Total intravenous anesthesia management with simultaneous use of remimazolam and propofol: A case series of three patients

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Abstract

Remimazolam is an ultra-short-acting benzodiazepine anesthetic agent. Because of pharmacodynamic interactions in the sedation effect between benzodiazepines and propofol, the combination of remimazolam and propofol may allow for a dose reduction of each agent while providing effective sedation for general anesthesia. We experienced three cases in which general anesthesia was induced with remimazolam and maintained with relatively small doses of remimazolam and propofol target-controlled infusion. In all cases, electroencephalogram changes associated with sedation induced by remimazolam were carefully observed during anesthesia induction before administration of propofol. The time required for recovery from anesthesia was 8–13 min. This is the first report in which remimazolam and propofol were concomitantly used for general anesthesia based on the concept of pharmacodynamic interaction. This anesthetic combination may be beneficial in reducing doses of each anesthetic and avoiding delayed recovery from anesthesia, although further study is needed to confirm this.

Introduction

In 2020, remimazolam, an ultra-short-acting benzodiazepine anesthetic agent, was launched in Japan. Immediately after that, the use of remimazolam was restricted due to a series of shipment adjustments associated with quality control. In addition, remimazolam and propofol were also in short supply due to the COVID-19 pandemic. Thus, we need to reduce the consumption of these anesthetics.

Modern general anesthesia is predominantly a balanced anesthesia approach using sedatives, analgesics, and muscle relaxants to achieve each of the three components of sedation, analgesia, and immobilization, respectively. When considering the sedative effects of anesthesia maintenance, inhaled anesthetics, propofol, or benzodiazepines such as midazolam are often used alone. However, combinations of multiple sedatives may be used to achieve sedation. For example, the combination of propofol and sevoflurane has been shown to exhibit additive interactions in loss of consciousness (LOC) and bispectral index.[1,2] This combination of anesthetic techniques is used clinically as a feasible alternative to propofol-based total intravenous anesthesia.[3,4] Such an approach utilizing drug interaction reduces both the amount of each drug used and their side effects, compared to single drug use.

Also, due to pharmacodynamic interactions in the sedation effect between benzodiazepines and propofol,[5–8] the combination of remimazolam and propofol may allow for a dose reduction of each agent while providing adequate sedation for general anesthesia maintenance.

In this case series, we report three cases in which anesthesia was induced with remimazolam and maintained with remimazolam and propofol while referring to patient state index (PSI) and raw electroencephalogram (EEG) obtained with a processed EEG monitor (SedLine® system, Masimo Corporation; Irvine, CA, USA). Written informed consent for publication was obtained from all patients.

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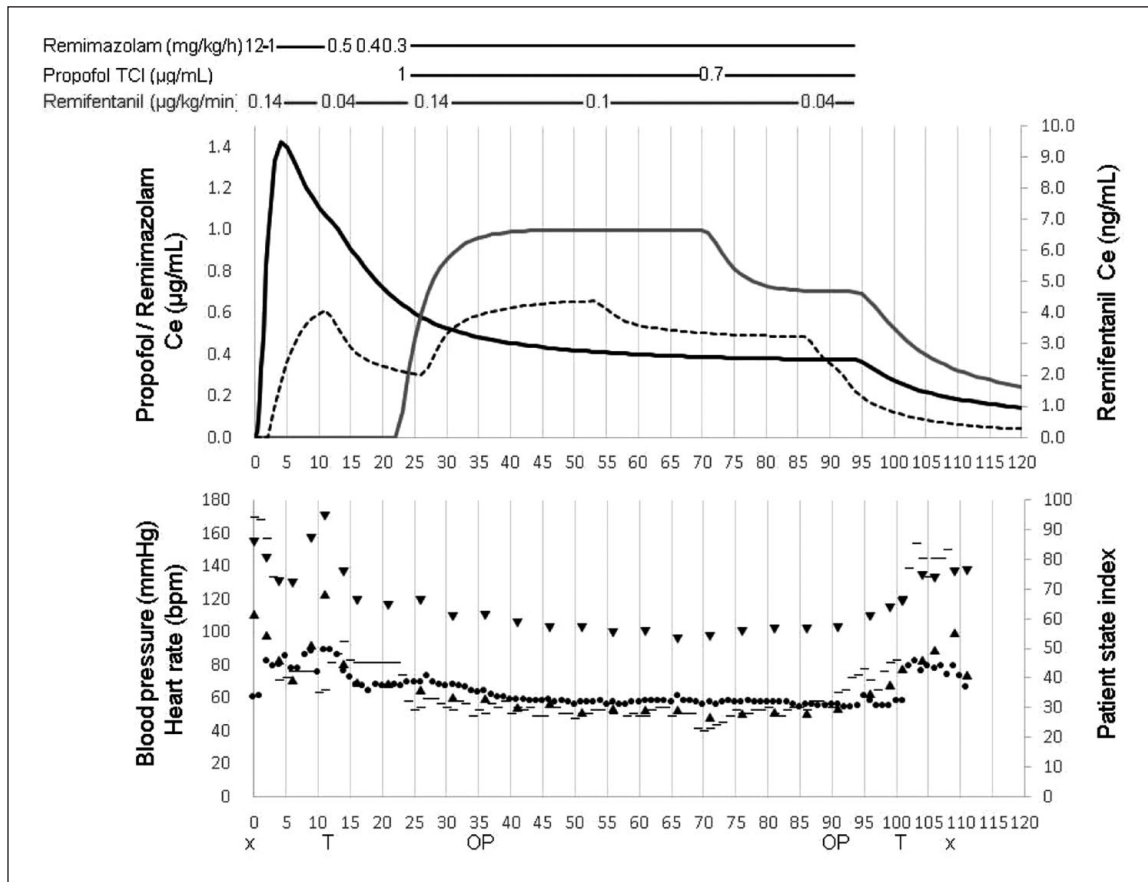Email: obashin99@gmail.com

