



Inadequate Efficacy of Remimazolam in Chinese Female Patients without Preoperative Benzodiazepine Exposure: A Report of Two Cases

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Remimazolam, a gamma-aminobutyric acid subtype A receptor agonist, serves as a benzodiazepine (BZD) anesthetic in monitored anesthesia care and general anesthesia. We present two cases in which patients not receiving regular BZD therapy maintained consciousness following the administration of remimazolam during monitored anesthesia care. Subsequent transition to propofol infusion successfully achieved adequate sedation. Our experience indicates that remimazolam efficacy may be influenced by factors other than prior BZD use. Variables, such as age, sex, and race, remain unclear in their impact. Alternative agents, such as propofol and ketamine, should be considered when remimazolam fails to achieve adequate sedation.

Key words: Remimazolam, benzodiazepine, monitored anesthesia care, inadequate efficacy, propofol

INTRODUCTION

Remimazolam, an ultrashort-acting benzodiazepine (BZD) gamma-aminobutyric acid subtype A (GABA_A) receptor agonist, is used for general anesthesia or monitored anesthesia care (MAC) due to its minimal cardiac and respiratory impact and available antagonists.¹ However, BZDs tolerance or inadequate response can be challenging. Previous reports documented four Japanese patients on long-term BZDs and one Chinese female without medication experiencing insufficient response to remimazolam.^{2,3} Here, we present the cases of two Chinese females without preoperative BZDs showing inadequate efficacy with remimazolam during MAC.

CASE REPORT

Case 1

A 76-year-old woman (height 138.5 cm, weight 48.1 kg, body mass index (BMI) 25.08 kg/m², adjusted body weight (ABW) 47 kg) was scheduled for left infraclavicular venous port implantation for rectosigmoid cancer therapy.

She reported no other systemic disease, regular medication, or anesthesia history. In the operating room, MAC with fentanyl 1.0 µg/kg (based on total body weight) and remimazolam 0.1 mg/kg (based on ABW) were administered for induction. The bispectral index (BIS) was 76, and the Observer Assessment of Alertness/Sedation Scale (OAA/S) was 5. Therefore, another dose of remimazolam 0.05 mg/kg (based on ABW) was given. A continuous infusion of remimazolam 0.3 mg/kg/h (based on ABW) was maintained. After 50 min, the patient remained awake (OAA/S five) with BIS in the 70s, and the total dose of remimazolam administered was 20 mg. Therefore, anesthesia with remimazolam was switched to propofol with a target-controlled infusion (TCI) machine at an effect-site concentration (Ce) of 1.0 µg/mL based on the Schneider model. The patient achieved a sedated state (OAA/S three), with the BIS value ranging between 40 and 65. At the end of the surgery, propofol infusion was discontinued, and the patient regained consciousness. Her anesthesia records are shown in Figure 1.

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Case 2

An 18-year-old girl (height 165 cm, weight 85 kg, BMI 31.22 kg/m², ABW 68 kg) was scheduled for Bartholin's cyst excision. She reported no systemic disease or anesthesia history. In the operating room, MAC was initiated with fentanyl 0.5 µg/kg (based on total body weight) and remimazolam 0.08 mg/kg (based on ABW) for induction. A continuous infusion of remimazolam 0.4 mg/kg/h (based on ABW) was maintained. However, within the next 10 min, due to inadequate sedation, two additional boluses of remimazolam at 0.08 mg/kg were administered at a 3-min interval. The total dosage of remimazolam reached 20 mg, and the patient's sedation level was maintained at OAA/S four. Therefore, MAC with remimazolam was switched to a TCI of propofol at Ce of 1.5 µg/mL, based on the Schneider model. The patient was then sedated, and propofol was maintained at Ce of 3.5 µg/mL. The surgery proceeded, and the patient spontaneously awoke at the end of the procedure. Her anesthesia records are shown in Figure 2.

