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Catecholamine-Refractory Vasoplegic Shock and Severe Abdominal Pain During Remimazolam Sedation in a Patient Receiving Capecitabine Chemotherapy: A Case Report and Literature Review

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Abstract **Case Report**

Refractory vasoplegic shock during procedural sedation poses a life-threatening challenge in perioperative medicine [1, 8]. Capecitabine, an oral prodrug of 5-fluorouracil (5-FU), is widely prescribed for gastrointestinal malignancies [2]. While fluoropyrimidine-induced coronary vasospasm is well recognized, its contribution to catecholamine-refractory vasoplegic shock remains poorly understood [2, 3]. A 73-year-old female with underlying diabetes mellitus, hypertension, and gallbladder cancer receiving adjuvant oral capecitabine underwent right foot extensor tendon repair under peripheral nerve block (PNB) and remimazolam sedation. Ten minutes following remimazolam administration, she developed sudden, profound hypotension (blood pressure < 50/30 mmHg). The hypotension was completely refractory to repeated boluses and continuous infusions of ephedrine, epinephrine, and norepinephrine, as well as 20% lipid emulsion (administered for suspected local anesthetic systemic toxicity [LAST]) and intravenous volume expansion. High-dose intravenous corticosteroids (methylprednisolone) were administered for suspected anaphylactic shock or acute relative adrenal insufficiency [5, 6]. The patient continuously complained of severe abdominal pain. Focused abdominal ultrasound, electrocardiography, and arterial blood gas analyses ruled out intra-abdominal hemorrhage, acute myocardial infarction, and severe metabolic acidosis. Hemodynamics spontaneously normalized in the intensive care unit (ICU) approximately 10 hours postoperatively. Capecitabine was held, and she was discharged without end-organ sequelae. Concurrent capecitabine therapy may induce subclinical vascular smooth muscle dysfunction and α_1-adrenoceptor desensitization [3]. When unmasked by remimazolam sedation [4], this state can trigger severe vasoplegic shock refractory to conventional catecholamines [1]. Early administration of stress-dose corticosteroids [6] and consideration of non-adrenergic vasopressors (e.g., vasopressin or methylene blue) [7, 8] are crucial therapeutic strategies.

Keywords: Capecitabine, Remimazolam, Vasoplegic shock, Catecholamine resistance, Corticosteroids, Abdominal pain.

INTRODUCTION

Vasoplegic shock is a form of distributive shock characterized by severe hypotension, reduced systemic vascular resistance, and blunted responsiveness to α-adrenergic vasopressors [1, 8]. While most commonly encountered following cardiopulmonary bypass or during severe sepsis, perioperative vasoplegia can unexpectedly occur during routine anesthesia induction or procedural sedation [1, 5]. Capecitabine is an oral fluoropyrimidine carbamate that undergoes a three-step enzymatic conversion to 5-fluorouracil (5-FU). Although 5-FU-associated cardiotoxicity, such as coronary artery vasospasm, is well-documented in up to 10% of patients [2], its systemic vascular effects—specifically vascular endothelial injury and smooth muscle desensitization—are far less recognized [3]. Remimazolam is an ultra-short-acting, ester-cleaved benzodiazepine favored for its superior hemodynamic stability compared to propofol [4]. However, isolated anaphylactoid collapse or synergistic blunting of sympathetic tone can still occur [4, 5]. Here, we report a rare case of profound, catecholamine-refractory vasoplegic shock accompanied by severe abdominal pain in a 73-year-old female undergoing active capecitabine therapy following remimazolam sedation. We further discuss the critical role of adjunctive corticosteroid therapy and review the underlying pathophysiological mechanisms. Written informed consent was obtained

from the patient for publication of this case report, and institutional ethical committee clearance was granted.

Case Report

A 73-year-old female (height: 152 cm, weight: 53 kg) presented for surgical repair of a right foot long extensor tendon and muscle injury. Her medical history included type 2 diabetes mellitus, hypertension, and mild cognitive impairment. Five months earlier, she had undergone surgery for gallbladder cancer and was receiving adjuvant oral capecitabine (originally 1,000 mg twice daily, adjusted to 1,000 mg three times daily starting 8 days before surgery). Standard American Society of Anesthesiologists (ASA) monitoring was established (blood pressure: 162/74 mmHg, heart rate: 50 beats/min, 〖"SpO" 〗_2: 97%). A popliteal and femoral peripheral nerve block (PNB) was performed using ropivacaine without immediate complications. For positioning and comfort, remimazolam sedation was initiated.

