy variable was the time from administration of sugammadex to recovery of the TOF ratio to 0.9.[14] Secondary efficacy variables were the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.7 (which was previously considered satisfactory clinical recovery)[15] and 0.8. Recurrence of NMB was defined as a decrease in the TOF ratio to < 0.9 after full recovery had been detected, or as a deterioration in the clinical signs of recovery from block.

After operation, oxygen saturation and respiratory rate were monitored for 7 h after administration of sugammadex in patients with normal renal function and for at least 24 h in patients with impaired renal function. All patients were assessed for clinical signs of recovery (5 s head lift test, diplopia, general muscle weakness and tongue depressor test)[15] after admission to the recovery room and 1, 2, 4, 6, 8, 12, 18 and 24 hours after administration of sugammadex. Renal patients were also assessed for clinical signs of recovery 36 and 48 h after administration of sugammadex. All subjects were assessed for adverse events (AEs) and serious adverse events (SAEs).[16]

For safety analysis, a urine sample for chemistry and sediment analysis was collected the day before surgery. Blood samples for blood biochemistry (sodium, potassium, chloride, ionized calcium, ionized magnesium, creatinine, blood urea nitrogen, alanine transaminase, aspartate transaminase, gamma-glutamyl transpeptidase, alkaline phosphatase, creatine kinase, lactate dehydrogenase, total bilirubin, total protein, albumin, fasting glucose, total cholesterol, fasting triglycerides and haptoglobin) and haematology (haematocrit, haemoglobin, erythrocyte count, leucocyte count, differential count and platelet count), were collected at induction of anaesthesia, and at 20 min and 4–6 hours after administration of sugammadex. Assessment of vital signs, blood chemistry and haematology analysis and urinalysis were repeated on the day after surgery and during a follow-up visit 2–4 weeks after surgery. All clinically relevant abnormal laboratory or vital signs were reported as AEs.

Statistical analysis

In previous trials (Organon database) in which a dose of 2.0 mg kg $^{-1}$ sugammadex was administered at reappearance of T2, the standard deviation (SD) of the times to recovery of the TOF ratio to 0.9 was 45 s. Thirteen patients per group would be required to show equivalence at a power of 81% (significance level α=0.05). Assuming a 10–15% dropout rate, 15 patients per group were required.

The confidence interval (CI) approach was used to demonstrate equivalence between patients with normal renal function and those with impaired renal function for the time to recovery of the TOF ratio to 0.7, 0.8 and 0.9 after reversal with sugammadex. With respect to induced recovery, a difference of 60 s or less between the two patient groups in the time to recovery of the TOF ratio to 0.7, 0.8 and 0.9 was considered not to be clinically relevant. Equivalence was established if the two-sided 95% CI for the difference between the two groups lay entirely within the range of –60 to +60 s. The 95% CI for the difference between the two groups was calculated from a two-way full analysis of variance (ANOVA), with patient group and trial site as factors. If the patient group by centre interaction was not statistically significant (significance level of 5%), a *post hoc* two-sided additive ANOVA model was also used to calculate the 95% CI.

Comparison of the physical characteristics of the two patient groups was performed by *post hoc* analysis using the Student's *t* test, $\chi 2$ test and the Fisher's exact test. A statistically significant difference was defined as $P<0.05$.

RESULTS

Fifteen renally impaired patients and 15 controls were enrolled and completed the trial between June 2005 and April 2006. The number of renally impaired and control patients was evenly distributed within each study site. There were no significant differences in age, weight, height, sex or ethnicity between the two groups (Table 1).

Table 1. Physical and baseline characteristics by patient group.
ASA, American Society of Anesthesiologists; CL_{CR}, total plasma creatinine clearance; SD, standard deviation.

		Patient group	
		CL_{CR} < 30 ml min^{-1} (*n*=15)	CL_{CR} ≥ 80 ml min^{-1} (*n*=15)
Age (yr), mean (range)		61 (29-81)	54 (32-70)
Weight (kg), mean (SD)		76 (13)	84 (15)
Height (cm), mean (SD)		170 (9)	170 (11)
Sex (n (%))	Female	7 (47)	9 (60)
	Male	8 (53)	6 (40)
Ethnicity (n (%))	Asian	2 (13)	0 (0)
	Caucasian	13 (87)	15 (100)
ASA Class (n (%))	Class I	0 (0)	5 (33)
	Class II	1 (7)	10 (67)
	Class III	14 (93)	0 (0)
CL_{CR} (ml min^{-1})	Mean (SD)	12 (5)	103 (24)
	Min – max	4 - 24	81 - 181

The majority of the renal patients were ASA class III (93%), whereas in the control group all patients were ASA I or II. The CL_{CR} in the renal failure group ranged from 4.3 ml min^{-1} to 24.1 ml min^{-1}. Ten of the 15 patients with end-stage renal failure were undergoing dialysis; one patient was having peritoneal dialysis and nine were undergoing haemodialysis at the time of the investigation. The mean CL_{CR} in the renally impaired group was 12 ml min^{-1} while in the control group it was 103 ml min^{-1}.

The time from administration of rocuronium to reappearance of T2 was 53.8 min (SD=22.4 min) in the renally impaired group and 40.6 min (SD=13.9 min) in the control group (P=0.06). The coefficient of variation in the renally impaired group was 41%.

In one subject (control), the TOF traces and recovery variables were unreliable due to poor recording. Data from this subject were excluded. Administration of sugammadex at reappearance of T2 after a bolus dose of rocuronium resulted in a mean time to recovery of the TOF ratio to 0.9 of 2.0 min for renal patients, and 1.65 min for control patients (Table 2). The estimated mean absolute difference in time from the start of administration of sugammadex to recovery of the TOF ratio to 0.9 between the renal patients and controls was +27.3 s. The corresponding 95% CI for this difference ranged from –10.9 to +65.5 s. The CI was not completely within the predefined equivalence interval of –60 to +60 s and equivalence could therefore not be claimed. However, since the interaction between trial site and subject group was not statistically significant (p=0.73), the *post hoc* additive ANOVA model excluding the group-by-centre interaction was applied. Using this approach the estimated mean absolute between-group difference was 20.1 s and the 95% CI (–12.1 to +52.3 s) was within the predefined equivalence interval.

Table 2. Time (min) from the start of administration of sugammadex to recovery of the TOF ratio to 0.7, 0.8 and 0.9 by patient group.

* One patient was excluded from the control group due to poor recording resulting in unreliable TOF traces and recovery variables. ANOVA, analysis of variance; CL_{CR}, total plasma creatinine clearance; NS, not significant; SD, standard deviation; TOF, train-of-four.

		Patient Group		
		CL_{CR} < 30 ml min^{-1} (*n*=15)	CL_{CR} ≥ 80 ml min^{-1} (*n*=14)*	ANOVA
Recovery to TOF ratio Mean (SD)	0.7	1.45 (0.47)	1.17 (0.38)	NS
	0.8	1.60 (0.57)	1.32 (0.45)	NS
	0.9	2.00 (0.72)	1.65 (0.63)	NS

The mean times from start of administration of sugammadex to recovery of the TOF ratios to 0.7 and 0.8 were 1.45 min *vs* 1.17 min and 1.60 min *vs* 1.32 min for renal patients and controls, respectively (Table 2). The estimated mean absolute difference between renal patients and controls for the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.7 and 0.8 was +20.6 s and +22.5 s, respectively. The corresponding 95% CI for these differences ranged from –2.4 to +43.6 s and –4.9 to +49.9 s, respectively. Both CIs were within the predefined equivalence interval of –60 to +60 s.

Recurrence of NMB was not observed in any of the patients during the neuromuscular monitoring or post-operative clinical monitoring period. In one control patient, a decrease in oxygen saturation was reported after operation. This was not considered a clinical sign of recurrence of NMB, but was attributed to the i.v. administration of meperidine on the recovery ward. This mild opioid-induced respiratory depression was successfully treated with oxygen (2 litre min^{-1}).

Blood biochemistry analysis showed hypocalcaemia in four patients (three renal patients, and one control). The lowest serum calcium measured, in a renal patient, was 1.17 mmol

litre^{-1} at 20 minutes after administration of sugammadex. In one control patient, elevated alanine transaminase (144 U litre^{-1}), aspartate transaminase (177 U litre^{-1}), bilirubin (44.5 µmol litre^{-1}) and gamma-glutamyl transpeptidase levels were recorded a day after surgery. At the follow-up assessment (postoperative day 19), the levels were within the safety ranges. One control patient had thrombocytopenia (68 x 10^9 litre^{-1}) 4–6 h after administration of sugammadex. The platelet counts at baseline, post-anaesthetic and follow-up visit were within normal ranges. None of these abnormal values was considered to be related to sugammadex. Haematology and blood biochemistry results were comparable between the two groups, except for serum creatinine and blood urea nitrogen levels, for which the differences existed at baseline.

The urinary variables were comparable between the two groups, except for *N*-acetyl glucosaminidase, beta-2 microglobulin and microalbumin, which are indicators of renal damage. For these variables, values above the safety ranges were seen pre-dominantly in the renally impaired group and were already present at the screening assessment.

Twenty patients had at least one AE perioperatively: eight patients in the renally impaired group and 12 patients in the control group. The most frequently reported AEs were nausea (*n*=6), procedural pain (*n*=6), pain (*n*=3), anaesthetic complications (coughing and movement during anaesthesia shortly after administration of sugammadex) (*n*=3), and hypocalcaemia (*n*=4). Five patients, two in the renally impaired group and three in the control group, experienced a total of eight AEs possibly related to sugammadex. These were diarrhoea (*n*=2), nausea (*n*=1), anaesthetic complications (*n*=3), headache (*n*=1) and decreased oxygen saturation (*n*=1). None of the patients were discontinued from the trial because of an AE.

SAEs were reported in two patients. One patient (renally impaired) experienced hypocalcaemia after parathyroidectomy and was re-admitted to hospital before recovering satisfactorily. The other (control) was involved in a road traffic accident on day 6 and suffered a high impact trauma, contusion of the knee and a forearm fracture. Neither SAE was considered to be related to the administration of sugammadex.

Five patients had abnormal changes in blood pressure from baseline (>20% decrease or increase) after administration of sugammadex. In the renally impaired group, two patients had a low systolic and one patient had a low diastolic blood pressure, whereas in the control group, one patient had a low and another patient had an elevated diastolic blood pressure. In all subjects, the blood pressure changes were considered to be clinically unimportant and returned to baseline after anaesthesia. No markedly abnormal heart rate values were observed.

DISCUSSION

NMB induced by rocuronium (0.6 mg kg^{-1}) was rapidly and effectively reversed by administration of sugammadex (2.0 mg kg^{-1}), both in renally impaired and in control patients. Although reversal of NMB by sugammadex tended to be slower in renal patients (not statistically significant), a mean value of 2.0 min for recovery of the TOF ratio to 0.9 in patients with impaired renal function is still good, especially as clinical signs of recurrence of NMB were not observed in any of the 30 patients. Furthermore, equivalence between groups was demonstrated with the *post hoc* statistical analysis.

This finding confirms that reversal of rocuronium-induced NMB by sugammadex can be attributed to rapid binding of rocuronium, which prevents it from acting at receptors, and is not dependent on its elimination by renal excretion.

This is consistent with an animal study which demonstrated that after complete interruption of renal perfusion in anaesthetized cats, sugammadex still caused a rapid reversal of rocuronium-induced NMB.[17] Although this animal model of acute renal failure is not a model for chronic renal insufficiency in humans, it did demonstrate that reversal of NMB by sugammadex is not dependent on renal excretion of the sugammadex-rocuronium complex.

Although available evidence suggests that the sugammadex-rocuronium complex will remain stable over time [7,18], there may be concerns for patients with renal insufficiency, who will retain the complex for a longer period than patients with normal renal function. For this reason, we monitored the renal patients during 48 hours for signs of recurarization, but none experienced recurrence of NMB.

It is of note that a recovery time of 2.0 min is quicker than the time to reversal of rocuronium-induced NMB by acetylcholinesterase inhibitors in healthy patients.[19,20] Sugammadex has already been shown to reverse rocuronium-induced NMB more rapidly than neostigmine. Sugammadex at a dose of 4 mg kg^{-1} for reversal of rocuronium-induced NMB achieved a TOF ratio of 0.9 in < 5 min, compared with only 5% of patients given neostigmine 70 µg kg^{-1}.[20]

Mechanomyography (MMG) has for many years been considered the 'gold standard' for quantification of NMB. An MMG TOF of 0.9 is considered necessary to exclude residual paralysis.[13,14] However, this method is now infrequently used and electromyography and AMG have largely replaced it in clinical research and practice.[13] The AMG and MMG methods cannot be used interchangeably, as a TOF ratio measured by AMG may overestimate recovery when compared with MMG.[21] Therefore, it must be accepted that slight levels of residual paralysis may not always be detected by the AMG.[21,22] The recently updated version of the Good Clinical Research Practice guidelines recommend that "Investigators using AMG should always report the time to an uncorrected (not normalized) TOF ratio of 0.9, but are encouraged to report the times to TOF ratio of 1.0". They also

state that more comparative data are needed to determine the impact of the practice of normalization, whereby the final TOF ratio becomes the control value, to improve the accuracy of AMG-derived recovery data.[13] The final TOF ratio in our study was almost identical to the baseline. In seven patients (three renal patients and four control patients) reversed fade (TOF ratio > 1.1) was recorded before administration of rocuronium. All patients returned to their baseline TOF level after administration of sugammadex.

As expected, the duration of clinical relaxation after rocuronium but before administration of sugammadex (time to reappearance of T2) tended to be longer in patients with impaired renal function, although this finding was not significantly significant. This observation and large between-patient differences in clinical response to rocuronium in renal failure have been reported in other studies.[10,23,24] The efficacy of sugammadex in patients with renal failure reported in this trial indicates that it may be useful in this patient group, where a prolonged duration of action of rocuronium and increased risk of post-operative residual paralysis and respiratory complications are more likely.[1,10]

As cyclodextrins are water soluble and do not possess direct intrinsic biological activity, they are unlikely to cause side-effects, although drug interactions could occur. Of the severe AEs reported in this trial, none were considered to be related to sugammadex. AEs possibly related to sugammadex were diarrhoea, nausea, headache and coughing or movement under anaesthesia. Coughing or movement after sugammadex has been reported in other studies.[8,25] This may be due to the rapid onset of effect of sugammadex in reversing NMB at a time of relatively light anaesthesia.

In conclusion, sugammadex at a dose of 2.0 mg kg^{-1} effectively and safely reverses NMB induced by rocuronium 0.6 mg kg^{-1}, in patients with normal or impaired renal function (CL_{CR} <30 ml min^{-1}). Recovery to the necessary TOF ratio of 0.9 before extubation occurred very rapidly and no signs of recurrence of NMB were reported. In patients with renal failure, sugammadex may be useful for limiting the risks of residual post-operative paralysis. Further safety studies on sugammadex in patients with severe renal impairment are warranted.

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Chapter 5

Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study

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ABSTRACT

Background

Sugammadex is a selective relaxant binding agent designed to encapsulate the neuromuscular blocking agent, rocuronium. The sugammadex-rocuronium complex is eliminated by the kidneys. This trial investigated the pharmacokinetics (PKs) of sugammadex and rocuronium in patients with renal failure and healthy controls.

Methods

Fifteen ASA class II–III renal patients (creatinine clearance (CL_{CR}) <30 ml min^{-1}) and 15 ASA I–II controls (CL_{CR} ≥ 80 ml min^{-1}) were included. After induction of anaesthesia, a single i.v. dose of rocuronium 0.6 mg kg^{-1} was given, followed by a single i.v. dose of sugammadex 2.0 mg kg^{-1} at reappearance of the second twitch of the train-of-four response. Plasma concentrations of rocuronium and sugammadex were estimated and PK variables determined using non-compartmental analyses. Percentages of sugammadex and rocuronium excreted in the urine were measured.

Results

PK data were obtained from 26 patients. Mean total plasma clearance (CL) of sugammadex was 5.5 ml min^{-1} in renal patients and 95.2 ml min^{-1} in controls ($P<0.05$). Rocuronium CL was 41.8 ml min^{-1} in renal patients and 167 ml min^{-1} in controls ($P<0.05$). The median amount of sugammadex and rocuronium excreted in the urine over 72 h in renal patients was 29% and 4%, respectively, and 73% and 42% over 24 h in controls.

Conclusions

Large differences in the PKs of sugammadex and rocuronium between patients with renal failure and healthy controls were observed. The effect of renal impairment on the PK variables of rocuronium was less than with sugammadex. Urinary excretion of both drugs was reduced in renal patients.

INTRODUCTION

Sugammadex is a modified γ-cyclodextrin and the first selective relaxant binding agent designed to encapsulate the aminosteroidal neuromuscular blocking agent (NMBA) rocuronium.[1–3] Cyclodextrins are cyclic oligosaccharides, capable of encapsulating lipophilic guest molecules such as steroids.[1] Sugammadex forms a 1:1 host-guest inclusion complex with rocuronium in the plasma. Free rocuronium molecules in the plasma are captured by sugammadex, resulting in a rapid decrease in the free rocuronium plasma concentration. This creates a concentration gradient between free rocuronium in the effect compartment (the neuromuscular junction (NMJ)) and the central compartment (the plasma and extracellular fluid). As a result, free rocuronium molecules return to the plasma, where they are captured by sugammadex, leading to a rapid reversal of neuromuscular block (NMB).[4]

Rocuronium is an NMBA with an intermediate duration of effect,[5] which is widely used in anaesthesia. Recovery from NMB occurs spontaneously as rocuronium diffuses away from the NMJ and is redistributed before being metabolized by the liver and/or eliminated in the bile and urine.

Administration of sugammadex leads to altered elimination of rocuronium. Sugammadex is a water-soluble molecule which is cleared mainly by the kidneys.[6] After encapsulation by sugammadex, rocuronium is confined to the space in which sugammadex resides and the plasma clearance of rocuronium assimilates into the plasma clearance of sugammadex.[6] Human studies have shown that the percentage urinary excretion of a dose of rocuronium increases up to a maximum of 68% over 24 h with increasing doses of sugammadex.[6]

This phase III trial was conducted to determine the efficacy, safety and pharmacokinetics (PKs) of sugammadex in patients with chronic renal failure, including patients on dialysis. The pharmacodynamic and safety findings of this study have already been reported.[7] This article describes the effect of severe to end-stage renal failure on the PKs of sugammadex and rocuronium and on the elimination of rocuronium encapsulated by sugammadex.

METHODS

Patient selection

The study protocol was approved by the Independent Ethics Committee of each trial centre (one in the UK, two in the Netherlands) and was conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, Good Clinical Practice and current regulatory guidelines. All patients provided written informed consent.

The study was performed between June 2005 and April 2006. Thirty patients aged ≥18 years were included in the trial: 15 ASA class II–III patients (American Society of Anesthesiologists physical status classification) with severe to end-stage renal failure (creatinine clearance (CL_{CR}) <30 ml min^{-1}) and 15 ASA class I–II control patients (CL_{CR} ≥80 ml min^{-1}). CL_{CR} was calculated using the serum creatinine value and the Cockcroft and Gault formula.[8] The pharmacodynamic and safety findings of this study have been reported previously.[7]
Patients were undergoing elective surgical procedures in the supine position under general anaesthesia, where it was anticipated that only one dose of rocuronium 0.6 mg kg^{-1} would suffice. Pregnant and breast-feeding women, patients with known or suspected neuromuscular disorders, those with a history of malignant hyperthermia, or allergy to narcotics, NMBAs, or other medication used during general anaesthesia were excluded, and also patients receiving medication known to interfere with the action of rocuronium, for example, aminoglycoside antibiotics, anticonvulsants or magnesium (Mg^{2+}).

Study procedures

An i.v. cannula was inserted solely for the administration of all anaesthetic drugs, including rocuronium and sugammadex. Anaesthesia was induced and maintained using i.v. infusions of propofol and opiates. Another i.v. cannula was inserted for blood sampling.
After induction of anaesthesia, a single i.v. dose of rocuronium 0.6 mg kg^{-1} was given. When maximal block had been achieved, tracheal intubation was performed and the lungs were ventilated with a mixture of oxygen and air. End-tidal CO_2 was maintained within 4.0–5.3 kPa. No potent inhalational agents were used.
Neuromuscular monitoring was performed continuously using acceleromyography of the adductor pollicis muscle and the TOF-Watch® SX (Schering-Plough, Dublin, Ireland). Surface paediatric ECG electrodes (Neotrode®, Conmed, Utica, NY, USA) were placed over the ulnar nerve near the wrist. A temperature sensor was attached to the ball of the thumb: peripheral temperature was maintained above 32°C.[9] Core body temperature was measured using a nasopharyngeal or rectal probe and maintained between 35°C and 37°C.[10]
At reappearance of the second twitch (T2) of the train-of-four (TOF) response a single i.v. dose of sugammadex 2.0 mg kg^{-1} was administered. Anaesthesia and neuromuscular monitoring were continued until the end of surgery and at least until recovery of the T4/T1 ratio of the TOF to 0.9, and for a minimum of 30 min after administration of sugammadex. Patients received dialysis during the study if indicated, according to usual practice.

Pharmacokinetic assessments

Plasma and urine sampling were conducted to determine the plasma concentration and the percentage of the administered dose of sugammadex and rocuronium excreted in the urine. Venous blood samples for determination of rocuronium concentration were

obtained pre-dose and at 2, 3, 5, 10, 15 and 20 min after administration of rocuronium. If reappearance of T2 occurred before all the post-rocuronium samples had been obtained, the remaining post-rocuronium samples were ignored. Venous blood samples to assess total rocuronium and sugammadex plasma concentrations were obtained directly before administration of sugammadex and at 2, 3, 5, 10, 15, 20, 30 and 60 min and 2, 4, 6, 8, 12, 18 and 24 h after administration of sugammadex. In patients with renal failure, further plasma concentrations of rocuronium and sugammadex were also determined at 36 and 48 h after sugammadex administration. The actual time of blood sampling was recorded in each instance. Additional pre- and post-dialysis samples were obtained if the patient underwent haemodialysis within 72 h of administration of sugammadex.

