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ORIGINAL ARTICLE

Can sugammadex save a patient in a simulated 'cannot intubate, cannot ventilate' situation?

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Summary

Recent studies have shown that the use of high dose rocuronium followed by sugammadex provides a faster time to recovery from neuromuscular blockade following rapid sequence induction than suxamethonium. In a manikin-based 'cannot intubate, cannot ventilate' simulation, we studied the total time taken for anaesthetic teams to prepare and administer sugammadex from the time of their initial decision to use the drug. The mean (SD) total time to administration of sugammadex was 6.7 (1.5) min, following which a further 2.2 min (giving a total 8.9 min) should be allowed to achieve a train-of-four ratio of 0.9. Four (22%) teams gave the correct dose, 10 (56%) teams gave a dose that was lower than recommended, four (22%) teams gave a dose that was higher than recommended, six (33%) teams administered sugammadex in a single dose, and 12 (67%) teams gave multiple doses. Our simulation highlights that sugammadex might not have saved this patient in a 'cannot intubate, cannot ventilate' situation, and that difficulties and delays were encountered when identifying, preparing and administering the correct drug dose.

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The first clinical use of sugammadex in humans to reverse neuromuscular blockade induced by rocuronium was reported in 2005 [1]. Since then, sugammadex has been shown to be clinically effective [2] and has become available for clinical use in hospitals throughout Europe [3]. Since its introduction into clinical practice, the role of sugammadex in rapid sequence induction has been investigated. In a recent review, no statistical difference in intubating conditions was found when suxamethonium was compared to high dose (1.2 $mg.kg^{-1}$) rocuronium administration during rapid sequence induction [4]. The main advantage of suxamethonium over rocuronium is the faster spontaneous recovery from neuromuscular blockade that occurs following the former's use; this characteristic has been a main indication for using suxamethonium despite its possible severe side-effects [5].

The possibility of rapidly reversing the effects of rocuronium has raised the question of whether suxamethonium is still necessary in clinical practice [6, 7]. High dose rocuronium administration can provide fast neuromuscular blockade that permits early tracheal intubation comparable to that found when using suxamethonium [8, 9]. Lee et al. [10] found that the intravenous administration of 16 $mg.kg^{-1}$ sugammadex, 3 min after giving 1.2 $mg.kg^{-1}$ rocuronium, resulted in reversal of neuromuscular blockade that was faster than the spontaneous recovery following 1 $mg.kg^{-1}$ suxamethonium.

Sugammadex has the potential to provide early reversal of profound neuromuscular blockade should a 'cannot intubate, cannot ventilate' situation arise following induction of anaesthesia [11]. However, as it still takes 2.2 min for the train-of-four (TOF) ratio (the ratio of magnitudes of the fourth to the first twitches) to recover to 0.9 following administration of sugammadex, the margin of safety is narrow in the event of failed tracheal intubation with inability to ventilate the patient's lungs manually [10]. In obese patients, critical haemoglobin desaturation has been shown to occur after 3.1 min [12].

We investigated the time it would take for anaesthetic teams at our teaching hospital to administer sugammadex following rapid sequence induction in order to reverse the effects of high dose rocuronium. We studied the total

time required for this process as measured from the time of the decision to use sugammadex to the intravenous administration of the drug. Factors that influenced the timing of sugammadex administration were also studied.

Methods

The study was undertaken at the VU University Medical Centre in Amsterdam, The Netherlands. This is a large teaching hospital with 18 operating theatres located on two sites within the hospital building. We closely observed anaesthetic teams preparing and administering sugammadex following the use of high dose rocuronium for rapid sequence induction in a manikin-based 'cannot intubate, cannot ventilate' simulation. Institutional Review Board approval was waived and informed consent was obtained from all participants for the study. Volunteers were recruited on the basis of their availability during a normal working day.

We created and simulated a normal operating theatre in an office room within our operating theatre complex. Standard materials and equipment (operating table, ventilator and monitors, fully equipped anaesthetic trolley) were made available. A standard training manikin (Laerdal™; Wappering Falls, New York, USA) was used. An intravenous cannula was present in the antecubital fossa of the manikin's left arm and an infusion of Hartmann's solution was in progress. All teams received the same briefing.

Participating teams consisted of both a staff anaesthetist and a nurse anaesthetist (specialist-nurse team), or an anaesthetic trainee and nurse anaesthetist (trainee-nurse team). We asked each team to reverse the effects of high dose rocuronium administration in the following scenario.

