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Isolated Refractory Circulatory Collapse after Remimazolam Induction: A Diagnostic Challenge Supported by Positive Intradermal Testing

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Abstract **Case Report**

Remimazolam is an ultra-short-acting benzodiazepine increasingly used for anesthetic induction due to its hemodynamic stability. However, as its use expands, reports of perioperative hypersensitivity reactions are accumulating. We report a case of isolated refractory circulatory collapse suspected to be caused by remimazolam during anesthetic induction. This case highlights the diagnostic challenge of distinguishing hypersensitivity reactions presenting solely as cardiovascular collapse from anesthesia-induced vasodilation. A 58-year-old male undergoing elective laparoscopic cholecystectomy developed severe hypotension within minutes of remimazolam administration. Due to previous encounters of remimazolam hypersensitivity reaction in our clinic, preventive measures for hypersensitivity were done before induction. Remimazolam was first diluted with normal saline using a filter needle and administration was done through an in-line filter. Despite these measures, the patient exhibited profound hypotension without bronchospasm, cutaneous signs, electrocardiographic abnormalities, or metabolic derangement. Anesthesia-induced vasodilation was initially suspected, but the condition progressed to non-measurable blood pressure and was refractory to repeated intravenous ephedrine boluses. Hemodynamics rapidly improved following administration of intravenous epinephrine. Although serum tryptase was not measured, intradermal testing three weeks later demonstrated a positive response to remimazolam. Though the concentration used during intradermal testing may have exceeded non-irritating thresholds, the relationship between remimazolam exposure and circulatory collapse, together with the prompt hemodynamic response to epinephrine was considered consistent with remimazolam-associated perioperative hypersensitivity. This case demonstrates that remimazolam hypersensitivity may present as isolated refractory circulatory collapse, highlighting the importance of considering hypersensitivity reaction in vasopressor-resistant hypotension during induction even in the absence of typical allergic features. This case also highlights the importance of structured postoperative allergy evaluation in providing clinically meaningful evidence in cases of diagnostically challenging perioperative shock.

Keywords: Remimazolam, Perioperative Hypersensitivity, Circulatory Collapse, Anesthetic Induction, Intradermal Test.

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INTRODUCTION

Remimazolam besylate is an ultra-short-acting benzodiazepine. It has a rapid onset and undergoes organ-independent metabolism via tissue esterases. It also provides relatively stable cardiovascular effects compared with other conventional induction agents. These pharmacological characteristics have contributed to its increasing use in anesthesia practice. However, as clinical use increases, cases of perioperative hypersensitivity reactions associated with remimazolam have been reported [1–3].

Perioperative anaphylaxis is a severe, rapid-onset systemic hypersensitivity reaction that might be life threatening. It typically involves multi-system manifestations such as bronchospasm, cutaneous signs, and cardiovascular instability. In anesthetized patients, however, clinical manifestations may be masked by controlled ventilation, surgical draping, and administration of various cardiac depressive anesthetic drugs. Consequently, circulatory collapse may be misinterpreted as anesthesia-induced vasodilation or relative hypovolemia, potentially delaying recognition and treatment [4].

In addition, due to the accumulating cases of hypersensitivity reactions associated with remimazolam, preventive strategies including the use of a filter needle during drug preparation and in-line filtration during administration are practiced in some clinics to reduce the risk of pseudoallergic reactions related to the excipient dextran [5]. However, the clinical effectiveness of these strategies remains uncertain.

We report a case of isolated refractory circulatory collapse following remimazolam induction despite these precautionary measures, with diagnostic evidence obtained from delayed intradermal testing.

Case Report

The Institutional Review Board of Presbyterian Medical Center approved this study and waived the requirement for informed consent because only the patient's medical records were reviewed (IRB no. PMC 2026-04-005).

A 58-year-old male patient (height 164 cm, weight 76 kg), classified as American Society of Anesthesiologists (ASA) physical status II, was scheduled for elective laparoscopic cholecystectomy under general anesthesia. The patient had a history of hypertension and no known allergies. He had previously undergone lumbar spine surgery under general anesthesia the previous year without any perioperative complications. Standard monitoring, including electrocardiography (ECG), non-invasive blood pressure (NIBP), pulse oximetry (SpO_2), and capnography was monitored upon arrival in the operating room. Baseline vital signs prior to anesthetic induction were recorded as NIBP of 185/95 mmHg, heart rate (HR) of 59 beats/min, and SpO_2 of 98% in room air.

After preoxygenation with 6 L/min of 100% oxygen, general anesthesia was induced with intravenous remimazolam administered at an initial infusion rate of 200 mL/hr after dilution in normal saline to a concentration of 1 mg/mL using a filter needle. The drug was delivered through a 0.22-µm in-line filter as a precautionary measure to reduce the risk of potential hypersensitivity reactions related to excipients. Continuous remifentanil target-controlled infusion was initiated concurrently. Tracheal intubation was performed uneventfully shortly after induction. Peak inspiratory pressure (PIP) and end-tidal carbon dioxide ($EtCO_2$) remained within normal limits, and no bronchospasm or ventilation difficulty was observed.