Plasma samples were stored in 4 ml heparin collection tubes. Within 15 minutes of collection, the plasma samples were centrifuged. If centrifugation could not be performed within 15 min, the tubes were stored in ice (0-4 °C). The heparin tubes were centrifuged for 15 min (2000 g-3000 g). Centrifuged plasma was stored in two hard plastic tubes (one for rocuronium and one for sugammadex) at -20 °C.

Urinary rocuronium and sugammadex concentrations and total amounts excreted were assessed from all healthy patients and those renal patients who still produced urine. Urine was collected at 6 h intervals, starting from administration of rocuronium to 6 h after administration of sugammadex and for 6–12 h, 12–18 h and 18–24 h after administration of sugammadex. In patients with renal failure, urine was also collected 24–36 h, 36–48 h and 48–72 h after administration of sugammadex. The actual collection times and volumes were recorded.

The collected urine was stored at 4 °C. Two samples of 1.0 ml of the collected urine for each interval were stored in a hard plastic tube: one for rocuronium and one for sugammadex. These tubes were stored at -20 °C. No preservatives were used.

Rocuronium and sugammadex concentrations in plasma and urine were determined using validated liquid chromatographic assay methods with mass spectrometric detection by the Department of Clinical Pharmacology and Kinetics, Schering-Plough, Oss, The Netherlands. The assays were carried out in full compliance with Good Laboratory Practice regulations. The lower limits of quantification (LLOQ) for the assays were: sugammadex 0.1 μg ml^{-1} (plasma) and 5 μg ml^{-1} (urine); and rocuronium 2.0 ng ml^{-1} (plasma) and 50 ng ml^{-1} (urine). The upper limits of quantification (ULOQ) for the assays were: sugammadex 40 μg ml^{-1} (plasma) and 200 μg ml^{-1} (urine); and rocuronium 1000 ng ml^{-1} (plasma) and 10.000 ng ml^{-1} (urine). All samples with a concentration >ULOQ were processed and analysed after an appropriate dilution to bring the concentration within the calibration range.

The assay methods do not differentiate between sugammadex and rocuronium in their free or complexed forms, as the sugammadex-rocuronium complex dissociates on the liquid chromatography column. Thus, plasma concentrations, urine concentrations and PK pa-

rameters pertain to total plasma and urine concentrations of sugammadex and rocuronium only and do not indicate the degree of encapsulation.

Pharmacokinetic parameter calculation

PK parameters were calculated using conventional non-compartmental analysis methods. For determination of terminal half-life, the slope ($-\lambda_z$) of the terminal log-linear phase of the concentration *vs* time curve was determined by linear regression. The log-transformed concentrations were fitted to a model with intercept and slope, starting with the last three points with measurable concentration (concentrations lower than LLOQ in the elimination phase were ignored). The procedure continued, adding preceding data points one at a time and fitting the regression equation sequentially. The terminal log-linear portion was defined by the data yielding the smallest mean square error term in the regression analysis. The elimination half-life ($t_{1/2,\beta}$) was then calculated as $\log_e 2/\lambda_z$.

The area under the concentration *vs* time curve (AUC) from time zero to t_{last} ($AUC_{0\text{-}tlast}$) was calculated by means of the linear trapezoidal rule, where t_{last} represents the last time point with a measurable concentration above the LLOQ within a subject. When a renal patient received dialysis during the study, t_{last} was the last pre-dialysis time point. This time point differed for each of the renally impaired patients. The AUC from time zero to infinity was calculated as $AUC_{0\text{-}\infty} = AUC_{0\text{-}tlast} + C_{tlast}/\lambda_z$, where C_{tlast} was the fitted concentration at time t_{last} using the regression line from which λ_z was calculated. With respect to the dialysed patients in the renally impaired group, $AUC_{0\text{-}\infty}$ was calculated by extrapolating from the pre-dialysis sample, ignoring plasma concentrations during and after dialysis.

The total plasma clearance (CL) was calculated as dose/$AUC_{0\text{-}\infty}$. The mean residence time (MRT) was calculated as (AUMC/$AUC_{0\text{-}\infty}$)–(duration administration dose/2), where AUMC is the area-under-the-moment-curve which is calculated from the product of concentration and time by means of the linear trapezoidal rule until t_{last} plus $(C_{tlast} \times t_{last}/\lambda_z) + (C_{tlast}/\lambda_z^2)$. The effective half-life ($t_{1/2,\ effective}$) was calculated as $\log_e 2 \times MRT$. The apparent volume of distribution at steady state was calculated as V_{ss} = CL x MRT.

In patients with renal failure who were treated with haemodialysis within 72 h after administration of sugammadex, the rocuronium and sugammadex plasma concentrations were assessed pre-dialysis ($C_{pre\text{-}dialysis}$) and post-dialysis ($C_{post\text{-}dialysis}$). A *post hoc* analysis was performed on the reduction ratio (RR) during dialysis, which was calculated as $RR=C_{post\text{-}dialysis}/C_{pre\text{-}dialysis}$.

From the sugammadex and rocuronium concentrations in urine and the urine volumes recorded for each collection interval, the amount excreted in urine (Ae) was calculated for each interval, assuming a urine density of 1.0 g ml^{-1}. The cumulative amount excreted in urine up to any time t ($Ae_{cum,\ t}$), where time *t* is the endpoint of a collection interval, was obtained by adding the total amounts excreted in each collection interval up to that time.

Statistical analysis

A power calculation was performed to calculate the number of patients needed to show pharmacodynamic equivalence.[7] A separate power analysis was not performed for the PK part of the study.

PK assessments were performed in the population of patients who received study medication, had no protocol violations interfering with the PK analysis, and for whom at least one PK parameter could be calculated. Linear regression analyses were performed of sugammadex and rocuronium CL *vs* CL_{CR} as a measure of renal function. Renal patients undergoing haemodialysis were excluded from this calculation, as CL_{CR} may be overestimated in this patient group, when calculated using the Cockroft and Gault formula. Correlation plots were made of CL *vs* CL_{CR} including regression lines.

The PK variables in the renal failure and control groups were compared using Student's *t* test on $\log_e$-transformed values. Point estimates and 95% confidence intervals for the ratio of renal failure to control means were calculated using geometric means. If there were no significant group effects, then the PKs were considered comparable between the renal failure group and the control group.

PK evaluation was performed using SAS version 8.2 (SAS Institute Inc, Cary, NC, USA) on a PC running under Windows XP v5.1 (Microsoft Corporation, Redmond, WA, USA).

Comparison of the physical characteristics and patient details of the two groups were performed by *post hoc* analysis using Student's *t*-test. Effects were considered statistically significant if $P \leq 0.05$.

RESULTS

Patients

Thirty patients were enrolled; 15 patients with renal failure (seven in Radboud University Nijmegen Medical Centre (RUNMC), six in Canisius-Wilhelmina Ziekenhuis (CWZ), Nijmegen and two in Liverpool) and 15 controls (seven in CWZ, six in RUNMC and two in Liverpool). In four patients (two renal patients and two controls), the data on the plasma and urine samples (time, date and patient number) did not correspond with those recorded on the Case Report Forms. These samples may have been reversed. For these subjects, no PK variables were calculated. Thus, 13 patients in each group were evaluable for PK assessment.

Table 1 shows the baseline characteristics of the 26 patients. There were no significant differences in age, weight, height or BMI between the two groups. The CL_{CR} in the renal failure group ranged from 4.3 ml min^{-1} to 24.1 ml min^{-1}.

All patients received propofol for induction and maintenance of anaesthesia, an intubating dose of rocuronium (median 0.6 mg kg^{-1}; range 0.59–0.61 mg kg^{-1}), and one dose

Table 1. Physical characteristics and patient data by patient group.
BMI, body mass index; CL_{CR}, total plasma creatinine clearance; SD, standard deviation. * Mean creatinine clearance may be overestimated in haemodialysis patients, when calculated using the Cockroft and Gault formula.

	Patient group		
	Renal Failure, CL_{CR} < 30 ml min^{-1} (n = 13)	Control, CL_{CR} ≥ 80 ml min^{-1} (n = 13)	
Age (yr), mean (range)	61 (29 – 81)	54 (32 – 70)	P=0.23
Weight (kg), mean (SD)	76.8 (13.8)	83.4 (16.0)	P=0.24
Height (cm), mean (SD)	170 (8.7)	168 (9.1)	P=0.68
BMI (kg m^{-2}), mean (SD)	26.6 (4.1)	29.5 (5.5)	P=0.06
CL_{CR} (ml min^{-1}), mean (SD)*	12.3 (5.7)	103.8 (26.0)	P=0.00

of sugammadex (median 2.0 mg kg^{-1}; range 1.99-2.05 mg kg^{-1}). The most frequently administered analgesic drugs were i.v. fentanyl and morphine. All patients were receiving concomitant medication. The drugs most frequently taken were alfacalcidol (10 of 15 renal patients) and acetaminophen (11 renal patients and 14 controls). None of the patients received an NMBA other than rocuronium, a second dose of rocuronium, or a reversal agent other than sugammadex.

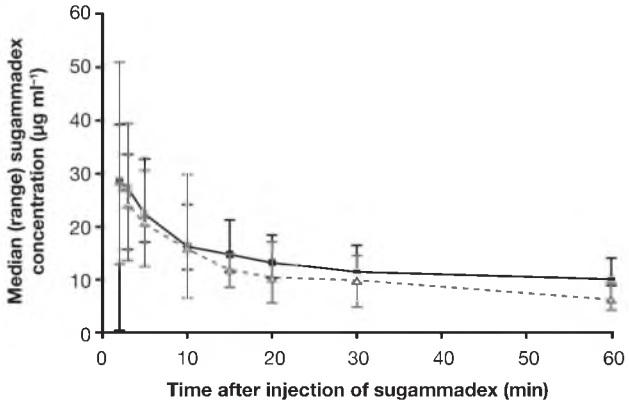
As previously reported, the mean (standard deviation) time from administration of rocuronium to reappearance of T2 was 53.8 min (22.4 min) in the renally impaired group and 40.6 min (13.9 min) in the control group.[7] Mean time (standard deviation) from the start of administration of sugammadex at reappearance of T2 to recovery of the TOF ratio to 0.9 was 2.0 min (0.72) for renal patients and 1.65 min (0.63) in healthy controls (not significant).[7] No clinical signs of recurarization were observed in any of the patients for up to 48 h.[7]

Plasma pharmacokinetics

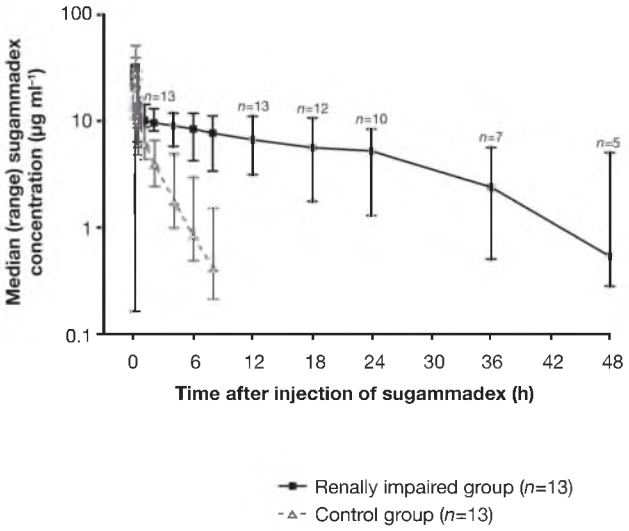
In one control patient, the rocuronium plasma concentration after 24 h was considered to be a PK outlier (laboratory error). The concentration at this time point was 3.94 ng ml^{-1}, although the plasma concentration after 12 h was 2.1 ng ml^{-1} and after 18 h was <2.00 ng ml^{-1}. This sample was excluded from all calculations. In one renal patient undergoing haemodialysis, the pre-dialysis plasma rocuronium concentration (24 h after administration of sugammadex) was also considered an outlier: the plasma concentration was 28.6 ng ml^{-1}, which was lower than the post-dialysis concentration (270 ng ml^{-1}). Therefore, the pre-dialysis sample was excluded from all calculations. For those patients in the renal failure group undergoing haemodialysis (nine patients), the samples obtained at time points after haemodialysis was started were excluded from the descriptive statistics.

Median plasma concentrations for sugammadex (Fig. 1A and B) and rocuronium (Fig. 2A and B) are presented by group. For the first 60 min after administration, median plasma

Figure 1: Sugammadex plasma concentrations *vs* time plots for patients with renal failure and control patients.



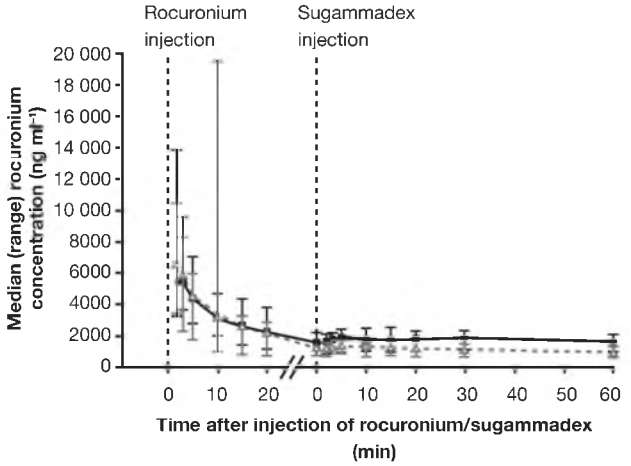
A. Median (range) sugammadex plasma concentration (μg ml^{-1}) vs time (min), for time points up to 60 min after injection of sugammadex.



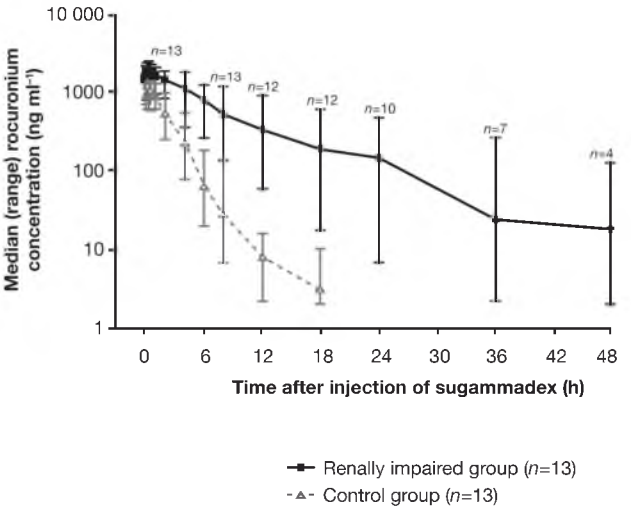
B. Semi-logarithmic plot: median (range) sugammadex plasma concentration (μg ml^{-1}) *vs* time (h), for time points up to 48 h after injection of sugammadex. Plasma concentrations were below the limit of quantification after 8 h in the control group. The numbers (*n*) of samples at each time point are given for the renally impaired group.

concentrations of sugammadex were similar in the control and renally impaired groups (Fig. 1A). At later time points, plasma concentrations of sugammadex showed a slower decline in the renally impaired group compared with the control group (Fig. 1B). A similar effect was seen for rocuronium (Fig. 2A and B). For both groups and both compounds, the concentration *vs* time curves showed a log-linear terminal decline.

Figure 2: Rocuronium plasma concentration *vs* time plots for patients with renal failure and control patients.



A. Median (range) rocuronium plasma concentration (ng ml^{-1}) *vs* time (min) after administration of rocuronium and sugammadex, for time points up to 60 min after injection of sugammadex.



B. Semi-logarithmic plot: median (range) rocuronium plasma concentration *vs* time, for time points up to 48 h after administration of sugammadex. Plasma concentrations were below the lower limit of quantification after 18 h in the control group. The numbers (*n*) of samples at each time point are given for the renally impaired group.

The main PK variables for sugammadex and rocuronium are given in Table 2.

Statistically significant differences ($P<0.05$) were observed between the control and the renal failure groups for sugammadex in total plasma CL, and the related parameters, AUC, $t_{1/2,\beta}$ and MRT (Table 2). Exposure ($AUC_{0-\infty}$), $t_{1/2,\beta}$ and MRT were 15 - 20 times higher and

the CL 17 times lower in the renal failure group compared with the control group. The V_{ss} did not differ significantly between the renal failure and the control groups.

Statistically significant differences ($P<0.05$) were also observed in these variables for rocuronium (Table 2). The exposure ($AUC_{0-\infty}$), $t_{1/2,\beta}$, and MRT were 2.5 -5 times higher and the CL was four times lower in the renally impaired group compared with the control group. Again, the V_{ss} of rocuronium did not differ significantly between the two groups.

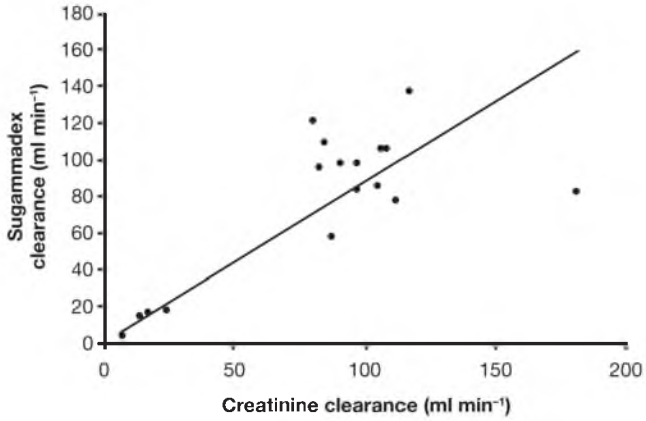
The effect of renal impairment on the PK variables was smaller for rocuronium than for sugammadex. The CL, AUC, $t_{1/2,\beta}$ and MRT of sugammadex were highly variable in patients with renal failure, with coefficients of variation >100%. The variability within renal failure patients in the PK parameters for rocuronium was smaller.

Table 2. PK variables for sugammadex 2.0 mg kg^{-1} and rocuronium 0.6 mg kg^{-1}.
Blood samples obtained before and after sugammadex administration were used to determine the rocuronium PKs. Data are presented as geometric mean (geometric coefficient of variation (%)) and overall ranges. AUC, area under the curve; CL, total plasma clearance; V_{ss}, volume of distribution at steady state; $t_{1/2,\beta}$, terminal elimination half-life; MRT, mean residence time. * Statistically significant (Student's *t*-test), $P< 0.05$ vs renal failure group.

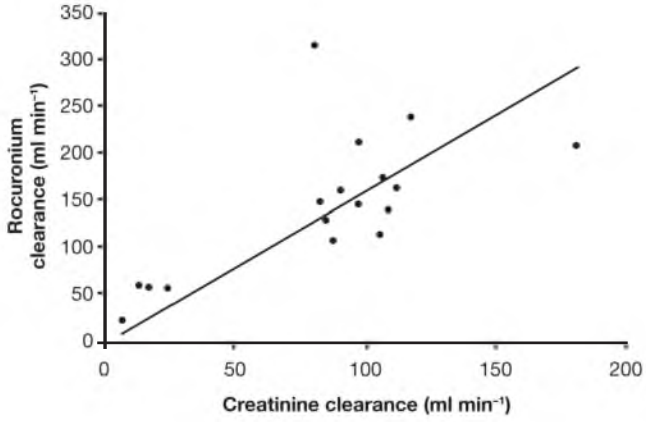
		Renal Failure	Control
Sugammadex kinetic variables			
$AUC_{0-\infty}$ (μg min ml^{-1})		27,500 (114)	1730 (34.8)*
	Range (μg min ml^{-1})	6480 – 147,000	1060 - 3330
CL (ml min^{-1})		5.5 (108)	95.2 (22.1)*
	Range (ml min^{-1})	1.15 – 18.1	58.3 - 138
V_{ss} (litre)		16.0 (35.5)	13.8 (20.5)
	Range (litre)	9.3 – 31.8	10.0 – 19.7
$t_{1/2,\beta}$ (h)		35.7 (121)	2.3 (44.4)*
	Range (h)	10.7 - 282	1.6 – 7.5
MRT (h)		48.2 (132)	2.4 (25.5)*
	Range (h)	13.2 - 399	1.8 – 4.0
Rocuronium kinetic variables			
$AUC_{0-\infty}$ (μg min ml^{-1})		1080 (53.8)	296 (37.4)*
	Range (μg min ml^{-1})	412 - 2370	143 - 538
CL (ml min^{-1})		41.8 (46.9)	167 (30.8)*
	Range (ml min^{-1})	23.2 – 88.8	108 - 314
V_{ss} (litre)		22.1 (29.9)	19.1 (28.3)
	Range (litre)	14.0 – 41.6	12.2 – 30.7
$t_{1/2,\beta}$ (h)		7.5 (39.9)	3.0 (67.5)*
	Range (h)	3.4 – 13.3	1.2 – 8.2
MRT (h)		8.8 (52.7)	1.9 (29.2)*
	Range (h)	3.7 – 19.7	1.2 – 3.3

Correlation plots were made of CL of sugammadex and rocuronium against creatinine clearance in controls and patients with renal insufficiency not yet on dialysis (Fig. 3). Regression analyses showed that both for sugammadex and for rocuronium, the correlation between CL and CL_{CR} is highly significant ($P<0.0001$).

Figure 3: Regression plots of total plasma clearance (CL) of sugammadex and rocuronium *vs* CL_{CR} (creatinine clearance) in normal controls and patients with renal insufficientcy not yet on dialysis.



A. Regression plot of sugammadex CL *vs* CL_{CR} (r=0.72)



B. Regression plot of rocuronium CL *vs* CL_{CR} (r=0.60)

Urinary excretion

In six patients with renal failure and four control patients, urine sampling was incomplete. Two patients with renal failure did not produce urine. Nine of 13 patients with renal failure underwent haemodialysis during the period of urine collection, which may have influenced urinary excretion of the drugs.