Figure 1 Time courses of remimazolam effect-site concentration (RzCe, black curve), propofol effect-site concentration (PCe, grey curve), remifentanil effect-site concentration (RfCe, dotted curve), systolic blood pressure (▼), diastolic blood pressure (▲), heart rate (•), and patient state index (—) in Case 1. Fentanyl 100 μg was administered at time 2 min. To calculate RzCe, we converted the fentanyl effect-site concentrations simulated using the Shafer model[12] toremifentanil equivalents[13] using a remifentanil:fentanyl equivalency ratio of 1:1.
OP: start and end of surgery; T: tracheal intubation and extubation; X: start and end of anesthesia.

Case presentations

Case 1

The patient was a 40-year-old man (height 176 cm, weight 81 kg) undergoing skin graft surgery following ring finger amputation. He had no history of medication. After performing a brachial plexus block, general anesthesia was induced with remimazolam 12 mg/kg/h (Figure 1). The patient lost responsiveness to repeated verbal stimuli (i.e., Modified Observer's Assessment of Alertness and Sedation [MOAA/S][9] of <3), and his PSI value decreased from 95 to 39. After confirming MOAA/S <3 and spindle wave EEG (Figure 2), the remimazolam dose was lowered to 1 mg/kg/h, and remifentanil 0.14 μg/kg/min, fentanyl 100 μg, and rocuronium 50 mg were administered. After tracheal intubation, remifentanil was reduced to 0.04 μg/kg/min. The remimazolam dose was then gradually reduced to 0.3 mg/kg/h while confirming that an arousal tendency was not observed on EEG. After that, the remimazolam dose was fixed, and propofol target-controlled infusion (TCI) (1 μg/mL) was

started. The remifentanil dose and propofol target concentration were titrated according to the surgical stimulus and PSI values, respectively. The effect-site concentrations of remimazolam (RzCe) and propofol (PCe) during maintenance were stabilized at approximately 0.38 μg/mL (Masui model[10]) and 1 μg/mL (Diprifusor system[11]), respectively. PSI remained at around 30 during surgery. Surgical procedures were completed in 56 min. The patient spontaneously recovered consciousness and was extubated 8 min after the end of remimazolam and propofol administration. No postoperative nausea and vomiting (PONV), postoperative delirium (POD), or intraoperative awareness and recall (IAR) was reported. The patient was discharged from hospital without any complications 2 days postoperatively.

