Anesthetic Management Using Remimazolam in a Hemodialysis Patient

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Remimazolam, an ultra-short-acting benzodiazepine, is a new intravenous anesthetic used for sedation and general anesthesia. Because remimazolam is primarily metabolized by carboxylesterases in the liver and other tissues including the lung and has metabolites with little or no bioactivity, its anesthetic effect is not significantly influenced by renal dysfunction. Therefore, remimazolam may be considered an appropriate agent for hemodialysis patients and may have added benefits beyond midazolam and propofol. Remimazolam has also been suggested to cause less cardiac depression than propofol. This case report presents an 82-year-old female hemodialysis patient with chronic heart failure who underwent partial glossectomy for squamous cell carcinoma of the tongue under general anesthesia with remimazolam and remifentanil. Hemodynamic control was stable during the anesthetic, which was safely completed without any adverse events and resulted in a rapid, clear emergence without flumazenil. Remimazolam and remifentanil may be appropriate as first-line general anesthetic agents for hemodialysis patients with heart failure.

Key Words: Remimazolam; Anesthetic management; General anesthesia; Hemodialysis; Heart failure; Oral surgery; Remifentanil.

INTRODUCTION

Remimazolam, an ultra-short-acting benzodiazepine, was developed as a new intravenous (IV) agent for general anesthesia and sedation. It is rapidly metabolized by carboxylesterases (CES) in the liver and other tissues including the lung. Combined with its rapid onset, remimazolam's unique metabolism facilitates easy and accurate titration, quick recovery, and few adverse events.[1] In recent clinical trials, the pharmacokinetics and pharmacodynamics, efficacy, and safety of remimazolam were evaluated in patients undergoing general anesthesia, demonstrating its usefulness as an IV anesthetic.[2–4] Remimazolam was approved in Japan for use via continuous IV infusion for general anesthesia in adult patients in 2020.[5]

Because remimazolam's metabolism is independent of organ (i.e., renal) function, it may be considered an appropriate agent for the anesthetic management of hemodialysis patients and may have added benefits beyond other IV anesthetics like midazolam and propofol. However, to our knowledge, there has been no report on general anesthesia using remimazolam in hemodialysis patients with heart failure. This case report presents the successful use of remimazolam for general anesthesia in a hemodialysis patient with a history of chronic heart failure undergoing oral surgery. Written informed consent was obtained from the patient for this report.

CASE PRESENTATION

An 82-year-old female (height, 147 cm; weight, 42.9 kg; body mass index, 19.85 kg/m^2) was scheduled to undergo partial glossectomy for T1N0M0 squamous cell carcinoma (SCC) of the tongue. The patient had hypertension, history of stroke, and end-stage kidney disease for which she had been undergoing hemodialysis for 4 years. In addition, she had a history of acute heart

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Table 1. Patient's Echocardiographic Data.

	Patient's values	*Abnormal cutoff values*[6]
Left ventricular ejection fraction, %	70	<50
Septal e′, cm/s	5.0*	<7.0
Lateral e′, cm/s	7.7*	<10.0
Septal E/e′	26.4*	>15.0
Mitral regurgitation (MR)	mild	
Aortic regurgitation (AR)	mild	
Tricuspid regurgitation (TR)	mild	
Peak velocity of TR, m/s	2.7	>2.8
TR pressure gradient (TRPG), mm Hg	30	>40

Echocardiography demonstrated preserved left ventricular function and diastolic dysfunction, although there were no congestive findings. The patient appeared to have had chronic diastolic heart failure with preserved ejection fraction. Her echocardiographic data had remained stable for over 1 year.

* Abnormal values.

failure 11 years earlier and a diagnosis of atrial fibrillation for which she was being followed by a cardiologist. Her regular medications were amlodipine (2.5 mg/day), diltiazem (200 mg/day), clopidogrel, ascorbic acid/pantothenic acid combination tablets, *Enterococcus faecium*/*Clostridium butyricum*/*Bacillus subtilis* combination powder, lanthanum carbonate, sennoside A+B, and nalfurafine.

An electrocardiogram and anterior-posterior chest radiograph obtained during preoperative examination ~1 week before the scheduled surgery showed atrial fibrillation and cardiomegaly, and her brain natriuretic peptide (BNP) level at that time was 882 pg/mL (normal <18.4 pg/mL). In addition to her BNP, we also performed echocardiography to assess her known heart failure. Echocardiography revealed her left ventricular function was preserved with an ejection fraction of 70% and diastolic dysfunction although there were no congestive findings. Other significant findings on echocardiography are presented in Table 1. Based on the patient's BNP level and echocardiography results, she appeared to have chronic diastolic heart failure. The echocardiography data had been maintained for a year with no significant changes, and she demonstrated no signs or overt symptoms of decompensation. Furthermore, the cardiologist judged that her heart function was stable and that surgery was feasible, thus we decided to proceed with the operation.