Urinary excretions of sugammadex and rocuronium were much lower in the renal failure group than in the control group. In renal failure patients (n=10), the median (range) total amount of sugammadex excreted in urine (in 72 h) was 29% (3.9 – 121%) of the administered dose. In the control group (n=11), renal excretion of sugammadex was almost complete in 24 h: median (range) total amount of sugammadex excreted was 73% (56 - 101%).

One renal patient was calculated to excrete 121% of the administered sugammadex dose, which reflects either an imprecision in the bioassay or in the urinary sampling. In nine of the 10 evaluable renal patients, the amount of sugammadex excreted over 72 h was <70%.

For rocuronium, a much smaller fraction of the dose was excreted in the urine than for sugammadex, both for the renally impaired group and the control group. Median (range) total amount of rocuronium excreted in urine was 4.4% (0.8 – 18) of the administered dose in 72 h in the renal failure group (n=10) and 42% (14 – 75) in 24 h in the control group (n=12).

Haemodialysis

Nine renal patients underwent haemodialysis between 0 and 72 h after administration of sugammadex. The plasma concentrations of sugammadex and rocuronium were measured pre- and post-dialysis. Median time for dialysis was 225 min.

In patients undergoing low-flux haemodialysis (n=7), no significant reductions in sugammadex plasma concentrations were observed after dialysis. The median (range) reduction ratio (RR) of sugammadex was 0.93 (0.87 – 1.20) and that of rocuronium was 0.65 (0.57 – 0.90). As there were only two patients undergoing high-flux haemodialysis, no conclusions regarding dialysability with these membranes can be presented from this study.

DISCUSSION

This multicentre, parallel-group, comparative trial was the first to investigate the PKs of sugammadex and rocuronium in patients with severe to end-stage renal failure. This phase III study showed large differences in the PKs of sugammadex and rocuronium between patients with renal failure and healthy controls. Plasma concentrations of sugammadex showed a slower decline in the renal failure group compared with the control group. Total plasma CL of sugammadex was 17 times lower and mean $t_{1/2,\beta}$ was 16 times higher in the renal failure group.

The effect of renal impairment on PK variables was less for rocuronium. Figure 2A shows no significant differences between renal patients and controls in rocuronium plasma concentrations before the administration of sugammadex. This is probably because re-

distribution of rocuronium, rather than CL, determines its plasma concentration during the initial 30-45 min after administration. However, after administration of sugammadex, total plasma CL of rocuronium was four times lower in the renal failure group than the control group.

Urinary excretion of sugammadex and rocuronium was also much lower in patients with renal failure.

In this investigation, venous sampling was performed for 48 hours in the renal failure patients and for 24 hours in the control group, which may have influenced the PK calculations. In renal failure patients, the calculated half-lives are longer than the sampling period, potentially making them inaccurate. However, the terminal elimination half life ($t_{½,\beta}$) and MRT for sugammadex are both greatly prolonged in renal failure compared with controls, suggesting a significant effect of renal impairment.

The major routes of elimination of rocuronium are biliary and urinary excretion.[11] Rocuronium is taken up by the liver and metabolized, excreted, or both in bile and faeces in high concentrations. The mean urinary recovery of rocuronium within 48 h of administration in subjects without a history of renal disease is 26%.[11] In patients with severe renal failure, CL of rocuronium is reduced by 33–39%, with a 66–84% increase in the MRT. [12 13] For sugammadex, a water-soluble molecule, renal excretion is the main route of elimination. In pre-clinical and clinical studies, renal excretion of the unchanged product was observed.[4 6 14]The plasma CL of sugammadex in healthy non-anaesthetized volunteers is ~ 120 ml min^{-1}, which is similar to the glomerular filtration rate.[6]

As urinary excretion is the main route of elimination of the sugammadex-rocuronium complex, the extrarenal route of elimination is expected to be unavailable for encapsulated rocuronium. After administration of sugammadex, the percentage of rocuronium excreted in the urine increases with increasing doses of sugammadex.[6 15] These data indicate that encapsulation by sugammadex diverts the elimination of rocuronium from its normal primary pathway of hepatic clearance to less effective renal clearance.[14] Such PK behaviour should have no consequences in surgical patients with normal renal function. However, patients with renal insufficiency will retain the sugammadex-rocuronium complex for a longer period of time and it is still unclear whether this prolonged exposure will have an impact on safety.

The plasma concentrations of rocuronium plateaued after administration of sugammadex. During the first hour after rocuronium injection, the plasma concentration of rocuronium decreased rapidly, mainly by redistribution and binding in the liver. After administration of sugammadex, the concentration of rocuronium showed a plateau or even an increase. This may be due to the fact that sugammadex attracts some rocuronium already bound in the liver back into the plasma, or that the assay cannot distinguish between free rocuronium and encapsulated rocuronium, thus leading to a higher total rocuronium concentration. In addition, the increased concentration gradient of non-encapsulated rocuronium mol-

ecules between the plasma and NMJ will result in free rocuronium at the NMJ returning to the plasma.

Available evidence suggests that the rocuronium-sugammadex complex remains stable over time.[1 16] The sugammadex-rocuronium complex exists in equilibrium with a very low dissociation rate (dissociation constant, K_d = 0.1 x 10^{-6} M) because of strong binding.[1 16] No drug interactions have been described between sugammadex and other agents used in general anaesthesia, such as opioids or propofol. In this trial, renal patients were monitored for 48 h after administration of sugammadex for clinical signs of recurarization. None of them experienced recurrence of NMB. Despite the large differences in the PKs of rocuronium and sugammadex between patients with renal failure and healthy controls, reversal of rocuronium-induced NMB by administration of sugammadex was rapid and effective in both patient groups.[7] It is appreciated, however, that the number of patients studied was small.

Cyclodextrins are water-soluble molecules, which are used as solubilizing agents for many drugs and foods. Sugammadex is biologically inactive and has been shown to be well tolerated. Toxicity studies on γ-cyclodextrins after oral or parenteral administration show that the drugs are well tolerated and safe to use in the dose ranges recommended for sugammadex.[17] No data based on prolonged follow-up are available on the safety of sugammadex in patients with renal failure, where elimination of the drug is compromised. In this study, the effect of renal impairment on the kinetic variables was smaller for rocuronium than for sugammadex. These data suggest that in patients with renal failure, extrarenal clearance of rocuronium does take place, in spite of complexation. However, we did not measure biliary concentrations of rocuronium, which would be necessary to determine if elimination, metabolism, or both by the liver of encapsulated rocuronium was continuing. Even after encapsulation of rocuronium by sugammadex, there may still be a low concentration of rocuronium unbound and available for hepatic metabolism and elimination. However, since the assay method cannot differentiate between encapsulated and free rocuronium, it is not possible at present to determine the plasma concentration of unbound rocuronium. If a higher dose of sugammadex had been administered even more rocuronium would have been encapsulated, and rocuronium clearance in renal patients would have more closely approximated the clearance of sugammadex in this patient group.

We obtained PK data in only four pre-dialysis patients with severe to end-stage renal failure and nine dialysis patients. In the latter group, the time of the first postoperative haemodialysis was patient specific and occurred before the last sampling time of 48 h after administration of sugammadex in eight patients. This might have influenced the PK parameters. The haemodialysis, together with the incomplete urine sampling, may have resulted in an underestimation of the urinary excretion of sugammadex and rocuronium.

Our study showed a significant correlation between sugammadex and rocuronium CL and creatinine clearance (P <0.0001), although it may not be linear. We did not investigate patients with mild renal failure (CL_{CR} 30–80 ml min^{-1}). Further PK studies in a larger patient group, in patients with different degrees of renal dysfunction and population PK approaches are needed to determine a more detailed profile of these drugs in such patients. After administration of sugammadex, an increase in rocuronium plasma concentration was detected. This has been described in other PK studies.[4 6 14 15] This is consistent with the rapid formation of the rocuronium-sugammadex complex in the plasma.[4] After administration of sugammadex, free rocuronium molecules in the plasma are encapsulated. This creates a concentration gradient of free rocuronium molecules between the NMJ and the central compartment. As they enter the plasma, more free rocuronium molecules are encapsulated by sugammadex. As the assay method cannot yet differentiate between free and encapsulated rocuronium, the complexation of rocuronium appears as an increase in total plasma rocuronium concentration.[14 15]

Dialysis membranes are classified into high and low flux, depending on their permeability. High-flux membranes are more porous non-cellulosic membranes with increased permeability, particularly to larger molecules.[18] Of the nine patients with renal failure who underwent haemodialysis during the investigation, seven were dialysed using low-flux membranes, which seemed almost ineffective in removing sugammadex from the circulation. However, the small number of subjects per filter type and the limited sampling means that the results must be viewed as preliminary. Further investigation is necessary to obtain more detailed information regarding dialysability of sugammadex and rocuronium.

In conclusion, large differences in the PKs of rocuronium and sugammadex were observed between patients with severe to end-stage renal failure and healthy controls. Total plasma CL of sugammadex and rocuronium was much lower in renal patients compared with controls. However, reversal of NMB induced by rocuronium 0.6 mg kg^{-1} with sugammadex 2.0 mg kg^{-1} was rapid and effective in both patient groups. No patient showed signs of recurarization.[7] The sugammadex-rocuronium complex is retained in the body for longer in patients with severe to end-stage renal failure and no clinical data on its long-term disposition are yet available. Furthermore, detailed studies should be conducted with a longer follow-up period, preferably with a higher dose of sugammadex, to determine more accurately whether prolonged exposure to sugammadex and the rocuronium-sugammadex complex has an impact on safety in patients with end-stage renal failure.

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Chapter 6

TOF ratio recovery often precedes twitch recovery when neuromuscular block is reversed by sugammadex

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ABSTRACT

Background

Sugammadex reverses rocuronium-induced neuromuscular block (NMB). In all published studies investigating sugammadex, the primary outcome parameter was a Train-of-Four (TOF) ratio of 0.9. Recovery time of T1 was not described. This retrospective investigation describes the recovery of T1 versus TOF ratio after reversal of NMB with sugammadex.

Methods

Two studies were analyzed. In study A, a phase II dose-finding study, ASA I-II patients received an IV dose of rocuronium 1.2 mg kg^{-1} followed by an IV dose of sugammadex (2.0, 4.0, 8.0, 12.0 or 16.0 mg kg^{-1}) or placebo (0.9% saline) after five minutes. In study B, a phase III trial comparing patients with renal failure and healthy controls, rocuronium 0.6 mg kg^{-1} was used to induce NMB; sugammadex 2.0 mg kg^{-1} was administered at reappearance of T2. Neuromuscular monitoring was performed by acceleromyography and TOF nerve stimulation. Primary efficacy variable was time from administration of sugammadex to recovery of the TOF ratio to 0.9. Retrospectively, time to recovery of T1 to 90% was calculated.

Results

After reversal of rocuronium-induced NMB with an optimal dose of sugammadex (16 mg kg^{-1} (A) or 2 mg kg^{-1} (B)), the TOF ratio recovered to 0.9 significantly faster than T1 recovered to 90%. Clinical signs of residual paralysis were not observed.

Conclusions

After reversal of NMB by sugammadex, full recovery of the TOF ratio is possible when T1 is still depressed. The TOF ratio as the only measurement for adequate reversal of NMB by sugammadex may not always be reliable. Further investigations for clinical implications are needed.

INTRODUCTION

Sugammadex is a modified γ-cyclodextrin that encapsulates the neuromuscular blocking agent (NMBA) rocuronium bromide, forming a 1:1 complex with a high affinity.[1] Chemical encapsulation of rocuronium promotes dissociation of rocuronium from the nicotinic acetylcholine receptor (nAChR), thereby rapidly reversing neuromuscular block (NMB) without the side effects associated with acetylcholinesterase inhibitors.[1-3] There are now numerous published clinical studies which show that sugammadex rapidly reverses rocuronium-induced NMB, at any depth of the block.[3-9]

Non-depolarizing NMBAs, such as rocuronium, block the transmission in the neuromuscular junction (NMJ) by inhibition of the nAChRs, both presynaptically and postsynaptically.[10-12] The presynaptic nAChR plays a role in mobilizing acetylcholine (ACh) from the intraneuronal reserve to the readily releasable pool of transmitter, in order that ACh release is proportional to the demand of the high frequencies of nerve impulses that are characteristic of transmission to striated muscle.[10] Blockade of these presynaptic nAChRs by NMBAs is thought to account for the so-called fade phenomenon that occurs during partial non-depolarizing NMB.[10] Fade, a gradual diminution of evoked response during repetitive nerve stimulation, is a typical phenomenon observed during recovery from NMB caused by non-depolarizing NMBAs, but not by depolarizing agents such as succinylcholine.[10]

During the last years the fade phenomenon, as expressed in the Train-of-Four (TOF) ratio, or height of the fourth evoked response as a fraction of the first evoked response in the same train (T4 /T1), is routinely used as the basic parameter of neuromuscular monitoring for recovery from NMB.[13] Studies have shown that the acceleromyographic TOF ratio must exceed 0.9 to exclude clinically important residual NMB.[13;14] It is even suggested that the uncorrected (not normalized) acceleromyographic TOF ratio should be 1.0, or even higher to exclude clinically significant residual paralysis.[15;16]

In the reported clinical trials about sugammadex the primary outcome parameter for adequate recovery of NMB was an acceleromyographic TOF ratio of 0.9. In none of the studies the recovery of the T1 response was reported.

As the TOF ratio reflects the effects of the NMBA at the presynaptic membrane of the neuromuscular junction (NMJ), the single twitch response reflects the events at the postjunctional membrane and is directly related to the force generated. During spontaneous recovery from non-depolarizing NMBAs the single twitch response and the T1 response of the TOF normally recover to baseline, while at this point the TOF ratio may still be no more than 0.7, which is nowadays considered insufficient recovery from NMB.[13;14;17] The same pattern occurs after reversal of non-depolarizing NMBAs with neostigmine.[18]

The aim of this retrospective analysis is to describe the temporal relationship of recovery of T1 and the TOF ratio, after reversal of rocuronium-induced NMB with sugammadex. The

data are derived from two prospective studies investigating the efficacy of sugammadex in reversing rocuronium-induced NMB, after placebo and different doses of sugammadex in healthy patients and after sugammadex 2 mg kg^{-1} in patients with severe renal dysfunction and healthy controls. Results of both clinical investigations have been published previously.[5;9]

METHODS

The first study (A) was designed as a multi-centre, randomized, assessor-blinded, placebo-controlled, phase II, parallel and dose-escalating dose-finding study in patients of ASA I-II.[5] The second study (B) was designed as a multicenter, parallel-group, comparative, phase III trial, in both ASA I-II patients with normal renal function and ASA II-III patients with severe to end-stage renal failure.[9] Both studies investigated the efficacy of sugammadex in reversing rocuronium-induced NMB after a single dose.

The studies were approved by the Central Ethics Committee and the Independent Ethics Committee of each trial centre. All patients provided written informed consent.

Methods of both investigations were published previously, including inclusion and exclusion criteria of both studies.[5;9] All patients were aged ≥ 18 years and were undergoing elective surgical procedures in the supine position under general anaesthesia where it was anticipated that only one dose of rocuronium given before tracheal intubation would be required. In study B, patients with renal failure included in the study had a creatinine clearance (CL_{CR}) < 30 ml min^{-1}, as calculated using the serum creatinine value and the Cockroft and Gault formula.[19] Healthy control patients had a CL_{CR} ≥ 80 ml min^{-1}.

Anaesthetic Technique

On arrival of the patient in the operating room an intravenous (IV) line was placed for anaesthetic administration, including rocuronium and sugammadex. Non-invasive arterial pressure, oxygen saturation, capnography, electrocardiography and core temperature were monitored. Anaesthesia was induced with propofol IV, followed by a continuous infusion of propofol and an opiate to maintain anaesthesia.

After induction of anaesthesia, neuromuscular function was monitored continuously by acceleromyography (AMG) at the adductor pollicis muscle using the TOF Watch® SX (Organon Ireland Ltd, now Merck, Dublin, Ireland). Surface paediatric ECG-electrodes (Neotrode®, Conmed, Utica, NY, USA) were placed over the ulnar nerve, near the wrist. A temperature sensor was attached to the ball of the thumb: peripheral temperature was maintained above 32°C. Core temperature was maintained above 35°C.[13] The AMG transducer was attached to the distal phalanx of the thumb, perpendicular to its movement. The arm and other fingers were immobilized on an arm board. After induction of anaesthesia,

a 5 s of 50 Hz tetanic stimulation was performed to reduce the time required to stabilize the response to subsequent TOF stimulation. This was followed by 2-5 min of TOF pulses at 2 Hz, repeated every 15 s, until the twitch response stabilized. The TOF Watch® SX device was then calibrated. After stabilization of the TOF signal and calibration, repetitive TOF stimulation was performed every 15s using supramaximal stimuli of 0.2 ms.

After calibration of the TOF-watch® SX, the patients received a bolus dose of rocuronium bromide 1.2 mg kg^{-1} (study A) or 0.6 mg kg^{-1} (study B), administered within 10 seconds into a fast running IV infusion. This was followed by endotracheal intubation and mechanical ventilation with a mixture of oxygen and air. In study A, five minutes after the administration of rocuronium to induce profound NMB, an IV bolus dose of either sugammadex (2.0, 4.0, 8.0, 12.0 or 16.0 mg kg^{-1}), or placebo (0.9% saline) was administered. In study B, at reappearance of the second twitch response (T2) of the TOF, a single IV dose of sugammadex 2.0 mg kg^{-1} was given. In both studies, anaesthesia and neuromuscular monitoring were continued until recovery of the TOF ratio to 0.9.

At the end of the surgical procedure, the patients were allowed to recover from anaesthesia and were transferred to the post anaesthesia care unit (PACU), where the possibility of postoperative recurrence of NMB was assessed by monitoring the patients' oxygen saturation, breathing pattern, breathing frequency and clinical signs of recovery.

In study A, the patients were monitored for at least 120 minutes after administration of sugammadex or placebo.[5] In study B, patients with normal renal function were observed on the PACU for 7 h after administration of sugammadex and patients with renal failure for at least 24 h. After sugammadex administration clinical signs of recovery were assessed for patients with normal renal function for 24 h, and for renal failure patients for 48 h.[5;9]

Efficacy Variables

The primary efficacy variable in both studies was the time from the start of the administration of either sugammadex or placebo, to recovery of the TOF ratio to 0.9.[5;9] *Post hoc* we retrieved the time from start of administration of sugammadex or placebo until recovery of T1 to 90% from the original recorded neuromuscular database of the patients included in these investigations.

All T1 recovery parameters were adjusted to the final, stable T1 value (normalization), as described in the guidelines for Good Clinical Research Practice in pharmcodynamic studies of NMBAs.[13] If, for example, the final T1 was 80%, a recorded T1 value of 72% implicated a 90% recovery of T1 (0.72 / 0.80). Also, the height of T1 at the time of recovery of the TOF ratio to 0.9 was recovered from all recordings. The *post hoc* analysis of these data was performed by 2 investigators.

Statistical analysis

Results were imported into an Excel database and analysed with SAS (SAS Inc, v 8.02, Cary, NJ, USA) statistical routines. Data are presented as mean values with SEM in parentheses. The difference in recovery times of the TOF ratio versus T1 were analyzed using Student's *t*-test for paired observations. To reduce inter-individual variability, differences between T1 and TOF ratio recovery times were analyzed as relative paired observations (difference/recovery time T1) within the groups.

The difference in recovery times of the TOF ratio and T1 between renal failure group and control group (in study B) were analyzed using Student's *t*-test for unpaired observations. The level of significance used was $p < 0.05$.

RESULTS

Study A

In study A, 43 patients were treated with either sugammadex or placebo.[5] Of these patients, 40 were eligible for analysis of recovery of NMB (one patient was excluded because of a sugammadex dosing error, in one patient the time to recovery of the TOF ratio to 0.9 was not available and one patient received neostigmine). Of these 40 patients, times to recovery of the TOF ratio to 0.9 have already been published.[5] In six out of 40 registrations, it was impossible to determine the time to recovery of T1 to 90%, due to poor recording or due to movement of the operating table. Data from these subjects were excluded from the retrospective analysis.

In all registrations the final TOF ratio was almost identical to the baseline TOF ratio, before administration of rocuronium. All patients returned to at least their baseline TOF level after the administration of sugammadex.

During recovery, a stable T1 response should be 80-120% of the baseline value.[13] In three patients, stable T1 response after recovery from NMB was lower than 80% of baseline T1 value (78%, 72% and 72%).

Results of the recovery times of the TOF ratio to 0.9 and our post hoc analyses of recovery times of the first twitch of the TOF are presented in Table 1.

When placebo is administered, a normal recovery pattern of NMB after a dose of rocuronium 1.2 mg kg^{-1} is seen. First T1 recovers to 90%, after a mean (SEM) time of 107.5 (2.2) minutes after administration of placebo. Recovery of the TOF ratio to 0.9 is significantly slower: 130.5 (4.7) min after administration of placebo. The mean difference between the recovery times is 23.0 min (P=0.018).

With sugammadex given 5 min after administration of rocuronium 1.2 mg kg^{-1}, the relative effect on TOF vs. T1 recovery depends on the dose of sugammadex administered. When a dose of sugammadex 2.0 mg kg^{-1} is given, the mean difference in time to recovery of the

Table 1: Recovery times of the TOF to 0.9 and T1 to 90%, in study A.

Summary of the recovery times (min) from start of the administration of sugammadex or placebo to recovery of the TOF ratio to 0.9 and the height of T1 to 90% of stable twitch height after a single dose of rocuronium 1.2 mg kg^{-1}, in study A.