Approximately 10 minutes post-sedation, the patient suffered an abrupt circulatory collapse with blood pressure dropping below 50/30 mmHg. Repeated intravenous boluses of ephedrine (10–20 mg) yielded no arterial blood pressure response [1]. Due to the recent PNB and rapid collapse, local anesthetic systemic toxicity (LAST) and remimazolam-induced anaphylactoid shock were considered [5]. A 20% intravenous lipid emulsion (1.5 mL/kg) bolus was infused, accompanied by intravenous epinephrine boluses (100 mcg twice), but no pressor response was observed. Continuous intravenous infusions of norepinephrine (0.1–0.3 mcg/kg/min) and epinephrine (0.1–0.2 mcg/kg/min) were maintained alongside 1,000 mL of crystalloid volume resuscitation. Given the refractory shock and suspicion of acute steroid deficit or severe anaphylaxis, high-dose intravenous corticosteroid (methylprednisolone 125 mg) was administered [6]. Throughout the event, despite baseline dementia, the patient distinctly and continuously complained of severe, diffuse abdominal pain.

The 1-hour surgery was completed under vasopressor infusions, and the patient was transferred to the intensive care unit (ICU). Bedside abdominal ultrasonography demonstrated no free fluid, abdominal aortic aneurysm, or intra-abdominal hemorrhage. Serial 12-lead ECGs revealed normal sinus rhythm without ischemic ST-T changes [2]. Cardiac troponin-I and arterial blood gas analysis demonstrated preserved oxygenation without severe uncompensated metabolic lactic acidosis or evidence of acute myocardial infarction. Approximately 10 hours after surgery, vascular resistance recovered spontaneously. Vasopressors were successfully weaned, and blood pressure normalized (165/68 mmHg). Capecitabine was temporarily withheld. The abdominal pain resolved completely upon hemodynamic restoration. The patient was transferred to the general ward the following day and discharged without neurological or end-organ sequelae.

Discussion

Capecitabine is rapidly absorbed from the gastrointestinal tract and converted to 5-FU via a three-step enzymatic pathway involving hepatic carboxylesterase, cytidine deaminase, and tumor-associated thymidine phosphorylase [2]. While the elimination half-life (t_(1/2)) of plasma capecitabine and parent 5-FU are short (< 1 hour), intracellular active fluoropyrimidine metabolites (e.g., FUMP, FUTP, dFUMP) persist in tissues for 12-24 hours [2, 3]. This persistence correlates with the 10-hour duration of refractory vasoplegia observed in our patient.

Fluoropyrimidines induce vascular toxicity through multifactorial pathways [2, 3]. First, Direct endothelial cytotoxicity may increase nitric oxide (NO) production via cyclic guanosine monophosphate (cGMP) signaling, causing vascular smooth muscle relaxation [3, 7]. Second, fluoropyrimidines impair intracellular calcium (〖"Ca" 〗^(2+)) influx in vascular smooth muscle cells, blunting actin-myosin cross-bridge formation [3]. Third, endothelial inflammation downregulates membrane-bound α_1-adrenergic receptors [1, 3]. Consequently, exogenous catecholamines (ephedrine, epinephrine, norepinephrine) fail to elicit vasoconstriction, manifesting as catecholamine-refractory vasoplegic shock [1, 8].

Figure 1. Proposed Pathophysiological Mechanism of Capecitabine-Induced Refractory Vasoplegic Shock and Ischemic Abdominal Pain. (A) Intracellular accumulation of fluoropyrimidine metabolites induces endothelial nitric oxide synthase (eNOS/iNOS) dysregulation, 〖"Ca" 〗^(2+) channel inhibition, and α_1-adrenoceptor desensitization. (B) Synergistic reduction in sympathetic tone by remimazolam precipitates catecholamine-refractory vasoplegic shock. (C) Splanchnic hypoperfusion results in non-occlusive mesenteric ischemia (NOMI) and severe abdominal pain, which reverses upon vascular tone recovery.