Surgery was scheduled for the day following one of her regular hemodialysis sessions. All her regular medications were continued preoperatively, and adherence to standard fasting guidelines were confirmed. In addition to the standard anesthetic monitoring, an arterial line was inserted into her right radial artery before induction of general anesthesia. The patient's blood pressure (BP) and heart rate (HR) before induction were 167/69 mm Hg and 65 beats per minute (bpm), respectively.

General anesthesia was induced with continuous IV infusions of remimazolam at 6 mg/kg/h and remifentanil at 0.25 μg/kg/min along with 100% oxygen (6 L/min) via facemask. After the patient lost consciousness, the remimazolam infusion rate was decreased to 1 mg/kg/h. Neuromuscular blockade was performed with an IV bolus of rocuronium (25 mg), and nasotracheal intubation was successfully performed without difficulty. Before tracheal intubation, the patient's lowest BP and HR were 118/55 mm Hg and 62 bpm, respectively. There were no significant hemodynamic changes during induction or after tracheal intubation. General anesthesia was maintained with continuous infusions of remimazolam at 0.3 to 0.4 mg/kg/h and remifentanil at 0.05 to 0.3 μg/kg/min along with oxygen/air (0.7/2.3 L/min). Ephedrine was administered via 4 mg boluses to raise the patient's BP twice, after induction and during surgery. Prior to the start of the surgical procedure, 4 mL of 2% lidocaine with 1:80,000 epinephrine was injected via infiltration into the surgical field at the start of the surgery, with an additional 1.5 mL given 1 hour later. The total dose of lidocaine and epinephrine were 110 mg and 68.75 μg, respectively. After local anesthetic injection, modest elevations in BP and HR temporarily occurred, ranging from a BP of 137/70 mm Hg and HR of 77 bpm to a BP of 161/73 mm Hg and a HR of 105 bpm. However, the patient's cardiovascular vital signs quickly returned to their normal ranges.

Immediately after completion of the surgery, the remimazolam and remifentanil infusions were discontinued. Because residual muscle relaxation remained as evident by the train-of-four (TOF) ratio of 0.38, an IV bolus of sugammadex (80 mg) was administered, and 5 minutes later, the TOF ratio was ~1. Twelve minutes after discontinuing the infusions, spontaneous breathing, cough reflex, eye opening, and obedience to verbal commands were observed, and the tracheal tube was immediately removed. Flumazenil was not required to help facilitate more rapid emergence from general anesthesia. The total duration of the surgical procedure was 1 hour and 13 minutes, and the total anesthesia time was 2 hours and 21 minutes. For postoperative analgesia, 600 mg of IV acetaminophen was administered at the end of surgery. Thereafter, additional doses (a total of 2) were administered at 6-hour intervals, producing adequate postoperative pain control.

Postoperatively, modest tachycardia (a HR of 100–120 bpm) was observed but improved with the administration of diltiazem (100 mg), one of the patient's regular medications. Thereafter, her HR remained around 70 to 80 bpm, and her cardiovascular

Table 2. Comparing Midazolam and Remifentanil Pharmacokinetic Parameters.

	Midazolam (0.075 mg/kg)	*Remimazolam (0.01–0.30 mg/kg)*
$t_{1/2}$ (hours)	4.290	0.597–0.804
CL (L/h)	23.02	70.24–75.35
V_{ss} (L/kg)	81.78	28.80–44.60

The $t_{1/2}$ of remimazolam is considerably more rapid, and its CL and V_{SS} are ~3 times and ~½ that of midazolam, respectively. Therefore, remimazolam is more rapidly metabolized and expected to promote more accurate titration and a faster recovery than midazolam. $t_{1/2}$, terminal phase half-life; CL, clearance; V_{SS}, volume of distribution at steady state.

condition stabilized rapidly during an otherwise unnoteworthy recovery. The patient was discharged from the hospital 12 days after the surgery.

DISCUSSION

In general, renal impairment can affect pharmacokinetics, including distribution, metabolism, elimination, and protein binding.[7] Chronic hemodialysis patients undergoing nonemergent surgeries are at significantly elevated risks for perioperative complications and death,[8] and anesthesiologists need to pay close attention to their perioperative management. Importantly, remifentanil and inhaled anesthetics like sevoflurane are not renally metabolized or excreted. However, IV anesthetics, other than remimazolam, as well as many other anesthesia-related drugs can accumulate due to impaired renal function, leading to enhanced or prolonged drug effects, delayed awakening, and other unexpected adverse events.[7]

Remimazolam is primarily metabolized by tissue CES, primarily carboxylesterase 1 (CES1), which is highly expressed in not only the liver but also the gallbladder and the lungs as well as other tissues. However, the liver has the highest genetic expression of CES1, while the lung is second highest. So, rapid metabolism of remimazolam is considered to be conducted in the liver and other tissues including the lung,[9] and its metabolic byproducts have virtually no relevant bioactivity.