At approximately 10 minutes after infusion initiation NIBP gradually decreased to 110/60 mmHg, accompanied by compensatory tachycardia (Figure 1.). At the next NIBP measurement, blood pressure became unmeasurable. Anesthetic-induced vasodilation was first suspected. Initial management included repeated attempts at blood pressure measurement, verification of monitor reliability, and intravenous administration of 10 mg of ephedrine. After another unmeasurable NIBP reading, 10 mg of ephedrine was again given, but hypotension persisted. As hemodynamic instability persisted, suspicion for another cause arose, and both remimazolam and remifentanil infusions were discontinued.

25 minutes after initiation of remimazolam infusion, invasive arterial blood pressure (IABP) monitoring was done with cannulation of the left radial artery. IABP monitoring showed profound hypotension, with blood pressure of 45/22 mmHg and a HR of 105 beats/min. SpO_2 remained above 93%, and PIP showed no increase. ECG revealed sinus tachycardia without ST-segment deviation, conduction abnormalities, or arrhythmias. No cutaneous signs of hypersensitivity, including urticaria or flushing, were observed.

Given the refractory hypotension and its association with remimazolam administration, perioperative hypersensitivity was suspected. An intravenous 0.05mg bolus of epinephrine was promptly administered followed by 125mg of intravenous methylprednisolone. This resulted in prompt hemodynamic improvement, with systolic blood pressure increasing to approximately 80 to 110 mmHg within minutes. Continuous norepinephrine infusion (4.5 mg diluted in 95.5 mL of normal saline) was started at a rate of 10 mL/hr to maintain hemodynamic stability. After hemodynamic stabilization, anesthesia was maintained with sevoflurane in combination with remifentanil infusion.

Approximately 40 minutes after infusion initiation, surgical team proceeded with the operation. Hemodynamic parameters remained stable during the operation with no recurrence of severe hypotension. Intraoperative fluid administration consisted of 1,300 mL of crystalloid and 300 mL of balanced colloid solution. Arterial blood gas analysis (ABGA) revealed no significant metabolic or respiratory abnormalities. The patient was transferred to the post-anesthesia care unit (PACU) in stable condition and subsequently to the general ward.

Serum tryptase levels were not measured in this case. However, intradermal testing performed three weeks later showed a positive wheal-and-flare response to remimazolam at a 1:10 dilution, whereas tests for other perioperative agents were negative. A notable limitation of this case is that the test concentration used may exceed established non-irritating thresholds, making it difficult to entirely rule out an irritant effect. However, the relationship between remimazolam exposure and circulatory collapse, together with the prompt hemodynamic response to epinephrine, was considered consistent with remimazolam-associated perioperative hypersensitivity presenting predominantly as isolated circulatory collapse.