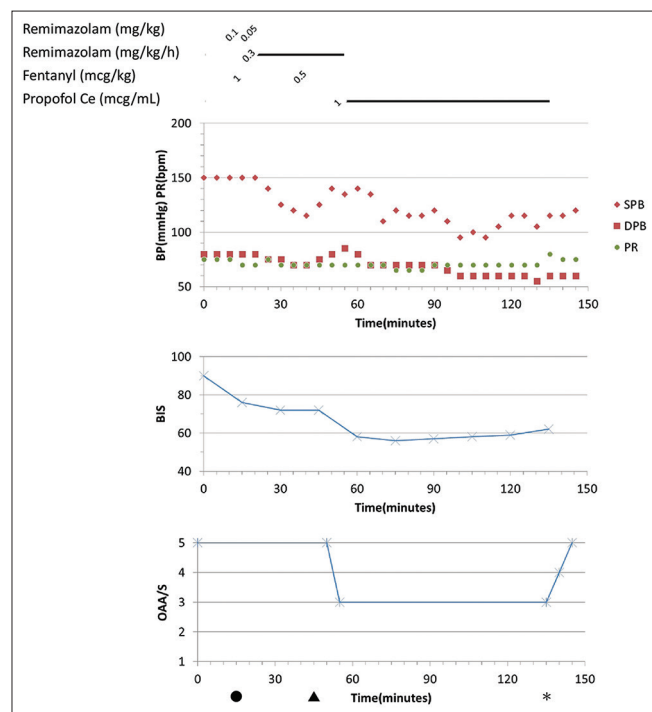


Figure 1: Anesthesia record of case 1. Hemodynamic parameters remained stable. Bispectral index (BIS) levels were sustained in the 70s, and the Observer Assessment of Alertness/Sedation Scale (OAA/S) remained at five following the administration of remimazolam. Subsequent propofol administration led to a swift reduction in both BIS and OAA/S. Ce: Effect site concentration, BP: Blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PR: Pulse rate, BIS: Bispectral index, OAA/S: Observer Assessment of Alertness/Sedation Scale. Circle sign: The start of anesthesia. Triangle sign: The start of the operation. Asterisk: The end of anesthesia and the operation. The time on the horizontal axis is the elapsed time of monitored anesthesia care in minutes

DISCUSSION

Remimazolam is known for its hemodynamic and respiratory stability during general anesthesia or MAC.¹ A case report by Lin *et al.* described the use of remimazolam combined with remifentanyl for procedural sedation during gastrointestinal endoscopy in a patient with morbid obesity and severe obstructive sleep apnea. The patient experienced no respiratory depression or hypotension.⁴

Reports of four Japanese patients on long-term BZDs indicated tolerance or inadequate response to remimazolam, and this could explain the poor efficacy of remimazolam.^{2,3} A similar case of a Chinese female without prior medical conditions was documented.³ We present the case reports of two more Chinese females with inadequate remimazolam efficacy, both without preoperative BZDs exposure, which may have shown an unexpected response due to individual differences or other underlying factors. This suggests that the effectiveness of remimazolam may vary depending on a patient's medication history and physiological characteristics. In case 1, adequate sedation was not achieved despite administering fentanyl, two boluses of remimazolam (0.1 and 0.05 mg/kg), and a continuous infusion at 0.3 mg/kg/h, totaling 20 mg. Similarly, in case 2, fentanyl with three boluses of remimazolam (0.08 mg/kg) and a continuous infusion at 0.4 mg/kg/h, totaling 20 mg, provided

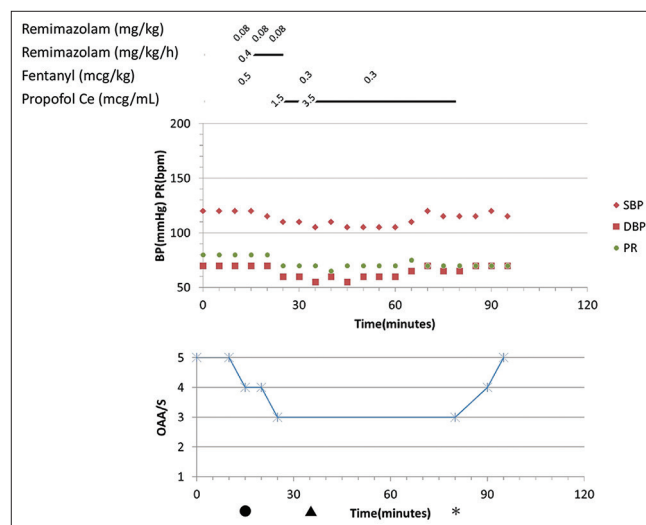


Figure 2: Anesthesia record of case 2. Hemodynamic parameters remained consistently stable. After remimazolam administration, the Observer Assessment of Alertness/Sedation Scale (OAA/S) was maintained at four. Subsequent propofol administration resulted in a further reduction in OAA/S. Ce: Effect site concentration, BP: Blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PR: Pulse rate, OAA/S: Observer Assessment of Alertness/Sedation Scale. Circle sign: The start of anesthesia. Triangle sign: The start of the operation. Asterisk: The end of anesthesia and the operation. The time on the horizontal axis is the elapsed time of monitored anesthesia care in minutes

insufficient sedation. Our targets for adequate sedation during monitored anesthesia care were a score of $\leq$ three on the OAA/S scale or the BIS value ranging between 40 and 70, and ensuring the patient remained motionless. Both patients achieved sedation after transitioning to propofol.