The anesthetic effects of remimazolam are not significantly influenced by renal dysfunction.[9] Regarding the effect of impaired renal function, the pharmacokinetics of remimazolam in patients with an estimated Glomerular Filtration Rate (GFR) (uncorrected GFR for body surface area) <30 mL/min were compared with otherwise healthy subjects by measuring the blood concentration of remimazolam up to 24 hours after bolus administration.[10] The results of that study indicated that remimazolam pharmacokinetics in patients with impaired renal function did not differ from healthy patients. Furthermore, there was no delay in awakening time and no adverse events in patients with renal impairment.[10] This suggests that remimazolam may be a useful alternative for patients with severely impaired renal function.

Midazolam, a short-acting benzodiazepine similar to remimazolam, is used worldwide as an IV agent for general anesthesia and sedation management. Unlike remimazolam, midazolam is metabolized in the liver by cytochrome P450 3A4, which leads to a slower comparative rate of metabolism. Comparing the key pharmacokinetic parameters for midazolam and remimazolam,[11] the terminal phase half-life of remimazolam is considerably more rapid, and its clearance and steady state volume of distribution are ~3 times and ~½ that of midazolam, respectively (Table 2).

Midazolam metabolism in patients with severely impaired renal function reportedly does not differ considerably from that in healthy subjects.[12] However, midazolam's pharmacologically active metabolite, α-hydroxymidazolam, is excreted by the kidneys.[13] Its elimination can be prolonged in patients with renal impairment.[14] On this point, the remimazolam's carboxylic acid metabolite (CNS7054) has a benzodiazepine binding site affinity ~300 times lower and exhibits almost no bioactivity.[1] Therefore, the actions of remimazolam and its metabolites are not affected by excretory ability of the kidneys. Remimazolam is more rapidly metabolized and expected to promote more accurate titration and a faster recovery than midazolam, even in patients with renal impairment.

Propofol is also often used as a general anesthetic and sedative agent because it is quickly redistributed into peripheral tissues and metabolized, resulting in the rapid onset and disappearance of its anesthetic effects. Unlike midazolam and remimazolam, propofol is not a benzodiazepine although it does similarly act as a positive allosteric modulator to enhance the actions of GABA at GABA-A receptors and induce an anesthetic action.[15] The action of propofol on the GABA-A receptors cannot be antagonized by a benzodiazepine receptor antagonist (flumazenil) due to the different binding sites that propofol and benzodiazepines have on GABA-A receptors.[15] Propofol is extensively metabolized in the liver through the cytochrome P450 system and glucuronidation, and less than 1% is excreted unchanged.[15] Because propofol exhibits a high systemic clearance that exceeds hepatic blood flow, other organs are thought to contribute to its extrahepatic clearance.[15] A past study[16] demonstrated that renal clearance of propofol was ~30% of total body clearance and suggested the human kidneys play an important role in

propofol elimination. However, another study[17] that investigated the influence of renal impairment on propofol metabolism reported that severe renal impairment did not significantly affect the pharmacokinetic and pharmacodynamic profiles of propofol. Therefore, propofol may also be considered a useful anesthetic agent when managing hemodialysis patients.

However, the patient in the present case had the added complication of chronic diastolic heart failure. Patients with chronic renal failure undergoing hemodialysis frequently have cardiovascular complications.[8] The occurrence of serious cardiovascular complications during anesthesia needs to be considered in patients with severely impaired renal function, especially hemodialysis patients. Because propofol has been demonstrated to depress cardiac function,[18] it should be administered cautiously to patients with heart failure. On the other hand, remimazolam was reported to have a lower incidence of hypotension and cumulative norepinephrine doses during induction of general anesthesia compared with propofol in patients undergoing cardiac surgery.[19] Furthermore, the safe anesthetic management of a patient with severe cardiovascular disease using remimazolam has also been reported.[20] These findings suggest that remimazolam causes less cardiac depression than propofol. Therefore, we considered remimazolam to be a more suitable option than propofol for the present patient with chronic diastolic heart failure.

