Case Report
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Sugammadex-induced bronchospasm: a case report

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Sugammadex has shown faster reversal of steroidal neuromuscular blockade (NMB) than neostigmine, a traditional reversal agent for NMB, even in the intense block phase. This efficiency is possible because of the unique mechanism of action by encapsulating the NMB molecules. Therefore, with the use of sugammadex, we can also expect to avoid direct interactions with the cholinergic system and its subsequent side effects, which are disadvantages of traditional drugs. However, despite these benefits and US Food and Drug Administration (FDA) approval in 2015, rare adverse events associated with sugammadex have been reported. Herein, we report a case of bronchospasm that developed immediately after sugammadex administration.

Keywords: Anaphylaxis; Bronchial Spasm; Neuromuscular Blockade.

INTRODUCTION

Sugammadex has been reported to have high efficacy with a rapid action time and the ability to reverse deep or intense block [1]. It is also indicated to reduce the overall postoperative complications with higher train-of-four ratio values at extubation compared to neostigmine [2]. Furthermore, unlike traditional reversal agents, due to its unique mechanism, sugammadex is known to avoid adverse effects from undesired activation of muscarinic receptors, such as bronchospasm [3]. However, although the etiology has not been fully understood or established, bronchospasm has been an adverse effect of sugammadex, as well as other events such as erythema, hypotension, and coronary spasm [4-10]. We report a case of bronchospasm that occurred immediately after sugammadex administration, without any other stimulation at emergence.

CASE REPORT

A 159 cm, 71 kg, 52-year-old woman was scheduled for mesiodens tooth extraction under general anesthesia. The patient had no relevant medical history. Her preoperative examination results were unremarkable, except for a slight increase in OT/PT to 31/69 due to a fatty liver. Standard monitoring devices were used in the operating room. Her initial vital signs were stable with blood pressure (BP), heart rate (HR), oxygen saturation (SpO_2), and body temperature of 121/68 mmHg, 80 bpm, 100%, and 35.9℃, respectively. Electrocardiography revealed normal sinus rhythm. An entropy sensor (Entropy EasyFit Sensor, GE Healthcare, Helsinki, Finland) was used for electroencephalogram (EEG) monitoring. Induction and maintenance of general anesthesia involved the use of 120 mg of propofol, 1-3 μg/ml of remifentanil, 50 mg of rocuronium, and 6 vol%

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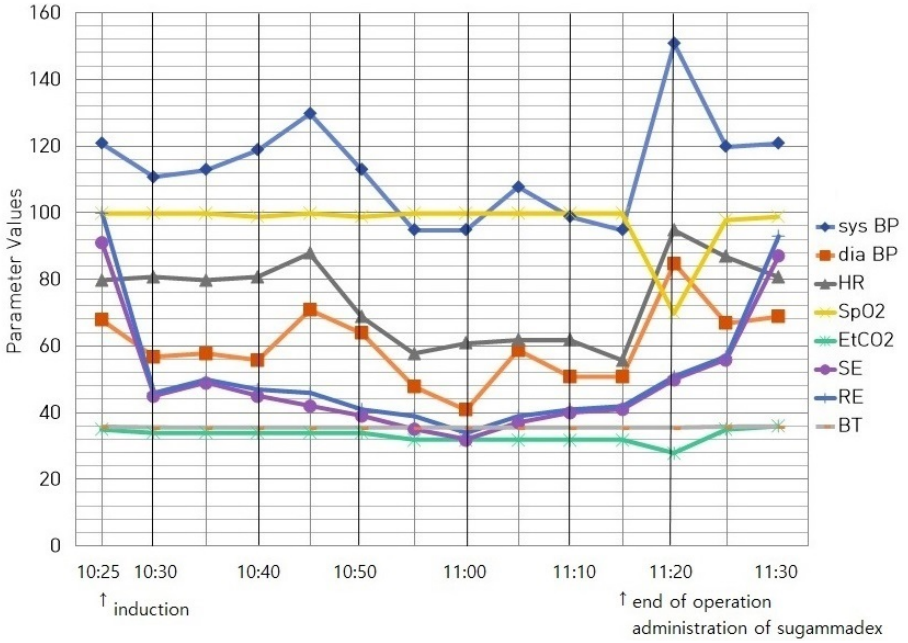