Cheng *et al.*⁵ reported variable individual responses to midazolam sedation, potentially influenced by GABA_A receptor complex heterogeneity, age, concurrent diseases and medications, liver and renal disease, overall health status, alcohol use, smoking, and hormonal status. Therefore, the effects of remimazolam may vary depending on different patient conditions. A phase I study in Chinese volunteers showed the sedative effects of remimazolam at 0.05 mg/kg, with deeper sedation at $\geq$ 0.075 mg/kg within 1–2 min.⁶ Optimal doses proposed by Chae *et al.*⁷ were 0.25–0.33 mg/kg for patients under 40, 0.19–0.25 mg/kg for those aged 60–80, and 0.14–0.19 mg/kg for patients over 80. A randomized trial in the Chinese population demonstrated that 0.2 mg/kg remimazolam was noninferior to 1.5 mg/kg propofol for gastroscopy sedation.⁸ Lu *et al.*⁹ recommended a 12 mg loading dose for painless colonoscopy, showing effective and rapid sedation. In ASA III/IV patients undergoing colonoscopy, the average remimazolam dose was 9.03 mg, and adverse events were comparable to placebo and midazolam groups.¹⁰ In studies with hepatically and renally impaired subjects, 0.1 mg/kg remimazolam caused sedation in 77.8% of healthy controls, 75% of moderately hepatically impaired, and 100% of severely hepatically impaired patients, while the renal impairment trial did not assess sedation due to lower doses.¹¹ Chen *et al.*¹² reported that intensive care unit patients on mechanical ventilation achieved satisfactory sedation with remimazolam 0.02–0.05 mg/kg loading followed by 0.20–0.35 mg/kg/h maintenance, with good respiratory and hemodynamic stability. In a transcatheter aortic valve replacement trial, remimazolam (12 mg/kg/min) anesthesia showed a lower incidence of hypotension and reduced ephedrine use compared to propofol.¹³ A study on septic shock patients demonstrated effective intraoperative sedation with remimazolam doses of 0.2–0.4 mg/kg, with stronger sedation at higher doses and dose-dependent postoperative recovery of hepatic and renal function.¹⁴ The two patients in our cases are relatively healthy, and more required remimazolam is expected. Our first patient, a 76-year-old, received 20 mg (0.4 mg/kg) of remimazolam with an opioid, while the second, an 18-year-old with a BMI of 31.22 kg/m², also received 20 mg (0.3 mg/kg based on ABW) with an opioid. Therefore, we consider the administered remimazolam dosages to be sufficient for achieving sedation.

Kitaura *et al.*² reported inadequate responses to remimazolam in two Japanese patients undergoing MAC with long-term BZD use. The first, an 82-year-old man, remained awake despite

receiving 0.1 mg/kg remimazolam followed by 1 mg/kg/h and three additional doses of 0.05 mg/kg, necessitating a switch to propofol. The second, an 89-year-old woman, required high doses of remimazolam (induced with 12 mg/kg/h, maintained with 1 mg/kg/h) to achieve sedation but showed multiple signs of arousal intraoperatively. Miyanishi *et al.*³ reported remimazolam tolerance during general anesthesia induction in two Japanese females (45 and 46 years old) using preoperative BZD, with a total remimazolam dose of 50 mg in the first case and the maximum dose rate of 2 mg/kg/h in the second case. They also noted insufficient sedation with remimazolam at 2 mg/kg/h during general anesthesia in a 44-year-old Chinese female without prior medical conditions or medication. They proposed that factors such as body movements, vital signs changes, regular medications, and race should be considered when estimating anesthesia depth with remimazolam. Miyanishi *et al.*³ proposed that racial factors influencing drug efficacy include genetic polymorphisms of drug-metabolizing enzymes, receptor sensitivity, pharmacokinetics, and medical practices. The impact of racial differences on these factors remains unknown for remimazolam. In previous studies,^{7,8,12–14} the sedation effect of remimazolam did not differ by gender. However, further research is warranted to confirm these findings. Propofol and ketamine may provide adequate sedation in patients insufficiently sedated with remimazolam, as propofol targets multiple sites, including the N-methyl-D-aspartate receptor,¹⁵ and ketamine acts as an N-methyl-D-aspartate receptor antagonist.

Besides prior BZD use and medical history, additional factors, including age, sex, and race, may potentially influence the effect of remimazolam, warranting further investigation. Diligent intraoperative sedation monitoring is crucial. Alternatives, such as propofol and ketamine, should be considered if remimazolam shows inadequate effects.

CONCLUSION

Remimazolam may show insufficient sedation in Chinese females without preoperative BZD use. Close sedation monitoring is essential for MAC or general anesthesia. Propofol and ketamine may be safer alternatives if remimazolam yields insufficient sedation.

Data availability statement

The data that support the findings of this study are available from the corresponding author, ZF Wu, upon reasonable request.

Declaration of patient consent

The authors certify that they have obtained all appropriate

patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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