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Cardiac Arrest Following Remimazolam-Induced Anaphylaxis: A Case Report

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Remimazolam is a recently approved benzodiazepine sedative. We report a case of a 72-year-old man who experienced a cardiac arrest due to severe anaphylaxis immediately after general anesthesia induction. Based on the results of skin tests, including those for dextran 40, an excipient in the remimazolam solution, and a review of drugs given during 3 anesthetics, remimazolam was identified as the probable causative agent. Although remimazolam is structurally similar to midazolam, the patient was not allergic to midazolam as demonstrated before and after anaphylaxis. This report highlights the potential risk of allergic reactions to remimazolam. (A&A Practice. 2022;16:e01616.)

GLOSSARY

ABP = intraarterial blood pressure; **ACLS** = advanced cardiovascular life support; **BP** = blood pressure; **dBP** = diastolic blood pressure; **EQUATOR** = enhancing the quality and transparency of health research; **HR** = heart rates; **ICU** = intensive care unit; **NIBP** = non-invasive blood pressure; **sBP** = systolic blood pressure

Remimazolam besylate (remimazolam) is a benzodiazepine sedative, first approved in Japan in January 2020 for general anesthesia induction and maintenance.[1] Remimazolam is structurally similar to midazolam (Figure 1).[2,3,4] Although the risk of allergic reactions to remimazolam remains unknown, it is suspected to be rare because hypersensitivity reactions to benzodiazepines are extremely rare.[5,6] To date, only 1 case of remimazolam-related anaphylactic shock, probably caused by cross-reaction between remimazolam and midazolam, has been reported.[7]

We describe the first reported case of cardiac arrest caused by anaphylaxis probably triggered by remimazolam. Our patient was not allergic to midazolam. Remimazolam-induced anaphylaxis was likely diagnosed based on skin test results and review of anesthetic drug usage.

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Our patient provided written consent for publication of this report. We adhered to all applicable EQUATOR guidelines.

CASE DESCRIPTION

The patient was a 72-year-old man (height, 166 cm; weight, 61 kg) who underwent elective video-assisted thoracoscopic left-lung segmentectomy for suspected lung cancer. His medical history included hypertension, benign prostatic hyperplasia, and herpes zoster viral infection. His allergic history included urticaria in response to acemetacin and *kikyosekko*, a Japanese herbal medicine. The anesthetics he had previously been exposed to included fentanyl, remifentanil, and rocuronium. All of these anesthetics were used when he underwent a robot-assisted gastrectomy under general anesthesia 2 years before the current consultation. Additionally, he had received intravenous sedation with midazolam for follow-up endoscopic gastric examinations multiple times. He did not have anaphylaxis during any of his previous treatments with anesthetics.

General anesthesia was induced with intravenous fentanyl (100 μg), remimazolam (12 mg), and rocuronium (70 mg). These medications were followed by a continuous intravenous infusion of remimazolam (600 mg/h) for anesthesia maintenance. Tracheal intubation was performed with a left-sided double-lumen endotracheal tube. Six minutes after tracheal intubation, his blood pressure sharply dropped and skin erythema appeared on his abdomen. Despite multiple boluses of phenylephrine and norepinephrine (30 μg), the systolic blood pressure decreased below 50 mm Hg until it became unmeasurable. His end-tidal CO_2 concentration decreased to 19 mm Hg, and his carotid artery pulse became undetectable.

Advanced cardiovascular life support (ACLS) was immediately initiated due to suspected anaphylactic cardiac arrest. The continuous intravenous infusion of remimazolam was discontinued. In parallel with chest compressions, we initiated ventilation with 100% oxygen, fluid resuscitation, and

