CASE REPORTS / CASE SERIES

Rocuronium-induced respiratory paralysis refractory to sugammadex in Charcot-Marie-Tooth disease

Un cas de paralysie respiratoire induite par rocuronium réfractaire au sugammadex dans la maladie de Charcot-Marie-Tooth

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Abstract

Purpose Prolonged postoperative neuromuscular respiratory paralysis after administration of a nondepolarizing neuromuscular blocking agent is a serious concern during anesthetic management of patients with Charcot-Marie-Tooth disease (CMTD). Some recent reports have described rocuronium use without respiratory paralysis in CMTD patients when sugammadex was used for its reversal. We report a case in which an induction dose of rocuronium caused a prolonged respiratory paralysis in a patient with undiagnosed type 1A CMTD (CMT1A).

Clinical features A 63-yr-old-male with an American Society of Anesthesiologists Physical Status score of III underwent a left hip arthroplasty under general anesthesia for osteoarthritis. Preoperative pulmonary function testing indicated a restrictive impairment. Anesthesia was induced with fentanyl, remifentanil, propofol, and 0.73 $mg \cdot kg^{-1}$ of rocuronium. The train-of-four (TOF) count was 0 for the 273-min duration of surgery. After repeated doses of sugammadex failed to recover the TOF count and spontaneous respirations, a total of 1,200 mg (17.3 $mg \cdot kg^{-1}$) of sugammadex, which was assumed to be a sufficient amount for capturing the residual rocuronium, was administered. Although the patient expressed that he was awake via eye blinking, he could not breathe. Thus, he was placed on mechanical ventilation for 18 hr after surgery. A postoperative neurology consultation revealed a delayed nerve conduction velocity of 20 $m \cdot sec^{-1}$ and a mutated duplication of the PMP22 gene; a diagnosis of CMT1A was made.

Conclusions Our case shows that rocuronium can cause a prolonged neuromuscular respiratory paralysis refractory to sugammadex in patients with CMT1A and impaired respiratory function. Our case may also indicate that restrictive pulmonary impairment and low nerve conduction velocity of 20 $m \cdot sec^{-1}$ are predictive factors that cause prolonged neuromuscular respiratory paralysis refractory to sugammadex in CMT1A.

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Résumé

Objectif La paralysie respiratoire neuromusculaire postopératoire prolongée après l'administration d'un bloqueur neuromusculaire non dépolarisant est une préoccupation sérieuse lors de la prise en charge anesthésique des patients atteints de la maladie de Charcot-Marie-Tooth (CMT). Certains comptes rendus récents ont décrit l'utilisation de rocuronium sans paralysie respiratoire chez les patients atteints de CMT lorsque le sugammadex était utilisé pour le neutraliser. Nous rapportons un cas dans lequel une dose d'induction de rocuronium a provoqué une paralysie respiratoire

prolongée chez un patient atteint de CMT de type 1A (CMT1A) non diagnostiquée.

Caractéristiques cliniques *Un homme de 63 ans avec un score de statut physique III selon la classification de l'American Society of Anesthesiologists a bénéficié d'une arthroplastie de la hanche gauche sous anesthésie générale pour son ostéo-arthrite. Les tests préopératoires de la fonction pulmonaire ont indiqué un syndrome restrictif. L'anesthésie a été induite avec du fentanyl, du rémifentanil, du propofol et 0,73 mg·kg-1 de rocuronium. Le décompte du train-de-quatre (TdQ) était de 0 pour toute la durée de la chirurgie, soit 273 minutes. Après l'échec de doses répétées de sugammadex qui n'ont pas réussi à rétablir un TdQ normal ni la respiration spontanée, un total de 1200 mg (17,3 mg·kg-1) de sugammadex (une quantité qu'on a présumé suffisante pour neutraliser le rocuronium résiduel) a été administré. Bien que le patient ait exprimé qu'il était éveillé en clignant des yeux, il ne pouvait pas respirer. Il a donc été placé sous ventilation mécanique pendant 18 heures après l'opération. Une consultation postopératoire en neurologie a révélé une vitesse de conduction nerveuse retardée de 20 m·sec-1 et une duplication mutée du gène PMP22; un diagnostic de CMT1A a été posé.*

Conclusions *Notre cas montre que le rocuronium peut provoquer une paralysie respiratoire neuromusculaire prolongée réfractaire au sugammadex chez les patients atteints de CMT1A et d'une altération de la fonction respiratoire. Notre cas pourrait également indiquer qu'un syndrome restrictif pulmonaire et une faible vitesse de conduction nerveuse de 20 m·sec-1 constituent des facteurs prédictifs provoquant une paralysie respiratoire neuromusculaire prolongée réfractaire au sugammadex dans les cas de CMT1A.*

