Adverse Drug Reaction: Midazolam-Induced Extrapyramidal Symptoms: A Case Report

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Midazolam is commonly used for sedation during procedures because of its relative safety and predictability. Still, some rare undesirable medication reactions have been described. We report a case in which midazolam given before a peripheral nerve block caused acute onset dyskinetic extrapyramidal symptoms. These symptoms ultimately resolved following reversal of the midazolam with flumazenil. Given the widespread and multidisciplinary use of midazolam, practitioners should be aware of the potential for rare adverse reactions and be prepared to manage these scenarios. (A&A Practice. 2020;14:e01248.)

GLOSSARY

CNS = central nervous system; **ECG** = electrocardiography; **EPS** = extrapyramidal symptoms; **GABA** = γ-aminobutyric acid; **IV** = intravenous; **LAST** = local anesthetic systemic toxicity; **ORIF** = open reduction internal fixation; **PCP** = primary care provider; **PICC** = peripherally inserted central catheter; **SSRI** = selective serotonin reuptake inhibitor

Midazolam is a short-acting benzodiazepine utilized in various clinical settings to provide sedation and anxiolysis and to induce general anesthesia in certain circumstances. Although midazolam is near ubiquitous in the perioperative and periprocedural environment due to its relative safety and predictability, rare untoward reactions following midazolam administration have been encountered and described, including paradoxic excitatory responses (anxiety, agitation, hostility) and unexpected motor disturbances (dystonia, dyskinesia, tremor, athetoid movements).[1–10] We report a case in which midazolam administration before a regional nerve block procedure resulted in the acute onset of dyskinetic extrapyramidal side effects, which terminated immediately on reversal with the benzodiazepine antagonist flumazenil. Written authorization patient consent was obtained for this case report.

CASE DESCRIPTION

A 60-year-old 50.4-kg woman was scheduled for an outpatient distal radius open reduction internal fixation (ORIF) surgery. Two weeks prior, the patient had tripped over a bathroom rug, falling onto an outstretched hand. Her medical history was significant for hypertension, moderate asthma, gastroesophageal reflux disease, depression, and active tobacco abuse. Her medications included diltiazem, valsartan, albuterol inhaler, omeprazole, paroxetine, and bupropion. She had previously undergone gastric bypass surgery (2015), resulting in a body mass index reduction from 48.5 to 20.7 over a 4-year period. Additional surgical history revealed an uncomplicated anesthetic for a laparoscopic cholecystectomy in 2015. She was advised to not take nonsteroidal anti-inflammatory drugs following her gastric bypass but did not endorse any medication allergies.

The anesthetic plan involved a combination of regional and general anesthesia. After thorough evaluation and informed consent, the patient underwent a preoperative, ultrasound-guided brachial plexus nerve block with an axillary approach. Per protocol, the patient was monitored with continual noninvasive blood pressure and continuous electrocardiography (ECG) and pulse oximetry. The patient was premedicated by the anesthesiologist with intravenous (IV) midazolam 2 mg and fentanyl 100 µg immediately before commencing the nerve block in the preoperative holding area. The skin was cleaned with chlorhexidine solution and punctured with a 2-inch 22-gauge Ultraplex 360 nonstimulating echogenic needle. Following negative aspiration, 5 mL of 0.5% bupivacaine with 1:200,000 epinephrine was injected and visualized appropriately filling around the musculocutaneous nerve. The patient was increasingly moving, and so before proceeding, the nerve block needle was removed and the patient was evaluated. She displayed distinct, persistent lip smacking but no facial twitching and repetitive, restless movements of the upper and lower extremities. The movements were fluid and not jerking in nature, with the lower extremities exhibiting an almost pedaling-like motion. This was accompanied by disorientation and unintelligible speech. Hemodynamic and ECG monitoring revealed no change from baseline during the injection and throughout the evaluation. Because the bedside examination was not most consistent local anesthetic systemic toxicity (LAST), flumazenil was immediately retrieved. A total dose of 0.3 mg flumazenil IV was administered in divided doses over 5–10 minutes, with further improvement of her symptoms

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following each dose. After the third and final dose, there was an immediate resolution of the dyskinetic movements and a return to baseline mental status. The patient was amnestic to the entire event. The remainder of the axillary nerve block was completed with an additional 25 mL of 0.5% bupivacaine with 1:200,000 epinephrine and 10 mL of 0.5% bupivacaine plain without incident. The patient proceeded to surgery under total IV anesthesia with a propofol infusion. The intraoperative course was uneventful.

In the postanesthesia care unit, the anesthesiologist spoke with the patient and her sister about the incident. During this conversation, the patient revealed that her father had noticed that she had recently been experiencing tremors. The patient was advised to follow-up with her primary care provider (PCP) and to consult a neurologist. In addition, the anesthesiologist conveyed the event to her PCP via electronic communication. The nerve block completely resolved after 24 hours. At the time of writing this report, our team and the PCP were unable to reach the patient.