Case 2

The patient was a 67-year-old man (height 167 cm, weight 72 kg) undergoing robot-assisted total prostatectomy for prostate cancer. He had a history of controlled hypertension.
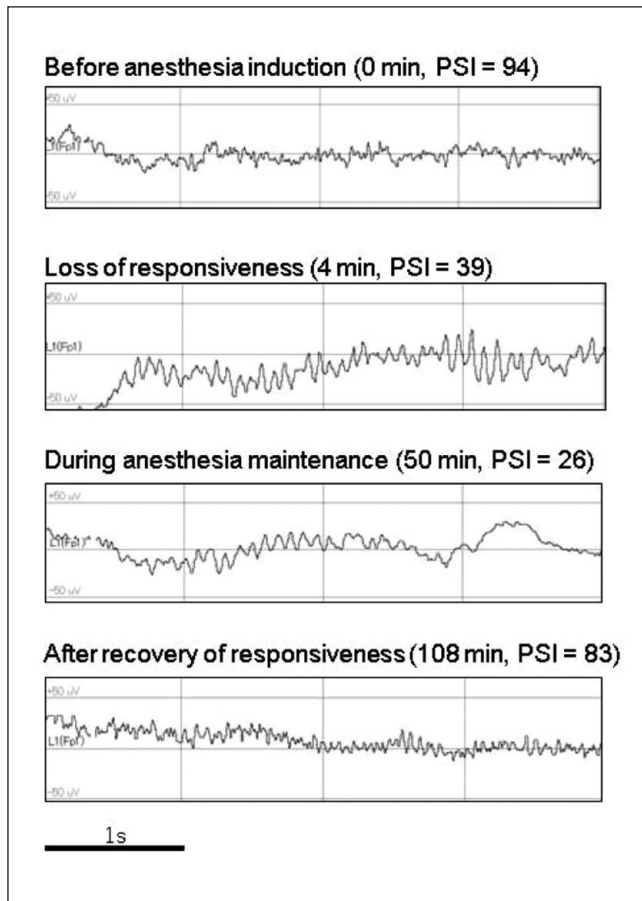
Figure 2. Raw electroencephalograms before anesthesia induction, after loss of responsiveness, during anesthesia maintenance, and after recovery of responsiveness (Case 2).

General anesthesia was induced with remimazolam 12 mg/kg/h (Figure 3) and his PSI value decreased from 95 to 42. After confirming MOAA/S <3 and spindle wave EEG, the remimazolam dose was lowered to 1 mg/kg/h, and remifentanil 0.12 µg/kg/min, fentanyl 100 µg, and rocuronium 50 mg were administered. After tracheal intubation, remifentanil was reduced to 0.05 µg/kg/min. Then, the remimazolam dose was gradually reduced to 0.3 mg/kg/h while confirming that an arousal tendency was not observed on EEG. After that, the remimazolam dose was fixed, and propofol TCI (1 µg/mL) was started. The remifentanil dose and propofol target concentration were titrated according to the surgical stimulus and PSI values, respectively. The RzCe and PCe during maintenance stabilized at approximately 0.34 and 1 µg/mL, respectively. PSI remained at 25–30 during surgery. Surgical procedures were completed in 277 min. The patient spontaneously recovered consciousness and was extubated 13 min after the end of remimazolam and propofol administration. No PONV, POD, or IAR was reported. The patient was discharged from hospital without any complications 10 days postoperatively.

Case 3

The patient was an 82-year-old woman (height 131 cm, weight 40 kg) undergoing molar extraction. She had a history of angina, which was treated by a coronary stent graft. General anesthesia was induced with remimazolam 12 mg/kg/h (Figure 4), and her PSI value decreased from 91 to 50. After confirming MOAA/S <3 and spindle wave EEG, the remimazolam dose was lowered to 1 mg/kg/h, and remifentanil 0.21 µg/kg/min, fentanyl 100 µg, and rocuronium 25 mg were administered. After tracheal intubation, remifentanil was reduced to 0.04 µg/kg/min. Then, the remimazolam dose was gradually reduced to 0.3 mg/kg/h while confirming that an arousal tendency was not observed on EEG. After that, the remimazolam dose was fixed, and propofol TCI (1 µg/mL) was started. The remifentanil dose was titrated according to the surgical stimulus. The RzCe and PCe during maintenance stabilized at approximately 0.29 and 1 µg/mL, respectively. PSI remained at 25–50 most of the time during surgery. Surgical procedures were completed in 70 min. The patient spontaneously recovered consciousness and was extubated 11 min after the end of remimazolam and propofol administration. Repeated bolus doses of ephedrine and phenylephrine were required (12 and 0.6 mg in total, respectively) to maintain blood pressure. No PONV, POD, or IAR was reported. The patient was discharged from hospital without any complications 3 days postoperatively.