The nurse anaesthetist was asked to enter the simulation room following which we explained the clinical situation: 'This female patient is scheduled for an acute laparoscopic cholecystectomy. She is 40 years old and has never received anaesthesia before. Her weight is 113 kg and her height is 169 cm. She is otherwise healthy. For rapid sequence induction you were instructed by the anaesthetist to administer 10 μg sufentanil, 200 mg propofol and 100 mg rocuronium intravenously after pre-oxygenation with 100% oxygen. Having done this, your team unexpectedly finds itself in a 'cannot intubate, cannot ventilate' situation. At this moment the anaesthetist is urgently called away for a resuscitation case elsewhere; however, you are immediately provided with assistance from a staff anaesthetist or trainee. All medications and equipment can be found in their normal location'. We provided a standard pre-anaesthetic chart with the patient's details and a standard list with monitor values and medications that had been given.

The staff anaesthetist or the anaesthetic trainee was briefed outside the simulation room and was told that there was an urgent 'cannot intubate, cannot ventilate' situation that had arisen in the operating room; their anaesthetic colleague has been called away urgently but it had already been decided that the only option was to continue difficult bag/mask ventilation and awaken the patient. The mission for the team was to antagonise the effects of high dose rocuronium administration using sugammadex as fast as possible. The door was subsequently opened and timing commenced.

At the time or our study, sugammadex was available in 2-ml ampoules (200 mg) in a fridge in a central storage room. The distances from our simulation room and the working operating theatres to this storage were comparable, with a one-way distance of approximately 50 m. The number of automatic sliding doors and fire prevention doors encountered on the way to the fridge were also comparable. To reduce the costs of the study we did not use real sugammadex, but another intravenous drug formulated in identical 2-ml ampoules (ketanserin 5 $mg.ml^{-1}$; Prostrakan Pharma™, Bergen op Zoom, Netherlands). The names on the labels were changed; however, the box containing the study medication was clearly marked as 'study drug' in order to reduce the risk that the drug could have been used in error by a clinician who was unaware of the study. The sugammadex information leaflets were enclosed in the box. While one team member ran to get the sugammadex from the fridge, the other tried to administer oxygen to the manikin through a facemask. The investigator remained in the theatre simulation throughout. To provide time pressure and enhance the stress of the scenario, they made remarks about dropping oxygen saturations and an audible timer was present which 'ticked' the sound of a heartbeat at 130 $beats.min^{-1}$. The times to intravenous administration of sugammadex were measured by stopwatch and recorded.

The study took place on a Wednesday during working hours with all the theatres busy undertaking their normal caseload. All participants were blinded to the study, with only the Head of Department of Anaesthetics and the research steering committee of our department being notified that the study was taking place. All participants were asked not to talk about the study so that future participants' performances would not be influenced. The anaesthetist or nurse anaesthetist participating in the study was temporarily replaced by a colleague so that routine patient care was not disturbed. At the end of the study all participants were asked to fill in a survey form on how to improve the use of sugammadex at our hospital.

Subsequently, we undertook a telephone survey in order to investigate ways in which sugammadex was

stored at the other seven academic hospitals in the Netherlands.

Statistical analysis was performed using SPSS software, version 12.0 for Windows (SPSS Inc., Chicago, IL, USA) to calculate differences between the study groups using student *t*-tests for unpaired data or chi-squared tests. A difference was regarded as significant when $p < 0.05$.

Results

Eighteen anaesthetic teams participated in the study. The first team was studied at 09.00, the last at 16.30. The correct dose of sugammadex for our manikin 'patient' should have been 113 (kg) × 16 ($mg.kg^{-1}$) = 1808 mg.

The dose of sugammadex administered by the study teams, the total times needed and problems encountered are displayed in Table 1. The mean (SD) total time until administration of sugammadex was 6.7 (1.5) min. Four (22%) teams gave the correct dose of 1800 mg, 10 (56%) teams gave a dose that was lower than recommended, four (22%) teams gave a dose that was higher than recommended, six (33%) teams administered sugammadex in a single dose, and 12 (67%) teams gave multiple doses.

Table 1 Administered doses of sugammadex, time to administration of sugammadex, and problems encountered, for each participating anaesthetic team.

	Sugammadex dose; mg	Time to administration; min	Problems encountered
Specialist-nurse teams			
1	2000	7.27	None
2	1600	5.48	None
3	300	4.35	Wrong assumption about concentration
4	2000	7.28	None
5	1000 + 600	6.95	None
6	1600	4.38	None
7	800 + 400 + 400	5.67	Calculation error
Trainee-nurse teams			
8	1800	5.97	None
9	1000 + 1000	5.58	None
10	1000 + 800	6.25	Wrong drug (rocuronium)
11	1000 + 800	8.00	None
12	800 + 1200	8.33	None
13	800 + 800	5.77	None
14	400 + 1200	6.30	Time lost through reading product information
15	800 + 400 + 200	9.55	Calculation error
16	1000 + 600	8.90	Time lost through looking for the drug by brand name 'Bridion'
17	600 + 600 + 600	7.88	None
18	400 + 400 + 800	7.00	Wrong assumption about concentration

There was a trend for specialist-nurse teams to be faster than trainee-nurse teams, taking a mean (SD) time of 5.9 (1.28) min vs 7.2 (1.37) min to administer the sugammadex, although this did not reach statistical significance ($p = 0.058$). The total team experience did not differ significantly between the two groups ($p = 0.101$) (Table 2).

