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Remimazolam-Induced Perioperative Anaphylaxis with Cardiac Manifestations Suggestive of Kounis Syndrome: A Case Report

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Abstract **Case Report**

Remimazolam is an ultra–short-acting benzodiazepine increasingly used for anesthetic induction because of its rapid onset and favorable hemodynamic profile. Although generally considered safe, reports of severe hypersensitivity reactions, including anaphylaxis, remain rare, and the underlying mechanisms are not fully elucidated. We describe a case of a 68-year-old man (ASA physical status III) scheduled for therapeutic laryngomicroscopic laser surgery who developed life-threatening anaphylaxis immediately after remimazolam induction. Within minutes of intravenous administration of 14 mg of remimazolam, the patient developed severe bronchospasm refractory to rocuronium, profound hypotension, and transient atrioventricular block, consistent with features of Kounis syndrome. Oxygen saturation and blood pressure became undetectable, indicating acute respiratory and circulatory collapse. Prompt administration of intravenous epinephrine (0.1 mg bolus followed by continuous infusion) resulted in rapid hemodynamic recovery. The patient had undergone uneventful general anesthesia with propofol and other agents 10 months earlier, strongly implicating remimazolam as the causative agent. Arterial blood gas analysis revealed no significant abnormalities after stabilization. Surgery was completed successfully, and the patient recovered without postoperative complications. Further allergy evaluation was recommended, but the patient declined additional diagnostic workup. This case highlights that remimazolam can trigger severe perioperative anaphylaxis with multisystem involvement, including rare cardiac manifestations suggestive of Kounis syndrome. Prior tolerance to other anesthetic agents does not preclude hypersensitivity reactions to remimazolam. Early recognition, differentiation from other intraoperative complications, and prompt administration of epinephrine are critical for successful management. As the clinical use of remimazolam expands, increased awareness and systematic post-event allergy evaluation are essential to improve patient safety.

Keywords: Remimazolam, Anaphylaxis, Kounis syndrome, Benzodiazepine hypersensitivity, Perioperative anaphylaxis, Atrioventricular block.

INTRODUCTION

Remimazolam is a recently introduced ultra-short-acting benzodiazepine used for intravenous induction of general anesthesia. It offers rapid onset, quick recovery, and favorable hemodynamic stability, making it a preferred agent for elderly patients or those with cardiovascular comorbidities [1]. While its safety profile is generally favorable, hypersensitivity reactions including anaphylaxis have been rarely reported, and their mechanisms remain poorly understood [2,3].

Severe reactions such as bronchospasm and circulatory collapse may resemble other complications during anesthetic induction, delaying early recognition as remimazolam use expands [3].

We report a case of a 68-year-old man who developed bronchospasm and cardiovascular collapse shortly after remimazolam induction and before neuromuscular blockade. His previous anesthesia history with other agents was uneventful, and the timing and clinical features implicate remimazolam as the likely cause. Notably, this case also demonstrated transient atrioventricular block consistent with Kounis syndrome a rare cardiac manifestation of anaphylaxis. This case highlights the importance of early recognition and prompt management of remimazolam-induced anaphylaxis.

Case Report

The Institutional Review Board of Presbyterian Medical Center approved the study and determined that informed consent was not required, under which the patients' medical records were reviewed. (IRB no. PMC 2025-11-016).

A 68-year-old man (162 cm, 57 kg), American Society of Anesthesiologists (ASA) physical status III, was scheduled for therapeutic laryngomicroscopic laser surgery under general anesthesia. He had a medical history of Parkinson's disease and mild cognitive impairment, with previous treatment for hyperthyroidism now normalized. The patient had no known allergies and had previously undergone the same surgical procedure ten months earlier under general anesthesia with propofol, rocuronium, remifentanil, and desflurane without adverse events.

Upon arrival in the operating room, standard monitoring was initiated, including three-lead electrocardiography (ECG), noninvasive blood pressure (BP), and peripheral oxygen saturation (SpO_2). Initial BP was 113/64 mmHg, and heart rate (HR) was 57 beats per minute. Preoxygenation was performed using 6 L of 100% oxygen. Remimazolam was prepared at a concentration of 1 mg/mL, and a total of 14 mg was administered intravenously. The patient lost consciousness within a few minutes, and bag-valve-mask ventilation was attempted. Despite no prior history or anatomical signs of a difficult airway, manual ventilation was unexpectedly impaired, suggesting acute bronchospasm. Target-controlled infusion of remifentanil had not yet been initiated. Rocuronium 40 mg was administered intravenously, but there was no improvement in lung compliance. As oxygen saturation began to fall and cyanosis developed, endotracheal intubation was performed promptly.