Fig. 1. Intraoperative changes in hemodynamic values of the patient.
*Abbreviations: BT, body temperature; dia BP, diastolic blood pressure; $EtCO_2$, end-tidal carbon dioxide concentration; HR, heart rate; RE, response entropy; SE, state entropy; SpO_2, oxygen saturation; sys BP, systolic blood pressure.

desflurane. The patient's vital signs remained stable throughout the operation, and there was no particular event of concern. At the end of the operation, BP, HR, SpO_2, body temperature, and EEG were 95/51 mmHg, 56 bpm, 100%, 35.5℃, and 45/40, respectively. Remifentanil was tapered, desflurane was turned off, and sugammadex was applied for emergence.

However, approximately 30 s after the administration of 200 mg sugammadex (2.8 mg/kg), the peak airway pressure (Ppeak) of the patient suddenly increased dramatically from 14 mmHg to 35 mmHg without any other stimulation. Desaturation to 70% occurred immediately despite the intubated status. Wheezing was heard on auscultation of both lungs. Her BP, HR, body temperature, and EEG were 151/85 mmHg, 95 bpm, 35.5℃, and 50/51, respectively (Fig. 1). Bronchospasm was suspected, and 100% oxygen was promptly administered via manual positive ventilation. Additionally, a salbutamol inhaler (Ventolin Evohaler™, GlaxoSmithKline) was given as first-line drug therapy. Two to three minutes later, Ppeak was restored to its original baseline level with 100% saturation and the patient was awake. Extubation was successfully performed and the patient was transferred to the recovery room without any other respiratory events.

No preoperative pulmonary function tests were performed because the patient was a non-smoker without any respiratory disease. Considering that both Ppeak and ventilator waveforms showed an obstructive pattern transiently only at the event, we decided not to perform the test in the postoperative phase. The patient showed no further symptoms or complications and was discharged on postoperative day three. Patient consent was obtained for the publication of this case report.

DISCUSSION

Neuromuscular blockade (NMB) is essential for maintaining general anesthesia. Therefore, reversing the status at the end of anesthesia in a safer and more effective manner is important. Cholinesterase inhibitors such as neostigmine and pyridostigmine are the conventional reversal agents that are still in use. However,

these traditional methods have disadvantages. First, due to their mechanism, increased acetylcholine can be associated with undesired muscarinic receptor stimulation which can result in hypersalivation with increased airway resistance, bronchospasm, and bradycardia. Therefore, anticholinergics such as atropine or glycopyrrolate should be co-administered to prevent this. Furthermore, cholinesterase inhibitors are effective only when administered at count 4 of the train-of-four superficial block phase. This is useless in the deeper phases. Paradoxical muscle weakness can occur if administered when NMB has fully recovered [11].

Compared to the ineffectiveness of cholinesterase inhibitors, the appearance of sugammadex seemed to be a game-changer. The mechanism of this new class of agents was simply to encapsulate the NMB agents, and it was unrelated to direct interaction with the cholinergic system. Therefore, adverse events due to the undesired activation of muscarinic receptors can be avoided. Additionally, it can reverse NMB even during the intense phase, with a faster recovery time. Kheterpal et al. [2] suggested in their multicenter cohort study that sugammadex reduced post-pulmonary complications by up to 30% with improved muscle tone of the upper airway, which is important for clearing secretions and decreasing alveolar collapse. Randomized controlled trials and retrospective cohort analyses have also suggested that sugammadex is comparably safe [1,3]. Consequently, the preference for sugammadex increased after its FDA approval in 2015.