Keywords Charcot-Marie-Tooth disease · Nondepolarizing neuromuscular agent · Rocuronium · Sugammadex · Respiratory paralysis

Charcot-Marie-Tooth disease (CMTD) is the most common primary genetic neuropathy, also termed hereditary sensory and motor neuropathy.[1,2] Charcot-Marie-Tooth disease is classified according to both the conduction velocity measured by electromyography (EMG) and inheritance pattern.[1,2] Predominantly based on nerve conduction velocity (NCV), it is classified into demyelinating (NCV < 35 m·sec^{-1}), axonal or non-demyelinating (NCV > 45 m·sec^{-1}), and dominant intermediate types (NCV 35-45 m·sec^{-1}).[1,2] With adding inheritance patterns, CMTD is currently categorized into the following five types: CMT1 (demyelinating type; autosomal dominant), CMT2 (axonal

degeneration type; autosomal dominant or recessive), CMT3 (severe infantile-onset or birth onset), CMT4 (demyelinating type; autosomal recessive), and CMTX (intermediate conduction velocities; X-linked inheritance). Each category is further classified according to mutated genetic etiology.[1,2] Charcot-Marie-Tooth disease occurs with an incidence of 1:2,500 (1:1,214-1:9,200), with type 1A CMTD (CMT1A) accounting for approximately 60% of cases.[1,2]

Type 1A Charcot-Marie-Tooth disease is caused by mutated duplications in the peripheral myelin protein 22 (*PMP22*) gene. Consequent overexpression of *PMP22* causes a demyelinating neuropathy, resulting in denervation and muscle atrophy.[1,2] Symptoms usually begin in the first or second decades of life and progress gradually, with marked variability between individuals.[1,2] In these patients, lower-limb muscular weakness is generally followed by whole-limb muscular weakness and peripheral sensory disturbances.[1,2] As the disease progresses, weakness of the respiratory muscles can also occur.[3-6]

Patients with CMTD may develop scoliosis, hip dysplasias, and foot deformities.[7,8] Therefore, they are often candidates for orthopedic surgery.[7,8] The most significant concern during anesthetic management of these patients is the potential for prolonged postoperative neuromuscular respiratory paralysis.[3,9] Recently, it has been reported that the nondepolarizing neuromuscular blocking agent (NMBA), rocuronium, can safely be used in patients with CMTD if sugammadex is used for its reversal.[10-13] Nevertheless, the utility of sugammadex in CMTD patients has not yet been established.[3] Here, we report a case in which an induction dose of rocuronium caused a prolonged respiratory paralysis that did not respond to a high dose of sugammadex in a patient with undiagnosed CMT1A. Written informed consent for the publication of this case report was obtained from the patient.

Case report

A 63-yr-old male patient with a height of 164 cm, weight of 68 kg, and American Society of Anesthesiologists Physical Status score of III was scheduled to undergo a left hip arthroplasty under general anesthesia for hip osteoarthritis. Prior to presentation, he had been experiencing bilateral hip pain and was referred to our hospital for management. The patient had a medical history of suspected chronic rheumatoid arthritis since the age of 56 yr and a ten-year history of diabetes mellitus managed with dietary therapy and oral medications. He had been

diagnosed with pneumonia four times since the age of 60 yr. He denied any relevant family history.

The patient's complete blood count showed a decreased hemoglobin concentration of 10.5 g·dL^{-1}; all of his other preoperative laboratory studies, including electrolytes, renal function, blood glucose, liver function studies, hemostasis evaluation, and urinalysis, were normal. Pulmonary function tests showed reductions of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) to 57.6% and 55.1% of the predicted normal values, respectively, and a preserved FEV1/FVC ratio of 0.79 (normal range, ≥ 0.7), indicating a restrictive pulmonary impairment. Furthermore, atrial fibrillation was noted on electrocardiography, and first-degree mitral regurgitation with mild left atrial and left ventricular enlargements were observed with echocardiography.

