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CASE REPORT

Postoperative recurarization undetected by neuromuscular monitoring

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Abstract

Background: Muscle relaxants and reversal agents, including sugammadex, should be administered according to the neuromuscular monitoring guidelines to prevent recurarization. However, recurarization may still occur with adequate neuromuscular monitoring. This case describes recurarization that occurred in the post-anesthesia care unit (PACU) where the patient's acceleromyography (AMG) train-of-four (TOF) ratio was 1.0 despite the use of sugammadex. **Case**: A 66-year-old woman completely recovered from general anesthesia using sugammadex but suddenly became unresponsive in the PACU. Her TOF ratio was 1.0, that we first suspected residual effects of benzodiazepines or opioids. However, there was no response to flumazenil or naloxone. Based on her symptoms, we suspected muscle relaxant recurarization with possibility of overestimation of uncalibrated TOF monitoring device and administered additional sugammadex, which immediately caused her to become responsive. Her symptoms were relieved completely after two additional doses of sugammadex. **Conclusions**: Despite the use of sugammadex, recurarization can occur without appropriate TOF monitoring.

Keywords

Neuromuscular blockade; Sugammadex; Benzodiazepine; Anesthesia

1. Introduction

Sugammadex safely and effectively reduces the risk of postoperative residual neuromuscular blockade. However, there have been several cases in which recurarization, a rapid increase in neuromuscular blockade after a period of recovery, occurs after the use of sugammadex [1–3]. Recurarization in the PACU can occur due to various factors and manifest diverse symptoms. It may lead to hypoxia, necessitating reintubation. Even without respiratory issues, patients may experience symptoms such as the inability to open their eyes or speak [4].

The American Society of Anesthesiologists recommended that neuromuscular monitoring should be performed during general anesthesia [5]. Even when neuromuscular blockade is reversed guided by TOF monitoring, a residual blockade or recurarization may occur. Here, we report a rare case in which the patient experienced recurarization undetected by TOF monitoring in the PACU after an adequate amount of sugammadex was administered based on neuromuscular monitoring during surgery.

2. Case presentation

A 66-year-old woman who was 167 cm tall and weighed 61 kg was scheduled for calcaneus metal removal under general anesthesia. She had a medical history of diabetes mellitus, subclinical hypothyroidism, and anxiety disorder. The patient was taking alprazolam 0.25 mg in the morning and before sleep at night. Preoperative laboratory testing showed she had a glycated hemoglobin (HbA1c) of 7.3% and a fasting blood glucose level of 116 mg/dL and was in a euthyroid state. She had undergone general anesthesia at our center three years prior with no particular issues.

On arrival in the operating room, standard monitoring by electrocardiogram, non-invasive blood pressure monitoring, and pulse oximetry were begun. General anesthesia was induced using propofol 1.6 mg/kg, remifentanil 0.1 μg/kg/min, and rocuronium 0.8 mg/kg. Sevoflurane 1.5–2 vol.% and remifentanil 0.03–0.1 μg/kg/min were used to maintain anesthesia.

We described management of neuromuscular blockade and reversal agents in Fig. 1. During the operation, a bispectral index (BIS) (Aspect Medical Systems, Inc., Natick, MA, USA) was used to monitor the patient's hypnotic state and a MechanoSensor kinemyography (KMG) (Datex Ohmeda GE Healthcare Neuromuscular transmission-electromyography: NMT-EMG, Helsinki, Finland) was used to monitor the neuromuscular blockade. Adequate anesthesia depth and neuromuscular blockade were maintained with a BIS of 40–60 and train-of-four (TOF) count below 1. One hour after anesthesia induction, the patient's TOF count was 2, so 10 mg of rocuronium was injected, and the surgery

