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CASE REPORT

Delayed emergence after general anesthesia using remimazolam for induction agent in laparoscopic cholecystectomy: a case report

Eun-Jin Ahn[1,2], Je Jin Lee[1,3], Chan Su Park[3], Min Kyoung Kim[1,2,*]

[1]Department of Anesthesiology and Pain Medicine, Chung-Ang University Gwangmyeong Hospital, 14353 Gwangmyeong-si, Republic of Korea
[2]Department of Anesthesiology and Pain Medicine, College of Medicine, Chung-Ang University, 06911 Seoul, Republic of Korea
[3]Department of Anesthesiology and Pain Medicine, Chung-Ang University Hospital, 06973 Seoul, Republic of Korea

***Correspondence**
ddolpaki86@naver.com
(Min Kyoung Kim)

Abstract

Remimazolam's ultrashort-acting properties, including reduced injection discomfort, minimal impact on respiratory and cardiovascular functions and rapid metabolism, have garnered significant attention in the field of anesthesia. However, despite its widespread acclaim, we encountered an unusual case in which a patient without hepatic or renal impairment experienced unexpected delays in regaining consciousness following a single intravenous induction dose of remimazolam. The patient, a 63-year-old undergoing laparoscopic cholecystectomy for gallbladder stones, had preoperative tests revealing atrial fibrillation and a reduced ejection fraction observed in an echocardiogram. Anesthesia induction included the administration of remimazolam (0.3 mg/kg), sufentanil and rocuronium. The surgery proceeded uneventfully and was maintained with desflurane and sufentanil. However, after the surgery, the patient experienced delayed emergence from anesthesia. Opioid overdose was ruled out, and we suspected a metabolic delay associated with remimazolam. In response to this suspicion, we administered flumazenil, which promptly restored consciousness and normal breathing. Subsequent post-anesthetic observation revealed no complications, and the patient was discharged two days after surgery. This case highlights the significant delayed emergence phenomenon linked to remimazolam, even when administered as a bolus. Instances of delayed emergence following remimazolam administration underscore the complexities in anesthesia responses, emphasizing the importance of vigilant clinical monitoring and the need for ongoing research in this area.

Keywords

Remimazolam; Flumazenil; Benzodiazepines; Delayed emergence; General anesthesia; Case report

1. Introduction

Remimazolam, which received approval from the United States Food and Drug Administration in 2020, belongs to the class of ultrashort-acting benzodiazepines [1–3]. Similar to remifentanil, remimazolam undergoes rapid hydrolysis into an inactive metabolite (CNS7054) within the body, facilitated by non-specific tissue esterases [4]. Remimazolam exhibits a relatively high clearance rate, a small steady-state volume of distribution, a short elimination half-life and a short context-sensitive half-life, which contribute to its fast onset and rapid recovery profile, making it easily manageable [1, 2, 5]. One notable advantage of remimazolam is its minimal impact on respiratory function, rendering it suitable for use outside the operating room, such as in endoscopy [6]. Additionally, it is known for causing minimal injection pain, and when compared to other anesthetic induction agents, remimazolam induces minimal cardiovascular depression, making it a preferred choice for anesthesiologists treating patients with cardiovascular disorders [2]. Remimazolam is particularly favored in cases involving end-stage liver disease, as its clearance and elimination processes remain unchanged [7]. Furthermore, in patients with hepatic or renal impairment, the maximum observed concentration after a bolus injection of remimazolam remains unaffected, indicating that dose adjustment is generally unnecessary [8].

Nonetheless, it is worth noting that several case reports have reported the occurrence of delayed emergence following the administration of remimazolam [9–11]. For instance, Singal *et al.* [9] reported its occurrence in a patient with end-stage liver disease, and other cases [10–12] incorporated remimazolam not only for anesthesia induction but also for maintenance, which diverges from our present case report where remimazolam was exclusively used for induction in a patient without hepatic or renal impairment, thereby allowing us to investigate the specific factors and potential causes associated with delayed emergence from anesthesia.

2. Case presentation

2.1 Patient history and preoperative assessment

A 63-year-old male patient was referred to our hospital after an abdominal CT (Computed Tomography) scan at another medical facility revealed gallbladder stones accompanied by chronic cholecystitis due to postprandial indigestion symptoms, following which he underwent laparoscopic cholecystectomy and experienced delayed emergence after general anesthesia. The patient had a history of hypertension but had only received temporary medication treatment in the past and was not currently taking any antihypertensive medications. However, he did report using carbamazepine and gabapentin to manage trigeminal neuralgia. Upon admission, his blood pressure was measured at 118/84 mmHg, and his heart rate was 81 beats per minute. A comprehensive physical examination revealed no abnormalities in other body systems.