Discussion

Remimazolam 50 mg (1 V) is generally diluted with 50 mL NS and administered using a syringe pump. Since the default maintenance dose is 1 mg/kg/h, the consumption of remimazolam tends to be generally high. Because the use of remimazolam was restricted as mentioned in the background section, we considered anesthesia methods with reduced maintenance doses of remimazolam and with propofol as an additional sedative, based on a multimodal anesthesia approach,[14] in which multiple anesthetics are used to maintain anesthesia. Many human studies on the combination of midazolam, typical benzodiazepine anesthetic, and propofol have shown synergistic effects.[5–8]

During general anesthesia, maintaining adequate sedation depth is critical to prevent IAR. It has been reported that some patients are resistant to the standard dose of remimazolam; thus, monitoring is required to confirm that the patient has been adequately sedated.[15–17] Regarding processed EEG monitoring during remimazolam use, a strong beta wave power at anesthesia induction[18] and a relatively high Bispectral index value during the anesthesia maintenance phase[19] are observed. In addition, typical EEG changes seen with propofol or inhalation anesthetics that have been used as de-facto standard anesthetics, including spindle wave EEG or decrease in PSI may not be observed, requiring careful interpretation. Therefore, in the present cases, general anesthesia
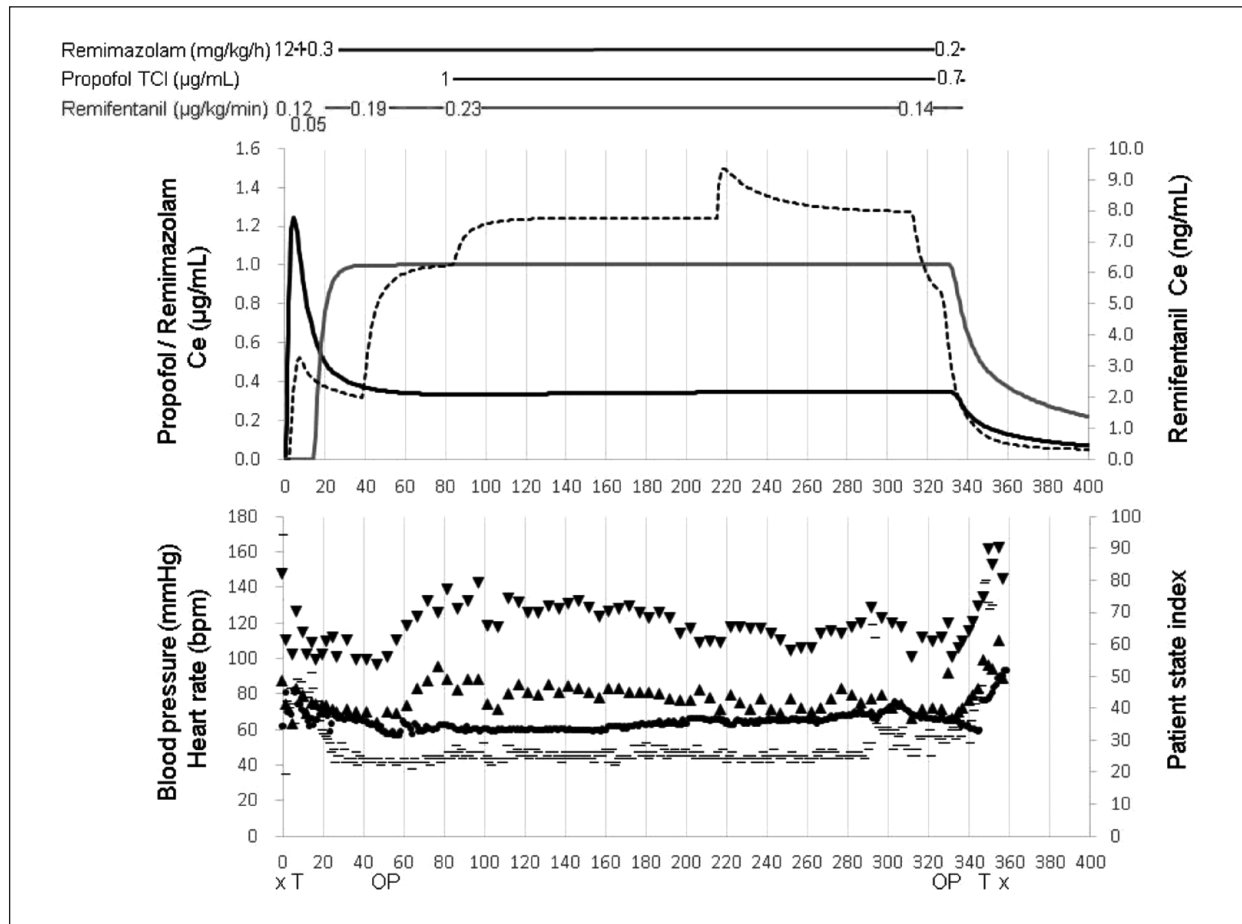
Figure 3. Time courses of remimazolam effect-site concentration (RzCe, black curve), propofol effect-site concentration (PCe, gray curve), remifentanil effect-site concentration (RfCe, dotted curve), systolic blood pressure (▼), diastolic blood pressure (▲), heart rate (●), and patient state index (–) in Case 2. Remimazolam dose was reduced from 1 to 0.5 mg/kg/h at 13 min, 0.5 to 0.4 mg/kg/h at 17 min, and 0.4 to 0.3 mg/kg/h at 21 min; not all of which are shown in the dosing history on the upper part of this graph. Fentanyl 100 μg was administered at times 2 min and 215 min. To calculate RzCe, we converted the fentanyl effect-site concentrations simulated using the Shafer model[12] to remifentanil equivalents[13] using a remifentanil:fentanyl equivalency ratio of 1:1.
OP: start and end of surgery; T: tracheal intubation and extubation; X: start and end of anesthesia.