Thorough chart review revealed that approximately 1 month later, the patient required a second surgery for revision distal radius ORIF. She underwent an uneventful preoperative ultrasound-guided axillary nerve block by the same regional anesthesiologist. Perioperative midazolam was avoided, and the patient exhibited no adverse reaction. Postoperatively, the patient developed a wound infection requiring peripherally inserted central catheter (PICC) line placement and outpatient IV antibiotic therapy. The patient then fell yet again and sustained a proximal humerus fracture that was managed nonoperatively. Three months after her initial distal radius ORIF surgery, the patient was scheduled for hardware removal. However, the procedure was postponed on the day of surgery due to uncontrolled hypertension. Attempts at preoperative blood pressure optimization were unsuccessful due to an inability to reach the patient by both the anesthesiologist preoperative clinic and the PCP. Two months later, the patient returned for hardware removal. Her blood pressure was again uncontrolled as she continued to be noncompliant with PCP follow-up. Therefore, the procedure was performed under local anesthesia by the surgeon without sedation.

DISCUSSION

Medication-induced extrapyramidal symptoms (EPS) represent a spectrum of abnormal movement disturbances (dyskinesias), including dystonias (involuntary contractions including torticollis, trismus, opisthotonus, oculogyric crisis), Parkinsonism (tremor, rigidity, bradykinesia), and akathisia (restlessness, repetitive movements).[11] These effects are a known potential sequelae of the acute or chronic administration of dopamine receptor blocking agents, most commonly associated with first-generation neuroleptic medications (ie, haloperidol, prochlorperazine) but observed with other agents as well (antidepressants including serotonin reuptake inhibitors and tricyclics; antiemetics including metoclopramide).[12,13] While the underlying neurobiologic mechanisms of medication-induced EPS are incompletely understood, they are presumed to involve neuronal dysfunction within the basal ganglia resulting from dopaminergic antagonism and neurotransmitter (dopamine, acetylcholine, serotonin, γ-aminobutyric acid [GABA]) imbalance.[8,11]

Benzodiazepines exert their sedative/anxiolytic effect by enhancing the inhibitory effects of GABA within the central nervous system (CNS).[9] Rarely, midazolam can also elicit paradoxical disinhibition[9,10] and dyskinetic motor disturbances.[1–8] Published data describing midazolam-induced dyskinetic reactions are limited to a small cohort of case studies, including acute dystonia in a 6-year-old girl receiving sedation with midazolam before removal of a foreign body,[2] EPS in an 82-year-old man receiving subcutaneous midazolam in a palliative care setting,[3] athetoid movements of the lower extremities in 2 geriatric patients premedicated with midazolam before epidural anesthesia,[4] dystonic reaction to IV midazolam in a 14-year-old boy before endoscopy,[5] and dyskinesias in a 58-year-old woman who received midazolam for epidural anesthesia.[6]

In each of the above cases, the unexpected motor disturbances were reversible and terminated either by cessation of midazolam itself or by administering alternate medications (antagonists such as flumazenil and physostigmine or alternate sedatives including propofol and, paradoxically, diazepam). In our case, the dyskinesias resolved with flumazenil. Like previous authors, we can only speculate regarding the etiology of symptoms that were observed. Interplay between dopamine and GABA receptors in the brainstem is implicated by Stolarek and Ford[5]; Prommer[1] evokes the structural heterogeneity of GABA receptors within the CNS and suggests that EPS and other "motoric phenomena" occur by benzodiazepine-enhanced GABA inhibition within the basal ganglia. Vorsanger and Roberts[4] hypothesize that anticholinergic activity by midazolam may also contribute, hence the capacity for physostigmine reversal. Our patient was managed on dual selective serotonin reuptake inhibitor (SSRI) medications, which can independently cause extrapyramidal reactions and parkinsonism.[13] Did a single dose of midazolam "tip the scales" to induce these symptoms? Furthermore, given our patient's admission of recent new-onset tremors, did we observe latent parkinsonian motor symptoms via some "unmasking" phenomena by midazolam? The patient's ongoing unsteadiness with frequent falls further supports the possibility of an underlying neurological disorder.

During our initial clinical evaluation of the patient, the differential diagnosis for the cause of her symptoms included LAST. However, aspiration before injection was negative; the 5 mL of local anesthetic injected appropriately filled around the musculocutaneous nerve; and there were no signs of increased heart rate, blood pressure, or ECG changes despite 1:200,000 of epinephrine in the solution. The patient never complained of symptoms such as metallic taste, tinnitus, or perioral numbness, although only approximately 15% of patients experienced prodromal symptoms with LAST.[14] Her extremity motor disturbances were not clonic, myoclonic, tonic, or tonic-clonic in nature, but, rather, were fluid dyskinetic movements. The patient also exhibited lip smacking, a well-known extrapyramidal symptom that more commonly presents in women.[15] Finally, her symptoms resolved in a dose-dependent manner with flumazenil. If this were LAST, one would expect that her symptoms would in fact worsen with the reversal of midazolam, as midazolam is used to treat neurologic symptoms of LAST.

In summary, this case report describes extrapyramidal side effects in response to premedication with midazolam, which terminated by reversal with flumazenil. This case illustrates potential patient risk factors for untoward reactions with benzodiazepines, including undiagnosed movement disorders and polypharmacy medication interactions. Given the widespread use of midazolam, practitioners should be aware of the potential for rare untoward reactions to occur and be prepared to manage these scenarios when necessary.

DISCLOSURES

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