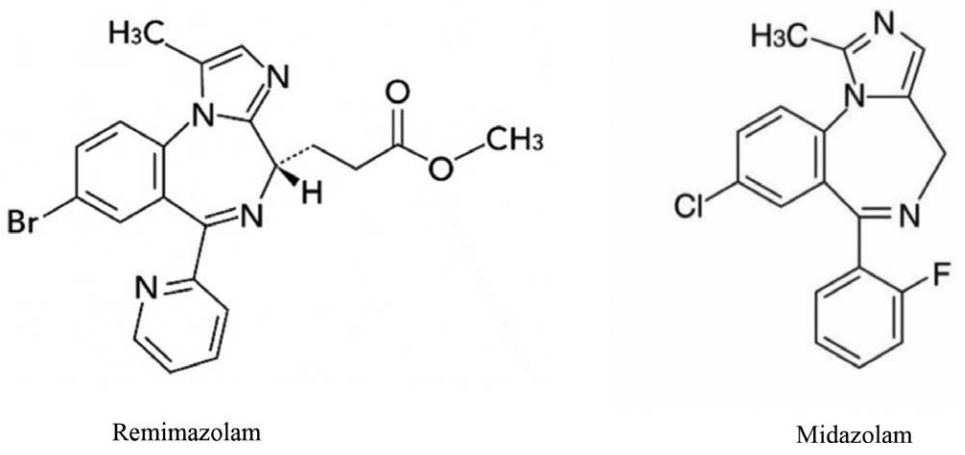

Figure 1. Chemical structures of the remimazolam and midazolam.

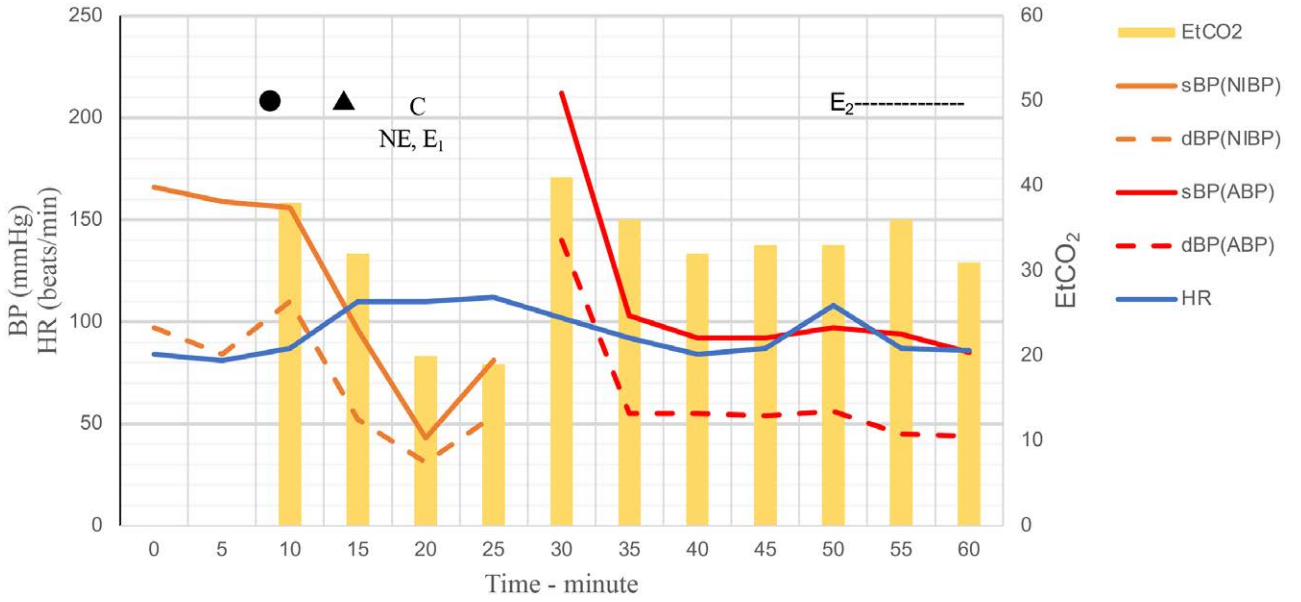

Figure 2. The patient's vital signs during the anesthetic. ABP indicates intraarterial blood pressure; BP, blood pressure; dBP, diastolic blood pressure; HR, heart rates; NIBP, non-invasive blood pressure; sBP, systolic blood pressure. $EtCO_2$, end-tidal carbon dioxide; ●, induction of anesthesia; ▲, intubation; C, cardiopulmonary resuscitation; NE, norepinephrine (30 mcg bolus infusion); E_1, adrenaline (1 mg bolus infusion); E_2, adrenaline (5 mcg/min continuous infusion).

arterial blood pressure monitoring with cannulation of the left radial artery. After 6 minutes of cardiopulmonary resuscitation, including an initial administration of epinephrine (1 mg), return of spontaneous circulation was observed. The patient's vital signs trends during the event are presented in Figure 2.