was induced with remimazolam alone while confirming the loss of responsiveness of the patient as well as a decrease in EEG frequency and PSI values, as shown in Figure 2. If we were not sure of sedation on EEG, we would have discontinued the use of remimazolam and replaced the anesthesia method since the sedation state would have been difficult to interpret. Then, the remimazolam dose was lowered and fixed to a level that did not cause arousal. This titration was performed at the discretion of the attending anesthesiologist based on the PSI values and visual inspection of raw EEG. In terms of the PSI, Chae et al.[20] showed a definitive dose–response relationship for PSI and the probability of LOC. However, they also indicated that PSI does not seem to be a reliable surrogate of LOC under remimazolam bolus injection based on their data, where a lowered PSI did not guarantee LOC occurrence. Recently, Zhao et al.[21] revealed that PSI could predict a patient's state of consciousness under sedation using remimazolam tosylate, despite the wide variability in

the correlation between PSI and MOAA/S. Therefore, PSI value may be considered as one of the decision-making factors, along with raw EEG, vital signs, and patient response.

In the present cases, according to pharmacokinetic simulations, after fixing the remimazolam dose, RzCe decreased steeply, then declined gradually, and stabilized approximately in 1 h. In the present cases, the increase in PCe with propofol administration coincided with the decrease in RzCe. The additional dose of propofol may have contributed as a "safety margin" for sedation, in case the fixed amount of remimazolam was inadequate due to changes in the required depth of sedation. Recently, Masui et al. published a remimazolam PK model.[10,22] Therefore, real-time simulation to precisely estimate the decrease in RzCe after fixing the remimazolam dose would be possible in future cases.