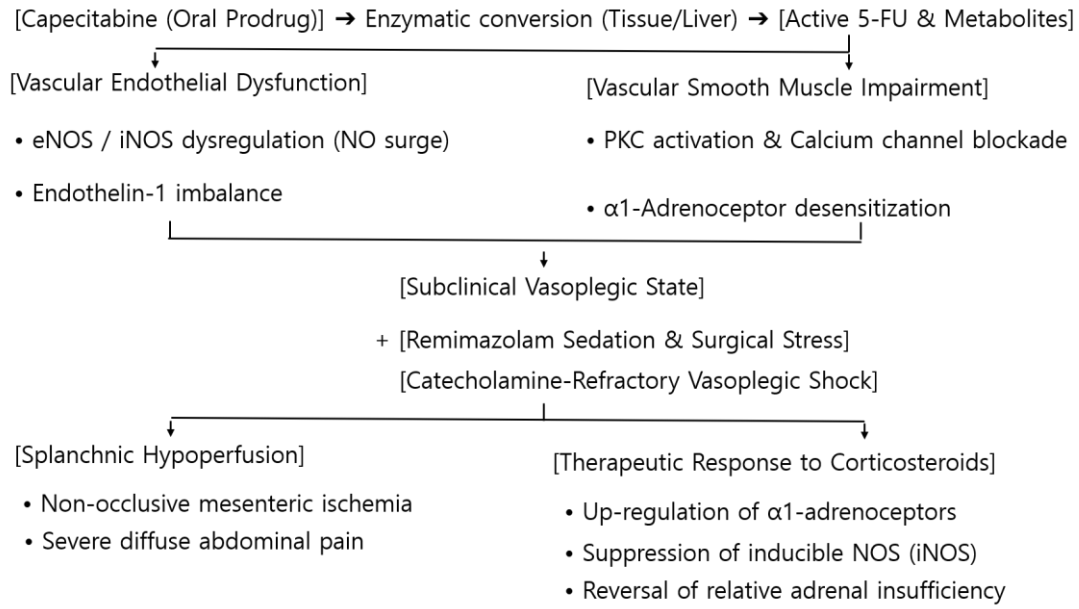

Figure 1: Proposed Pathophysiological Mechanism of Capecitabine-Induced Refractory Vasoplegic Shock and Ischemic Abdominal Pain

Remimazolam acts on 〖"GABA" 〗_A receptors to produce sedation [4]. Although its esterase-mediated metabolism typically preserves hemodynamic stability [4], reduced central sympathetic tone can precipitate catastrophic circulatory collapse in a vascular system rendered labile by capecitabine-induced endothelial desensitization [3, 5].

Methylprednisolone played a multimodal role in managing refractory vasoplegic shock [6]. Glucocorticoids increase the transcription and cell-surface expression of α_1-adrenergic receptors, directly reversing catecholamine resistance [1, 6]. Furthermore, corticosteroids suppress pro-inflammatory cytokines and downregulate inducible nitric oxide synthase (iNOS), curtailing elevated NO levels [6, 7]. They also provide coverage for relative adrenal insufficiency (RAI), as cancer patients undergoing surgical stress frequently exhibit impaired hypothalamic-pituitary-adrenal axis responsiveness [6].

The patient's severe abdominal pain without structural abnormalities on ultrasound is best explained by splanchnic hypoperfusion (non-occlusive mesenteric ischemia [NOMI]) [1, 8]. Severe vasoplegia causes selective vasoconstriction of the splanchnic circulation to preserve cerebral and coronary perfusion. Transient bowel ischemia, combined with direct capecitabine-induced gastrointestinal mucosal irritability [2, 3], manifests as severe abdominal pain that completely resolves upon hemodynamic restoration.

Differential diagnoses included remimazolam anaphylaxis, LAST, and acute adrenal crisis. Remimazolam anaphylaxis was considered due to sudden collapse post-sedation, but the absence of cutaneous signs, bronchospasm, and complete non-responsiveness to epinephrine made it less likely [5]. LAST was ruled out based on the lack of pressor response to 20% lipid emulsion and absence of cardiac arrhythmias or seizures. While acute adrenal crisis aligned with chronic malignancy, surgical stress, and resistant shock, the spontaneous full recovery without long-term steroid requirement supported drug-induced vasoplegia as the primary mechanism [6].

Clinically, the timing of the last chemotherapy dose should be routinely assessed. A 24-hour drug holiday prior to elective surgery should be considered after multidisciplinary consultation [2, 3]. When vasoplegic shock is unresponsive to catecholamines, non-adrenergic vasopressors should be initiated early: vasopressin ("V" _1-receptor agonist, dose: 0.01–0.04 units/min) directly contracts smooth muscle by bypassing desensitized adrenoceptors [1, 8], and methylene blue (bolus dose: 1–2 mg/kg IV) inhibits soluble guanylyl cyclase and NOS, blocking the NO-cGMP vasodilatory pathway [7, 8]. Early stress-dose corticosteroids (hydrocortisone 100–200 mg/day or methylprednisolone 1–2 mg/kg IV) are also strongly recommended [6].

CONCLUSION

Active oral capecitabine therapy can induce subclinical vascular endothelial dysfunction and catecholamine refractoriness [2, 3]. Under remimazolam sedation [4], this blunted vascular state can unmask catastrophic, refractory vasoplegic shock accompanied by splanchnic ischemic pain [1, 8]. Anesthesiologists should maintain a high index of suspicion, consider early stress-dose corticosteroids [6] alongside non-adrenergic agents (vasopressin/methylene blue) [7, 8], and

recognize that complete recovery aligns with the tissue clearance timeline of the chemotherapeutic agent [2, 3].

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