Despite successful intubation, positive pressure ventilation remained challenging due to stiff lungs, and the patient's face became increasingly cyanotic. SpO_2 was undetectable, and no BP or peripheral pulse was measurable. ECG revealed a transition from normal sinus rhythm to 38 bpm with atrioventricular (AV) block. Given the suspected hypotension, ephedrine 20 mg was administered intravenously without effect. Subsequently, 0.1 mg of epinephrine was administered intravenously, after which BP and SpO_2 became measurable at 60/40 mmHg and 64%.

To stabilize hemodynamics, an additional 0.1 mg of epinephrine was administered, and a continuous infusion of epinephrine was initiated. (Figure 1.) Invasive arterial monitoring was established via radial artery cannulation, and intravenous fluid resuscitation was administered through a 16-gauge peripheral IV line. Blood samples were collected through the arterial line immediately following cannulation for further analysis, including arterial blood gas analysis (ABGA).

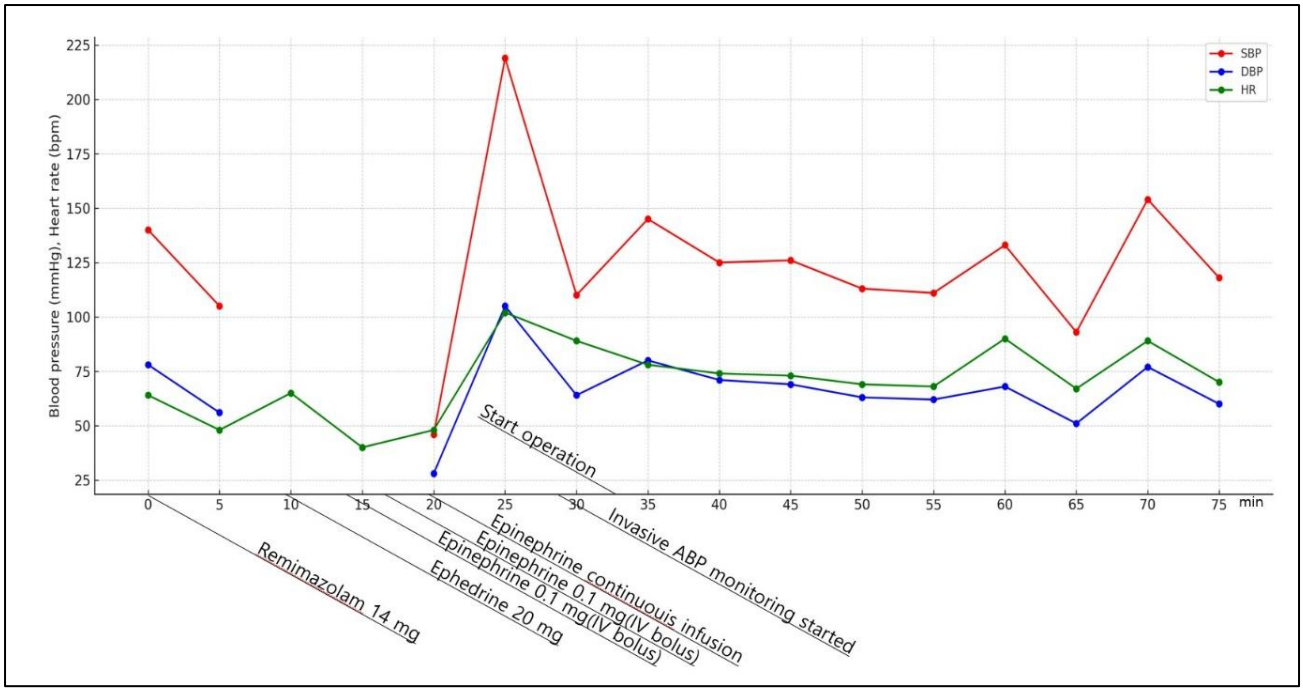

Figure 1: Time course of hemodynamic changes during anesthetic induction and management of remimazolam-induced anaphylaxis. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) are shown over time. Severe hypotension and bradycardia developed shortly after remimazolam administration and were refractory to ephedrine but responded promptly to intravenous epinephrine bolus followed by continuous infusion

ABGA revealed no significant abnormalities: pH 7.42, $PaCO_2$ 39 mmHg, PaO_2 170 mmHg, HCO_3^- 25.3 mmol/L, base excess 0.8 mmol/L, and lactate 3.0 mmol/L. During the management of presumed

anaphylaxis, there was no increase in peak airway pressures, chest auscultation remained unremarkable, and SpO_2 was maintained between 93-95%. Following hemodynamic stabilization, the surgical procedure was carried out as planned and completed without further complications.