High-dose opioids used concomitantly during anesthesia may decrease EEG frequency,[23] resulting in the overestimation of the sedative effect. In the present cases, during
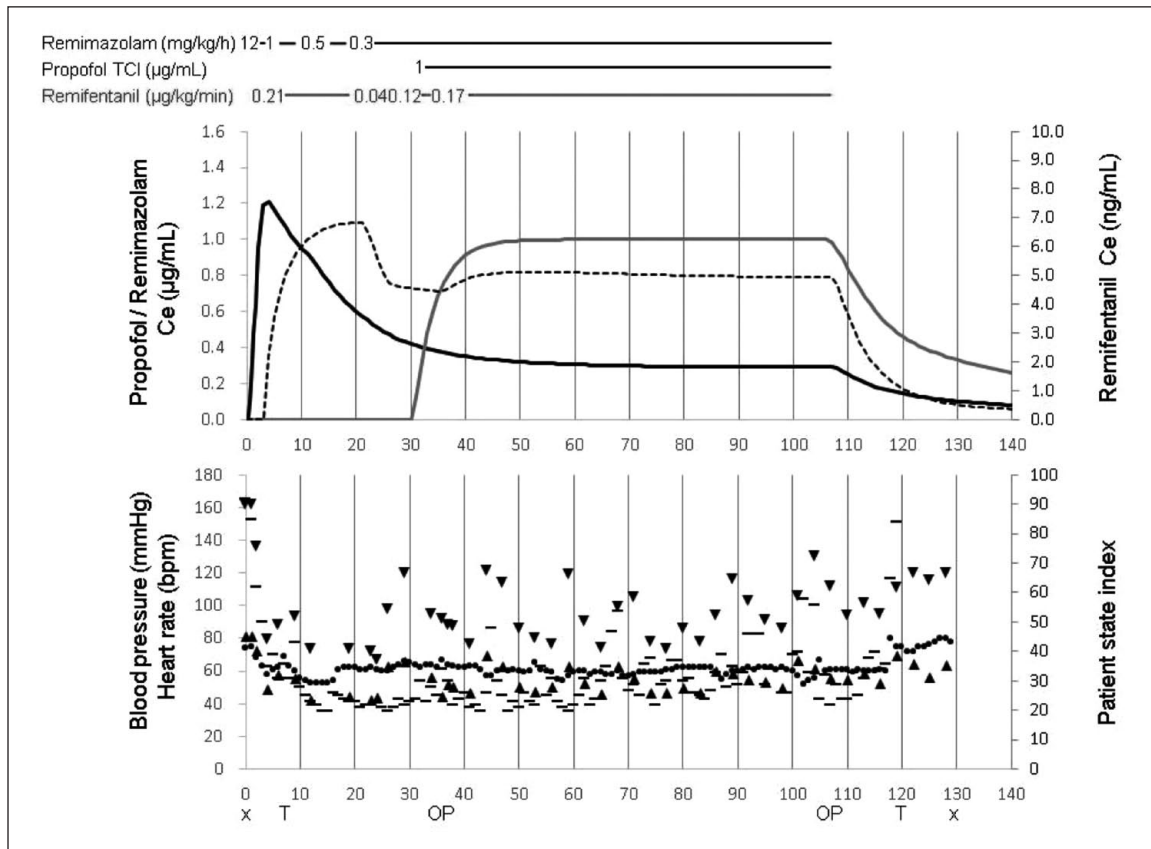
Figure 4. Time courses of remimazolam effect-site concentration (RzCe, black curve), propofol effect-site concentration (PCe, gray curve), remifentanil effect-site concentration (RfCe, dotted curve), systolic blood pressure (▼), diastolic blood pressure (▲), heart rate (•), and patient state index (–) in Case 3. Fentanyl 100 μg was administered for 3 min. To calculate RzCe, we converted the fentanyl effect-site concentrations simulated using the Shafer model[12] to remifentanil equivalents[13] using a remifentanil:fentanyl equivalency ratio of 1:1.

OP: start and end of surgery; T: tracheal intubation and extubation; X: start and end of anesthesia.

anesthesia induction, remifentanil was used for tracheal intubation, after which it was lowered to a dose that was not expected to affect EEG (i.e., remimazolam effect-site concentration of <6.2 ng/mL[23]). This contributed to accurately estimating the dose of remimazolam and propofol required to adequately sedate each patient before the surgical procedure, with reference to EEG unaffected by opioids.

Previous phase II/IIIb studies have reported a median remimazolam maintenance dose of 1 mg/kg/h when a sufficient amount of remifentanil for analgesia was administered.[24] The package insert for remimazolam also indicates that anesthesia maintenance should be started at 1 mg/kg/h then increased or decreased as needed and that the maximum maintenance dose is 2 mg/kg/h. The insert does not state a minimum dose. Clinically, pharmacokinetic or pharmacodynamic variabilities may lead to the possibility that the actual dose may be less than the starting dose (i.e., 1 mg/kg/h). Indeed, cases have been reported in which the minimum dose of remimazolam required during maintenance of anesthesia was 0.1–0.3 mg/kg/h.[25–28] In the present cases, after the remimazolam dose was lowered to 0.3 mg/kg/h and

maintained, the PSI value increased slightly. Therefore, the dose was not lowered any further, and propofol was additionally administered. Also, the attending anesthesiologists had background knowledge of pharmacokinetic/pharmacodynamic simulation that the resultant RzCe of 0.25 μg/mL corresponds to remimazolam 0.3 mg/kg/h, indicating that the probability of the MOAA/S ≤1 (i.e., equal or deeper than the level where a subject responds only after painful trapezius squeeze) is less than 5%,[29] which may have dictated clinical behavior. It is undeniable that remimazolam 0.3 mg/kg/h alone could have been maintained without the addition of propofol. In the present cases, propofol was added for the "safety margin" for the sedation, as mentioned earlier.