Anesthesia was induced with 100 μg of fentanyl, 0.4 μg·kg^{-1}·min^{-1} of remifentanil, and a target-controlled infusion (TCI) of 3.0 μg·mL^{-1} of propofol. Rocuronium (50 mg [0.73 mg·kg^{-1}]) was administered to facilitate tracheal intubation. Anesthesia was maintained with 0.12-0.4 μg·kg^{-1}·min^{-1} of remifentanil and a propofol TCI of 1.7 μg·mL^{-1}. An acceleration-sensing muscle relaxation monitor (TOF-Watch^{TM}, MSD/Organon, Dublin, Ireland) was used to monitor the neuromuscular blockade. The accelerometer sensor was attached to the tip of the left thumb, and electrical stimulation was performed at the ulnar nerve proximal to the wrist. The train-of-four (TOF) was measured at a 2-Hz stimulation frequency with a current amplitude of 50 mA and a pulse width of 0.2 msec. Monitoring was initiated after the administration of rocuronium; therefore, the baseline single twitch amplitude (T1) was not obtained. The initial TOF count was already 0. No additional rocuronium was administered during the 273-min surgery. Since the TOF count of the left arm remained at 0 throughout the surgery, the accelerometer of TOF-Watch was temporarily moved to the right arm. Nevertheless, the TOF count of the right arm was also 0. Therefore, 300 mg of sugammadex was administered at the end of the surgery. Nonetheless, the TOF count and posttetanic contraction count (PTC) after five minutes were 0 and 2, respectively. Therefore, 200 mg of sugammadex was administered, followed by 200 mg then 300 mg within 20 min, and then 200 mg at 60 min after surgery. The patient was able to communicate that he was awake by blinking his eyes at ten minutes after cessation of intravenous anesthesia. Nevertheless, he could not breathe. Even after administering a total sugammadex dose of 1,200 mg, the TOF ratio of the left adductor pollicis muscle was 0, and the PTC was 6. Thus, he remained intubated and mechanical ventilation was initiated under continuous midazolam sedation at 3 mg·hr^{-1}, while maintaining the Richmond Agitation Sedation Scale at -1

to -2. Adverse events including hypotension, bradycardia, bronchospasm, hypersensitivity reactions were not observed during administration of sugammadex. Eighteen hours after rocuronium administration, the patient was again able to breathe spontaneously. At that time, although the TOF ratio of the right adductor pollicis muscle was recovered to > 0.9, the TOF ratio of the left adductor pollicis muscle remained at 0. Nevertheless, he was able to grip with his hands; thus, his trachea was extubated. Arterial blood gases ten minutes after extubation, on oxygen administration via face mask, were: pH, 7.40; partial pressure of carbon dioxide, 45 mm Hg; partial pressure of oxygen, 178 mm Hg; and base excess, 2.1.

A postoperative physical examination confirmed superficial sensory loss predominantly in the distal parts of both feet, *pes cavus*, and weakness of both the tibial and upper limb muscles. In a postoperative interview, he noted that muscle loss that had become apparent during the last five years, and more recently, an inability to open the lid of a plastic bottle and stumbling during walking. Due to suspicion of a neuromuscular disease, he was referred to the neurology department at a tertiary hospital and diagnosed with CMT1A, based on a conduction delay in the nerve transmission velocity of 20 m·sec^{-1} and mutated duplication of the *PMP22 gene*.

Discussion

Brief literature reviews on anesthetics

No consensus has been established regarding anesthetic management of patients with CMTD.[11-13] Some sporadic case reports have noted that propofol, remifentanil, and midazolam can safely be used in these patients if NMBAs are withheld.[14,15] In addition, previous case reports have reported that regional anesthesia is safe in these patients,[16,17] although the advantages and disadvantages of this approach should be carefully weighed.[18] The importance of appropriate anesthetic management for possible hemodynamic instability due to the dysfunction of the autonomic nervous system in CMTD has also been emphasized.[15] As for depolarizing muscle relaxants, one study reported that succinylcholine was safely administered without the occurrence of malignant hyperthermia in all the 41 CMTD patients for its use.[19]

In patients with CMTD, the primary concern during anesthesia is the potential for development of a prolonged postoperative neuromuscular blockade caused by administration of a nondepolarizing NMBA.[3,9,20] Although a report described near-normal responses to mivacurium in five patients,[21] prolonged effects of NMBAs[20] and a postoperative need for artificial

ventilation after administering the NMBAs have been reported.[3,9] Recently, it was reported that rocuronium could safely be administered to patients with CMTD if it was antagonized by sugammadex.[11-13] Nevertheless, our case shows that high-dose sugammadex could not protect a patient with CMTD from a rocuronium-induced neuromuscular respiratory paralysis.