In the past studies,[3,4] the initial remimazolam infusion rate for general anesthesia was 6 or 12 mg/kg/h until loss of consciousness, followed by an infusion maintenance rate of 1 mg/kg/h. This method was applied during this case without any significant hemodynamic changes being observed during the induction of anesthesia, and the patient's hemodynamics were generally stable throughout. There was no delay in awakening from general anesthesia and no need to consider administering flumazenil. In the present case, anesthetic management was performed safely using the combination of remimazolam and remifentanil.

CONCLUSION

The effects and pharmacokinetics of remimazolam are independent of renal function, and it appears that remimazolam can be used safely for hemodialysis patients with heart failure. In addition, the combination of remimazolam and remifentanil produced a rapid and clear emergence from general anesthesia without the need for reversal agents. Remimazolam and remifentanil may be appropriate as first-line agents for the anesthetic management of hemodialysis patients with heart failure.

REFERENCES

1. Kilpatrick GJ, Mclntyre MS, Cox RF, et al. CNS 7056: a novel ultra-short-acting benzodiazepine. *Anesthesiology*. 2007;107:60–66.

2. Schuttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers: part I. pharmacokinetics and clinical pharmacodynamics. *Anesthesiology*. 2020;132:636–651.

3. Doi M, Hirata N, Suzuki T, Morisaki H, Morimatsu H, Sakamoto A. Safety and efficacy of remimazolam in induction and maintenance of general anesthesia in high-risk surgical patients (ASA Class III): results of a multicenter, randomized, double-blind, parallel-group comparative trial. *J Anesth*. 2020; 34:491–501.

4. Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. 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.

5. Masui K. Remimazolam besilate, a benzodiazepine, has been approved for general anesthesia!! *J Anesth*. 2020;34:479–482.

6. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314.

7. Kanda H, Hirasaki Y, Iida T, et al. Perioperative management of patients with end-stage renal disease. *J Cardiothorac Vasc Anesth*. 2017;31:2251–2267.

8. Gajdos C, Hawn MT, Kile D, Robinson TN, Henderson WG. Risk of major nonemergent inpatient general surgical procedures in patients on long-term dialysis. *JAMA Surg*. 2013;148:137–143.

9. Kilpatrick GJ. Remimazolam: non-clinical and clinical profile of a new sedative/anesthetic agent. *Front Pharmacol*. 2021;12:690875.

10. Stohr T, Colin PJ, Ossig J, et al. Pharmacokinetic properties of remimazolam in subjects with hepatic or renal impairment. *Br J Anaesth*. 2021;127:415–423.

11. Antonik LJ, Goldwater DR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled Phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): part I. safety, efficacy, and basic pharmacokinetics. *Anesth Analg*. 2012;115:274–283.

12. Vinik HR, Reves JG, Greenblatt DJ, Abernethy DR, Smith LR. The pharmacokinetics of midazolam in chronic renal failure patients. *Anesthesiology*. 1983;59:390–394.

13. Mandona JW, Tuk B, Van Steveninck AL, Breimer DD, Cohen AF, Danhof M. Pharmacokinetic-pharmacodynamic

modeling of the central nervous system effects of midazolam and its main metabolite a-hydroxymidazolam in healthy volunteers. *Clin Pharmacol Ther*. 1992;51:715–728.

14. Zaporowska-Stachowiak I, Szymański K, Oduah MT, Stachowiak-Szymczak, Łuczak J, Sopata M. Midazolam: safety of use in palliative care: a systematic critical review. *Biomed Pharmacother*. 2019;114:108838.

15. Vanlersberghe C, Camu F. Propofol. In: Schüttler J, Schwilden H. *Modern Anesthetics (Handbook of Experimental Pharmacology)*. Berlin: Springer; 2008:227–252.

16. Takizawa D, Hiraoka H, Goto F, Yamamoto K, Horiuchi R. Human kidneys play an important role in the elimination of propofol. *Anesthesiology*. 2005;102:327–330.

17. Ickx B, Cockshott ID, Barvais L, et al. Propofol infusion for induction and maintenance of anaesthesia in patients with end-stage renal disease. *Br Jr Anaesth*. 1998;81: 854–860.

18. Coetzee A, Fourie P, Coetzee J, et al. Effects of various propofol plasma concentrations on regional myocardial contractility and left ventricular afterload. *Anesth Analg*. 1989;69:473–483.

19. Liu T, Lai T, Chen J, et al. Effect of remimazolam induction on hemodynamics in patients undergoing valve replacement surgery: a randomized, double-blind, controlled trial. *Pharmacol Res Perspect*. 2021;9:e00851.

20. Satoh T, Nishihara N, Sawashita Y, Ohno S, Hirata N, Yamakage M. Remimazolam anesthesia for mitraClip implantation in a patient with advanced heart failure. *Case Rep Anesthesiol*. 2021;2021:5536442.