However, despite its high efficacy and comparable safety, adverse events associated with sugammadex have been steadily reported and remain unresolved. Although the types and severity of symptoms differ, they commonly manifest as hypersensitivity, including anaphylactic-like reactions such as erythema, hypotension, bronchospasm, and even coronary spasm. Sugammadex-related adverse reactions seem to be more frequent at higher clinical doses (16-96 mg/kg) in earlier studies [12,13]. However, according to Menendez-Ozcoidi et al. [4] and Godai et al. [5], these reactions can rarely occur even with the usual lower clinical doses (1.9-3.2 mg/kg) with disastrous results. Min et al. [6] performed a study on the hypersensitivity incidence in response to sugammadex administration in healthy people. According to a randomized controlled trial, hypersensitivity after sugammadex administration can develop even without previous exposure, and the incidence seems to be similar across the doses used. However, it was significantly higher than that of the placebo, which means that the possibility of hypersensitivity should be considered when using sugammadex.

Considering bronchospasm was one of the undesired adverse results of muscarinic activation by neostigmine, theoretically, sugammadex was expected to have the benefit of avoiding this event [3]. Ironically, however, a rare but still sugammadex-related bronchospasm has been noticed [7-9] and its mechanism is so far not fully understood. The time of onset of bronchospasm varies among published reports. Thus, it is difficult to determine whether sugammadex itself or the sugammadex-rocuronium complex causes bronchial muscle retraction in bronchospasms. Using a rat model, Yoshioka et al. [14] demonstrated that sugammadex itself has no direct contractile effect on bronchial smooth muscles, even at the highest concentration. Therefore, they concluded that other factors, such as the activation of mast cells and stimulation of cholinergic nerves, should be considered. However, in a clinical study involving healthy volunteers, Min et al. [6] reported that hypersensitivity to sugammadex is unlikely to be mediated by immunoglobulin G or E-related mast cell stimulation. Additionally, considering the very short time of onset, direct activation by sugammadex was suspected to be the cause of bronchospasm, rather than mast cell activation or the clathrate complex.

The patient's pulmonary condition appeared to be an important factor. Although pulmonary conditions, such as infection or asthma, are more vulnerable to broncho-spasm, they have also been reported to occur even in the absence of pulmonary disease [7,8]. In these cases, desflurane is commonly used, as in our case. While

sevoflurane has a moderate bronchodilatory effect with decreasing respiratory resistance, desflurane has irritant characteristics and is even constrictive in patients with a current smoking history. Thus, Baronos et al. [8] suggested that the irritant properties of desflurane may interact with those of sugammadex. We hypothesized that the rapid reversal of bronchial smooth muscle by sugammadex could interact with the remnant desflurane during awakening. However, the interactions between sugammadex and desflurane remain unclear [15]. When the minimal alveolar concentration of desflurane was decreased to 1.0, airway resistance was not significantly high and returned to baseline. In addition, bronchospasms, even with sevoflurane, have been reported by Trivedi et al. [9], which makes sugammadex itself more focused on as the main cause of bronchospasm, rather than the type of inhalation agent used.

In the present case, the bronchospasms developed immediately after sugammadex administration. Considering that there were no other significant anesthetic or surgical changes at the time, sugammadex was highly suspected to be the main cause. It is important to focus on the fact that the event occurred at a low clinical dose in healthy patients without any other potential stimulator except desflurane, which is controversial. Therefore, despite its increased popularity, staying vigilant while using sugammadex is mandatory for maintaining a safe and stable hemodynamic status. Further research is required to understand the mechanisms of adverse side effects for better clinical outcomes.

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AUTHOR CONTRIBUTIONS

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CONSENT: The ethical approval was granted by the Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB file number: KNUH 2023-07-039). The patient provided informed consent for publication of this article.

The authors have no conflicts of interest to disclose.

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