The difference is the mean (SEM) absolute difference in recovery times of TOF ratio to 0.9 and T1 to 90%. $P<0.05$ = statistically significant

		Placebo	Sugammadex (mg kg^{-1})				
			2.0	4.0	8.0	12.0	16.0
N		3	5	3	10	6	6
TOF ratio to 0.9	Mean (SEM) (min)	130.5 (4.7)	56.5 (2.4)	18.1 (14.3)	2.7 (0.2)	1.5 (0.1)	1.1(0.1)
	Min - Max	123.5–139.5	50.5 – 65.1	3.3 – 46.6	2.2 – 3.6	1.1 – 1.9	0.7-1.5
T1 to 90%	Mean (SEM) (min)	107.5 (2.2)	39.3 (4.9)	13.7 (9.6)	4.9 (0.9)	2.9 (0.7)	2.2(0.4)
	Min - Max	104.4 -111.8	24.3 – 52.0	4.0 – 32.9	2.4 – 10.9	1.9 – 6.3	1.2 – 4.3
Difference (min)	Mean (SEM)	-23.0 (3.2)	-17.3 (4.2)	-4.4 (4.7)	2.2 (0.8)	1.5 (0.7)	1.1(0.4)
	Min - Max	-27.8 - (-17.0)	(-26.3) – (-2.8)	(-13.8) –0.8	(-0.5) – 7.5	0.25 -4.8	0.5 – 3.0
Significance		*P*=0.018	*P*=0.014	*P*= 0.445	*P*=0.021	*P*=0.084	*P*=0.040

TOF to 0.9 and recovery of T1 to 90% is 17.3 minutes (Table 1). Recovery of T1 to 90% occurs statistically significantly earlier than recovery of the TOF ratio to 0.9 (p=0.014). After a dose of sugammadex 4.0 mg kg^{-1}, this mean difference in recovery times is 4.4 minutes (T1 first, than TOF ratio), however, this difference is not statistically significant (p=0.445). After a dose of 8, 12 and 16 mg kg^{-1} the recovery of the TOF ratio to 0.9 occurs earlier than the recovery of T1 to 90%. There is a statistically significant difference in recovery times of T1 to 90% and TOF ratio to 0.9 in the dose groups of 8.0 mg kg^{-1} (p=0.021) and 16.0 mg kg^{1} (p=0.040).

After an optimal dose of sugammadex (16 mg kg^{-1}) was administered, at the time of recovery of the TOF ratio to 0.9, T1 had recovered to a mean of 53%.

Figure 1 is a graphic depiction of the recovery times from administration of sugammadex or placebo to recovery of the TOF ratio to 0.9 and T1 to 90% and the different doses of sugammadex.

Signs of residual NMB or recurrence of NMB were not observed in any of the patients.

Study B

In study B two patient groups were examined: patients with severe to end-stage renal failure and healthy ASA I-II controls.[9] Fifteen renal patients and 14 healthy controls were eligible for full analysis of recovery of NMB. In one control patient, the recovery variables were unreliable due to poor recording. Data from this subject were excluded. In this study, sugammadex 2.0 mg kg^{-1} was administered at reappearance of T2.

In all patients in study B the stable T1 response during recovery of NMB was within the predefined limits (80-120% of baseline T1 value).[13] In all registrations the final TOF ratio was almost identical to the baseline TOF ratio, before administration of rocuronium.

Results of the recovery times of the TOF ratio to 0.9 and our *post hoc* analyses of recovery times of T1 are presented in Table 2.

In both patient groups, recovery of T1 to 90% was significantly slower than recovery of the TOF ratio to 0.9. In patients with normal renal function the mean (SEM) difference between recovery of the TOF ratio to 0.9 and recovery of T1 to 90% was 79.4 (19.5) seconds (p=0.0013). In patients with renal impairment, this difference was even larger: mean (SEM) difference was 157.6 (23.4) seconds (p<0.0001).

In the renal patient group, at the time the TOF ratio had recovered to 0.9, T1 had recovered to a mean of 72%. In the control group, T1 had recovered to a mean of 71% when the TOF ratio had recovered to 0.9.

Recovery times to a TOF ratio of 0.9 were not statistically different between the renal failure patients and the controls, as published previously.[9] However, the time to recovery of T1 to 90% was statistically significantly faster for the patients with normal renal function, compared to the patients with renal insufficiency (p=0.001). Also, the difference in recovery times between recovery of the TOF ratio to 0.9 and T1 to 90% was significantly

smaller for the patients with normal renal function, compared to renal failure patients (p=0.017).

Recurrence of NMB was not observed in any of the patients.

Figure 1: Recovery times of the TOF ratio to 0.9 and T1 to 90% after different doses of sugammadex, in study A.

X-axis: administered dose of sugammadex to reverse profound rocuronium-induced neuromuscular block (NMB), in mg kg^{-1}.

Y-axis: mean time from administration of sugammadex to recovery of the train-of-four (TOF) ratio to 0.9 or recovery of the first twitch of the TOF (T1) to 90%, in minutes.

After a low dose of sugammadex (2 or 4 mg kg^{-1}) or placebo is administered to reverse a profound rocuronium-induced NMB, T1 recovers to 90% before the TOF ratio recovers to 0.9.

At a sugammadex dose of around 6 mg kg^{-1}, the recovery of the TOF ratio to 0.9 and recovery of T1 occur at about the same time.

At high doses of sugammadex (8 mg kg^{-1} and higher), recovery of the TOF ratio to 0.9 occurs earlier than the recovery of T1 to 90%.

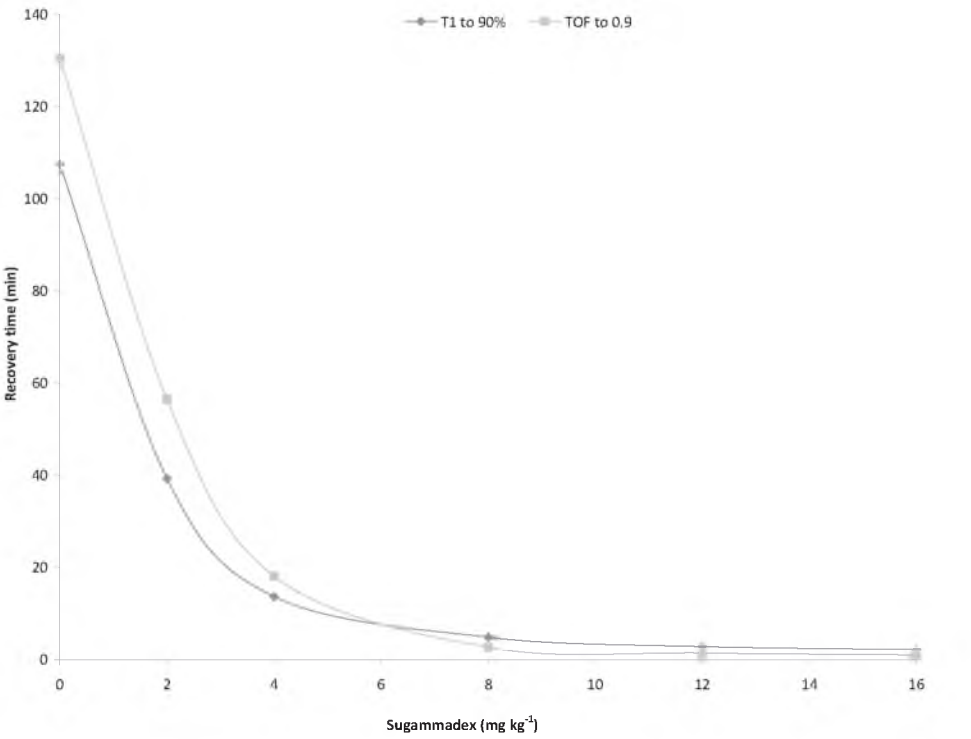

Table 2: Recovery times of the TOF to 0.9 and T1 to 90%, in study B.
Summary of the recovery times (sec) from start of the administration of sugammadex to recovery of the TOF ratio to 0.9 and the height of T1 to 90% of stable twitch height after a single dose of rocuronium 0.6 mg kg^{-1}, in study B.
The difference is the mean (SEM) absolute difference in recovery times of TOF ratio to 0.9 and T1 to 90%.
$P<0.05$ = statistically significant

		Renal failure Patients	Control Patients
N		15	14
TOF ratio to 0.9	Mean (SEM) (sec)	123.7 (12.3)	99.4 (10.2)
	Min - Max	69 – 221	58 - 185
T1 to 90%	Mean (SEM) (sec)	281.3 (22.0)	178.8 (18.3)
	Min - Max	145 – 476	102 - 281
Difference (sec)	Mean (SEM)	157.6 (23.4)	79.4 (19.5)
	Min - Max	(-30) – 315	(-75) - 180
Significance		<0.0001	0.0013

DISCUSSION

Nowadays neuromuscular monitoring is an evidence-based practice and should routinely be used whenever a non-depolarizing NMBA is administered. Such monitoring can improve patient outcome.[20] Measurement of the TOF ratio is considered the standard, with a normalized acceleromyographic TOF ratio of 0.9 now accepted as safe with regard to postoperative risk of respiratory complications, such as aspiration and hypoxia. Several studies clearly show that airway protection and respiratory control have not fully recovered until an adductor pollicis TOF ratio of 0.9 has been reached.[21;22]
However, TOF fade (expressed by the TOF ratio) represents presynaptic receptor blockade, whereas postsynaptic receptor block is expressed by depression of the single twitch response or T1.[10] The two phenomena represent two different physiological sites of action, and may not be used interchangeably in all conditions.
It has been demonstrated by Ali et al., using mechanomyography, that when the single twitch height had recovered to baseline after recovery from NMB, the TOF ratio varied between mean 64 and 74%, depending on the NMBA.[23] Mc Coy et al reported that at a TOF ratio of 0.6 or greater, single twitch had returned to 90%.[24] Hence, as considerable residual paralysis may still be present at full recovery of the single twitch height, it is considered misleading to use the single twitch monitoring as the single criterion for return of neuromuscular function.
Although there is difference between currently used NMBAs in their ability to produce fade, during spontaneous recovery from NMB the fade effect persists longer than twitch depression.[25] [26-28] Fade disappears and TOF ratio recovers to >0.9 only after normalisa-

tion of T1 tension.[24] When antagonizing with classical reversal agents (anticholinesterase drugs) the time course of recovery from NMB is identical: first full return of T1 and then recovery of the TOF ratio to 70 and 90%.[23]

The present study shows that after reversal of rocuronium-induced NMB by sugammadex the return of a normal TOF ratio can, dose-dependently, precede the return of a normal twitch height. When the dose of sugammadex is high enough for fast reversal of deep rocuronium-induced NMB (8 mg kg^{-1} and higher), the recovery of the TOF to 0.9 precedes the recovery of T1 to 90%, sometimes by minutes. This is also the case when the recommended dose of sugammadex (2.0 mg kg^{-1}) is administered at reappearance of T2 (moderate NMB). In healthy patients the mean difference in reversal time (TOF vs. T1) was 79 seconds, but could take as long as 3 minutes, and in renal patients the mean difference in reversal time was 157 seconds, but could take as long as 5 minutes.

This study shows that after reversal with an adequate dose of sugammadex, the traditional relationship between TOF ratio and T1 recovery is no longer valid. Recovery of the TOF ratio to 0.9 precedes the recovery of T1, and the TOF ratio may be fully recovered when this is not yet the case for T1. Therefore, the TOF ratio as the only measurement for adequate reversal of NMB, is no longer reliable in all cases after reversal with sugammadex, and twitch height has to be taken into account as well.

Bom and Thomson showed in the mouse hemi-diaphragm during TOF stimulation that sugammadex in a lower concentration produced a faster recovery from rocuronium-induced NMB of T1 than T4, while after a higher concentration the recovery of T1 and T4 were rather similar and the TOF ratio even reached 0.9 when T1 was still depressed.[29] They suggested that the TOF ratio might be an unreliable indicator of recovery in those situations. The present study is the first to show in humans that after reversal of rocuronium-induced NMB by sugammadex a full recovery of the TOF ratio is possible when T1 is still depressed.

The transmitter ACh, in addition to acting on the postjunctional nicotinic ACh receptor (nAChR), also acts on the prejunctional nAChR to mobilize ACh from the reserve to the readily releasable store, so that the availability for release can keep up with the demands of high frequencies of nerve impulses that are characteristic of transmission to striated muscle.[10] Blockade of these presynaptic receptors will thus impair mobilization and accounts for the so-called "fade" that occurs during partial non-depolarizing NMB. Normal single twitches may be produced in the presence of 75 - 80% receptor occlusion by a NMBA, but it is necessary for about 50% of the receptors to be unoccupied by NMBAs before tetanic fade at 100Hz is no longer evident.[30] How then can it be explained that after the administration of sugammadex, a recovery to a TOF ratio of 0.9 precedes the recovery of T1 to 90%?

Non-depolarizing NMBAs, such as rocuronium, block nAChRs located in the NMJ in a competitive manner. Muscle nAChRs are assembled from four different subunits arranged as the pentamer $(\alpha 1)_2\beta 1\delta\varepsilon$.[31;32] At NMJ the receptors are composed of two α1-subunits in

combination with one each of β1-, δ-, and ε-subunits. Non-depolarizing NMBAs compete with ACh to bind to an α subunit of the receptors. Under these conditions, the ion channel will not open and no current will flow through it. Also, the presynaptic axon terminals are equipped with nAChRs. These neuronal nAChRs include homomeric and heteromeric receptors, where the heteromeric receptors are formed by a combination of α2-6 and β2-4.[32] It has been shown that inhibition of the presynaptic α3β2 nAChR subtype at the motor nerve end induces tetanic fade.[33] Therefore it is likely that the fade phenomenon seen during non-depolarizing NMB is due to an inhibition of this α3β2 nAChR subtype. Jonsson et al. showed that non-depolarizing NMBAs inhibit neuronal nAChRs and that the inhibitory mechanism differs between individual receptor subtypes and NMBAs.[34] The NMBAs had individual action profiles on different receptors. The clinically used NMBAs inhibited the α3β2 nAChR subtype, which provides a molecular explanation for the tetanic and TOF fade seen during NMB by non-depolarizing NMBAs.[34] Also, succinylcholine, which does not produce TOF fade, does not block the α3β2 nAChR subtype.[35]

Different non-depolarizing NMBAs produce different degrees of fade response.[25,26;27] This is probably due to a difference in potency of the NMBAs in blocking the neuronal presynaptic nAChR. In vitro studies showed that non-depolarizing NMBAs have a much higher affinity for the postsynaptic α1β1εδ nAChR subtype compared with the presynaptic α3β2 subtype.[34] In the presence of high concentrations of sugammadex, only a low concentration of free rocuronium molecules remains in the NMJ and will preferentially block the postsynaptic nAChR. This could explain why after an optimal dose of sugammadex, the fade phenomenon disappears very fast, while the postsynaptic single twitch is still depressed, even when the TOF ratio has recovered to 0.9.

After an effective dose of sugammadex, full recovery of T1 followed recovery to a TOF ratio of 0.9 within a few minutes, and it is not known yet if this will have clinical implications. In the present study, none of the subjects showed clinical signs of residual paralysis after reversal of a rocuronium-induced NMB by sugammadex, even when reversal of T1 was significantly slower than reversal of the TOF ratio. After a lower dose of sugammadex, which does not produce fast recovery of deep NMB (4 mg kg^{-1} or less), the recovery of TOF to 0.9 did not precede the recovery of T1 and thus behaved like after spontaneous recovery from rocuronium-induced NMB. This means there is no reason to expect that the absence of the TOF fade response may be misleading in such circumstances. Therefore it is not likely, when a low dose of sugammadex is given, that a recovery to a TOF ratio of 0.9 would carry the risk of incomplete recovery of the muscle strength.

However, patients taking medication known to interfere with the postsynaptic response of NMBAs (for example aminoglycoside antibiotics [36;37] or magnesium [38]), were excluded from the studies here described. Patients with known or suspected neuromuscular disorders were also excluded, such as patients with diseases involving the AChR, for example myasthenia gravis.[39] It is possible that in patients receiving such medication or suffering

from such a disease, recovery of the single twitch response after administration of sugammadex, will be remarkably slower, and there could be a risk of residual paralysis, even though the TOF ratio has recovered to 0.9. Further investigation is necessary.

Also, for the renal patients in study B, recovery of T1 to 90% was significantly slower compared to the patients with normal renal function. Renal patients may therefore be more vulnerable for developing residual paralysis, even when a TOF ratio of 0.9 has been reached.

In conclusion, after reversal of rocuronium-induced NMB with an optimal dose of sugammadex, the TOF ratio recovered to 0.9 significantly faster than T1 recovered to 90%. A full recovery of the TOF ratio was possible when T1 was still depressed. Therefore, after reversal with sugammadex the TOF ratio as the only measurement for adequate reversal of NMB may not always be reliable and twitch height has to be taken into account as well.

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Chapter 7

Sugammadex reverses neuromuscular block induced by 3-desacetyl-vecuronium, an active metabolite of vecuronium, in the anaesthetised rhesus monkey

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ABSTRACT

Background

3-Desacetyl-vecuronium is an active metabolite of the neuromuscular blocking agent (NMBA) vecuronium, which might lead to residual paralysis after prolonged administration of vecuronium in critically ill patients with renal failure. This study investigated the ability of sugammadex to reverse 3-desacetyl-vecuronium-induced neuromuscular block (NMB) in the anaesthetised rhesus monkey.

Methods

Experiments were performed in anaesthetised female rhesus monkeys. After bolus intravenous injection of vecuronium (n=8) or 3-desacetyl-vecuronium (n=8) 10 μg kg^{-1} (ED_{90}), a continuous infusion of the same NMBA was started to maintain the first twitch of the Train-of-Four (TOF) at 10% of baseline value. The infusion was stopped and NMB recovered spontaneously. The procedure was repeated, but immediately after stopping the infusion an intravenous bolus dose of sugammadex 0.5 or 1.0 mg kg^{-1} was given. For each NMBA, four placebo experiments were performed, in which the second recovery from NMB was also spontaneous. For all experiments time to recovery of the TOF ratio to 90% was retrieved.

Results

After administration of sugammadex for reversal of 3-desacetyl-vecuronium-induced NMB, recovery was significantly faster than spontaneous recovery. Mean time to recovery of TOF to 90% was 3.2 min (sugammadex 0.5 mg kg^{-1}) and 2.6 min (1.0 mg kg^{-1}), compared to spontaneous recovery (17.6 min). For vecuronium-induced NMB mean time to recovery of TOF to 90% was 17.1 min (0.5 mg kg^{-1}) and 4.6 min (1.0 mg kg^{-1}), compared to spontaneous recovery (23.4 min).

Conclusions

Sugammadex rapidly and effectively reversed 3-desacetyl-vecuronium-induced NMB in the rhesus monkey, at a lower dose than needed to reverse vecuronium-induced NMB.

INTRODUCTION

Vecuronium is an aminosteroidal neuromuscular blocking agent (NMBA), with a high safety profile, which is used in many surgical cases and for facilitation of mechanical ventilation. Like all other NMBAs, it may cause residual paralysis, resulting in hypoventilation, airway obstruction, pulmonary complications and hypoxia.[1, 2] Therefore, reversal of neuromuscular block (NMB) is important for the acceleration of patient recovery and prevention of residual paralysis and prolonged mechanical ventilation. Sugammadex, a selective relaxant binding agent, was specifically designed to encapsulate and inactivate the aminosteroidal NMBA rocuronium, thereby rapidly reversing NMB.[3-7] It has also been shown to be effective in reversing vecuronium-induced NMB.[8-10]

Vecuronium is associated with residual paralysis, with an increased risk after cumulative doses and long-term administration.[11,12] Segredo *et al.*[12] described two critically ill patients with renal failure and prolonged NMB lasting many hours after discontinuation of long-term administration of vecuronium. High plasma concentrations of 3-desacetyl-vecuronium (also known as 3-hydroxy-vecuronium), the principal metabolite of vecuronium, were found in these patients. 3-Desacetyl-vecuronium has significant neuromuscular blocking potency, up to 80% of its parent compound vecuronium.[13,14] It was likely that accumulation of the metabolite 3-desacetyl-vecuronium was the main cause of the residual paralysis in the patients described.[12]

It is important to know if such a residual paralysis can be terminated with sugammadex. Although sugammadex is effective in binding rocuronium and vecuronium, it is not known whether sugammadex is also capable of encapsulating 3-desacetyl-vecuronium. Theoretically, after reversal of vecuronium-induced NMB by sugammadex, 3-desacetyl-vecuronium might, thus, cause residual paralysis, should sugammadex not be capable of inactivating this active metabolite. To demonstrate the ability of sugammadex to also reverse 3-desacetyl-vecuronium-induced NMB, the present study was designed in the anaesthetised rhesus monkey. To assess a possible difference in reversing power of sugammadex for 3-desacetyl-vecuronium versus vecuronium, identical experiments were performed with a NMB induced by vecuronium.

METHODS

These in-vivo experiments were performed in the research laboratories of the Department of Anaesthesiology, Pain and Palliative Medicine at the Radboud University Nijmegen Medical Centre in Nijmegen, The Netherlands.

Female rhesus monkeys (CSIMS, Beijing, China) were sedated with ketamine 10 mg kg^{-1} (Nimatek; Eurovet, Bladel, the Netherlands) administered by intramuscular injection. Two

intravenous (i.v.) lines were inserted; one for the administration of anaesthetics, including vecuronium or 3-desacetyl-vecuronium, the other for sugammadex administration. Anaesthesia was induced by i.v. bolus injection of pentobarbital sodium 25 mg kg^{-1} (Ceva Sante Animale) and a subsequent continuous infusion of 5-10 mg kg^{-1} h^{-1}. The trachea was intubated and the lungs were mechanically ventilated with a mixture of oxygen and nitrous oxide at a ratio of 2:3, to maintain normoventilation, as determined by capnography. Heart rate and oxygen saturation were determined at the ear using a pulse oximeter (Ohmeda Biox; Ohmeda, Madison, USA). Blood pressure was determined non-invasively with a cuff placed around the tail (Ohmeda, Finapres). Body temperature was kept constant at 37–38°C.[15]

For monitoring neuromuscular transmission, the median nerve of the right arm was stimulated supramaximally near the wrist using needle electrodes.[15] Stimulation was performed with 2 ms square wave pulses in a Train-of-Four (TOF) sequence of 2 Hz with a train interval of 15 s, delivered by a Grass S88 Stimulator (Grass Medical Instruments, Quincy, Massachusetts, USA). The resulting contractions of the thumb muscles were quantified with a force displacement transducer, and recorded on a polygraph. The level of 10% recovery of the first twitch response (T1) of the TOF was chosen as the point for reversal. This point was chosen in analogy of previous experiments with sugammadex.[15] Each time a TOF stimulus was triggered (every 15 s), all variables were requested by the measuring computer from both the pulse oximeter and the blood pressure device.