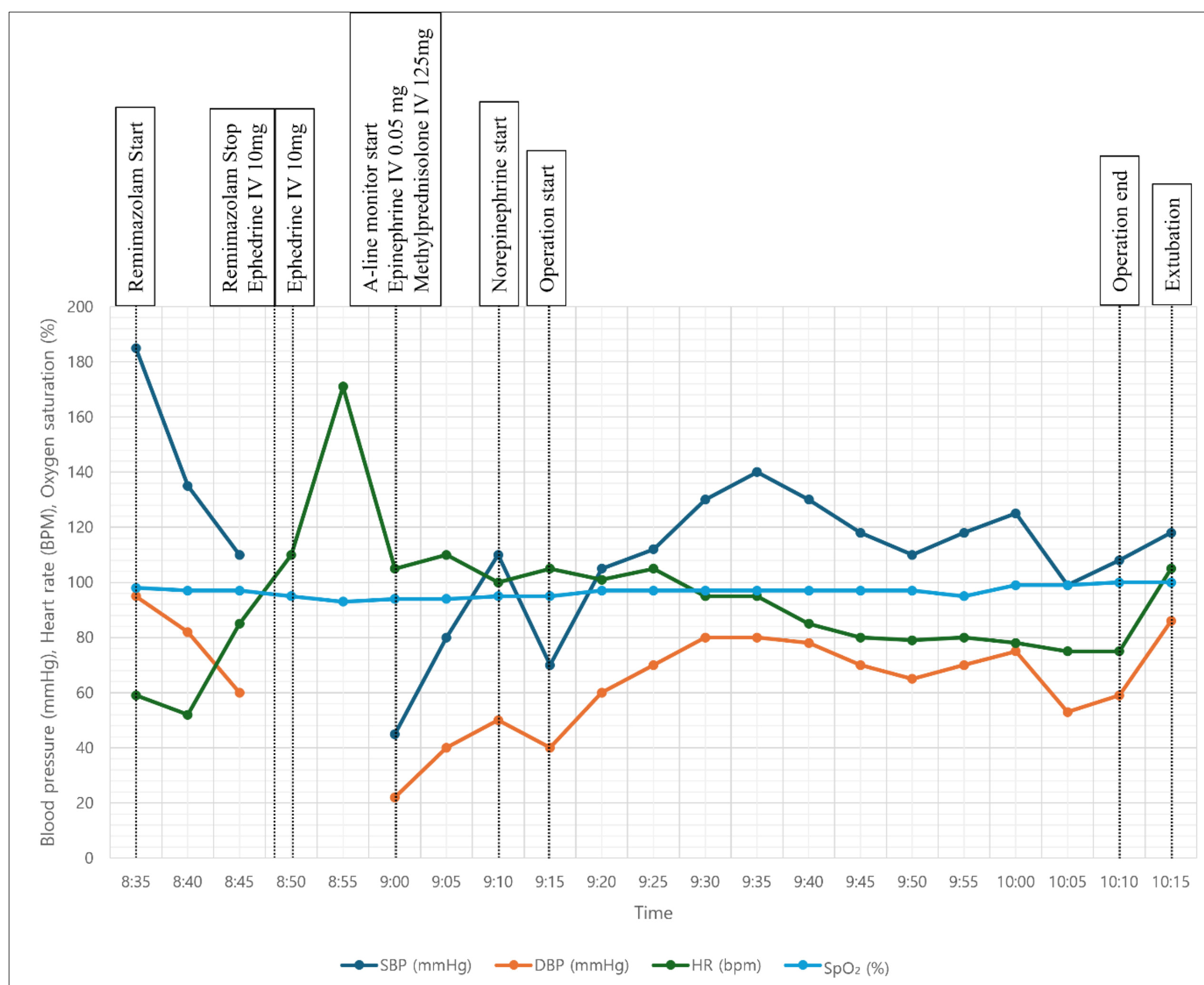

Figure 1: Time course of hemodynamic changes during anesthetic induction

Severe hypotension developed after initiation of remimazolam infusion and was refractory to repeated ephedrine administration. Improvement in systolic blood pressure was observed following intravenous epinephrine administration.

DISCUSSION

There are various reports of remimazolam associated hypersensitivity presenting with multi-system manifestations, including bronchospasm, cardiac conduction abnormalities, or cardiac arrest [1–3, 7]. However, perioperative hypersensitivity reactions may present with diverse clinical manifestations, and typical multi-system involvement may not always be evident. In anesthetized patients especially, cutaneous signs may go unnoticed from surgical draping, while respiratory manifestations such as bronchospasm can be subtle or absent due to controlled ventilation and pharmacologic effects from anesthetic agents. Therefore, sudden circulatory collapse may present as predominant or sole manifestation of perioperative hypersensitivity [4-6].

This case expands the clinical spectrum by demonstrating that remimazolam-related reactions may manifest predominantly as isolated refractory circulatory collapse, thereby posing a significant diagnostic challenge during anesthetic induction. Recognition of this potential diagnostic pitfall is important, as delayed identification and treatment of perioperative hypersensitivity reactions may result in life-threatening hemodynamic deterioration.

In the event of a hypersensitivity reaction, prompt administration of epinephrine is crucial, as it directly counteracts the underlying pathophysiology of systemic vasodilation and increased vascular permeability. The rapid hemodynamic improvement following intravenous epinephrine not only represents effective treatment but also provides diagnostic evidence of an anaphylactic mechanism.

The diagnosis in this case was further supported by a positive intradermal skin test performed three weeks after the event. Current recommendations generally suggest allergy testing after a four-to-six-week interval to minimize the risk of false-negative results during the refractory period [8]. It is worth noting that the skin test findings should be interpreted with caution as testing at higher drug concentrations may produce irritant

responses. Nevertheless, overall clinical findings were considered consistent with remimazolam-associated hypersensitivity. The absence of perioperative serum tryptase measurement is a limitation, as the lab result could have strengthened the diagnosis. However, tryptase elevation may be absent in a subset of hypersensitivity reactions, particularly when sampling is delayed or when non–IgE-mediated mechanisms are involved [9].

Another noteworthy aspect is the effectiveness of precautionary measures such as the use of filter needles and in-line filtration. Remimazolam formulations contain excipient dextran, which is associated with complement-mediated pseudoallergic reactions and cardiovascular instability [5]. Although such preventive strategies are sometimes adopted in clinical practice, their effectiveness remains uncertain. As illustrated in this case, filtration alone may not reliably eliminate the risk of severe perioperative reactions.

Anesthesia providers should consider perioperative hypersensitivity when encountering unexplained vasopressor-resistant hypotension during anesthetic induction, even in the absence of typical respiratory or cutaneous manifestations. Early recognition and proper management are essential for hemodynamic stabilization and optimizing patient outcome. Structured postoperative allergy evaluation also plays a critical role in identifying the causative agent and guiding future anesthetic management.

Conclusion

This case demonstrates that remimazolam-associated perioperative hypersensitivity may cause isolated refractory circulatory collapse during anesthesia induction. While preventive filtration strategies might reduce the risk of such reactions, anesthesia providers should always remain highly alert as early recognition and prompt epinephrine administration is critical for hemodynamic stabilization and optimal patient outcome. This case also highlights the importance of postoperative allergy evaluation, as it offers evidence for identifying the causative agent and guiding future anesthetic management.

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