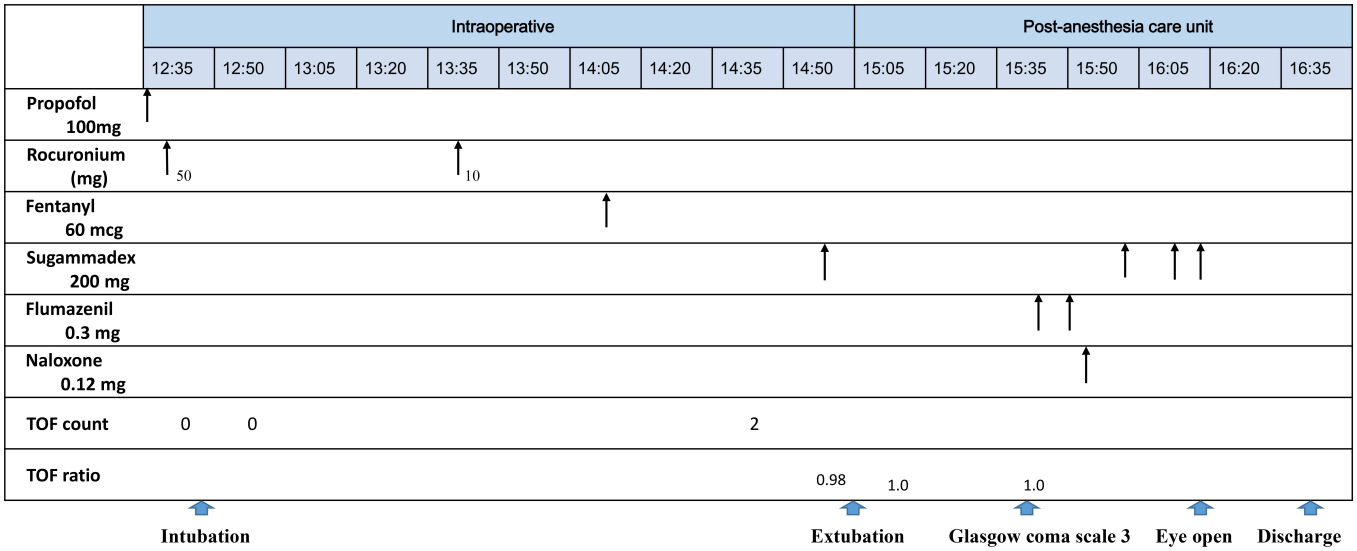

FIGURE 1. Timeline of propofol, rocuronium, fentanyl, sugammadex, flumazenil, naloxone administration and train-of-four (TOF) count and ratio during surgery and in the post-anesthesia care unit.

proceeded uneventfully. Normothermia was maintained during the operation and the patient's temperature was 36.8 °C at the end of the operation. Fifty minutes before the end of anesthesia, 1 μg/kg of fentanyl was injected. Bristurn prefilled sugammadex (23006, Bristurn prefilled inj., Hanlim Pharm. Co. Ltd., Yongin, South Korea) 3.3 mg/kg for a total of 200 mg was administered when the patient's TOF count was 2 after which it recovered to TOF ratio of 0.9 or more. Then her BIS exceeded 90, her spontaneous breathing was adequate, and she opened her eyes and nodded in response to a verbal command. The endotracheal tube was extubated 1 minute after sugammadex injection after which the patient was transferred to the PACU. The total anesthesia time was 141 minutes.

On arrival in the PACU, the patient was calm and breathing spontaneously. 30 minutes after arrival in the PACU, she was breathing spontaneously but suddenly stopped responding to verbal commands, pain and any external stimuli; had a Glasgow Coma Scale score of 3, tympanic temperature of 36.8 °C, and blood sugar test of 132 mg/dL; arterial blood gas analysis showed that her blood pH level was 7.450, partial pressure of carbon dioxide was 34.5 mmHg, partial pressure of oxygen was 87.9 mmHg, bicarbonate was 24 mmol/L, arterial oxygen saturation was 95% in room air, and other serum electrolytes were within their normal ranges; and a Stimpod NMS 450 acceleromyography (AMG) device (Xavant Technology, Pretoria, South Africa) showed that her TOF ratio was 1.0.

Considering that the patient was taking alprazolam twice per day, we administered flumazenil 0.3 mg intravenously, but her condition did not change for the next five minutes. We then administered naloxone 0.12 mg and flumazenil 0.3 mg intravenously, but her condition still did not change. Next, even though she had a TOF ratio of 1.0, we administered sugammadex 200 mg because the AMG may have overestimated her TOF. Right after administering the sugammadex, the patient started to move her fingers in response to verbal commands and pain stimuli with her eyes closed. Following this slight improvement of symptoms, we administered sugammadex 200 mg again. She immediately opened her eyes slightly in response to a verbal command, weakly grasped our hands, and made efforts to move her body. We asked her if she could not speak after which she nodded weakly, pointed her index finger at her neck, and slightly moaned. At this point, a neurologist came to conduct a neurological examination. In the neurologist's opinion, she did not exhibit any pathologic reflexes but did seem to have paralysis symptoms. We decided to further administer sugammadex 200 mg. Afterward, she fully recovered her motor and verbal abilities. She reported that she wanted to move and speak but could not and experienced significant pain at the surgical site. There were no further events during the hospital stay.

3. Discussion

There are a few reports of recurarization after administration of the recommended dose of sugammadex. Our case poses novelty that recurarization occurred after sugammadex administration while the patient's TOF ratio was measured as 1.0. Also, the patient exhibited recurarization symptoms of inability to move while maintaining spontaneous breathing, and required a fairly large amount of additional sugammadex to fully recover.