The study drugs vecuronium and 3-desacetyl-vecuronium were provided by Organon, now a part of Merck Sharp & Dohme BV, Oss, the Netherlands. Vecuronium was supplied as commercially available Norcuron® and 3-desacetyl-vecuronium was supplied as a powder which was dissolved in NaCl 0.9%. The 3-desacetyl-vecuronium as supplied was at least 99% pure.

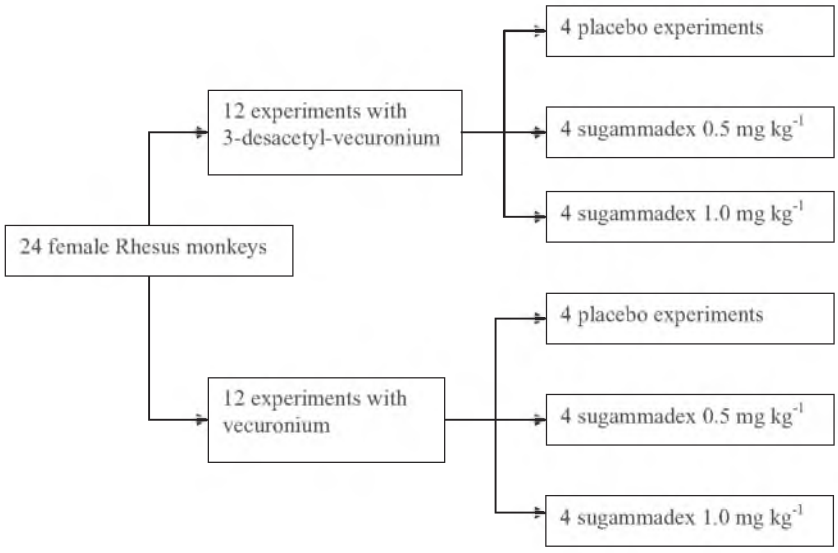
In this study in female rhesus monkeys, 12 experiments were planned using vecuronium and 12 using its metabolite 3-desacetyl-vecuronium as the NMBA. A flowchart of the study protocol is shown in Figure 1. After i.v. bolus injection of about the ED_{90} dose (in the rhesus monkey) of either vecuronium (10 µg kg^{-1})[16] or 3-desacetyl-vecuronium (10 µg kg^{-1}, known from pilot experiments to be the ED_{90}), a continuous infusion of vecuronium or 3-desacetyl-vecuronium was started in order to maintain T1 at approximately 10 % (± 5%) of its baseline value. After a constant NMB had been maintained for about 10 min, the infusion was stopped and the NMB was allowed to recover spontaneously. After full recovery of the TOF ratio (height of T4 versus height of T1 or T4/T1) one extra hour of recovery was allowed, before a second bolus of NMBA was given and the process was repeated. At the time the second infusion of NMBA was stopped, sugammadex either 0.5 or 1.0 mg kg^{-1} was administered as a rapid bolus i.v. (n=4 for each dose of sugammadex; eight experiments with 3-desacetyl-vecuronium and eight with vecuronium).

To verify that these data could be compared in a paired fashion, these experiments were preceded by eight placebo experiments (four for vecuronium and four for 3-desacetyl-vecuronium), in which the second recovery from NMB was spontaneous (instead of administration of sugammadex; Fig. 1).

From all experiments the time intervals from stopping the infusion to recovery of the TOF ratio to 90% were measured. After the response had recovered to baseline values, TOF monitoring was continued for an extra hour, to evaluate possible recurrent paralysis, as the effect of sugammadex may disappear 60 minutes after administration.[17]

At the end of the experiments, the animals recovered from anaesthesia, in a guarded recovery area. They were monitored in the presence of a warming lamp until normal behaviour had fully restored.

Figure 1: Flowchart of the study protocol.



Ethics

Ethical approval for this study (protocol number 1999-64B and 2000-62) was provided by the Radboud University Nijmegen Animal Experiment Committee, Nijmegen, the Netherlands (Professor Dr P. Zwart, October 27, 2000) which is governed by the Dutch law on Animal Experiments (revision 5/2/1997) and is based on the guidelines of the EU Directive 86/609. The two authors holding the animal lab authorization to perform this investigation were Dr J van Egmond (licensed in 1999 for article 9 of the cited Dutch law) and Ms F van de Pol (licensed in 1988 for article 12 of the same law).

Statistical analysis

The placebo experiments were used to show that two consecutive spontaneous recoveries for a single rhesus monkey, with sufficient recovery time in between, in a single experiment were reproducible.

Recovery times with (R2) and without (R1) the reversal agent were compared for the same NMBA and the same dose of sugammadex or placebo, in a Student's *t* test for paired observations. To eliminate more interindividual variance than simple paired observations, the recovery times were scaled to the first value (i.e. comparison of the difference/first value, (R2-R1)/R1, with 0). All values of the recovery times are presented as mean (SEM).

To compare recovery times of two different doses of sugammadex with the same NMBA, the ratio (R2-R1)/R1 was compared in a Student's *t*-test for unpaired data. Similarly, recovery times at the same sugammadex dose were compared between the two NMBAs.

P-values < 0.01 were considered statistically significant.

RESULTS

The experiments were performed in 24 different female rhesus monkeys (body weight 5.2 – 7.0 kg). Twelve experiments were conducted using vecuronium (four placebo experiments, four with sugammadex 0.5 mg kg^{-1} and four with sugammadex 1.0 mg kg^{-1}) and 12 using 3-desacetyl-vecuronium (four placebo experiments, four with sugammadex 0.5 mg kg^{-1} and four with sugammadex 1.0 mg kg^{-1}). (Fig. 1) To maintain T1 at 10%, infusion rates varied between 7.4 and 39.0 µg kg^{-1} h^{-1} for vecuronium and between 12.9 and 54.4 µg kg^{-1} h^{-1} for 3-desacetyl-vecuronium.

Recovery times for either 3-desacetyl-vecuronium or vecuronium are presented in Table 1. In the placebo group, after the second administration of the NMBA the spontaneous recovery times did not change statistically significantly, compared to recovery times after the first administration of the NMBA. Figure 2 shows a representative recording of a TOF registration of a placebo experiment (spontaneous recovery) with vecuronium in one animal. The overlap figure in Fig. 2 shows that there is no difference in spontaneous recovery pattern after the first and second administration of vecuronium in a representative experiment in the placebo group. From these data it is clear that the two consecutive spontaneous recoveries for a single monkey in a single experiment are reproducible, allowing evaluation of the effect of a reversal agent in a paired fashion as described.

Table 1 also presents the results of the experiments in which sugammadex was administered after the second administration of the NMBA. Recovery to a TOF ratio of 90% from both 3-desacetyl-vecuronium-induced and vecuronium-induced NMB was significantly faster after injection of sugammadex 1.0 mg kg^{-1}, compared to spontaneous recovery.

Table 1: Recovery times of neuromuscular block, spontaneous and after administration of sugammadex.

Mean (SEM) time intervals (min) from stop of the continuous administration of 3-desacetyl-vecuronium or vecuronium to recovery of the train-of-four (TOF) ratio to 90% after spontaneous recovery or reversal with sugammadex 0.5 mg kg^{-1} or sugammadex 1.0 mg kg^{-1}. Spontaneous recovery: after the first administration of the neuromuscular blocking agent (NMBA) and after the second administration of the NMBA in the placebo experiments. Reversal with sugammadex: after the second administration of the NMBA.

[a] Unpaired comparison of these groups showed no significant difference in 90% recovery time (p=0.84). [b] Unpaired comparison of these groups showed a significant reduction of 90% recovery time for the highest sugammadex dose (p=0.0069). Statistically significant P<0.01.

Drug	Recovery (min) First administration	Recovery (min) Second administration	Comparison (P)
3-Desacetyl-vecuronium (n=12)			
Placebo (n=4)	19.8 (1.61)	19.3 (0.77)	0.81
Sugammadex 0.5 mg kg^{-1} (n=4)	20.5 (3.58)	3.2 (1.17)[a]	0.0004
Sugammadex 1.0 mg kg^{-1} (n=4)	17.6 (1.51)	2.6 (0.94)[a]	0.0003
Vecuronium (n=12)			
Placebo (n=4)	23.9 (2.00)	25.3 (2.83)	0.36
Sugammadex 0.5 mg kg^{-1} (n=4)	25.4 (2.95)	17.1 (3.99)[b]	0.0487
Sugammadex 1.0 mg kg^{-1} (n=4)	23.4 (1.86)	4.6 (0.78)[b]	<0.0001

In 3-desacetyl-vecuronium-induced NMB, mean time to recovery of the TOF ratio to 90% was 3.2 minutes after administration of sugammadex 0.5 mg kg^{-1}, compared to 2.6 minutes after sugammadex 1.0 mg kg^{-1}. The higher dose of sugammadex provided a slightly faster reversal, however, not statistically significantly so (p=0.84).

In vecuronium-induced NMB, reversal by the administration of sugammadex 0.5 mg kg^{-1} was considerably slower than by sugammadex 1.0 mg kg^{-1}. Mean time to recovery of the TOF ratio to 90% was 17.1 minutes after sugammadex 0.5 mg kg^{-1}, compared to 4.6 minutes after sugammadex 1.0 mg kg^{-1}, which difference is statistically significant (p=0.0069). This is typically shown in Figures 3 and 4, presenting TOF ratio registrations for vecuronium and 3-desacetyl-vecuronium, respectively. Figure 3b clearly shows a faster recovery of vecuronium-induced NMB after administration of sugammadex 1.0 mg kg^{-1}, compared to sugammadex 0.5 mg kg^{-1} (Fig. 3a). Figure 4a shows a slightly faster reversal of 3-desacetyl-vecuronium-induced NMB after sugammadex 1.0 mg kg^{-1}, compared to sugammadex 0.5 mg kg^{-1} (Figure 4b).

Comparison of the recovery times after reversal with sugammadex 0.5 mg kg^{-1} shows that the reversal of 3-desacetyl-vecuronium-induced NMB is significantly faster than reversal of vecuronium-induced NMB with the same dose of sugammadex (p=0.0059). However, reversal with sugammadex 1.0 mg kg^{-1} of 3-desacetyl-vecuronium-induced NMB is not significantly faster than reversal of vecuronium-induced NMB with the same dose of sugammadex (p=0.31).

Monitoring for another hour did not reveal any signs of residual paralysis or recurrence of NMB. Heart rate and blood pressure did not change more than 20% of baseline values. The body temperature of the animals stayed between 37° and 38°C during the experiments. The recoveries from anaesthesia were uneventful in all rhesus monkeys.

Figure 2: TOF registration of vecuronium-induced neuromuscular block in a rhesus monkey (placebo experiment).

In this experiment, vecuronium 10 μg kg^{-1} i.v. was administered, followed by continuous infusion of vecuronium to maintain T1 at approximately 10% of the baseline value. When the infusion of vecuronium was stopped, the neuromuscular block (NMB) recovered spontaneously. This experiment was repeated in the same animal, again without reversal. The small insert figure is an overlap registration of both TOF ratio registrations of the first and second NMBA administration in the same animal. TOF, train-of-four.

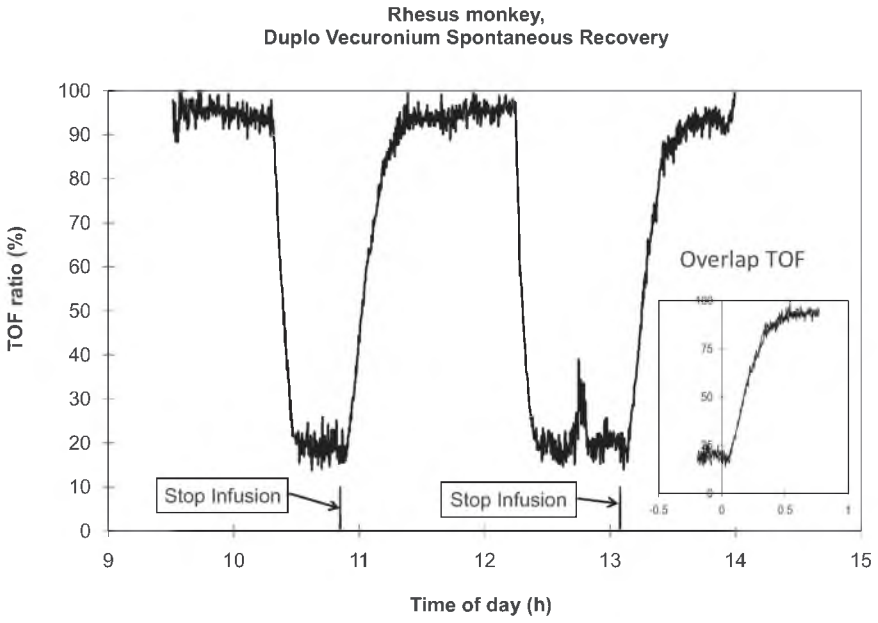


Figure 3: Overlap of two registrations of the train-of-four (TOF) ratio versus time curve in the same animal after vecuronium administration.

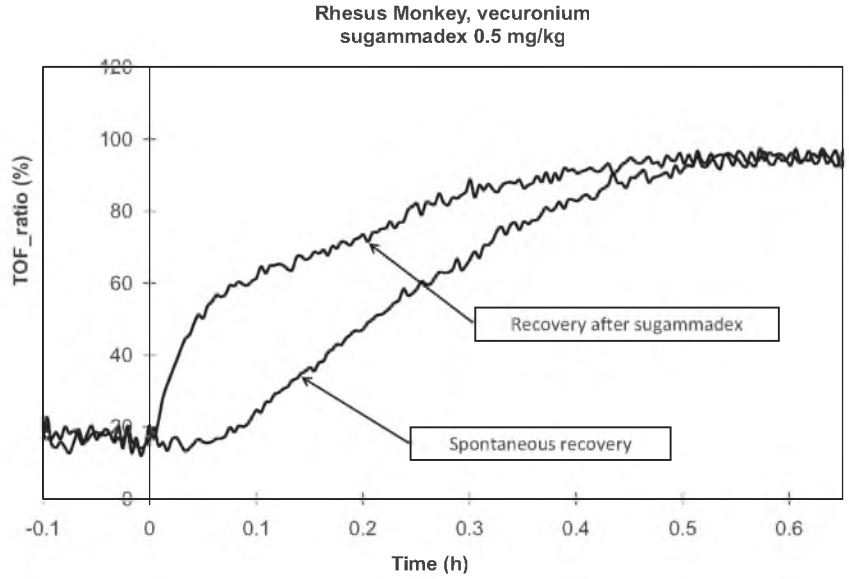


Figure 3a: spontaneous recovery of vecuronium-induced neuromuscular block (NMB) compared with recovery after administration of sugammadex 0.5 mg kg^{-1} iv.

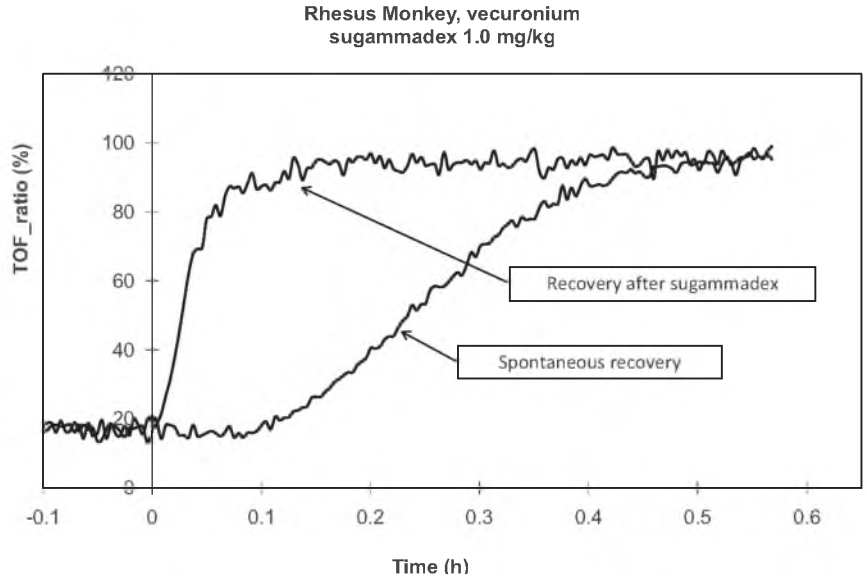


Figure 3b: spontaneous recovery of vecuronium-induced NMB compared with recovery after administration of sugammadex 1.0 mg kg^{-1} intravenously.

Figure 4: Overlap of two registrations of the train-of-four (TOF) ratio versus time curve in the same animal after 3-desacetyl-vecuronium administration.

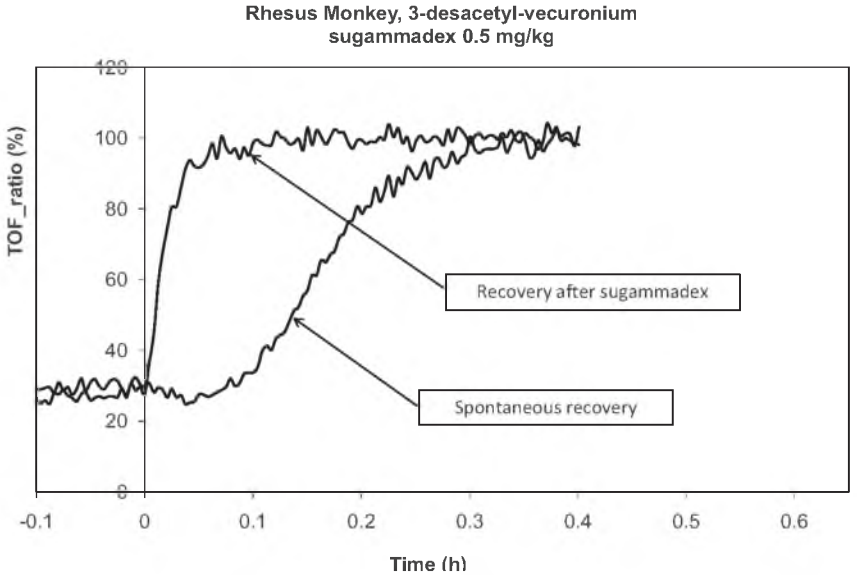


Figure 4a: spontaneous recovery of 3-desacetyl-vecuronium-induced neuromuscular block (NMB) compared with recovery after administration of sugammadex 0.5 mg kg^{-1} intravenously.

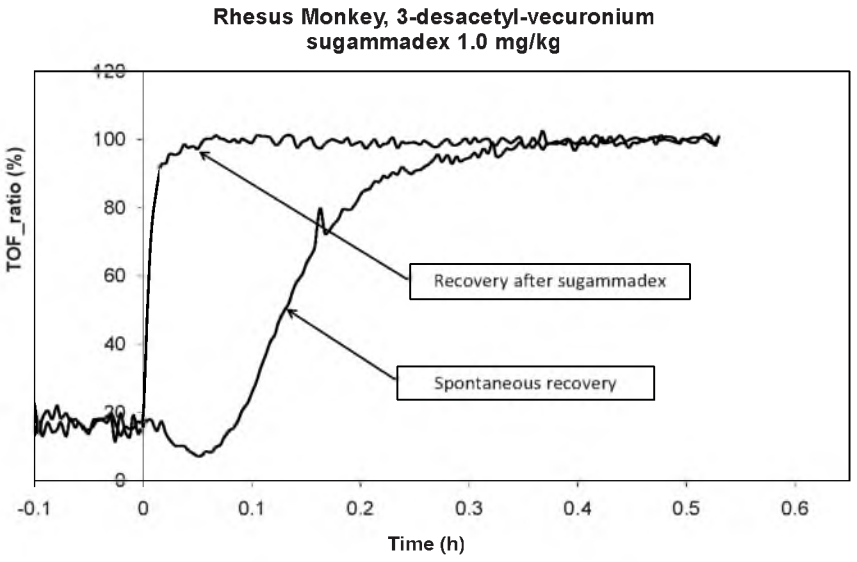


Figure 4b: spontaneous recovery of 3-desacetyl-vecuronium-induced NMB compared with recovery after administration of sugammadex 1.0 mg kg^{-1} intravenously.

DISCUSSION

Vecuronium undergoes hydrolysis to three pharmacologically active metabolites, 3-desacetyl-vecuronium, 17-desacetyl-vecuronium and 3,17-desacetyl-vecuronium.[18] The most potent metabolite, 3-desacetyl-vecuronium, accounts in humans for approximately 12% of the total clearance of vecuronium.[14] It has significant neuromuscular blocking potency, up to 50-70% in cats and 80% in humans, of its parent compound vecuronium.[13,14] Therefore, 3-desacetyl-vecuronium is a potent NMBA and is probably responsible for reported episodes of prolonged NMB after long-term administration of vecuronium in critically ill patients or patients with renal failure.[11,12,19]

The present study shows that NMB induced by 3-desacetyl-vecuronium in rhesus monkeys, like that produced by vecuronium, can be effectively and rapidly reversed by sugammadex. The rhesus monkey model was chosen because it is not allowed to administer 3-desacetyl-vecuronium in humans. Both sugammadex dosages administered (0.5 mg kg^{-1} and 1.0 mg kg^{-1}) were adequate in reversing the effect of 3-desacetyl-vecuronium within 4 minutes. There was no significant difference in recovery times between the two different doses of sugammadex, indicating that sugammadex 0.5 mg kg^{-1} is close to the optimal dose for reversing a 90% 3-desacetyl-vecuronium-induced NMB.