Seventeen nurse anaesthetists were sent to collect the sugammadex from the storage room while the doctors continued bag/mask ventilation. One junior trainee decided to get the drug herself and leave the difficult airway management to a senior nurse anaesthetist.

To our surprise, the majority of the trainee-nurse teams (10/11, 91%) were inclined to give multiple doses of sugammadex because they did not know the initial correct dose, while only two of the seven (29%) specialist-nurse teams gave multiple doses ($p = 0.006$).

Only four teams administered the correct dose. None of the specialist-nurse teams gave the correct dose vs four of the eleven trainee-nurse teams. One specialist-nurse team only administered 300 mg sugammadex due to an erroneous assumption of the drug concentration in each ampoule.

We observed additional problems during the process of accessing and preparing the sugammadex. One specialist-nurse team initially calculated the required dose of sugammadex to be 800 mg; however, this mistake was subsequently realised and an extra 800 mg given. Problems encountered by the trainee-nurse teams included: a calculation error (recognised and corrected by the team); time delay whilst reading the product information leaflets to identify the correct dosage; searching for sugammadex under the brand name rather than the generic name; and the potentially life-threatening near miss of administering more rocuronium. A contributing factor to the latter was identified as being the storage of rocuronium next to the sugammadex in the fridge. Fortunately, while preparing the drug, the team realised this mistake and administered the correct drug.

At the end of the day we also participated in the study. Our time was fastest, as one would expect, giving the correct dose after 2.17 min. This would have been a few

Table 2 Time to administration of sugammadex and experience of the study groups. Values are mean (SD).

	Specialist-nurse teams	Trainee-nurse teams	p value
Time; min	5.91 (1.28)	7.23 (1.37)	0.058
Experience of doctors; years	14.6 (9.59)	2.0 (1.41)	< 0.05
Experience of nurses; years	13 (9.83)	14.8 (11.80)	0.739
Total team experience; years	27.6 (13.75)	16.8 (12.18)	0.101

seconds faster but for the nurse-anaesthetist (CH) bumping into a closed door before running to the fridge.

Having completed the simulation, we undertook a telephone survey in order to review the manner in which sugammadex was stored at the other seven academic hospitals in the Netherlands. We found that sugammadex was available in the difficult intubation trolley at two hospitals, one of which also stored the drug in a 'crash trolley' in the intensive care unit. In both hospitals, ampoules were available in sufficient quantities for clinical use. In another hospital sugammadex was available on the anaesthetic trolley in the operating theatre and in two others it was stored in a fridge at a central depository. One hospital stored the drug outside a fridge in a central depository, and one did not have sugammadex available at the time of our survey.

Discussion

In our difficult airway simulation it took a mean of 6.7 min to prepare and administer intravenous sugammadex in order to reverse the neuromuscular blocking effects of high dose rocuronium. Current evidence suggests that it would take an additional 2.2 min following administration to achieve a TOF ratio of 0.9 [10], giving a total time of 8.9 min to reverse the effects of high dose rocuronium completely.

It is vital that clinicians appreciate the time consuming process of preparing and administering sugammadex in the correct dose, even for experienced anaesthetic teams. This is exacerbated by the fact that sugammadex is a novel drug that is used infrequently, thus making the process more susceptible to errors. Only four (22%) teams gave the correct dose of sugammadex. Ten (56%) teams gave a dose lower than currently advised and four (22%) teams administered an overdose; there are currently, however, no reports of side-effects or complications from administering a higher dose of sugammadex than is recommended. Sugammadex is dosed on real body weight and not on lean body weight; this is somewhat confusing, since most medications are dosed on lean body mass and this may explain why many teams (56%) gave a lower than recommended dose.

We found that costly time was lost because sugammadex was not directly available in the operating theatre. This decision was made at a managerial level because sugammadex is an expensive drug that is used infrequently. While our anaesthetic teams knew where to find the drug, important time was lost while collecting it from the fridge and calculating and preparing the correct dose. Our patient required a dose of 1800 mg, which meant that nine ampoules of 2 ml (200 mg) needed to be prepared. Our findings underline the fact that it is important to have sugammadex directly available at the site where high dose rocuronium is administered to patients.

It is well recognised that medication errors increase with time pressure and during stressful situations, particularly when novel medication or equipment is used [13, 14]. Our study identified calculation errors, drug dosing errors and misidentification of drug ampoules under these challenging circumstances. In particular, we identified that the drug information leaflet was hard to read due to the small sized letters, and that time was lost in finding the correct language.