Soehle et al. demonstrated that, for the recommended ranges of the PSI (25–50), the corresponding PCe ranges between 1.2 and 2.6 μg/mL.[30] In the present cases, the target concentration for propofol was started at 1 μg/mL. This is a reasonable initial dose because a previous study[4] in which sevoflurane and propofol were concomitantly administered as sedatives used the same propofol target concentrations (i.e., 1 μg/mL). If sedation had been inadequate, the higher

PCe would have been targeted; however, this was unnecessary in all three of the present cases.

In the present cases, the doses of remimazolam (0.2–0.3 mg/kg/h) and PCe (1 µg/mL) were much smaller than their respective standard doses, which may be due to pharmacodynamic interaction between remimazolam and propofol. In the present cases, the combination of remimazolam 0.3 mg/kg/h propofol 1 µg/mL was sufficient to maintain anesthesia, but considering the pharmacokinetic/pharmacodynamic variability, this combination is unlikely to be appropriate for all patients. The authors aim for a concept report; the authors do not recommend this particular dose combination.

In addition, the time from discontinuation of remimazolam to eye-opening (8–13 min) in the present cases was shorter than the average of 14 min in nonelderly patients (age 64 years or younger) in a previous phase II study,[19] and flumazenil was unnecessary in all patients because of spontaneous recovery of consciousness. It was presumed that the sedative effect obtained by the interaction of remimazolam and propofol diminished more rapidly after administration than after the maintenance of anesthesia with remimazolam alone and the termination of administration. Future pharmacodynamic studies are required to demonstrate this quantitatively.

The use of local or regional anesthetics used for neuraxial blockade has been found to reduce the requirement of midazolam and propofol for general anesthesia,[31–34] probably by decreasing ascending sensory input into the brain. From this context, the requirement of each of the concomitantly used remimazolam and propofol may be reduced when regional anesthesia technique is additionally performed, although further study with larger populations is required.

To the best of our knowledge, this is the first report in which remimazolam and propofol were concomitantly used for general anesthesia based on their pharmacodynamic interaction. This anesthetic combination may be beneficial in reducing the doses of each anesthetic and avoiding delayed recovery from anesthesia, although further study is needed to confirm this.

Conclusions

We experienced three cases in which general anesthesia was induced with remimazolam and maintained with relatively small doses of remimazolam and propofol TCI. The time required for recovery from anesthesia was 8–13 min. This anesthetic combination may be beneficial for reducing doses of each anesthetic and avoiding delayed recovery from anesthesia, although further study is needed to confirm these findings.

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References

1. Schumacher PM, Dossche J, Mortier EP, et al. Response surface modeling of the interaction between propofol and sevoflurane. *Anesthesiology* 2009; 111: 790–804.
2. Diz JC, Del Río R, Lamas A, et al. Analysis of pharmacodynamic interaction of sevoflurane and propofol on Bispectral Index during general anaesthesia using a response surface model. *Br J Anaesth* 2010; 104: 733–739.

3. Wolf A, Selpien H, Haberl H, et al. Does a combined intra-venous-volatile anesthesia offer advantages compared to an intravenous or volatile anesthesia alone: a systematic review and meta-analysis. *BMC Anesth* 2021; 21: 52.

4. Hensel M, Fisch S, Kerner T, et al. Combined use of inhalation anaesthetics and propofol for maintenance of general anaesthesia [Gibt es eine Rationale für die kombinierte Anwendung von volatilen Anästhetika und Propofol zur Aufrechterhaltung der Narkose?]. *Anasthesiol Intens* 2019; 60: 45–55.

5. Hendrickx JF, Eger EI 2nd, Sonner JM, et al. Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. *Anesth Analg* 2008; 107: 494–506.

6. Minto CF, Schnider TW, Short TG, et al. Response surface model for anesthetic drug interactions. *Anesthesiology* 2000; 92: 1603–1616.

7. Short TG and Chui PT. Propofol and midazolam act synergistically in combination. *Br J Anaesth* 1991; 67: 539–545.

8. Vinik HR, Bradley EL Jr. and Kissin I. Triple anesthetic combination: propofol-midazolam-alfentanil. *Anesth Analg* 1994; 78: 354–358.

9. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. *J Clin Psychopharmacol* 1990; 10: 244–251.

10. Masui K, Stöhr T, Pesic M, et al. A population pharmacokinetic model of remimazolam for general anesthesia and consideration of remimazolam dose in clinical practice. *J Anesth* 2022; 36: 493–505.

11. Glen JB and Servin F. Evaluation of the predictive performance of four pharmacokinetic models for propofol. *Br J Anaesth* 2009; 102: 626–632.