It has already been shown in human experiments that reversal of vecuronium-induced NMB by sugammadex is efficient and safe.[8-10] In the present study, reversal of vecuronium-induced NMB by sugammadex 1.0 mg kg^{-1} was also significantly faster than spontaneous recovery. However, after administration of sugammadex 0.5 mg kg^{-1}, mean time to reversal to a TOF ratio of 90% was still 17.1 minutes, which is a significantly slower recovery than recovery of vecuronium-induced NMB with sugammadex 1.0 mg kg^{-1} (p=0.0069), indicating that sugammadex 0.5 mg kg^{-1} is not yet the optimal dose. The vecuronium experiments in this study were performed to assess a possible difference in efficacy of sugammadex for reversing 3-desacetyl-vecuronium-induced NMB and vecuronium-induced NMB. Both doses of sugammadex provided an adequate recovery of 3-desacetyl-vecuronium-induced NMB, whereas the low dose of sugammadex did not for vecuronium-induced NMB. It also has to be taken into account that the infusion rates for 3-desacetyl-vecuronium in these experiments were higher, and therefore probably also the amount of NMBA molecules present in the rhesus monkey. These data suggest a difference in affinity of sugammadex for the NMBA molecules.

The equilibrium affinity constant (K_A) of vecuronium for sugammadex is 10.000.000 M^{-1} (compared to the K_A of rocuronium for sugammadex: 25.000.000 M^{-1}).[20] The exact K_A of 3-desacetyl-vecuronium is not known, as an isothermal microcalorimetry was not performed.

However, the efficacy of reversal of NMB depends not only on the affinity of sugammadex for the NMBA molecule, but also on the distribution kinetics and potency of the NMBA

and the number of NMBA molecules that need to be encapsulated to reverse NMB, that is, the plasma concentration of the NMBA at the time of reversal. Furthermore the efficacy depends on the number of sugammadex molecules present, that is, at a higher concentration the probability is greater for the two molecules to meet and form a complex. In this experiment, plasma concentrations of the NMBAs and sugammadex were not measured. In the rhesus monkeys that received vecuronium, part of the NMBA probably could have been metabolised into 3-desacetyl-vecuronium, at the time of reversal by sugammadex. Also other factors could play a role, such as differences in speed of diffusion of the NMBAs from the neuromuscular junction to the extravascular volume.

Conclusions regarding the difference in reversing power of sugammadex for the two NMBAs based on the results of this study must be made with caution and should be substantiated with further experiments.

No complete data are available on the potency and duration of effect of 3-desacetyl-vecuronium in rhesus monkeys, compared to the parent compound vecuronium. In the present study, the ED_{90} of both compounds proved to be about the same. The spontaneous recovery experiments of the present study show that recovery from 90% constant NMB induced by vecuronium is longer than that for the same NMB depth induced by 3-desacetyl-vecuronium. Mean time (SEM) to spontaneous recovery to a TOF 90% is 24.2 (1.24; n=12) minutes after vecuronium, compared to 19.2 (1.32; n=12) minutes after 3-desacetyl-vecuronium.

Prolonged NMB due to its metabolite 3-desacetyl-vecuronium has been reported after repeated or continuous administration of vecuronium for days in the ICU.[12,19] Risk factors for this prolonged paralysis are high concentrations of 3-desacetyl-vecuronium and renal failure.[12,19,21] For 3-desacetyl-vecuronium, the liver is the main organ of elimination and renal clearance accounts for 20% of the total drug clearance.[12,14] This means that hepatic failure could also lead to an accumulation of 3-desacetyl-vecuronium and prolonged NMB, which has been shown in animal studies.[22] The results of the present study show that reversal of such a state of prolonged NMB should be possible with sugammadex, as sugammadex also efficiently, and even more so, reverses 3-desacetyl-vecuronium-induced NMB. It should be realised that the present study, performed in the rhesus monkey, is different from the situation of critically ill humans in the ICU, who could possibly also suffer from muscle weakness due to critical illness polyneuromyopathy (CIP) or sepsis-induced myopathy.[23,24] The use of NMBAs itself has been described as a risk factor for developing CIP.[23] However, vecuronium is still used in many ICUs throughout the world for facilitation of mechanical ventilation in patients resisting such ventilation.

Human studies have shown that sugammadex is effective in reversing vecuronium-induced NMB.[8-10] However, if sugammadex was not capable of encapsulating and inactivating the metabolite 3-desacetyl-vecuronium, there would be a risk that after successful reversal of long duration vecuronium-induced NMB by sugammadex, the patient would develop

residual paralysis due to the active metabolite 3-desacetyl-vecuronium. The present results show that there is little chance that such residual paralysis will occur after administration of sugammadex.

Sugammadex is a water-soluble molecule, which is excreted mainly by the kidneys. In preclinical and clinical studies, renal excretion of the unchanged product was observed.[6,7,25] After sugammadex administration in renal failure patients, clearance of sugammadex was much reduced and the terminal elimination half-time and mean residence time of sugammadex was 15-20 times higher in the renal failure group compared to the control group.[26] Sugammadex is biologically inactive, and has been shown to be well tolerated. However, at present no data are available on long-term safety aspects of sugammadex in patients with renal failure or critically ill patients in the ICU.

It should be realised that this investigation was performed in the rhesus monkey and that extrapolation of these results to humans, especially patients in ICU with organ failure, is not straightforward. However, although volume of distribution and potency of the NMBA may differ in the rhesus monkey compared to humans, the affinity of the NMBA for sugammadex is not species-dependent.

In conclusion, sugammadex rapidly and effectively reverses NMB induced by 3-desacetyl-vecuronium in the rhesus monkey. It provides a rapid reversal of NMB at a lower dose of sugammadex than the dose needed to reverse NMB induced by vecuronium. As prolonged NMB after administration of vecuronium in critically ill patients and patients with renal failure has been attributed to high plasma concentrations of 3-desacetyl-vecuronium, the results of this investigation indicate that sugammadex should also be able to reverse NMB in such circumstances.

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Chapter 8

General Discussion and Conclusions

REVERSAL OF NEUROMUSCULAR BLOCK BY SUGAMMADEX

Rocuronium and vecuronium are aminosteroidal neuromuscular blocking agents (NMBAs) widely used in anaesthesia and intensive care medicine.[1] They are used for facilitation of endotracheal intubation and to allow surgical access to body cavities, in particular the abdomen and thorax, without hindrance from voluntary or reflex muscle movement. Also NMBAs are sometimes needed for patients in the intensive care unit (ICU) to facilitate compliance with mechanical ventilation, when sedation alone has proved inadequate. [1]
Recovery from rocuronium- or vecuronium-induced neuromuscular block (NMB) occurs spontaneously, as the NMBA diffuses away from the effect site, the neuromuscular junction (NMJ), and is metabolized in the liver and/or eliminated in the bile or the urine.[1] However, there is a large inter-individual variability in duration of action of the NMBAs. As with all other non-depolarizing NMBAs, this includes the risk of residual paralysis at the end of surgery. Postoperative residual curarization (PORC) is defined as an acceleromyographic Train of Four ratio (TOF ratio) < 0.9.[2-5] PORC is a risk factor for postoperative pulmonary complications, such as aspiration and hypoxia, which contribute to anaesthesia related morbidity and mortality.[6-8] Conventionally, acetylcholinesterase inhibitors (in combination with muscarinic agonists) were used for the prevention and treatment of PORC, but these drugs have many side-effects and are also ineffective in reversing a profound NMB.[9;10]
Sugammadex is a new selective relaxant binding agent, designed to encapsulate and inactivate the aminosteroidal NMBAs, especially rocuronium.[11] It provides a rapid recovery from NMB, even when a profound NMB is present, and it has minimal side effects.[12-14] This thesis describes the use of sugammadex as a reversal agent in renal failure.

THE EFFICACY OF SUGAMMADEX IN RENAL FAILURE

Prolonged NMB has been reported after administration of rocuronium in patients with renal failure, compared with patients with normal renal function, although not consistently.[15-17] Inter-individual variability is also increased in renal failure patients, resulting in a less predictable duration of action.[18] As patients with renal failure are more vulnerable for developing a prolonged NMB, sugammadex may be very useful in this patient group, as PORC and postoperative respiratory complications are more likely (**chapter 2**).
The animal study performed in the cat (**chapter 3**) investigated the efficacy of sugammadex in reversing rocuronium-induced NMB in an animal model of acute renal failure. After complete interruption of renal perfusion, sugammadex rapidly and effectively reversed the neuromuscular blocking effect of rocuronium.
This finding was later confirmed in the clinical study on efficacy of sugammadex in patients with renal failure (creatinine clearance (CL_{CR}) < 30 ml min^{-1}) compared with patients

with normal renal function (**chapter 4**). The rocuronium-induced NMB was rapidly and effectively reversed by administration of sugammadex 2.0 mg kg^{-1}. Mean time to recovery of the TOF ratio to 0.9 was 2.0 minutes for the renal failure patients, compared to 1.65 minutes for the controls, which was not a statistically significant difference. Clinical signs of recurrence of NMB were not observed in any of the patients.

The findings in both investigations confirm that reversal of rocuronium-induced NMB by sugammadex depends on the rapid binding of rocuronium and not on its renal elimination. The free rocuronium molecules in the plasma are rapidly encapsulated by sugammadex, forming a complex with a high affinity. As a result the concentration of free rocuronium molecules in the plasma will rapidly decrease. Due to the concentration gradient more rocuronium molecules will diffuse from the NMJ (the effect site) to the plasma, and NMB is reversed.[19] In conclusion, it is rather the redistribution of the rocuronium molecules than elimination of the drug by renal excretion, which is responsible for the rapid recovery from NMB. Further investigation is necessary to test the ability and dose requirement of sugammadex in reversing a profound NMB in renal failure patients.

The duration of action of vecuronium is not prolonged in renal failure patients. However, residual paralysis has been described after cumulative doses and after long-term administration in critically ill patients on the ICU, who suffered from renal failure.[20-22] High plasma concentrations of 3-desacetyl-vecuronium, the principal metabolite of vecuronium were found in these patients.[20;21] 3-Desacetyl-vecuronium has a significant neuromuscular blocking potency, and accumulation of this metabolite was held responsible for the residual paralysis described. An animal study performed in the rhesus monkey (**chapter 7**) showed that sugammadex rapidly and effectively reversed NMB induced by 3-desacetyl-vecuronium. These results indicate that the described state of prolonged NMB can be reversed with sugammadex.

PHARMACOKINETICS OF SUGAMMADEX IN RENAL FAILURE

Administration of sugammadex leads to an altered distribution and elimination of rocuronium. The major routes of elimination of rocuronium are biliairy and urinary excretion.[23] Rocuronium is mainly taken up by the liver and metabolized and/or excreted in the bile and faeces in high concentrations. In the absence of sugammadex, only a limited amount of rocuronium is excreted via the renal route.[23]

Sugammadex is a water soluble molecule, and is rapidly and dose-dependently excreted in the urine.[24] When sugammadex was administered after administration of rocuronium, sugammadex was found to increase the urinary excretion of rocuronium in a dose dependent manner. This indicates that sugammadex enhances the renal clearance of rocuronium.[19;25]

After administration of sugammadex, the plasma clearance of rocuronium assimilates into the plasma clearance of sugammadex, with increasing doses of sugammadex.
It is suggested that the extrarenal route of elimination is unavailable to rocuronium encapsulated by sugammadex.[12] The plasma concentration of total rocuronium (free plus encapsulated) decreases less rapidly after administration of sugammadex. This implies that the elimination of rocuronium is even slowed by the administration of sugammadex. Encapsulation by sugammadex diverts the elimination of rocuronium from its normal pathway of hepatic clearance to the less effective renal clearance.[25] This makes the use of sugammadex in renal failure patients questionable. Nevertheless the reversal is effective since the complex of rocuronium and sugammadex has a high affinity constant.
The clinical study performed on the pharmacokinetics of rocuronium and sugammadex in renal failure patients compared to patients with normal renal function showed large differences in the pharmacokinetics of both drugs between the two patient groups (**chapter 5**). For the first 60 min after administration, median plasma concentrations of sugammadex were similar in the control and renally impaired groups. At later time points, plasma concentrations of sugammadex showed a slower decline in the renally impaired group compared with the control group. A similar effect was seen for rocuronium.
Total plasma clearance of sugammadex was 17 times lower in the renal failure group. The mean terminal elimination half-life ($t_{½,\beta}$) of sugammadex was 2.3 hours in the control group, whereas it was 35.7 hours in the renal failure group. This effect was less for the pharmacokinetic variables of rocuronium. After the administration of sugammadex, the total plasma clearance of rocuronium was four times lower in the renal failure group than in the control group. Regression analyses showed that both for sugammadex and rocuronium the correlation between clearance of the drug and creatinine clearance is highly significant. Also urinary excretion of both sugammadex and rocuronium was much reduced in the renal failure group compared to the control group.
It is clear that patients with renal insufficiency retain the rocuronium-sugammadex complex for a longer period of time than patients with normal renal function. However, the effect of renal impairment on the pharmacokinetic variables was smaller for rocuronium than for sugammadex. This suggests that in patients with renal failure, extrarenal clearance of rocuronium does take place, in spite of encapsulation by sugammadex. Even after encapsulation of rocuronium by sugammadex, there may still be a low concentration of free rocuronium available for hepatic clearance.
One of the problems of this pharmacokinetic study was, that the assay method used could not distinguish between free rocuronium and rocuronium encapsulated by sugammadex, as the sugammadex-rocuronium complex dissociates on the liquid chromatography column.[24] Therefore, all measured concentrations in urine and plasma, are total concentrations and do not indicate the degree of encapsulation. This makes it impossible to determine

whether there are still some free rocuronium molecules left, which are available for the hepatic elimination route.
More research is needed to determine the long-term disposition of the sugammadex-rocuronium complex in patients with renal failure. Also, investigations should be performed to determine whether rocuronium is still eliminated by the liver, after administration of sugammadex.

SAFETY OF SUGAMMADEX IN RENAL FAILURE

Available evidence suggests that the rocuronium-sugammadex complex will remain stable over time. The complex exists in equilibrium with a very high association constant (K_A $=25x10^6$ M^{-1}).[11;26] However, there may be concerns for patients with severe renal failure, who will retain the complex for a longer period of time than patients with normal renal function. These patients may suffer more from possible side effects of sugammadex. More importantly, should the sugammadex-rocuronium complex dissociate, there would be a risk of recurrence of NMB.
In the clinical study (**chapter 4**), the patients with renal failure were monitored for at least 24 hours using oxygen saturation and respiratory rate monitoring. They were also monitored for 48 hours for clinical signs of PORC. Recurrence of NMB was not observed in any of the patients during the neuromuscular monitoring or postoperative clinical monitoring period.
In the study on the efficacy of sugammadex in cats with ligated renal pedicles (**chapter 3**), there was a tendency towards a decrease in heart rate after the administration of sugammadex (not statistically significant). This could be interpreted as a restoration of the increase in heart rate caused by the preceding injection of rocuronium. In the clinical study in humans (**chapter 4**) and the study on the reversal of 3-desacetyl-vecuronium by sugammadex in rhesus monkeys (**chapter 7**), such a heart rate decreasing effect was not observed.
The adverse events possibly related to sugammadex in the clinical study (**chapter 4**) were diarrhoea (*n*=2), nausea (*n*=1), headache (*n*=1), and coughing and movement under anaesthesia (*n*=3). Coughing and movement after sugammadex has been reported in other studies as well.[13;25;27] This may be due to the rapid onset of effect of sugammadex in reversing NMB at a time of relatively light anaesthesia. In such a situation stimulation of the trachea by the endotracheal tube is more likely to be the cause of coughing and subsequent movement.
Urinary N-acetyl-glucosaminidase (NAG) is a measure of proximal renal tubule damage. In several clinical studies on sugammadex, abnormal values of NAG were documented in a few patients who received sugammadex.[13;25;28] One study also documented microalbu-

minuria and abnormal urine β_2–microglobulin values.[25] It is uncertain what the clinical relevance is of these findings and how this should be interpreted. In the clinical study described in this thesis (**chapter 4**), urinary NAG, microalbuminuria and β_2–microglobulin values above the safety ranges were seen predominantly in the renally impaired group and were already present at the pre-operative screening assessment.

No data on prolonged follow-up are available on the safety of sugammadex in patients with renal failure, where elimination of the sugammadex-rocuronium complex is compromised. No data on its long-term disposition are available yet. Sugammadex is a modified γ–cyclodextrin, an oligosaccharide forming a cylindrical capsule with a lipophilic internal cavity and a hydrophilic exterior.[11] Cyclodextrins are water-soluble molecules, which are used as solubilising agents for many drugs and foods. They do not possess any intrinsic biological activity and it is therefore unlikely that side effects will occur. Sugammadex has been shown to be well tolerated in many clinical trials in humans.[12-14;25;27] Also, high doses of sugammadex, up to 96 mg kg^{-1}, were tolerated well in healthy volunteers. The most common adverse event was dysgeusia (a bitter or metallic taste).[29]

Toxicity studies on γ-cyclodextrins after oral or parenteral administration show that the drugs are well tolerated and safe to use in the dose ranges recommended for sugammadex.[30] The clinical safety profile is comparable to other cyclodextrins used as carrier agents, for example for voriconazole and itraconazole.[31] In rats, it was observed that sugammadex can bind to mineralized tissues (hydroxy-apatite) such as bones and teeth, although a single dose of sugammadex is unlikely to create any long-lasting effect.[31;32]

It is important to know the final disposition of sugammadex in renal patients who cannot excrete the molecule. Adverse reactions have occurred with drugs and intravenous fluids depositing in tissue, for example the deposition of hydroxyethyl starch (HES) in dermal and endoneural tissues, causing pruritus sometimes weeks or months after HES exposure.[33] Further investigations of the long-term safety aspects of sugammadex in renal failure patients are needed.

SUGAMMADEX AND HAEMODIALYSIS

Haemodialysis membranes are classified into high and low flux membranes, depending on their permeability. High flux membranes are more porous non-cellulosic membranes with increased permeability, particularly to larger molecules.[34]

In the clinical study in humans (**chapter 5**), nine out of the 15 patients with renal failure underwent haemodialysis at the time of the investigation. In patients undergoing low-flux haemodialysis (n=7) no significant reductions in sugammadex plasma concentrations were observed after dialysis. The median reduction ratio (RR) of sugammadex was 0.93. In patients undergoing high-flux haemodialysis (n=2), the median RR of sugammadex was

0.58.[35] The low flux membranes seemed almost ineffective in removing sugammadex from the circulation, whereas high-flux membranes reduced the sugammadex plasma concentration by more than 40%. Due to the small number of subjects included, these results must be viewed as preliminary. However, they were in agreement with the results of an *in vitro* study on the dialysability of sugammadex, which concluded that sugammadex could be efficiently removed from the plasma by dialysis using a high flux membrane but not a low flux membrane.[36]
Further investigation is necessary to obtain more detailed information regarding the dialysability of sugammadex.

SUGAMMADEX AND NEUROMUSCULAR MONITORING

In all published studies investigating sugammadex, the primary efficacy parameter was time to recovery of an acceleromyographic TOF ratio to 0.9. Time to recovery of the first twitch of the TOF (T1) was not described.
Fade, a gradual diminution of evoked response during repetitive nerve stimulation, is expressed by the TOF ratio and it represents presynaptic acetylcholine receptor (nAChR) blockade. Postsynaptic acetylcholine receptor blockade is expressed by the depression of the single twitch response or T1.[37] During spontaneous recovery from NMB induced by a non-depolarizing NMBA, the fade effect persists longer than the depression of T1. Fade disappears and the TOF ratio recovers to > 0.9 only after normalization of the twitch height.[38] When a NMB is reversed by anticholinesterases, the time course of reversal from NMB is the same: first full recovery of T1, and then recovery of the TOF ratio to 0.9.[1]
As described in **chapter 6**, after reversal of a rocuronium-induced NMB by an optimal dose of sugammadex, the recovery of the TOF ratio to > 0.9 precedes the return of T1 to 90%. The TOF ratio may be fully recovered, when T1 is still depressed. It can be concluded that the TOF ratio as the only measurement for adequate reversal from NMB is no longer reliable in all cases after reversal with sugammadex. Twitch height has to be taken into account as well. This phenomenon may be explained by a difference in affinity of rocuronium for the different nAChRs in the NMJ: the neuronal presynaptic nAChR (which is responsible for the fade phenomenon) and the postsynaptic muscle nAChR (which is responsible for the single twitch height).[39]
The clinical implications of this finding, however, are not clear. In the investigation described in **chapter 6**, full recovery of T1 followed recovery of the TOF ratio within a few minutes. In the patients with renal impairment, recovery of T1 was significantly slower compared to patients with normal renal function. Also the differences in recovery times between TOF ratio and T1 were larger in this patient group. Renal patients may therefore be more vulnerable for the development of residual paralysis, even when a TOF ratio of

0.9 has been reached. Further studies need to be conducted to investigate the clinical implications of this finding.

FUTURE OF SUGAMMADEX

Sugammadex is capable of antagonizing an aminosteroidal-induced NMB from any level of NMB at any time. This gives the anaesthetist the possibility to apply anaesthesia methods best suitable for the individual patient. It diminishes the importance of inter-individual variability in the duration of action of the NMBAs; it may not be relevant anymore if a NMB lasts longer than the operation. In an individual patient we can reverse the aminosteroidal-induced NMB at any time needed. The introduction of sugammadex may change the use of NMBAs in the context of balanced anaesthesia.[40;41]

However, there are still some questions to be answered regarding sugammadex. The European registration authorities (EMEA) registered sugammadex for clinical use in July 2008, but the FDA (Food and Drug Administration, USA) has asked more data on hypersensitivity testing, as there have been reports on possible allergic reactions to sugammadex, one of which has been substantiated by a positive skin test.[29;31] There were reports of two cases of serious adverse events related to bronchospasm after administration of sugammadex.[27] Even though both cases had a history of asthma, these complications might also suggest the risk of allergic or hypersensitivity reactions following sugammadex.