Preoperative laboratory tests showed no abnormalities apart from elevated blood urea nitrogen 22 mg/dL (reference range, 6.5–20.9 mg/dL) and lactate dehydrogenase 315 IU/L (reference range, 0–225 IU/L). However, his preoperative electrocardiogram (ECG) showed evidence of atrial fibrillation, and following additional questioning, the patient reported experiencing vague chest discomfort for the past few days. In response to this, he underwent an echocardiogram, which revealed an ejection fraction of 40.9%, global hypokinesia, biatrial enlargement and minimal aortic, mitral and tricuspid regurgitation, while coronary angiography revealed no abnormalities.

2.2 Anesthesia and surgery

Based on the comprehensive preoperative assessment, in collaboration with a cardiologist, it was decided to incorporate edoxaban and bisoprolol into the patient's medication regimen before proceeding with the planned surgery. Continuous monitoring of the patients was performed using ECG, pulse oximetry, non-invasive blood pressure, bispectral index (BIS), and train-of-four (TOF) measurements. To induce anesthesia, an effect-site target-controlled infusion (TCI) of sufentanil was maintained at 0.2 ng/mL, and remimazolam was administered at 0.3 mg/kg, along with rocuronium at 0.6 mg/kg. The endotracheal intubation was successfully performed with minimal impact on vital signs, allowing for a reduction in the sufentanil infusion concentration to 0.1 ng/mL. For the maintenance of anesthesia, desflurane was administered at a total gas flow of 2 L/min with an FiO_2 of 0.3. To ensure an appropriate depth of anesthesia, the desflurane concentration was adjusted to maintain BIS values between 40–60. Additionally, the effect-site TCI of sufentanil was adjusted between 0.05 and 0.1 ng/mL to maintain the vital signs within 20% of baseline values throughout the surgery, which comprised laparoscopic cholecystectomy with the use of three ports. The surgical procedure was successfully completed without any adverse events 40 minutes after the induction of anesthesia. Immediately after the surgery, desflurane administration was discontinued, and to reverse any residual muscle relaxation, an intravenous injection of sugamadex 200 mg was administered. At 50 minutes after anesthesia induction, the end-tidal desflurane concentration reached 0 vol%, and the TOF ratio was 98%. However, the patient did not exhibit spontaneous recovery of breath and consciousness.

2.3 Delayed emergence and administration of flumazenil

Since there were no prior neurological or medical conditions that could account for the delayed recovery from anesthesia, we decided to wait a bit longer to allow for adequate recovery time. However, 55 minutes after anesthesia induction, the patient's BIS value consistently remained between 40–50, there were no signs of spontaneous breathing, and the modified observer's assessment of alertness/sedation (MOAA/S) score remained at 0. Consequently, we performed a thorough differential diagnosis to identify the cause of this delayed anesthesia recovery, with a special focus on the impact of the drugs administered during the general anesthesia.

The possibility of opioid overdose was ruled out based on several factors: the patient's limited opioid use during surgery, the absence of pinpoint pupils, and the presence of pupil reflexes. Given these findings and considering the potential delay in metabolism associated with a single dose of remimazolam used for anesthesia induction, the decision was made to administer 0.2 mg of flumazenil intravenously, following which we observed a notable increase in BIS values. Within a minute, the patient exhibited spontaneous recovery of consciousness and breathing, as indicated by a MOAA/S score of 4 (Fig. 1). Consequently, we diagnosed the delayed emergence from anesthesia as being due to remimazolam. During a one-hour observation period in the post-anesthetic care unit, there were no instances of re-sedation. Subsequently, the patient was discharged on the 2nd day after the surgery without any complications.

3. Discussion

Delayed emergence from anesthesia, which refers to a condition where a patient does not regain consciousness within 30 to 60 minutes after undergoing general anesthesia, remains a significant challenge for anesthesiologists [3, 13–15]. Such conditions, especially under general anesthesia, could occur due to several factors. Firstly, patient-related factors such as age, gender, genetic variations and underlying health conditions can contribute to this phenomenon [3]. Secondly, drug-related factors, including the timing of drug administration, how drugs are metabolized, potential drug toxicity, and interactions with other drugs, should be considered. Thirdly, surgical and anesthetic factors, such as low oxygen levels, low blood pressure, the use of muscle relaxants, and surgical complications, can also be considered [3], as well as metabolic factors such as acidosis, hypothermia, central anticholinergic syndrome and hepatic and renal failure [3]. The following factors represent potential contributors to delayed emergence after general anesthesia [16, 17]:

- Old age (year) >64
- Body Mass Index (kg/m^2) ≥ 25
- Being diploma of anesthesia provider

