



# Midazolam-Induced Hyperactivity Treated with Flumazenil

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## Abstract

Benzodiazepines are characteristically anxiolytic, amnestic, and sedative. However, paradoxical reactions may cause agitation or aggression. We report a case in which a postoperative paradoxical reaction to midazolam was successfully managed with flumazenil (a benzodiazepine-receptor antagonist). Whilst the aetiology of benzodiazepine-induced hyperactivity remains unclear, this report demonstrates that even small amounts of flumazenil is an effective treatment. Despite the risks associated with the use of flumazenil we recommend its use for both diagnostic and therapeutic purposes.

**Keywords:** Midazolam, Benzodiazepine, Flumazenil

## Introduction

Benzodiazepines are characteristically anxiolytic, amnestic, and sedative. However, paradoxical reactions may result in restlessness, agitation, or aggression. This case report describes successful management of a postoperative paradoxical reaction to midazolam with the benzodiazepine-receptor antagonist flumazenil.

## Case Report

68-year-old Caucasian male with prostate cancer presented for elective robot-assisted laparoscopic prostatectomy. He also had osteoarthritis, hypertension, hypercholesterolemia, obesity, coronary artery disease (post coronary artery bypass graft) and obstructive sleep apnoea (not requiring CPAP). His regular medications included aspirin, atorvastatin, finasteride, losartan, metoprolol, mometasone furoate, nitroglycerin, terazosin, and meloxicam. He denied previous adverse drug reactions and had not had any previous complications with general anaesthesia.

He was premedicated with midazolam (2 mg i.v.) and, notably, was relaxed and drowsy thereafter. The patient was induced without incident using fentanyl 200 mcg, propofol 250 mg and

vecuronium 10 mg. Anaesthesia was maintained with isoflurane, remifentanyl infusion and intermittent boluses of morphine (total 10 mg). Dexamethasone and diphenhydramine were administered for prophylaxis against postoperative nausea and vomiting. The prostatectomy was extremely difficult and was aborted after two hours. Residual neuromuscular blockade was reversed, isoflurane was stopped and the patient was extubated uneventfully.

Prior to transfer to the post-anaesthesia care unit (PACU), the patient became agitated and aggressive. He insisted on using the restroom to urinate despite having a urinary catheter in situ. He pulled at the oxygen facemask and required manual restraint to prevent self-harm from falling out of bed. After administration of 1 mg of midazolam the agitation increased. He struggled against the restraints and continued to try to get out of bed, despite reassurance that he had a catheter in his bladder. His vital signs remained stable throughout this period. Ten minutes later another 1 mg of midazolam was given and he appeared to settle, so transfer to the PACU was initiated. En route he became more restless and struggled against his physical restraints; so, another 1 mg of midazolam was

given. On arrival in the PACU, the patient's vital signs were all stable (BP 147/83 mmHg, HR 75 beats per minute, SaO<sub>2</sub> 96%, RR 14 breaths per minute, T 36.4 °C) and there was no focal neurological deficit but physical restraint was still required. Despite a further 1 mg of midazolam the patient continued to struggle.

Ultimately, flumazenil 0.5mg was given in divided doses to reverse the effects of midazolam. Within three minutes the patient calmed, stopped struggling, answered all questions appropriately and asked for removal of the restraints. He subsequently denied having any recollection of the preceding events.

## Discussion

The aetiology and mechanism of benzodiazepine-induced paradoxical hyperactivity have yet to be elucidated, although a central cholinergic mechanism has been suggested [1]. This report and others [1] demonstrate even small amounts of flumazenil can be effective in treating this. Despite the risks associated with the use of flumazenil we recommend its use for both diagnostic and therapeutic purposes.

## References

1. Thurston TA, Williams CGA (1996) Reversal of a paradoxical reaction to midazolam with flumazenil. *Anesthesia and Analgesia* 83: 192.



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