The FDA also expressed concerns regarding the potential of sugammadex to bind to bone and teeth of developing rats and implied that safety was not well established in paediatric populations.[32] More paediatric registration studies are needed to get valid paediatric documentation of the use of sugammadex in different clinical scenarios.[40]

Currently succinylcholine is the NMBA of choice when performing a rapid sequence induction (RSI) of anaesthesia, for example when the patient has a full stomach. A dose of succinylcholine 1.0 mg kg^{-1} provides superior intubating conditions within 1 minute after administration.[42] Rocuronium, when administered in a high dose (1.2 mg kg^{-1}) provides similar intubating conditions in a similar speed.[42] However, when rocuronium is administered in such a high dose, the duration of action is much prolonged, and can take more than 1 to 1.5 hours. Therefore, until recently, a RSI with rocuronium was only performed in case of contra-indications for succinylcholine. Succinylcholine has many side effects and is contra-indicated in several diseases, such as burn trauma, muscle crush injuries, muscle denervations, myotonic dystrophy and malignant hyperthermia.[43;44]

To compare the time of sugammadex reversal of profound rocuronium-induced NMB with time to spontaneous recovery from succinylcholine, a randomized study was performed. Patients received either rocuronium 1.2 mg kg^{-1} or succinylcholine 1.0 mg kg^{-1}. Sugammadex 16 mg kg^{-1} was administered 3 minutes after rocuronium administration. This study

showed that with sugammadex the mean time to recovery of the first twitch (T1) of the TOF from profound rocuronium-induced NMB was 6.2 minutes, which was significantly shorter than the time to spontaneous recovery from succinylcholine-induced NMB (10.9 minutes).[45]

In conclusion, with the availability of sugammadex, rocuronium has become a good alternative for succinylcholine when the anaesthetist has to perform a RSI, even for short procedures. Future trials are needed to establish the efficacy and safety of sugammadex in situations such as *cannot intubate cannot ventilate* and failed intubation during RSI using high-dose rocuronium.

In the trials investigating sugammadex, patients with known or suspected neuromuscular diseases were excluded. The use of NMBAs in patients with these disorders is of great concern. Depolarizing NMBAs are contra-indicated, because of the risk of hyperkalemia, rhabdomyolysis or even cardiac arrest.[46] Non-depolarizing NMBAs may have a prolonged duration of action in these patients, which may result in PORC.[44;47] Patients with neuromuscular disorders would benefit from a reversal agent such as sugammadex which does not interfere with acetylcholinesterase in the NMJ. Some case reports have already been published on the successful use of sugammadex as a reversal agent for NMB in patients with Duchenne muscular dystrophy, myotonic dystrophy and myasthenia gravis.[48-50]

Many clinicians are aware of the relatively high costs of sugammadex, especially compared to the classical reversal combination of neostigmine and atropine. Will the routine reversal of profound NMB by sugammadex be cost-effective in terms of time savings in operating theatre programs?[51;52] However, the most important question on the use of sugammadex is whether the routine reversal of NMB by sugammadex will decrease postoperative pulmonary complications, such as atelectasis and pneumonia. Further research is required to determine the effects of sugammadex on predictability of recovery from NMB and efficient use of resources; but most importantly on patient safety and outcome.

CONCLUSION: CLINICAL IMPLICATIONS FOR RENAL FAILURE PATIENTS

Sugammadex rapidly and effectively reverses NMB induced by rocuronium, even when renal function is severely impaired. It is the redistribution of rocuronium molecules which is responsible for the rapid recovery from NMB, and not the elimination of the drugs by renal excretion. However, there are large differences in pharmacokinetics of rocuronium and sugammadex between patients with normal renal function and patients with severe renal impairment. Total plasma clearance of sugammadex is 17 times lower in renal failure patients compared to controls, and $t_{1/2,\beta}$ of sugammadex is more than 15 times prolonged. Urinary excretion of sugammadex and rocuronium is much reduced in renal failure patients.

Although sugammadex was tolerated well by patients with severe renal failure, long-term follow up on the safety of sugammadex in renal patients is needed, as the sugammadex-rocuronium complex is retained longer in the body and the disposition of the drug is not known.

Because renal patients are more at risk of developing PORC after the use of aminosteroidal NMBAs, they would benefit from the use of sugammadex, as this would decrease the risk of PORC and subsequently the incidence of postoperative pulmonary complications. Benzylisoquinolines are not dependent on renal function, and often recommended as NMBAs in renal failure patients. However, they may evoke histamine release. Also the duration of action of the benzylisoquinolines shows inter-individual variations, and the risk of developing PORC remains. Succinylcholine has many unwanted side effects in renal failure patients, most importantly hyperkalemia. Other NMBAs with a short duration of action are not available.

Although the use of sugammadex in patients with renal failure is questionable, the advantages of sugammadex for patients with renal insufficiency probably outweigh the risks of possible long-term effects of sugammadex.

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Chapter 9

Summary
Samenvatting

SUMMARY

This thesis describes the influence of renal failure on the efficacy and safety of reversal of neuromuscular block (NMB) induced by aminosteroidal neuromuscular blocking agents (NMBAs) by the reversal agent sugammadex. It also describes the pharmacokinetics of rocuronium and sugammadex in patients with severe to end-stage renal failure compared to healthy controls.

Chapter 1 provides a general introduction to the research presented in this thesis. Rocuronium and vecuronium are aminosteroidal NMBAs used in anaesthesia and intensive care medicine. The effect of all NMBAs is variable in intensity and duration. This frequently results in the occurrence of postoperative residual paralysis, which is a major risk factor in the development of postoperative pulmonary complications, such as atelectasis and pneumonia. Reversal of NMB can be achieved by administration of acetylcholinesterase inhibitors, but these have many side effects.
Sugammadex, a modified γ-cyclodextrin, is a selective relaxant binding agent, designed to reverse the neuromuscular blocking effects of the aminosteroidal NMBAs, especially rocuronium. Sugammadex encapsulates the NMBA molecules in the plasma, forming a complex with a high affinity, which leads to a rapid decrease of the concentration of free NMBA molecules in the plasma. As a result of the concentration gradient of free molecules between plasma and the effect site, the neuromuscular junction (NMJ), steroidal NMBA molecules rapidly diffuse away from the NMJ into the plasma. This leads to a rapid recovery of NMB.
Sugammadex is a water-soluble molecule, cleared by the kidneys. Also, the sugammadex-rocuronium complex is cleared by the kidneys. To investigate the implications for the efficacy and safety of sugammadex in patients with renal failure, the studies presented in this thesis were conducted.

Chapter 2 is an introductory chapter, with an historic overview on the use of NMBAs and reversal agents. A number of important issues associated with the administration of NMBAs and reversal agents in patients with renal failure are discussed.
Inter-individual variability in the effect of the aminosteroidal NMBAs is increased in renal failure patients, resulting in a less predictable duration of action. Prolonged NMB after administration rocuronium has been reported in patients with renal failure. Residual paralysis has also been described after long-term administration of vecuronium in critically ill patients with renal failure. 3-Desacetyl-vecuronium, an active metabolite of vecuronium, which has 80% of the potency of the parent compound vecuronium, was held responsible for this prolonged NMB. Therefore, patients with renal insufficiency have an increased risk of residual paralysis and postoperative respiratory complications.

In this chapter, the development and the mechanism of action of sugammadex is also described. Sugammadex does not appear to undergo metabolism and is primarily excreted in the urine as the unchanged drug. Also the sugammadex-rocuronium complex is mainly excreted by the kidneys. When sugammadex is administered after a dose of rocuronium, urinary excretion of rocuronium increases with increasing doses of sugammadex. The normal route of elimination for rocuronium, hepatic elimination, is expected to be unavailable for encapsulated rocuronium.
This raises concerns regarding the safety of sugammadex in patients with renal failure: when the elimination pathway of rocuronium is diverted from hepatic clearance to renal clearance after administration of sugammadex, what will happen to the complex when renal clearance is decreased? Will the reversal of rocuronium-induced NMB by sugammadex be effective? Is there a possible risk, when rocuronium is not cleared from the body, that paralysis will recur? The investigations presented in this thesis were conducted to answer these questions.

The study described in **chapter 3** investigated the influence of renal failure on the efficacy of reversal of rocuronium-induced NMB by sugammadex. An animal model in the cat was used: both renal pedicles of anaesthetized cats were ligated to create a model of acute renal failure. Neuromuscular monitoring was performed by single twitch monitoring. Rocuronium was administered to induce NMB, and after this first administration NMB recovered spontaneously. Then the renal pedicles of the cats were ligated. Directly after induction of NMB by a second dose of rocuronium, in Group 1 placebo and in Group 2 sugammadex was administered. Sugammadex reversed rocuronium-induced NMB significantly faster than spontaneous recovery ($p<0.0001$). The reversal of NMB by sugammadex was rapid and effective, even after interruption of the renal perfusion in these anaesthetized cats. This demonstrates that reversal of NMB is not dependent on the renal elimination of the sugammadex-rocuronium complex.

After the study in animals, a clinical study in humans was performed, which is presented in **chapters 4 and 5**. Thirty adult patients, undergoing elective surgery under general anaesthesia, were included in this trial: 15 ASA class II–III patients with severe renal failure (creatinine clearance (CL_{CR}) <30 ml min^{-1}) and 15 ASA class I–II control patients. Neuromuscular function was monitored continuously by acceleromyography and the Train-of-Four (TOF). A single i.v. dose of rocuronium 0.6 mg kg^{-1} was administered. At reappearance of the second twitch response (T2), a single i.v. dose of sugammadex 2.0 mg kg^{-1} was given. Primary efficacy variable was the time to recovery of the TOF ratio to 0.9. Plasma and urine sampling were conducted to determine the plasma concentration of sugammadex and rocuronium and the percentage of the administered dose of sugammadex and rocuronium excreted in the urine.

Chapter 4 describes the efficacy and safety results of this clinical trial. Administration of sugammadex at reappearance of T2 after a bolus dose of rocuronium resulted in a mean time to recovery of the TOF ratio to 0.9 of 2.0 min for renal patients, and 1.65 min for controls. This was not a significant difference. Recurrence of NMB was not observed in any of the patients during a 48 hour postoperative monitoring period. These findings confirm that reversal of rocuronium-induced NMB by sugammadex can be attributed to rapid binding of rocuronium and is not dependent on its elimination by renal excretion.
Five patients, two in the renally impaired group and three in the control group, experienced a total of eight adverse events (AEs) possibly related to sugammadex. These were diarrhoea (*n*=2), nausea (*n*=1), anaesthetic complications (coughing and movement during anaesthesia shortly after administration of sugammadex) (*n*=3), headache (*n*=1) and decreased oxygen saturation (*n*=1). This decreased oxygen saturation was not considered a clinical sign of recurrence of NMB, but was attributed to the i.v. administration of opioids in the recovery ward and was successfully treated with oxygen. Coughing or movement after sugammadex has been reported in other studies. This may be due to the rapid onset of the effect of sugammadex in reversing NMB at a time of relatively light anaesthesia. No sugammadex-related serious adverse events (SAEs) were reported.
In **chapter 5** the pharmacokinetics (PKs) of rocuronium and sugammadex in patients with renal failure and healthy controls are described. PK parameters were calculated using conventional non-compartmental analysis methods. Of the 30 patients enrolled in the study, PK data could be obtained in 26 patients.
This study showed large differences in the PKs of sugammadex and rocuronium between patients with renal failure and healthy controls. For the first 60 min after administration, median plasma concentrations of sugammadex were similar in the control and renally impaired groups. At later time points, plasma concentrations of sugammadex showed a slower decline in the renally impaired group compared with the control group. A similar effect was seen for rocuronium.
Statistically significant differences were observed between the control and the renal failure groups for sugammadex in total plasma clearance (CL), and the related parameters, elimination half-life ($t_{1/2,\beta}$) and mean residence time (MRT). MRT was 20 times higher, $t_{1/2,\beta}$ was 15.5 times higher and CL was 17 times lower in the renal failure group compared with the control group.
Statistically significant differences were also observed in these variables for rocuronium. The MRT was 4.6 times higher, $t_{1/2,\beta}$ was 2.5 times higher and CL was four times lower in the renally impaired group compared with the control group. Regression analyses showed that both for sugammadex and for rocuronium, the correlation between CL and CL_{CR} was highly significant ($P<0.0001$).
Urinary excretions of sugammadex and rocuronium were much lower in the renal failure group than in the control group. In renal failure patients, the median total amount of

sugammadex excreted in urine (in 72 h) was 29% of the administered dose, compared to 73% (in 24 h) in the control group. For rocuronium, a much smaller fraction of the dose was excreted in the urine than for sugammadex, both for the renally impaired group and the control group. Median total amount of rocuronium excreted in urine was 4.4% of the administered dose in 72 h in the renal failure group and 42% in 24 h in the control group. As urinary excretion is the main route of elimination of the sugammadex-rocuronium complex, the extrarenal route of elimination is expected to be unavailable for encapsulated rocuronium. Encapsulation by sugammadex diverts the elimination of rocuronium from its normal primary pathway of hepatic clearance to renal clearance. As the effect of renal impairment on the PK variables was smaller for rocuronium than for sugammadex, it is suggested that in patients with renal failure, extrarenal clearance of rocuronium does take place, in spite of complexation.

Chapter 6 describes the temporal relationship of recovery of the first twitch of the TOF (T1) and the TOF ratio, after reversal of rocuronium-induced NMB with sugammadex. The TOF ratio reflects the effects of the NMBA at the presynaptic membrane of the NMJ and the T1 response reflects the events at the postjunctional membrane. During spontaneous recovery from non-depolarizing NMBAs the T1 response of the TOF normally recovers to baseline, while at this point the TOF ratio may still be no more than 0.7, which is considered insufficient recovery from NMB. The same pattern occurs after reversal of non-depolarizing NMBAs with acetylcholinesterase inhibitors.
The data in **chapter 6** are derived from two prospective studies investigating the efficacy of sugammadex in reversing rocuronium-induced NMB. Retrospectively, the times to recovery of T1 to 90% were retrieved from the original recorded neuromuscular database of the patients included in these investigations.
After reversal of rocuronium-induced NMB with an optimal dose of sugammadex (16 mg kg^{-1} for profound NMB or 2 mg kg^{-1} after reappearance of T2), the TOF ratio recovered to 0.9 significantly faster than T1 recovered to 90%. This means that after reversal of rocuronium-induced NMB by sugammadex the return of a normal TOF ratio can, dose-dependently, precede the return of a normal T1 twitch height and the traditional relationship between TOF ratio and T1 recovery is no longer valid. Therefore, the TOF ratio as the only measurement for adequate reversal of NMB, is no longer reliable in all cases after reversal with sugammadex, and twitch height has to be taken into account as well. Further investigation for the clinical implications of this finding is needed.

Chapter 7 describes a study in anaesthetized rhesus monkeys, investigating the ability of sugammadex to reverse a NMB induced by 3-desacetyl-vecuronium. 3-Desacetyl-vecuronium is the principal metabolite of the aminosteroidal NMBA vecuronium, and has significant neuromuscular blocking potency. The use of vecuronium is associated

with residual paralysis, with an increased risk after cumulative doses and long-term administration in critically ill patients with renal failure. Accumulation of this metabolite 3-desacetyl-vecuronium is considered the main cause of residual paralysis in these patients. It is important to know if such a residual paralysis can be terminated with sugammadex. Also, theoretically, after reversal of a vecuronium-induced NMB by sugammadex, 3-desacetyl-vecuronium might cause residual paralysis, should sugammadex not be capable of inactivating this active metabolite.
Experiments were performed in anaesthetized female rhesus monkeys. A NMB was induced by either vecuronium or 3-desacetyl-vecuronium. After the first administration of the NMBA the NMB was allowed to recover spontaneously. Then the procedure was repeated. After the second administration of NMBA a bolus dose of sugammadex 0.5 or 1.0 mg kg^{-1} was given. For each NMBA placebo experiments were performed in which the second recovery from NMB was also spontaneous. For all experiments, the time to recovery of the TOF ratio to 90% was retrieved. Sugammadex rapidly and effectively reversed NMB induced by 3-desacetyl-vecuronium in the rhesus monkey: recovery was significantly faster than spontaneous recovery. Sugammadex also provided a rapid reversal of NMB at a lower dose of sugammadex than the dose needed to reverse NMB induced by vecuronium. The results of this investigation indicate that sugammadex should be able to reverse NMB due to high plasma concentrations of 3-desacetyl-vecuronium after long-term administration of vecuronium.

Chapter 8 presents the general discussion and conclusions of the thesis. In this chapter also the future of sugammadex and implications for further research are discussed.
Sugammadex rapidly and effectively reverses a rocuronium-induced NMB, even when renal function is severely impaired. Therefore, reversal of NMB by sugammadex depends on the rapid binding of the NMBA and not on its renal elimination. It is rather the redistribution of the rocuronium molecules than elimination of the drug by renal excretion, which is responsible for the rapid recovery from NMB.
From the pharmacokinetic study on sugammadex and rocuronium, it can be concluded that patients with renal insufficiency retain the rocuronium-sugammadex complex for a longer period of time than patients with normal renal function. Sugammadex was well-tolerated by all patients, both renal patients and controls, and recurrence of NMB was not observed in any of the patients. However, no data on prolonged follow-up are available on the safety of sugammadex in patients with renal failure, where elimination of the sugammadex-rocuronium complex is compromised. No data on its long-term disposition are available yet. The Food and Drug Administration has asked more data on hypersensitivity testing and expressed concerns regarding the potential of sugammadex to bind to bone and teeth tissue. Further investigation is needed.

As patients with renal failure are more at risk of developing residual paralysis after the use of aminosteroidal NMBAs, they would benefit from a reversal agent such as sugammadex. Although the use of sugammadex in patients with renal failure is still matter of discussion, the advantages for patients with renal insufficiency probably outweigh the risks of possible long-term effects of sugammadex.

SAMENVATTING

Dit proefschrift beschrijft de invloed van nierinsufficiëntie op de effectiviteit en veiligheid van de antagonist sugammadex in het opheffen van spierrelaxatie, ofwel een neuromusculaire blokkade (NMB), geïnduceerd door een spierrelaxans van de groep van de aminosteroiden. Het proefschrift beschrijft ook de pharmacokinetiek van rocuronium en sugammadex bij patiënten met ernstig tot terminaal nierfalen in vergelijking met gezonde controles.

Hoofdstuk 1 geeft een algemene introductie op het onderzoek dat wordt gepresenteerd in dit proefschrift. Rocuronium en vecuronium zijn spierrelaxantia van de groep van de aminosteroiden, die regelmatig worden gebruikt in de anesthesiologie en de intensive care geneeskunde. De werkingsduur en de intensiteit van effect van alle spierrelaxantia is zeer variabel. Dit heeft regelmatig het optreden van postoperatieve restverslapping tot gevolg, een belangrijke risicofactor op het ontwikkelen van postoperatieve longcomplicaties, zoals atelectase en pneumonie. Het opheffen van NMB is mogelijk door het toedienen van acetylcholinesterase remmers, maar deze hebben veel bijwerkingen.
Sugammadex, een gemodificeerd γ-cyclodextrine, is een selectieve antagonist van spierrelaxantia en is ontwikkeld om het spierverslappende effect van de aminosteroidale spierrelaxantia, in het bijzonder van rocuronium, op te heffen. Sugammadex kapselt de spierrelaxans moleculen in die aanwezig zijn in het plasma (encapsulatie), waarbij een complex wordt gevormd met een hoge affiniteit. Dit leidt tot een snelle daling van de concentratie van vrije spierrelaxans moleculen in het plasma. Als gevolg van de concentratiegradiënt van de vrije moleculen die ontstaat tussen plasma en de plaats van effect, de neuromusculaire junctie (NMJ), diffunderen de spierrelaxans molecules weg van de NMJ naar het plasma. Dit leidt tot het snel opheffen van de neuromusculaire blokkade.
Het sugammadex molecuul is wateroplosbaar en wordt geklaard door de nieren. Ook het sugammadex-rocuronium complex wordt uitgescheiden door de nieren. De studies die worden gepresenteerd in dit proefschrift zijn uitgevoerd om de implicaties voor de effectiviteit en veiligheid van sugammadex in patiënten met nierinsufficiëntie te onderzoeken.

Hoofdstuk 2 is een inleidend hoofdstuk, met daarin een historisch overzicht van het gebruik van spierverslappers en antagonisten. Een aantal belangrijke zaken aangaande het gebruik van spierrelaxantia en antagonisten bij patiënten met nierinsufficiëntie worden besproken.
Bij patiënten met nierfalen is de inter-individuele variabiliteit in het effect van aminosteroidale spierrelaxantia verhoogd, met als gevolg een minder voorspelbare werkingsduur. Verlengde NMB is beschreven na de toediening van rocuronium aan nierpatiënten. Ook na langdurige toediening van vecuronium aan kritisch zieke patiënten met nierinsufficiëntie

is restverslapping beschreven. Voor deze verlengde NMB wordt 3-desacetyl-vecuronium verantwoordelijk gehouden, een actieve metaboliet van vecuronium, met 80% van de potentie van vecuronium zelf. Concluderend, patiënten met nierinsufficiëntie hebben een verhoogd risico op restverslapping en daarmee postoperatieve longcomplicaties.
In dit hoofdstuk wordt tevens de ontwikkeling en het werkingsmechanisme van sugammadex beschreven. Sugammadex lijkt niet gemetaboliseerd te worden en wordt primair als onveranderd molecuul uitgescheiden in de urine. Ook het sugammadex-rocuronium complex wordt voornamelijk door de nieren uitgescheiden. Wanneer sugammadex wordt toegediend na een dosis rocuronium, neemt de uitscheiding van rocuronium in de urine toe, met stijgende doses sugammadex. Men neemt aan dat de gebruikelijke uitscheidingsroute voor rocuronium, via de lever, niet mogelijk is voor rocuronium dat een complex heeft gevormd met sugammadex.
Dit roept vragen op over de veiligheid van sugammadex bij patiënten met nierinsufficientie: als de uitscheidingsroute van rocuronium zich heeft verplaatst van de lever naar de nieren nadat sugammadex is toegediend, wat gebeurt er dan met het complex als de nierfunctie is verminderd? Zal het opheffen van NMB geïnduceerd door rocuronium nog effectief zijn met sugammadex? Is er een mogelijk risico op het heroptreden van spierverslapping, als rocuronium niet uitgescheiden kan worden uit het lichaam? Om deze vragen te beantwoorden werden de onderzoeken uitgevoerd, die worden gepresenteerd in dit proefschrift.