The patient regained consciousness uneventfully in the postoperative period and was transferred to a general ward. The patient was informed of the suspected drug-related hypersensitivity reaction. To evaluate for hypersensitivity reactions, comprehensive allergy work-up including serum tryptase measurement, skin testing, and consultation with an allergy specialist was recommended to identify the causative agent and guide future anesthetic management. However, the patient declined further diagnostic evaluation.

DISCUSSION

Remimazolam besylate is an ultra-short-acting benzodiazepine increasingly used for anesthetic induction because of its favorable hemodynamic profile [1]. Although generally considered safe, rare cases of severe hypersensitivity reactions, including anaphylaxis, have been reported [2,3]. In the present case, the differential diagnosis during induction focused on distinguishing drug-induced anaphylaxis from other causes of acute ventilatory failure. Opioid-induced chest wall rigidity was unlikely, as no opioid, including remifentanil, had been administered at the time of symptom onset, and severe bronchospasm persisted despite neuromuscular blockade with rocuronium [4]. In addition, profound hypotension developed that was unresponsive to ephedrine but rapidly reversed by intravenous epinephrine, a hemodynamic response characteristic of anaphylactic shock [5]. The combination of refractory bronchospasm, circulatory collapse, and prompt epinephrine responsiveness strongly supported the diagnosis of remimazolam-induced anaphylaxis rather than other intraoperative complications.

A distinctive feature of this case was the near-simultaneous occurrence of severe bronchospasm and transient AV block. ECG demonstrated a transition from normal sinus rhythm to junctional bradycardia with AV conduction disturbance, an uncommon cardiac manifestation of perioperative anaphylaxis. This presentation is consistent with type I Kounis syndrome, in which allergic mediators induce coronary vasospasm and conduction abnormalities without underlying coronary artery disease [6].

The coexistence of respiratory and cardiac manifestations highlights the multisystem nature of severe hypersensitivity reactions and may complicate intraoperative diagnosis. Although the AV block in our patient was transient and resolved promptly after epinephrine administration, this underscores reaction severity and the need for vigilance regarding cardiac involvement during anaphylaxis. Careful cardiovascular monitoring should be considered in patients presenting with hypotension or arrhythmias in suspected perioperative anaphylaxis [6].

Remimazolam anaphylaxis may involve immune mechanisms beyond IgE-mediated pathways. Formulation components, particularly dextran-40, have been implicated in non–IgE-mediated pseudoallergic reactions through complement activation [7,8]. These reactions are indistinguishable from IgE-mediated anaphylaxis. Although allergy testing was not performed, negative skin testing has been reported, indicating that causality cannot be excluded by skin testing alone. Prior tolerance to other benzodiazepines or anesthetics does not guarantee safety, underscoring the need for vigilance despite unremarkable allergy history [1,8].

This case reinforces key clinical principles in perioperative anaphylaxis management. Early recognition during induction is critical, particularly when symptoms follow drug administration. Prompt intravenous epinephrine remains the cornerstone of treatment; in our patient, an initial bolus followed by continuous infusion achieved rapid hemodynamic stabilization, consistent with current recommendations [5]. Airway management, oxygen supplementation, fluid resuscitation, and vasopressor support are essential adjuncts.

Slower remimazolam infusion rates have been suggested to reduce peak drug and excipient exposure and potentially lower hypersensitivity risk, although supporting evidence is limited [3]. Given its expanding clinical use, heightened vigilance during induction is warranted. A limitation of this report is the absence of confirmatory allergy testing. Nevertheless, the temporal relationship between drug administration and symptom onset, exclusion of alternative causes, and multisystem involvement, including Kounis syndrome, strongly support remimazolam as the causative agent.

CONCLUSION

This case demonstrates that remimazolam, despite its favorable safety profile, can cause life-threatening anaphylaxis with multisystem involvement, including rare cardiac manifestations such as Kounis syndrome. Clinicians should maintain a high index of suspicion during induction and administer epinephrine promptly as first-line treatment. Prior tolerance to other anesthetics does not exclude hypersensitivity to remimazolam. As its clinical use expands, continued vigilance and post-event evaluation are essential to improve patient safety.

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