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CASE REPORTS/CASE SERIES

Recurarization after sugammadex reversal in an obese patient
Recurarisation après décurarisation avec le sugammadex chez une patiente obèse

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Abstract

Purpose *We report a case that involved immediate postoperative respiratory failure necessitating tracheal intubation, which was possibly related to recurarization after sugammadex reversal.*

Clinical findings *A 54-yr-old woman weighing 115-kg was scheduled for laparoscopic repair of abdominal dehiscence under general anesthesia. Muscle relaxation was induced and maintained with rocuronium (170 mg iv total dose). At the end of the 170-min procedure, two twitches were visualized after supramaximal train-of-four (TOF) stimulation at the adductor pollicis muscle, and the patient's central core temperature was 35.6°C. Sugammadex 200 mg iv (1.74 mg·kg^{-1}) was administered. With the patient fully awake, a TOF ratio 0.9 was obtained five minutes later. The tracheal tube was then removed, and the patient was transferred to the postanesthesia care unit. Ten minutes later, the patient presented respiratory failure necessitating tracheal intubation and sedation with propofol. One TOF response only was visualized at the adductor pollicis muscle. Another dose of sugammadex 200 mg iv was administered. Forty-five minutes later, the patient was fully awake and her trachea was extubated after repeated measures of the TOF ratio (≥ 0.9) at the adductor pollicis muscle. The patient fully recovered without sequelae, further complication, or prolonged hospital stay.*

Conclusion *Shortly after tracheal extubation, an obese patient experienced respiratory failure necessitating tracheal intubation and an additional dose of sugammadex. This occurred despite initial reversal of neuromuscular blockade with an appropriate dose of sugammadex 2 mg·kg^{-1} iv given at two responses to TOF stimulation.*

Résumé

Objectif *Nous décrivons un cas de détresse respiratoire survenu en postopératoire immédiat nécessitant l'intubation de la trachée, possiblement lié à une recurarisation après une décurarisation pharmacologique avec du sugammadex.*

Éléments cliniques *Une femme de 54 ans, pesant 115 kg, était programmée pour le traitement chirurgical d'une éventration de la paroi abdominale par laparoscopie sous anesthésie générale. La curarisation était induite et entretenue par du rocuronium (dose totale 170 mg iv). À la fin de l'intervention, durant 170 min, deux réponses étaient visualisées après une stimulation supra-maximale par un train-de-quatre (Td4) à l'adducteur du pouce, et la température centrale était de 35,6°C. Une dose de 200 mg iv de sugammadex (1,74 mg·kg^{-1}) a été administrée pour la décurarisation pharmacologique. Un rapport de Td4 à 0,9 à l'adducteur du pouce était obtenu cinq minutes plus tard permettant le retrait de la sonde d'intubation et le transfert en salle de réveil, la patiente répondant aux ordres simples. Dix minutes plus tard, elle présentait une détresse respiratoire nécessitant l'intubation de la trachée et une sédation au propofol. Une seule réponse était visualisée au Td4 à l'adducteur du pouce. Une dose supplémentaire de 200 mg iv de sugammadex a été administrée. Quarante-cinq*

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minutes plus tard, la sonde d'intubation était à nouveau retirée, après l'observation répétée à l'adducteur du pouce d'un rapport de Td4 supérieur ou égal à 0,9 et avec une patiente répondant aux ordres simples. La patiente a récupéré complètement, sans autre complication, sans séquelle, ni prolongation de la durée de séjour à l'hôpital.

Conclusion *Malgré une décurarisation initiale avec une dose de sugammadex adaptée au monitorage (2 mg·kg^{-1} après deux réponses au TOF), une patiente obèse a présenté très rapidement une défaillance respiratoire, nécessitant une nouvelle intubation de la trachée et une dose supplémentaire de sugammadex.*

The dose of sugammadex required for reversal depends on the depth of neuromuscular blockade at the end of the procedure. When two twitches are visible after a train-of-four (TOF) stimulation at the ulnar nerve, the recommended dose is 2 mg·kg^{-1} *iv*. This is also the level of neuromuscular blockade at which reversal with acetylcholinesterase inhibitors is possible.[1] After sugammadex 2 mg·kg^{-1} *iv*, the median time to obtain a TOF ratio (TOFR) $\geq$ 0.9 was reported as 1.4(0.9-5.4) min and 2.1(1.6-64.2) min for rocuronium[2] and vecuronium,[3] respectively. After neostigmine 50 µg·kg^{-1} *iv*, this delay was reported as 18.5(3.7-106.9) min and 21.9(2.9-76.2) min for rocuronium[2] and vecuronium,[3] respectively.

As previously reported in a Phase II study, there is a risk of recurarization when the dose of sugammadex is inadequate.[4] This risk was confirmed recently in a study where a dose of sugammadex 1 mg·kg^{-1} *iv* was administered to 30 patients 15 min after the last dose of rocuronium without previous assessment of neuromuscular recovery.[5] Incomplete neuromuscular recovery (TOFR $<$ 0.9) was observed in three patients (10%), and recurarization occurred in four other patients (13%) after first obtaining a TOFR $\geq$ 0.9.[6]

To date, no case of recurarization with major clinical consequences has been reported after recommended doses of sugammadex and adequate monitoring. The patient gave written informed consent before the publication of this case.