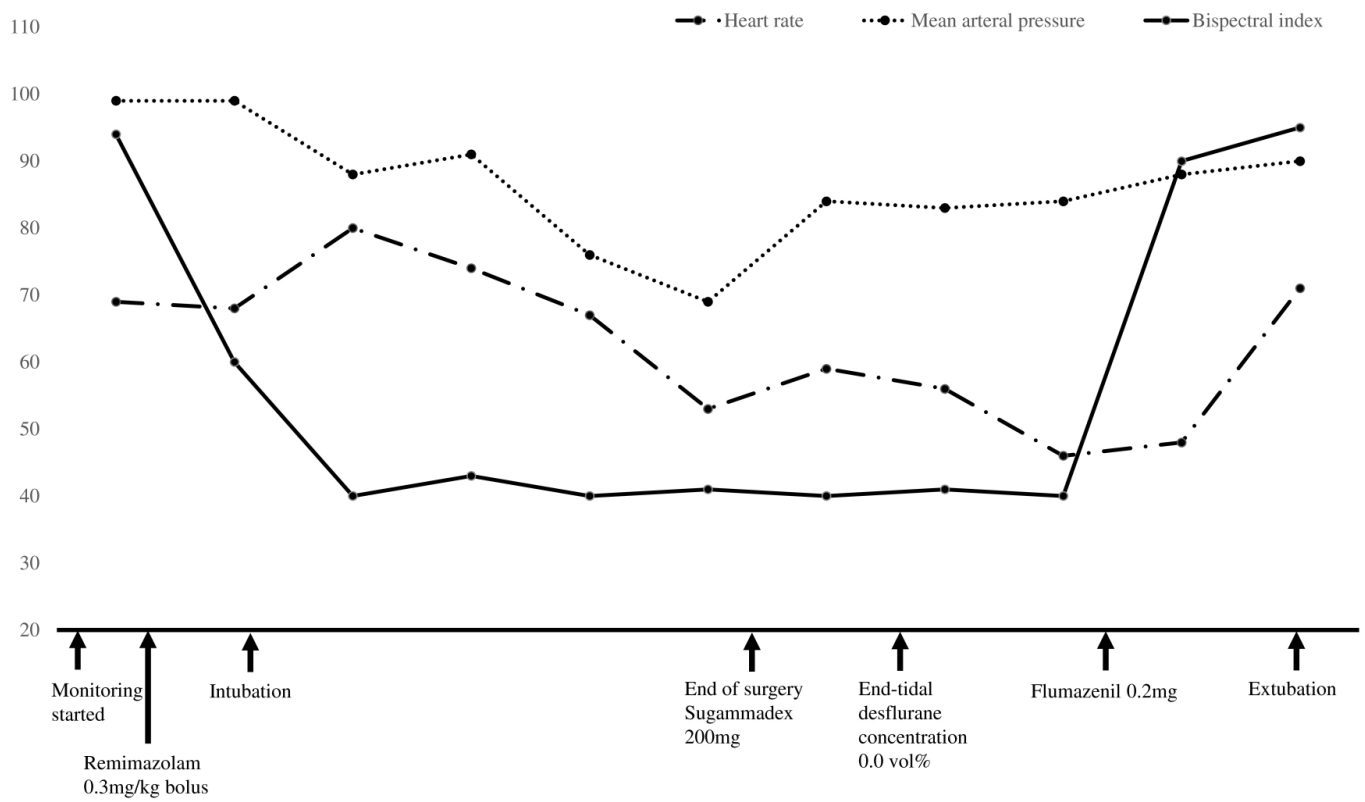

FIGURE 1. Graph of vital signs according to timeline.

- Metabolic equivalents of task <4
- Use of Intraoperative strong opioids
- Intraoperative hypotension
- Surgical time (min) >120
- Duration of anesthesia (min) ≥230
- Estimated blood loss (mL) >1500
- Intraoperative flued used (mL) >3000
- Preoperative fasting time (hour) >12

In our present case, none of the mentioned risk factors in the table were applicable, except for the use of opioids. Notably, the surgical procedure was of short duration, and the patient's vital signs remained stable throughout the surgery. Therefore, we focused on investigating drug-related factors among the various possibilities mentioned earlier. Initially, we examined the impact of desflurane, but this factor was ruled out since the exhaled gas concentration reached 0 vol% within just 10 minutes after the surgery. Next, they considered the possibility of residual opioid effects due to the use of sufentanil. However, we excluded this factor because the patient did not exhibit pinpoint pupils, and the administered sufentanil dose was relatively low. Our third suspicion was residual muscle relaxation, but in this patient's case, sugammadex had been administered, and the train-of-four (TOF) ratio had already recovered to a level above 90%, eliminating this as a contributing factor. Finally, to eliminate the potential influence of remimazolam used during induction, we administered flumazenil. Shortly after receiving flumazenil, the patient's BIS value increased to 90, and he rapidly regained consciousness.