Immediate transthoracic echocardiography showed no evidence of cardiogenic shock. As anaphylaxis was strongly suspected based on the clinical presentation, a histamine H_1-receptor antagonist (chlorpheniramine maleate, 5 mg), a histamine H_2-receptor antagonist (famotidine, 20 mg), and hydrocortisone (100 mg), were administered intravenously after initial cardiovascular stabilization. The operation was canceled, and the patient was transferred to the intensive care unit (ICU) while still intubated. Neurological functioning was confirmed. Then, he was extubated 4 hours after ICU admission. Although vasopressor treatment was required for 15 hours, he was moved to the general ward the following day and was discharged from the hospital 2 days later.

The blood samples taken within 1 hour after the suspected anaphylactic reaction showed elevated serum tryptase (8.7 µg/L, compared with a baseline concentration of 4.8 µg/L) and histamine (24.1 ng/mL) concentrations. Four weeks after the event, dermatologists performed skin tests, including skin prick and intradermal tests, for suspected allergens. Of these allergens, only remimazolam solution (the reconstituted remimazolam preparation from the vial obtained by adding 0.9% sodium chloride injection) returned a positive result in intradermal tests (wheals of 11 × 11 mm and 9 × 6 mm accompanied by flares at dilutions of 1:100 and 1:10 in saline, respectively) (Supplemental Digital Content, Figure 1 and Table 1, http://links.lww.com/AACR/A484, http://links.lww.com/AACR/A490). Additional skin tests of dextran 40, an excipient in the remimazolam solution, tested negative (Supplemental Digital Content, Figures 2–5 and Table 2, http://links.lww.com/AACR/A483, http://links.lww.com/AACR/A485, http://links.lww.com/AACR/A486, http://links.lww.

com/AACR/A487, http://links.lww.com/AACR/A491). The irritant nature of remimazolam solution in healthy volunteers is shown in Supplemental Digital Content, Figure 6 and Table 3, http://links.lww.com/AACR/A488, http://links.lww.com/AACR/A492.

The postponed operation was attempted again. However, this time, general anesthesia was established without remimazolam. All other drugs (fentanyl, remifentanil, and rocuronium) were administered at full therapeutic doses and no allergic reaction was observed. The patient remained stable and had no complications perioperatively. He was discharged 2 days after the surgery. The patient was successfully sedated with midazolam during an endoscopic gastric examination 6 months later.

DISCUSSION

Remimazolam besylate is a new benzodiazepine sedative characterized by its ultra-short duration of action.[1,3,4] Remimazolam and midazolam have similar chemical structures (Figure 1) and clinical characteristics. Both induce mild cardiovascular depression and their anesthetic effects are antagonized by flumazenil.[4]

Perioperative benzodiazepine-induced anaphylaxis is extremely rare.[5,6] Remimazolam-associated anaphylaxis is predicted to be rare as well. However, this is not an established fact owing to the lack of widespread use. Here, we document the first reported case of cardiac arrest due to likely remimazolam-induced anaphylaxis.

Tsurumi et al[7] previously reported a case of remimazolam-induced anaphylactic shock probably caused by a cross-reaction between remimazolam and midazolam. Skin prick tests yielded simultaneous positive reactions to both remimazolam and midazolam. Contrarily, in our case, despite our patient's previous exposure to midazolam for sedation, such cross-reaction did not cause anaphylaxis because midazolam did not provoke harmful reactions when it was administered during his endoscopy, which occurred after the anaphylaxis.

Another distinguishing feature of our patient from that reported by Tsurumi et al[7] was the need for full ACLS for our patient. Because our patient's systolic blood pressure dropped below 50 mm Hg, his carotid pulse was absent, and his end-tidal CO_2 concentration was below 20 mm Hg, his cardiac arrest was categorized as grade IV (the highest severity) on the scale of perioperative allergic reactions published by Ring and Messmer.[8] ACLS, including external cardiac massage and 1 mg epinephrine administration, was appropriate.[9]