Clinical features

A 58-yr-old woman was scheduled for laparoscopic repair of abdominal wound dehiscence one month after a sleeve gastrectomy was performed for the treatment of obesity. The patient's medical conditions included hypertension (treated with irbesartan), type II diabetes (on an appropriate diet), sleep apnea syndrome (requiring non-invasive ventilation at night), and morbid obesity (weight, 115 kg; height, 154 cm; body mass index, 48 kg·m^{-2}). There was no renal failure (plasma creatinine 75 µmoL·L^{-1}).

Pulse oximetry, electrocardiogram (EKG), and non-invasive arterial blood pressure monitoring were applied when the patient arrived in the operating room. An intravenous cannula was inserted, and cefazoline 2 g *iv* was injected for surgical infection prophylaxis. After preoxygenation, anesthesia was induced with sufentanil 15 µg *iv*, propofol 200 mg *iv*, and succinylcholine 120 mg *iv* to facilitate tracheal intubation. Anesthesia was maintained with a intermittent doses of sufentanil 10 µg *iv* and desflurane (expired fraction: 1.3-4.8%) in an air-oxygen mixture.

Monitoring of neuromuscular blockade was performed with kinemyography (NMT®, General Electric Healthcare^{TM}, Buc, Yvelines, France), a device which evaluates the level of neuromuscular block by measuring the bending of malleable strip with a small piezoelectric sensor.[7] Two EKG electrodes were placed on the patient's wrist at the ulnar nerve, and the evoked muscle response at the adductor pollicis (AP) muscle was measured by the displacement of the probe positioned between the patient's thumb and forefinger. After automatic calibration, supramaximal TOF stimulation ($>$ 50 mA) was applied every 15 sec, and TOF ratio (TOFR) values were displayed on the monitor screen. When neuromuscular recovery was confirmed following administration of succinylcholine, further muscle relaxation was provided with intermittent doses of rocuronium (170 mg *iv* total) to maintain at the AP muscle less than five visual responses after post-tetanic stimulation (deep neuromuscular blockade).

Surgery was uneventful and lasted 170 min. Analgesia was started during the procedure with nefopam 20 mg *iv* and paracetamol 1 g *iv*. Postoperative nausea and vomiting prophylaxis was provided with dexamethasone 4 mg *iv*.

At the end of the procedure and 40 min after the last dose of rocuronium, two twitches were visualized on the kinemyography monitor after application of supramaximal TOF stimulation at the AP. The patient's central core temperature was 35.6°C. Sugammadex 200 mg *iv* (1.74 mg·kg^{-1}) was administered, and a TOFR $\geq$ 0.9 at the AP derived from kinemyography monitoring was obtained five minutes later, allowing removal of the endotracheal tube with the patient responding to verbal command and attempting a sitting position on the operating table. The patient was then transferred from the operating room to the postanesthesia care unit (PACU) with nasal oxygen supply (3 L·min^{-1}) and oxygen saturation (SpO_2) monitoring. During the five-minute transfer, no event occurred and SpO2 was $>$ 95%.

Ten minutes after the patient was admitted to the PACU (i.e., 20 min after sugammadex), she experienced bradypnea.

This was immediately followed by respiratory arrest, with the patient expressing her inability to breathe with her hands. The SpO2 was still > 95%. We decided to perform tracheal intubation with a single bolus dose of propofol followed by a continuous infusion for maintenance of sedation. At the same time, one visual response was observed after supramaximal TOF stimulation at the AP with an acceleromyographic monitor (TOF-Watch®, Schering Plough™, Courbevoie, France) set up without prior calibration. Another dose of sugammadex 200 mg *iv* was administered. In less than three minutes, a TOFR ≥ 0.9 was obtained. Sedation was maintained until her core temperature increased to > 36.5°C. Forty-five minutes after the episode of respiratory failure and after repeated observations of TOFR ≥ 0.9, the tracheal tube was removed while the patient answered verbal commands. No clinical sign of residual paralysis was observed. The patient reported explicit memory of the critical event, including the inability to breathe on arrival in the PACU. The patient recovered without sequelae. She did not experience any other complication related to the anesthetic or surgical procedure, and her hospital stay was not prolonged.

Discussion

The cause of the episode of respiratory failure experienced by the patient is likely related to recurarization after reversal of neuromuscular blockade with sugammadex. This is evidenced by an adequate quantitative TOFR measurement at the end of the procedure followed by a depressed response in the PACU. At the end of the procedure, only a single TOFR measurement was taken because of the immediate and sudden awakening of the patient which required immediate extubation. Repeated TOFR measurements were prevented under these conditions.