Prolonged respiratory paralysis refractory to sugammadex

The total of 1,200 mg (17.3 mg·kg^{-1}) of sugammadex administered to our patient seemed sufficient to encapsulate the residual rocuronium molecules. This dose was higher than the 16 mg·kg^{-1} dose of sugammadex that has been shown to reverse a neuromuscular blockade immediately after administration of 1 mg·kg^{-1} of rocuronium.[22] Therefore, it is difficult to attribute the prolonged respiratory paralysis in our patient to residual rocuronium. Also, since the patient regained consciousness at ten minutes after cessation of anesthesia, a central respiratory depression resulting from propofol, fentanyl, and remifentanil was also unlikely to have caused his respiratory depression. Finally, the midazolam used for sedation was also unlikely to have caused the respiratory depression because spontaneous breathing was recovered during its use.

Although sugammadex can reverse a neuromuscular blockade from rocuronium more rapidly and reliably than neostigmine can,[22] it should be noted that, unlike cholinesterase inhibitors, sugammadex does not increase the acetylcholine concentration at the neuromuscular junctions.[22] Therefore, if acetylcholine release from presynaptic nerve endings is reduced, sugammadex only has a negligible effect on enhancing neuromuscular transmission. An animal model of CMT1A suggests that abnormal synaptic transmission caused by pre- and postsynaptic dysfunction exists at the diaphragm of CMT1A patients.[23] Accordingly, the prolonged rocuronium-induced disturbance of excitatory transmission of acetylcholine at the neuromuscular junctions may have occurred in our patient via mechanisms not attributable to residual rocuronium.

Impairment of the phrenic nerve and diaphragm

CMTD can cause atrophy of the diaphragm due to denervation, with respiratory failure occurring in the advanced stages of the disease.[4-6] In our case, the restrictive spirometry pattern and the history of repeated pneumonias suggest that this patient's phrenic nerves were affected, which may have contributed to his prolonged neuromuscular respiratory paralysis. The degree of phrenic nerve impairment and the extent of subsequent diaphragmatic muscular atrophy seem to be critical factors in prolonging neuromuscular respiratory paralysis. In patients with CMTD, restrictive pulmonary dysfunction should be viewed as a potentially alarming indicator of phrenic nerve impairment.

Difficulties in monitoring muscle relaxation

Our patient had a difference between the TOFs of his left (TOF ratio of 0) and right (TOF ratio of > 0.9) adductor pollicis muscle after spontaneous breathing was recovered. The reason for the 0 value of TOF ratio in the left adductor pollicis muscle remains unclarified because of the lack of data on the amplitude of evoked responses before administration of rocuronium in our patient. In an animal model of CMT1A, sustained nerve stimulation decreased acetylcholine release from nerve endings and temporarily impaired neuromuscular transmission.[23] The repetitive nerve stimulation of the left adductor pollicis muscle during anesthesia and artificial ventilation might have decreased acetylcholine release from presynaptic terminals in our patient.

Difficulties monitoring neuromuscular blockade have been reported in patients with CMT1 due to impaired peripheral nerves.[13] The possible slowing of NCV and reduced amplitude of the muscles in CMT1 may impair EMG assessment of neuromuscular transmission.[21] Therefore, acceleromyography reflecting the actual muscular contraction may be more beneficial in monitoring neuromuscular function.[21] As for the monitoring site, facial muscles such as the orbicular oculi may be used in patients with suspected ulnar nerve demyelination.[20,21] Nevertheless, objective measurements such as TOF should be used for facial muscles because the subjective evaluation of facial muscle function could underestimate residual neuromuscular block.[24]

Preanesthetic cautions

This patient's muscular weakness and gait disturbance were thought to be attributable to osteoarthritis of the hips and rheumatoid arthritis preoperatively. Nevertheless, *pes cavus* and hammer fingers and toes are the characteristic findings of CMTD and should be differentiated from rheumatoid arthritis.[1,25] When anesthesiologists encounter such foot deformities accompanied by muscular weakness in the extremities and peripheral sensory deficits preoperatively, CMTD should be suspected and thorough examinations should be performed by consulting neurologists.[1,25]

Conclusion

Our case shows that rocuronium can cause a prolonged neuromuscular respiratory paralysis refractory to sugammadex in patients with CMT1A and a restrictive pulmonary impairment. Systematic studies are needed to clarify the types of CMTD and associated co-morbidities or conditions that put CMTD patients at risk for prolonged paralysis after receiving rocuronium with sugammadex.

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