De studie die wordt beschreven in **hoofdstuk 3** onderzocht de invloed van nierinsufficientie op de effectiviteit van sugammadex in het opheffen van een NMB geïnduceerd door rocuronium. Er werd gebruik gemaakt van een diermodel in de kat: om een model van acuut nierfalen te creëren werden beide nierpedikels geligeerd van katten onder algehele anesthesie. Neuromusculaire monitoring werd uitgevoerd door middel van single twitch zenuwstimulatie. Om NMB te induceren werd rocuronium toegediend, en na deze eerste toediening herstelde de NMB zich spontaan. Daarna werden de nierpedikels van de katten afgebonden. Direct na inductie van de NMB door een tweede dosis rocuronium, werd in Groep 1 een placebo en in Groep 2 sugammadex toegediend. Sugammadex maakte de NMB ten gevolge van rocuronium significant sneller ongedaan dan de spontane hersteltijd ($p<0.0001$). Het opheffen van de spierverslapping door sugammadex was snel en effectief, zelfs na onderbreking van de nierperfusie. Dit toont aan dat het opheffen van NMB niet afhankelijk is van de uitscheiding van het sugammadex-rocuronium complex via de nieren.

Na deze dierstudie werd een klinische studie bij mensen uitgevoerd, welke wordt gepresenteerd in **hoofdstukken 4 en 5**. Dertig volwassen patiënten, die electieve chirurgie onder algehele anesthesie ondergingen, werden in deze trial geincludeerd: 15 ASA klasse II–III patiënten met ernstige nierinsufficiëntie (creatinine klaring (CL_{CR}) <30 ml min^{-1}) en 15 ASA

klasse I–II controle patiënten. Neuromusculaire functie werd continu bewaakt middels acceleromyografie en de Train-of-Four (TOF). Een eenmalige dosis rocuronium 0.6 mg kg^{-1} werd i.v. toegediend. Na het verschijnen van de tweede twitch (T2) van de TOF werd een eenmalige dosis sugammadex 2.0 mg kg^{-1} i.v. toegediend. Primaire variabele voor de effectiviteit was de tijd tot het herstel van de TOF ratio tot 0.9. Er werden bloedafnames gedaan om plasma concentraties te bepalen van sugammadex en rocuronium en er werd urine verzameld om het percentage van de toegediende dosis sugammadex en rocuronium te bepalen dat werd uitgescheiden in de urine.

Hoofdstuk 4 beschrijft de resultaten van deze klinische trial wat betreft effectiviteit en veiligheid. De toediening van sugammadex na het optreden van T2 na een eenmalige dosis rocuronium, resulteerde in een gemiddelde tijd tot het herstel van de TOF ratio tot 0.9 van 2.0 minuten bij nierpatiënten en 1.65 minuten bij controle patiënten. Dit verschil was niet significant. Bij geen enkele patiënt werd het heroptreden van spierverslapping gezien tijdens de bewakingsperiode tot 48 uur postoperatief. Deze resultaten bevestigen dat het opheffen van NMB geïnduceerd door rocuronium met sugammadex toegeschreven kan worden aan de snelle binding van rocuronium en dat dit onafhankelijk is van de uitscheiding van het complex door de nieren.

Vijf patiënten, twee in de groep nierpatiënten en drie in de controlegroep, hadden in totaal acht *adverse events* die mogelijk gerelateerd waren aan sugammadex. Het ging om diarree (n=2), misselijkheid (n=1), anesthesie complicaties (hoesten en bewegen onder anesthesie kort na de toediening van sugammadex) (n=3), hoofdpijn (n=1) en gedaalde zuurstofsaturatie (n=1). Deze gedaalde zuurstofsaturatie werd niet gezien als een klinisch teken van het heroptreden van NMB, maar werd toegeschreven aan de i.v. toediening van opioiden op de verkoeverkamer en werd succesvol behandeld met zuurstof. Hoesten en bewegen na de toediening van sugammadex is gerapporteerd in andere studies. Dit is mogelijk ten gevolge van de snelle inwerking van sugammadex en het opheffen van de spierverslapping op een moment van relatief lichte anesthesie. Er werden geen *serious adverse events* gerapporteerd die gerelateerd waren aan sugammadex.

In **hoofdstuk 5** wordt de pharmacokinetiek (PK) van rocuronium en sugammadex in nierpatiënten en gezonde controles beschreven. PK parameters werden berekend door middel van conventionele non-compartiment analyse methoden. Van de 30 patiënten die werden geincludeerd in de studie, konden er van 26 patiënten PK data worden verkregen.

Deze studie toonde grote verschillen aan in de PK van sugammadex en rocuronium tussen nierpatiënten en gezonde controles. In de eerste 60 minuten na de toediening waren de mediane plasmaconcentraties van sugammadex gelijk in controles en nierpatiënten. Op latere tijdstippen lieten de plasmaconcentraties van sugammadex een langzamere daling zien in de groep nierpatiënten ten opzichte van de controlegroep. Een soortgelijk effect werd gezien voor rocuronium.

Tussen de controles en de groep nierpatiënten werden er voor sugammadex statistisch significante verschillen gezien voor totale plasma klaring (CL), en voor gerelateerde parameters eliminatie halfwaardetijd ($t_{1/2,\beta}$) and *mean residence time* (MRT). MRT was 20 keer verhoogd, $t_{1/2,\beta}$ was 15.5 keer verhoogd en de CL was 17 keer verlaagd in de groep nierpatiënten vergeleken met de controle groep. Ook voor rocuronium werden er statistisch significante verschillen gezien voor deze variabelen. De MRT was 4.6 maal verhoogd, $t_{1/2,\beta}$ was 2.5 maal verhoogd en de CL was vier maal lager in de groep nierpatiënten vergeleken met de controle groep. Regressie analyses toonden aan dat de correlatie tussen CL en CL_{CR} zeer significant was zowel voor sugammadex als voor rocuronium ($P<0.0001$).
De uitscheiding van sugammadex en rocuronium in de urine was veel lager in de groep nierpatiënten dan in de controle groep. In de patiënten met nierinsufficiëntie was de mediane totale hoeveelheid sugammadex dat werd uitgescheiden in de urine 29 % van de toegediende dosis (in 72 uur), vergeleken met 73% (in 24 uur) in de controlegroep. Van rocuronium werd een veel kleinere fractie van de dosis in de urine uitgescheiden dan van sugammadex, zowel in de groep nierpatiënten als in de controlegroep. Mediane totale hoeveelheid rocuronium die werd uitgescheiden in de urine van de groep nierpatiënten was 4.4% van de toegediende dosis in 72 uur, en 42% in 24 uur in de groep controles.
Aangezien urinaire excretie de belangrijkste route is voor de uitscheiding van het sugammadex-rocuronium complex, wordt aangenomen dat de extrarenale route onmogelijk is geworden voor rocuronium dat een complex heeft gevormd met sugammadex. Encapsulatie door sugammadex verplaatst de eliminatie van rocuronium van de normale route van uitscheiding via de lever naar uitscheiding via de nieren. Het effect van nierinsufficiëntie op de PK variabelen is kleiner voor rocuronium dan voor sugammadex, wat suggereert dat bij patiënten met nierfalen er toch uitscheiding van rocuronium plaatsvindt buiten de klaring via de nieren, ondanks de vorming van het sugammadex-rocuronium complex.

Hoofdstuk 6 beschrijft de tijdsrelatie tussen het herstel van de eerste twitch van de TOF (T1) en de TOF ratio, na het opheffen door sugammadex van een NMB geïnduceerd door rocuronium. De TOF ratio weerspiegelt het effect van het spierrelaxans op de presynaptische membraan van de NMJ en T1 weerspiegelt het effect op de postjunctionele membraan. Tijdens het spontane herstel van een niet-depolarizerend spierrelaxans, herstelt eerst T1 van de TOF naar het oorspronkelijke niveau, terwijl op dat moment de TOF ratio nog niet altijd hersteld is tot 0.7, wat aangeeft dat de spierkracht dan nog onvoldoende is hersteld. Hetzelfde patroon treedt op na opheffen van een niet-depolarizerende NMB met acetylcholinesterase remmers.
De data in hoofdstuk 6 werden afgeleid uit twee prospectieve studies, die de effectiviteit van sugammadex onderzochten in het opheffen van een NMB geïnduceerd door rocuronium. De tijden tot het herstel van T1 tot 90% werden retrospectief verkregen uit de

originele neuromusculaire database van de patiënten die geïncludeerd waren in deze studies.
Na het opheffen van de NMB geïnduceerd door rocuronium met een optimale dosis sugammadex (16 mg kg^{-1} in geval van een diepe NMB of 2 mg kg^{-1} na het verschijnen van T2), herstelde de TOF ratio significant sneller naar 0.9 dan dat T1 herstelde naar 90%. Dit betekent dat, na het opheffen van een rocuronium-geïnduceerde NMB door sugammadex, het herstel van een normale TOF ratio vooraf kan gaan aan het herstel van de T1 twitch tot een normale hoogte, afhankelijk van de dosering sugammadex. De traditionele relatie tussen herstel van TOF ratio en T1 is dan niet langer geldig. Om deze reden is de meting van de TOF ratio als enige meting van het adequaat herstel van NMB niet langer in alle gevallen betrouwbaar na het opheffen van NMB door sugammadex. Er zal ook rekening gehouden moeten worden met de twitch hoogte. De klinische consequenties van deze bevinding dienen verder onderzocht te worden.

Hoofdstuk 7 beschrijft een studie waarin het vermogen werd onderzocht van sugammadex om een NMB geïnduceerd door 3-desacetyl-vecuronium op te heffen, in rhesusapen onder algehele anesthesie. 3-Desacetyl-vecuronium is de belangrijkste metaboliet van het aminosteroidale spierrelaxans vecuronium, en heeft een significante spierverslappende werking. Het gebruik van vecuronium is geassocieerd met restverslapping, met een verhoogd risico na cumulatieve doses en na langdurige toediening aan kritisch zieke patiënten met nierfalen. Restverslapping in deze patiënten wordt meest waarschijnlijk veroorzaakt door stapeling van deze metaboliet 3-desacetyl-vecuronium. Het is belangrijk om te weten of zulke restverslapping kan worden opgeheven met sugammadex. Ook zou het theoretisch mogelijk zijn dat 3-desacetyl-vecuronium restverslapping zou kunnen veroorzaken na het opheffen van een vecuronium-geïnduceerde NMB, mocht sugammadex niet in staat zijn om deze actieve metaboliet te inactiveren.
Er werden experimenten uitgevoerd in vrouwelijke rhesusapen onder algehele anesthesie. Een NMB werd geïnduceerd door ofwel vecuronium ofwel 3-desacetyl-vecuronium. Na de eerste toediening van het spierrelaxans herstelde de NMB zich spontaan. Deze procedure werd herhaald. Na deze tweede toediening van het spierrelaxans werd nu een eenmalige dosis sugammadex 0.5 of 1.0 mg kg^{-1} toegediend. Voor elk spierrelaxans werden tevens placebo experimenten uitgevoerd, waarbij het tweede herstel van NMB spontaan verliep. Bij alle experimenten werd de tijd tot herstel van de TOF ratio tot 0.9 bijgehouden. Sugammadex beëindigde een NMB geïnduceerd door 3-desacetyl-vecuronium snel en effectief in de rhesusapen: het herstel was significant sneller dan spontaan herstel. Sugammadex zorgde ook voor een snel herstel van NMB met een lagere dosis sugammadex dan de dosis die nodig was om een NMB geïnduceerd door vecuronium op te heffen. De resultaten van dit onderzoek wijzen erop dat het mogelijk is om een NMB ten gevolge van hoge

plasmaspiegels 3-desacetyl-vecuronium, na langdurige toediening van vecuronium, op te heffen met sugammadex.

Hoofdstuk 8 geeft de algemene discussie en de conclusies van dit proefschrift weer. In dit hoofdstuk worden tevens de toekomst van sugammadex en de implicaties voor verder onderzoek besproken.
Sugammadex heft snel en effectief een door rocuronium geïnduceerde NMB op, zelfs wanneer de nierfunctie ernstig is beschadigd. Hieruit blijkt dat het opheffen van de NMB door sugammadex afhankelijk is van de snelle binding van het spierrelaxans en niet van de uitscheiding van het spierrelaxans via de nieren. Het is eerder de redistributie van de rocuronium moleculen die verantwoordelijk is voor het snelle herstel van de NMB, dan de uitscheiding van rocuronium via de nieren.
Uit de pharmacokinetische studie naar sugammadex en rocuronium kan worden geconcludeerd dat patiënten met nierinsufficiëntie het sugammadex-rocuronium complex langere tijd vasthouden dan patiënten met een normale nierfunctie. Sugammadex werd goed verdragen door alle patiënten, zowel door nierpatiënten als controles, en bij geen enkele patiënt werd heroptreden van de NMB geobserveerd. Van de andere kant zijn er nog geen data beschikbaar over lange termijn follow-up wat betreft de veiligheid van sugammadex in patiënten met nierinsufficiëntie, bij wie de uitscheiding van het sugammadex-rocuronium complex is vertraagd. Er zijn ook nog geen data over of en waar sugammadex op de lange termijn in het lichaam wordt opgeslagen. De Food and Drug Administration heeft meer data gevraagd over hypersensitiviteit en heeft haar zorgen geuit over de mogelijkheid dat sugammadex zou binden aan bot- en tandweefsel. Meer onderzoek is noodzakelijk.
Aangezien patiënten met nierinsufficiëntie meer risico lopen op het ontwikkelen van restverslapping na het gebruik van aminosteroidale spierrelaxantia, zouden juist zij profiteren van een antagonist zoals sugammadex. Hoewel het gebruik van sugammadex bij nierpatiënten nog discutabel is, wegen de voordelen voor patiënten met nierinsufficiëntie waarschijnlijk wel op tegen de nadelen van mogelijke lange termijn effecten van sugammadex.

Chapter 10

Dankwoord
Curriculum Vitae
List of publications

DANKWOORD

Een proefschrift schrijven doe je nooit alleen. "Mijn" boekje is nu klaar, maar dit zou zeker niet mogelijk zijn geweest zonder de hulp van vele anderen. In dit meest gelezen deel van het proefschrift wil ik dan ook de patiënten, collega's, vrienden en familieleden bedanken die er in de afgelopen 6 jaar voor gezorgd hebben dat ik dit promotietraject tot een goed einde kon brengen. Een aantal personen wil ik in het bijzonder noemen:

Prof. dr. Leo Booij, mijn promotor. In 2001 werd ik door u aangenomen voor de opleiding tot anesthesioloog, en daarmee was ik een van de laatste assistenten anesthesiologie van "uw" lichting. Uw encyclopedische kennis over spierverslappers en antagonisten was natuurlijk al legendarisch en werkte op mij zeer inspirerend. Bedankt dat u het op u heeft genomen om mijn promotor te zijn.

Dr. Jacques Driessen, mijn copromotor. Beste Jacques, vanaf het eerste moment dat ik werd betrokken bij de sugammadex studies was jij mijn vaste begeleider. Ik kon altijd bij je terecht voor vragen en hulp, de deur stond altijd open. Jouw enthousiasme voor onderzoek werkte aanstekelijk en ik zal dan ook zeker niet de laatste promovendus zijn die door jou wordt begeleid. Naast de gezamenlijke sugammadex-missie heb je me ook enthousiast gemaakt voor de kinderanesthesiologie. Dank voor alle leerzame momenten.

Dr. Jan van Egmond, mijn copromotor. Beste Jan, jij was al vanaf de eerste dierexperimentele onderzoeken betrokken bij de ontwikkeling van sugammadex. Je was altijd bereid jouw (enorme) kennis over "jouw kindje" te delen. Daarnaast was je steeds beschikbaar als statistische vraagbaak. Je bent nu met pensioen, maar ik kan me niet voorstellen dat je onderzoeksdrang nu ten einde is.

Dr. Marc Snoeck, mijn copromotor. Beste Marc, dank voor al je hulp bij de klinische nierstudie en de uitwerking daarvan in de verschillende artikelen. Je hebt me laten zien dat onderzoek doen in de periferie zeker niet onderdoet voor onderzoek in de academie! Bovendien was het erg gezellig samenwerken.

Prof. dr. Frans Russel wil ik bedanken dat hij voorzitter wilde zijn van de manuscriptcommissie.

Prof. dr. Hans van der Hoeven. Beste Hans, bedankt dat je zitting wilde nemen in de manuscriptcommissie. Daarnaast zijn we tijdens het uitvoeren van de klinische studie geweldig ondersteund door de Research Unit van de Intensive Care.

Prof. dr. Jennifer Hunter. Dear Jennie, many thanks for your help during the clinical trial and for your support and constructive criticism when writing the articles. I would also like to thank you for sharing your extensive knowledge on muscle relaxants and organ failure. I greatly appreciate that you are a member of the manuscript committee.

Prof. dr. Gert Jan Scheffer, voor het grootste deel van mijn assistententijd mijn opleider. Uiteindelijk is het allemaal begonnen met jouw vraag of ik geïnteresseerd was in het doen van onderzoek. Bedankt voor de kansen die je mij hebt gegeven, vooral in het combineren van mijn opleiding met het doen van onderzoek.

Dr. Hans de Boer. Beste Hans, op jouw uitstekende onderzoekswerk naar sugammadex, was het voor mij gemakkelijk voortborduren. Je adviezen en mental coaching zijn voor mij zeer waardevol geweest.

Francien van de Pol. Beste Francien, ik vraag me af hoe hoofdstuk 3 en 7 er uit zouden hebben gezien zonder jouw uitstekende werk op het dierenlab. Ik ben je uitermate dankbaar voor je inzet en jouw geweldige geheugen!

De mensen bij Organon, later Schering-Plough, en weer later MSD: dr. Anton Bom, de "uitvinder" van sugammadex, Marten Heeringa, Michiel van den Heuvel, Martine Prins, Gerard Kuiper en vele anderen. Dank voor jullie hulp tijdens het uitvoeren van de studies en bij het schrijven van de artikelen. Zelfs in de laatste weken voordat sommigen van jullie (noodgedwongen) Organon moesten verlaten, bleven jullie behulpzaam. Ik bewonder jullie inzet en wens jullie allen veel succes in de toekomst.

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De afdeling nefrologie van het UMC St. Radboud, vooral prof. dr. Jack Wetzels, dr. Henk van Hamersvelt en dr. Ruud de Sévaux. Jullie nefrologische blik tijdens het uitvoeren van de klinische nierstudie en het schrijven van de artikelen was voor mij als anesthesioloog soms hard nodig.

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inmiddels een carrière begonnen als physician assistant in de Radboud. Ze zullen jouw gedrevenheid in het CWZ vast heel erg missen!

Dr. Elizabeth Flockton. Dear Liz, thank you very much for your dedicated work performing the renal trial in Liverpool. And thanks a lot for your great sense of humour, when we were both nervously waiting to give our presentation at the ESA congress in Munich.

Alle anesthesiologen, arts-assistenten, anesthesiemedewerkers, doktersassistenten, operatie-assistenten, verkoeververpleegkundigen, chirurgen en poli-medewerkers van het UMC St. Radboud wil ik hartelijk bedanken voor hun medewerking tijdens de klinische studie. Iedereen hield altijd zijn ogen open voor mogelijke "kandidaten". Bovendien waren jullie allemaal zeer geduldig en coöperatief als ik weer eens aan kwam zetten met mijn meetarm of als er bij een onderzoekspatiënt op de PACU een heel schema aan bloedafnames verricht moest worden.

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Michiel Vaneker, mijn paranimf. Niet alleen volgden we samen de opleiding tot anesthesioloog, ook stapten we allebei in een promotietraject. Dankzij jouw inzet kregen we zelfs een eigen onderzoekskamer, met bovendien eerste rang uitzicht op de landingsplaats van de traumahelikopter (niet geheel toevallig). Ik bewonder jouw enorme energie en enthousiasme.

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CURRICULUM VITAE

Lonneke Staals werd geboren op 19 maart 1976 te Maarheeze. In 1994 behaalde zij haar gymnasium diploma aan het Bisschoppelijk College te Weert. Aangezien zij uitlootte voor de studie geneeskunde in Nederland, maakte zij de overstap naar België, waar zij startte met de opleiding geneeskunde aan de Katholieke Universiteit Leuven. In 1997 behaalde zij daar de graad kandidaat arts, en in 2001 de graad arts, met grote onderscheiding. Gedurende het laatste jaar van de opleiding volgde zij een zogenaamde pre-specialisatie in de Anesthesie en Reanimatie aan de afdeling Anesthesie van het Universitair Ziekenhuis Gasthuisberg te Leuven (diensthoofd prof. dr. E. Vandermeersch).

Na het afronden van de opleiding was zij kortdurend werkzaam als poortarts in het Sint Jans Gasthuis te Weert. In 2002 werkte zij als assistent geneeskundige niet in opleiding (AGNIO), eerst op de afdeling Intensive Care en later op de afdeling Anesthesiologie van het Universitair Medisch Centrum St. Radboud te Nijmegen. In 2003 werd zij hier aangenomen voor de opleiding tot anesthesioloog, met als opleider prof. dr. L.H.D.J. Booij en later prof. dr. G.J. Scheffer. Tijdens deze opleidingsperiode werd zij als onderzoeker betrokken bij de studies naar sugammadex die werden uitgevoerd op deze afdeling, wat uiteindelijk zou leiden tot dit proefschrift.

Na in 2008 de opleiding tot anesthesioloog te hebben afgerond, volgde zij in hetzelfde ziekenhuis een fellowship in de kinderanesthesiologie. Sinds augustus 2009 is zij werkzaam als anesthesioloog in het Sophia Kinderziekenhuis van het Erasmus Medisch Centrum te Rotterdam.

Lonneke woont samen met Bart Smits. Zij hebben 2 kinderen, Tom en Sofie.

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