We diagnosed our patient with probable remimazolam-induced anaphylaxis for the following reasons: First, our patient met the World Allergy Organization's clinical criteria for diagnosis of anaphylaxis.[10] The clinical criteria that he satisfied included acute onset of circulatory collapse and an erythematous rash. Our patient's positive serum tryptase test result also indicated that the event was caused by an allergic reaction. Second, intradermal tests yielded positive results for the remimazolam solution only. Although the methodology for remimazolam skin testing has not been standardized, our patient's intradermal tests resulted in the appearance of a wheal of 11 mm in width accompanied by a flare, thereby satisfying the generally accepted positive threshold for intradermal tests[5,6] (Supplemental Digital Content, Figure 1 and Table 1, http://links.lww.com/AACR/A484, http://links.lww.com/AACR/A490). For these tests, we used 1:10 and 1:100 remimazolam solution dilutions in saline, which matched the dilutions used in the standardized protocol for midazolam skin testing.[11] Third, our patient's history of anesthetic drug exposure also indicated that remimazolam solution was the causative allergen. All of the other drugs had been administered to the patient previously (Table). Furthermore, for his subsequent surgery, the previously administered drugs apart from remimazolam were used at full therapeutic doses without provoking allergic reactions. According to Garvey et al,[12] potential allergen drugs administered at therapeutic doses without provoking allergic reactions can be ruled out as causative agents of anaphylaxis with confidence, thereby leaving remimazolam solution as the only remaining allergen solution that was responsible for our patient's anaphylaxis. Finally, further investigation revealed that dextran 40, which is an excipient contained in the remimazolam solution and is frequently associated with anaphylaxis,[6,13,9] was not the culprit behind anaphylaxis. In the skin tests, we used Low Molecular Dextran L Injection (Otsuka Pharmaceutical Factory, Inc., Tokyo, Japan) which includes dextran 40 as the main component. Despite the fact that dextran 40 concentration in 1:10 diluted and undiluted Low Molecular Dextran L Injection was higher than that in the remimazolam solution, with 10, 100, and 3.95 mg/mL, respectively, the results of the skin tests for each solution were all negative (Supplemental Digital Content, Figures 2–5 and Table 2, http://links.lww.com/AACR/A483, http://links.lww.com/AACR/A485, http://links.lww.com/AACR/A486, http://links.lww.com/AACR/A487, http://links.lww.com/AACR/A491). According to the pharmaceutical label indication, the remimazolam solution contains lactose monohydrate, hydrochloric acid, sodium hydroxide, remimazolam, and dextran 40. As the former 3 components seem unlikely to be the causative allergens, our investigation leaves remimazolam itself as the likely allergen.

Table. The Patient's Prior Exposure to Anesthetics

Anesthesia during anaphylaxis[a]	Previous anesthesia[b]	Subsequent anesthesia[c]
Before the reaction	-	-
Remimazolam	-	Remifentanil
Remifentanil	Remifentanil	Fentanyl
Fentanyl	Fentanyl	Rocuronium
Rocuronium	Rocuronium	Latex[d]
Latex[d]	Latex[d]	-
After the reaction	-	
Phenylephrine	Phenylephrine	Phenylephrine
Norepinephrine	-	-
Epinephrine	-	-
	Propofol	Propofol
	Sevoflurane	Sevoflurane
	Ephedrine	Ephedrine
	Sugammadex	Sugammadex
	Acetaminophen	Acetaminophen

[a]For video-assisted thoracoscopic left-lung segmentectomy.
[b]For robot-assisted gastrectomy 2 years earlier.
[c]For the subsequent surgery.
[d]The urethral catheter contained latex.

Our study had the following limitations. First, we only used a vial preparation of the remimazolam solution not pure remimazolam itself in the skin tests. Hence, it is possible that we may have overlooked other possible culprits if unreported ingredient or contaminants had existed. Second, the dextran 40 used in the skin tests might not have been completely the same as that in the remimazolam solution because they are from a different pharmaceutical company, although its significance is unverifiable.

In conclusion, our patient experienced severe anaphylaxis during the induction of general anesthesia. The anaphylaxis resulted in cardiac arrest and necessitated resuscitation with ACLS. Based on the skin test results and a review of drug usage in our patient's exposure to general anesthesia, we concluded that anaphylaxis was certainty caused by remimazolam vial preparation and probably by remimazolam itself. Further research on the safety profile of remimazolam is needed.

DISCLOSURES

Name: Yudai Hasushita, MD.
Contribution: This author helped provide intraoperative care and management for anaphylaxis, prepare for the reattempted surgery, and write the original draft.
Name: Megumi Nagao, MD.
Contribution: This author helped investigate and interpret the results of the dermatological examinations and review the draft.
Name: Yoshihide Miyazawa, MD.
Contribution: This author helped provide intraoperative care for the reattempted surgery and review the draft.
Name: Kazuma Yunoki, MD.
Contribution: This author helped provide intraoperative care for reattempted surgery, provide guidance, and revise the draft.
Name: Hiroyuki Mima, MD.
Contribution: This author helped provide guidance and revise the draft.
This manuscript was handled by: BobbieJean Sweitzer, MD, FACP.

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