We suspected that the patient's sudden loss of responsiveness in the PACU was due to the residual effects of benzodiazepine. Rarely, benzodiazepine may induce expressive aphasia [6]. It potentiates the effect of anesthetics, especially propofol, by activating gamma-aminobutyric acid. The clinical features accompanying expressive aphonia vary from inability to open the eyes to quadriplegia-like weakness, which completely recover after flumazenil administration. In previous case, patient chronically medicated with benzodiazepine had delayed awakening with no response to pain stimuli in the PACU [7]. Our patient was taking alprazolam twice per day, leading us to suspect aphonia due to benzodiazepine.

However, flumazenil was ineffective and repeated dosing of sugammadex caused immediate recovery, so we determined that the cause of unresponsiveness was muscle relaxant recurarization.

Recurarization after sugammadex administration can occur because rocuronium is distributed from peripheral compartments to the central compartment or there is a lack of sufficient free sugammadex in the plasma [8]. Various factors that can cause to these conditions, but the most common are patient comorbidities such as obesity and being elderly, pharmacological interactions, inappropriate sugammadex dosing, and lack of dosing guided by quantitative neuromuscular monitoring [1]. With regard to pharmacological interations, the sugammadex's effectiveness can be compromised by steroid structure drugs, such as toremifene, flucloxacillin and fusidic acid, leading to reoccurrence of muscular blockade after sugammadex administration [9].

In our present case, we most suspect overestimation of uncalibrated AMG and KMG devices. In previous studies, AMG and KMG produced higher TOF ratios than EMG and mechanomyography, with AMG overestimating the EMG TOF ratio by at least 0.15 [10–12]. Khandkar *et al.* [13] (2016) reported that KMG TOF measurements were 0.08 higher than EMG measurements (95% confidence interval: −0.12, 0.27) measured during recovery with a TOF ratio of 0.80–0.99. Thus, a KMG TOF ratio of 1.0 may be as low as 0.73 when measured by EMG, which cannot exclude residual neuromuscular blockade. Liang *et al.* [10] (2013) also reported that residual blockade cannot be excluded with an AMG TOF ratio of either 0.9 or 1.0. In our case, we used KMG during the operation and AMG in the PACU, but did not calibrate the devices to establish a baseline TOF ratio before induction of general anesthesia. Therefore, the patient's TOF ratio measured by either KMG or AMG might not have been accurate, given her symptoms. An uncalibrated AMG ratio of 1.0 can indicate a wide and clinically significant degree of residual paralysis.

Our patient was breathing well but unable to open her eyes or grip with her hand. Based on her symptoms, we estimated the neuromuscular junction receptor occupancy to be around 50%. Muscles have varying sensitivities to muscle relaxants due to different levels of blood flow, acetylcholine receptor densities, acetylcholine release rates, acetylcholinesterase activity levels, muscle fiber compositions, numbers of neuromuscular junctions, and temperatures [14]. We only used the right hand's adductor pollicis muscle to check neuromuscular blockade, which may not have had similar relaxation levels as other major muscles.

Our patient required a considerable amount of additional sugammadex. The patient received rocuronium 60 mg and sugammadex 800 mg. Theoretically, rocuronium (molecular weight: 610 Daltons) and sugammadex (molecular weight: 2178 Daltons) bind in a 1:1 molar ratio, so sugammadex 3.57 mg would be needed for rocuronium 1 mg [8]. Several previous cases noted that muscle paralysis was reversible with sugammadex 10.9–17.3 mg/kg administration, which is a relatively large dose [15, 16]. We cannot identify the exact reason because the patient's rocuronium and sugammadex plasma concentrations were not measured, but the patient may have been an extreme outlier in terms of sugammadex resistance or the sugammadex did not rapidly respond to the rocuronium in the plasma and interstitial tissue for some reason.

When muscle relaxant recurarization is suspected, vital signs should be checked immediately and physical examination and quantitative assessment of neuromuscular functioning should be carried out. EMG can be used in the PACU because EMG devices do not need to be calibrated. If there is evidence of recurarization, additional reversal agents should be administered. Hypothermia and pH abnormalities should be treated and any complications owing to recurarization, such as hypoxemia, should be managed.

4. Conclusions

Although rare, a TOF ratio >0.9 as measured by uncalibrated AMG or KMG cannot preclude recurarization due to the overestimation of the TOF monitoring device. Anesthesiologists must always be aware of the possibility of postoperative recurarization in the PACU.

AVAILABILITY OF DATA AND MATERIALS

The data are available on request from the corresponding author.

AUTHOR CONTRIBUTIONS

GN—wrote the first version of the manuscript. KMK—provided help and advice on editing the manuscript. SL—edited the first version of the manuscript. IJJ—wrote the manuscript and approved the final version of the manuscript. All authors contributed to editorial changes in the manuscript and all authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The institutional review board approval has been waived from Ethics committee of Sanggye paik hospital. Written informed consent was obtained from the patient for the publication of this case report.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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