The choice of sedatives is based on various criteria, and the recently introduced remimazolam is becoming a preferred choice among anesthesiologists for several compelling reasons. In the case of this patient, who had a history of heart disease, blood tests revealed no significant abnormalities. However, due to the patient's lower-than-normal cardiac output (Ejection Fraction = 40.9%) and the presence of atrial fibrillation, there were concerns regarding the possibility of hypotension following the induction of general anesthesia. Consequently, the decision was made to utilize remimazolam as the anesthetic induction agent instead of propofol [18]. Furthermore, for effective postoperative pain control, a target-controlled infusion of sufentanil was administered during anesthesia induction instead of remifentanil, as pain following surgery could worsen atrial fibrillation [19].

For this patient, we opted for remimazolam as the anesthetic induction agent because of its favorable characteristics, such as quick onset and offset of action, as well as minimal impact on blood pressure and heart rate. Typically, a continuous infusion concentration of 6–12 mg/kg/h is recommended for anesthesia induction [20]. However, for practical reasons, various studies have explored the effectiveness and safety of using single bolus dose [9, 18, 21, 22]. A dose of 0.3 mg/kg has been found to induce loss of consciousness during anesthesia induction in a similar time frame to propofol without causing significant changes in blood pressure or heart rate [9, 21]. In previous research involving remimazolam, the time it took for patients to fully recover varied, ranging from approximately 12.3 to 31.5 minutes, depending on the study and the dosage used [2, 23, 24]. In our reported case, the patient experienced delayed emergence from anesthesia despite receiving only a 0.3 mg/kg bolus dose for anesthesia induction without additional

maintenance doses.

Some studies have documented instances of re-sedation after the administration of flumazenil, suggesting that the duration of remimazolam's effects may surpass the effects of flumazenil [10, 12]. For instance, in a case described by Takemori *et al.* [10], a patient who underwent radical prostatectomy and was given remimazolam for general anesthesia experienced re-sedation that persisted for nearly 12 hours after the surgery. While the availability of the antagonist flumazenil is a notable advantage of remimazolam, the possibility of re-sedation underscores the importance of remaining vigilant and continuously monitoring patients when delayed emergence is observed. In such situations, it is crucial to maintain awareness of this potential issue and to conduct ongoing observation.

The exact reasons for the delayed effects of remimazolam remain unclear, but several possibilities can be considered. Firstly, an overdose of remimazolam might be a factor, although in this case, remimazolam was administered as a bolus during induction, not as an infusion, and the dosage of 0.3 mg/kg used was not indicative of an overdose. Overdose typically results in lower BIS readings, but in this present case, the BIS values were consistently maintained between 40–60. Secondly, the impact of remimazolam on drug metabolism may play a role. Studies [25, 26] have suggested that variations among individuals, either due to genetic differences or interactions with other drugs, could lead to differences in the efficiency of hydrolysis by carboxylesterase, the enzyme responsible for metabolizing remimazolam. Similar to findings that show carbamazepine can inhibit carboxylesterase [27], in this case, the patient's concurrent use of carbamazepine for trigeminal neuralgia might have potentially inhibited carboxylesterase, resulting in a potential delay in remimazolam metabolism. Lastly, the patient's underlying medical condition could also influence remimazolam metabolism. Our patient had signs of congestive heart failure, which could have led to a delay in drug metabolism due to decreased cardiac output resulting from heart failure. Although severe liver dysfunction was not evident in this patient, it has been reported that in individuals with significant liver impairment, the metabolism of remimazolam could be delayed [8].

Taken together, potential factors for this present case could include drug interactions between the patient's medications and remimazolam, individual variability in the efficiency of carboxylesterase-mediated hydrolysis, or a delay in drug metabolism attributable to the underlying congestive heart failure. Despite numerous studies on delayed emergence in general anesthesia, this phenomenon continues to pose a substantial challenge for anesthesiologists in the field of anesthesia and pain medicine, thereby urging the need for further research to explore the underlying mechanisms associated with delayed emergence in patients receiving remimazolam.

4. Conclusions

Remimazolam, a sedative preferred by anesthesiologists in recent pain management practices, is recognized for its rapid onset, short duration, and minimal side effects such as injection pain and respiratory and cardiovascular suppression. However, caution should be exercised due to potential risks associated with overdose, patient enzymatic issues or delayed metabolism due to drug interaction or underlying medical issues. Additionally, in situations where a patient experiences delayed recovery following general anesthesia involving remimazolam, it should raise suspicion of a possible connection with the drug. Further research is necessary to uncover the underlying causes of delayed metabolism.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

MKK and EJA—designed the study. EJA, CSP and JJL—contributed to manuscript writing and data collection. MKK—contributed to editing and supervision of this work. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study has been approved by the Institutional Review Board of Gwang-Myung Chung-Ang University Hospital (IRB number: 2308-104-088). Written informed consent was waived 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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