The following factors suggest the diagnosis of recurarization: a patient capable of responding to verbal commands on arrival in the PACU; no sign of opioid residual effect (the last dose of sufentanil 10 μg *iv* had been administered 70 min before the first dose of sugammadex); the inability to breathe, probably because of upper airway obstruction; the possibility to perform tracheal intubation without muscle relaxant; the presence, at that time, of only a single response to TOF stimulation at the AP; and the efficacy of an additional dose of sugammadex documented by repeated measures of TOFR ≥ 0.9. It follows that the first suggamadex dose was inadequate and represented under-dosage in this patient. Other factors could have contributed to this recurarization, including the history of sleep apnea that may exacerbate the effects of residual paralysis of the upper airway; the use of halogenated agents; and moderate hypothermia at the time of the first administration of sugammadex.

The use of halogenated agents for maintenance of anesthesia does not alter the efficacy of sugammadex. This was demonstrated in a study designed to compare the efficacy of sugammadex in reversing rocuronium-induced block in patients in whom anesthesia was maintained with propofol or sevoflurane. In that study, the time from administration of sugammadex 2 $mg \cdot kg^{-1}$ *iv* to the reappearance of two twitches at the AP to TOFR ≥ 0.9 was similar in both groups, i.e., 1.8(0.7) min.[8] However, in that study, the time delay to visualize two responses after TOF stimulation at the AP was significantly longer with sevoflurane than with propofol, i.e., 51.8(22.7) min *vs* 33.0(8.8) min, respectively.

In this case report, two different methods of neuromuscular blockade measurement were used, i.e., kinemyography (allowing both visual and quantitative assessment) in the operating room and acceleromyography (allowing both visual and quantitative assessment) in the PACU. The different methods were used because the equipment available in the two locations was not the same. In our view, the two methods are probably comparable in the clinical setting. However, two studies[7,9] comparing the reliability of kinemyography with mechanomyography demonstrated that kinemyography is unreliable in terms of both onset time and maximum effect of neuromuscular blockade. Likewise, kinemyography proved unreliable for determining a TOFR ≤ 0.7 when compared with mechanomyography. Two letters to the editor have emphasized these drawbacks.[10,11] To summarize, kinemyography is not recommended for research purposes, but it is a valuable option and commercially available for routine monitoring.

Monitoring of neuromuscular blockade was carried out throughout the procedure. A value of TOFR ≥ 0.9 was measured in the operating room by kinemyography before extubation. Respiratory arrest was concomitant of visualization of a single response after TOF stimulation with another method of monitoring (acceleromyography). The recurarization observed could be explained by an inadequate dose of sugammadex. The dose given based on the patient's actual body weight was 1.74 $mg \cdot kg^{-1}$ *iv*, slightly below the recommended dose (2.0 $mg \cdot kg^{-1}$ *iv*) at the time of reappearance of two responses at the AP after TOF stimulation. No data are currently available to determine if the dose of sugammadex in obese patients should be calculated on the actual or ideal body weight. However, the current product monograph recommends calculating the dose on the patient's actual body weight, even in the obese patient.[12] The distribution of sugammadex is restricted to the intravascular space due to the low volume of distribution at steady state estimated at 0.16 $L \cdot kg^{-1}$.[13] Thus, as is the case for non-depolarizing muscle relaxants, it might be relevant to determine the dose of sugammadex based on the ideal body weight and not on the actual body weight.[14]

The affinity of sugammadex for rocuronium is high, so unbinding of sugammadex-rocuronium complexes is unlikely. One molecule of sugammadex binds to one molecule of rocuronium or vecuronium. Therefore, the most likely hypothesis is that the number of sugammadex molecules was not sufficient to bind to most rocuronium molecules present in the body. Termination of action of rocuronium occurs chiefly because of redistribution to deep sites. Such redistribution must have been extensive in our patient because a large total dose (170 mg *iv*) was given. When the first sugammadex dose was given, it had access to the rocuronium molecules in the intravascular space and nearby areas, such as the neuromuscular junction, thus restoring neuromuscular function. This decrease in free rocuronium concentration presumably caused rocuronium to shift from the peripheral compartments to the intravascular space. The additional rocuronium could not bind to sugammadex because of the inadequate dose of the latter. One molecule of sugammadex encapsulates one molecule of rocuronium, but the former molecule is larger than the latter, thus 200 mg of sugammadex *iv* binds to only 55 mg of rocuronium *iv*. Thus, when a large dose of rocuronium was given followed by an inadequate dose of sugammadex, the possibility was to be expected that the previously redistributed rocuronium might be mobilized to produce delayed neuromuscular blockade.

In conclusion, sugammadex is more rapid and reproducible than neostigmine in restoring neuromuscular function[15]; however, this property can induce overconfidence in its effectiveness. Therefore, anesthesiologists must follow basic principles for adequate use, specifically, adjust the dose of sugammadex to the level of spontaneous recovery, and assess its efficacy with objective neuromuscular monitoring.[6,16-19]

Conflicts of interest Benoît Plaud has participated in the clinical development of sugammadex as a co-investigator in two Phase III studies funded by Merck Sharp & Dohme, The Netherlands, and he has given paid lectures and attended conferences for the same company. Frédérique Le Corre, Salmi Nejmeddine, Chérif Fatahine, Claude Tayar, and Jean Marty have no conflict of interest.

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