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ORIGINAL ARTICLE

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 i.v. was administered. After spontaneous recovery from neuromuscular block, both renal pedicles were ligated. A second dose of rocuronium 0.5 mg/kg 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 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) min (Group 2) versus 31.1 (5.0) min (Group 1) ($p < 0.0001$). No signs of recurrence of neuromuscular block were observed for 90 min 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.

Keywords Kidney failure · Neuromuscular block · Antagonism · Rocuronium · Sugammadex · Cat

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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 toward 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 h 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) [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 and ketamine (Ketaset®, Willows Francis) 5 mg/kg, intramuscularly. Alpha chloralose (BHD) 90 mg/kg was administered intraperitoneally, followed by intravenous administration of 10 mg/kg 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); 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°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 use of 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 $2\times$ ED_{90} (0.5 mg/kg). 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 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 min after complete neuromuscular block was induced by the second dose of rocuronium. In Group 2 ($n = 7$), 5.0 mg/kg sugammadex was administered, 1 min 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 min after complete twitch restoration.

Blood pressure and heart rate were recorded for analysis at four time points: before injection of rocuronium (both groups), 1 min after rocuronium (both groups), before sugammadex (Group 2), and 1 min 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 at 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 Fig. 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 the 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 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,

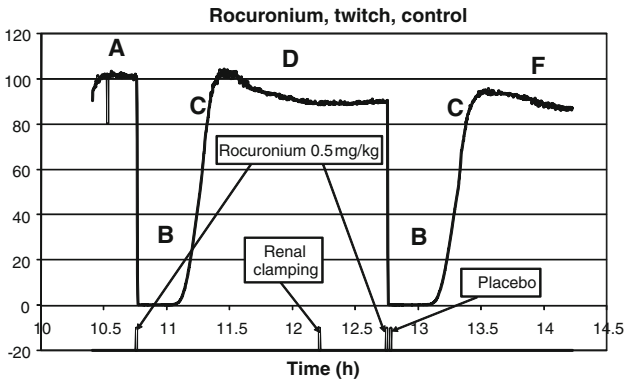

Fig. 1 Experimental time course in Group 1 (controls). Twitch response after administration of rocuronium 0.5 mg/kg. After spontaneous recovery, renal arteries were clamped. Thirty minutes after renal clamping, a second dose of rocuronium 0.5 mg/kg was administered. One minute after disappearance of 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

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

In Group 2, 30 min after renal clamping, sugammadex 5.0 mg/kg was administered 1 min after disappearance of the twitches after the second dose of rocuronium 0.5 mg/kg. After renal pedicle ligation, time to complete recovery of rocuronium-induced neuromuscular block was significantly shorter after administration of sugammadex 5.0 mg/kg. Mean time (SEM) to recovery to 90% of the twitch height was 4.7 (0.25) min in the 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.

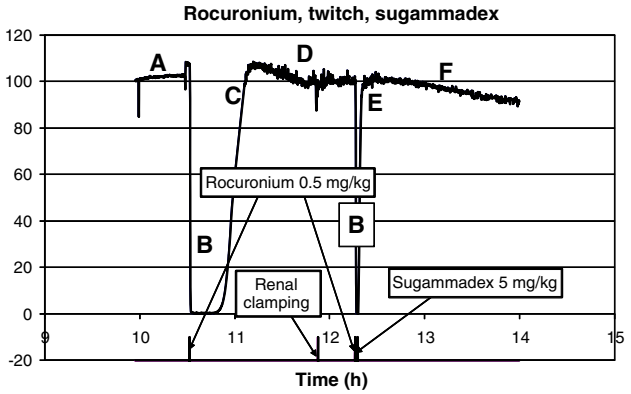

Fig. 2 Experimental time course in Group 2 (sugammadex). Twitch response after administration of rocuronium 0.5 mg/kg. After spontaneous recovery, renal arteries were clamped. Thirty minutes after renal clamping, a second dose of rocuronium 0.5 mg/kg was administered. One minute after disappearance of the twitches, sugammadex 5.0 mg/kg 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

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

During neuromuscular monitoring for 90 min 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 toward a decrease

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

	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

In Group 1, after the second administration of rocuronium, placebo (0.9% saline) was administered 1 min after complete neuromuscular block. In Group 2 sugammadex 5.0 mg/kg was administered 1 min 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. 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)

ns, not significant

Level of significance: $p < 0.05$

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 min 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 to reverse the neuromuscular blocking effect of rocuronium 0.6 mg/kg 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 is normally 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 [6–8, 10, 14]. In our study there was a tendency toward a decrease in heart rate after administration of sugammadex, which could be interpreted as 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 [16–18]. In patients with no or minimum renal function, the clinical duration and recovery time of rocuronium 0.6 mg/kg increased significantly [16–18]. 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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Conflict of interest LM Staals received travel fees from MSD. HD De Boer received speaker fees from MSD. AH Bom is employed by MSD and holds stocks in MSD. F Hope was employed by MSD. LHDJ Booij was a member of the scientific advisory board of MSD and received speaker fees from MSD. J van Egmond, F van de Pol and J Driessen do not have conflicts of interest.

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