12. Shafer SL, Varvel JR, Aziz N, et al. Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. *Anesthesiology* 1990; 73: 1091–1102.

13. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; 86: 10–23.

14. Egan TD and Svensen CH. Multimodal general anesthesia: a principled approach to producing the drug-induced, reversible coma of anesthesia. *Anesth Analg* 2018; 127: 1104–1106.

15. Yoshikawa H, Hosokawa M, Kashima Y, et al. Remimazolam tolerance in long-term benzodiazepine users: a case report of 2 cases. *A&A Pract* 2021; 15: e01460.

16. Kida K, Taguchi M, Uchiyama K, et al. Tolerance to remimazolam at a high effect-site concentration. *J Anesth* 2023; 37: 168–169.

17. Miyanishi M, Yaguramaki T, Maehara Y, et al. Three cases of difficulty in achieving definitive loss of consciousness with remimazolam. *JA Clin Rep* 2022; 8: 4.

18. Eisenried A, Schüttler J, Lerch M, et al. Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers: Part II. Pharmacodynamics of electroencephalogram effects. *Anesthesiology* 2020; 132: 652–666.

19. Doi M. Remimazolam. *JJSCA (Japanese manuscript with English abstract)* 2014; 34: 860–866.

20. Chae D, Kim H-C, Song Y, et al. Pharmacodynamic analysis of intravenous bolus remimazolam for loss of consciousness in patients undergoing general anaesthesia: a randomised, prospective, double-blind study. *Br J Anaesth* 2022; 129: 49–57.

21. Zhao TY, Chen D, Xu ZX, et al. Comparison of bispectral index and patient state index as measures of sedation depth during surgeries using remimazolam tosilate. *BMC Anesth* 2023; 23: 208.

22. Masui K and Hagihira S. Equilibration rate constant, k(e0), to determine effect-site concentration for the Masui remimazolam population pharmacokinetic model in general anesthesia patients. *J Anesth* 2022; 36: 757–762.

23. Abad-Torrent A, Martínez-Vázquez P, Somma J, et al. Remifentanil pharmacodynamics during conscious sedation using algometry: a more clinically relevant pharmacodynamical model. *Br J Anaesth* 2022; 129: 868–878.

24. Doi M, Morita K, Takeda J, et al. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. *J Anesth* 2020; 34: 543–553.

25. Kido T, Suzuki Y and Nishida K. General anesthesia with remimazolam and peripheral nerve blocks is useful for femoral surgery in patients with severe aortic stenosis: a case report. *A&A Pract* 2023; 17: e01702.

26. Aoki Y, Ida M, Takatani T, et al. Motor-evoked potentials monitoring with remimazolam during thoracic descending aortic aneurysm surgery: a case report. *J Anesth* 2023; 37: 315–318.

27. Ito H, Kameyama A, Furuta M, et al. Anesthetic management using remimazolam for transcatheter edge-to-edge repair of the mitral valve in patients with reduced ejection fraction: a case report of two cases. *Cureus* 2022; 14: e30706.

28. Satoh T, Nishihara N, Sawashita Y, et al. Remimazolam anesthesia for mitraclip implantation in a patient with advanced heart failure. *Case Rep Anesth* 2021; 2021: 5536442.

29. Obara S. Simulation of residual sedation effect of remimazolam: pharmacokinetic-pharmacodynamic simulation can be an additional standard anesthesia monitoring method. *J Anesth* 2022; 36: 167–170.

30. Soehle M, Kuech M, Grube M, et al. Patient state index vs bispectral index as measures of the electroencephalographic effects of propofol. *Br J Anaesth* 2010; 105: 172–178.

31. Ingelmo PM, Ferri F and Fumagalli R. Interactions between general and regional anesthesia. *Minerva Anestesiol* 2006; 72: 437–445.

32. Tverskoy M, Shifrin V, Finger J, et al. Effect of epidural bupivacaine block on midazolam hypnotic requirements. *Reg Anesth* 1996; 21: 209–213.

33. Agarwal A, Pandey R, Dhiraaj S, et al. The effect of epidural bupivacaine on induction and maintenance doses of propofol (evaluated by bispectral index) and maintenance doses of fentanyl and vecuronium. *Anesth Analg* 2004; 99: 1684–1688.

34. Senturk M, Pembeci K, Menda F, et al. Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by bispectral index. *Br J Anaesth* 2002; 89: 849–852.