The specialist-nurse teams demonstrated a trend to being faster than trainee-nurse teams though this was not significant ($p = 0.058$) and did not appear to be due to differences in the total team experience ($p = 0.101$). We observed that the staff anaesthetists were clearer in their orders to the nurse anaesthetists. Interestingly, trainee-nurse teams were inclined to give multiple doses of sugammadex; we do not know why they used this technique, but it was significantly different to that of the staff anaesthetists.

In order to identify how sugammadex was stored at the other seven academic teaching hospitals in our country we undertook a telephone survey which showed that not every teaching hospital in the Netherlands was prepared for the use of sugammadex in urgent situations. We suspect that this may be a worldwide phenomenon.

It is possible that the introduction of sugammadex into our department could have been better. The process undertaken included a representative from the manufacturer of sugammadex who introduced the new drug during a meeting attended by staff members and trainees; this was followed by a demonstration of its clinical use in theatre at different time points for patients treated with rocuronium. On the other hand, the evaluation of the introduction of sugammadex was not our primary goal and, in the past, new devices and medications have been introduced at our hospital without problems. The errors that we elucidated seemed to result primarily from the lack of familiarity and limited education of the anaesthetic teams, a situation that is compounded due to the drug's being new, expensive and not readily accessible to teams. We feel that the introduction of infrequently used, emergency medications should be undertaken according to a strict protocol, with emphasis on patient safety and acknowledgement of factors that may contribute to human error.

Our study has several limitations. It is unlikely that a new anaesthetic team would be expected to manage a 'cannot intubate, cannot ventilate' scenario having not been involved with the preceding anaesthetic management. The decision to use the induction agents including

rocuronium, and the steps before making the decision to awaken the patient, were excluded from the scenario. In addition, it is unlikely that the anaesthetist in charge would be called away to another emergency in the midst of one of the most critical events encountered in anaesthetic practice. Nevertheless, this scenario could arise at our hospital, where the anaesthetist in charge has duties in addition to supervising theatre anaesthesia including, for example, providing emergency assistance in the paediatric intensive care units. The teams consisted of only two members who were required to locate, prepare, and administer the correct dose of sugammadex. In an airway emergency occurring at a large teaching hospital, a number of anaesthetists and anaesthetic providers would normally be available to help with all of these tasks. However, during busy periods outside normal working hours this situation could arise at our hospital. Despite clear instructions for the study participants to antagonise the rocuronium, many of our study teams were considering alternative intubation methods in order to salvage the situation. In our judgment this did not create bias, as the relevant teams were immediately instructed that the single mission of the simulation was to antagonise the rocuronium as fast as possible. Finally, as our study took place in a simulation, it may not reflect how the teams would have performed under real circumstances.

Our study has highlighted a number of issues regarding the safe use of sugammadex from which we have produced recommendations and adjusted local protocols (Table 3). Some of the errors we observed highlight that general strategies to prevent drug administration errors were not applied well [15]. Two such errors, the substitution and dosing errors, emphasise the continued need to reduce the likelihood of drug dosing errors in anaesthetic practice [16]. We believe that simulation scenarios may play an important role in the further development of risk reduction strategies.

Table 3 Recommendations from the VU University Medical Centre for the use of high dose rocuronium in combination with sugammadex for rapid sequence induction.

Use the larger ampoule of sugammadex when high dose rocuronium is used for rapid sequence induction
Advice to the manufacturer: make a short and clear information leaflet containing emergency dosages by weight and provide bigger ampoules or a prefilled syringe
Have sugammadex available in the anaesthetic trolley
Calculate the exact dose of sugammadex for your patient before using high dose rocuronium
Introduce infrequently used emergency medications in a different way from other drugs
It is not necessary to store sugammadex in a fridge
Provide a reminder that the correct dose of sugammadex is calculated according to measured (i.e. actual) body weight
To prevent medication errors, do not store rocuronium and sugammadex alphabetically

We would warn against a false sense of security developing from the knowledge that sugammadex is available in the theatre complex, should problems arise when using high dose rocuronium for rapid sequence induction; the mean time to administer sugammadex in our study was 6.7 min following which one could predict that a further 2.2 min would be required to achieve a TOF ratio of 0.9.

There is no doubt that the development of sugammadex to reverse the neuromuscular blocking actions of rocuronium is an advance in anaesthetic practise. However, we conclude that in a 'cannot intubate, cannot ventilate' simulation at our teaching hospital, our anaesthetic teams demonstrated delayed administration of the correct dose of sugammadex, a situation which could have proved fatal in a real clinical situation.

Competing interests

No competing interests declared. The financial support for this work, all materials and resources, were provided by the department of Anesthesiology, VU University Medical Centre, Amsterdam, the Netherlands.

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