Paradoxical Reactions to Midazolam in a Term Parturient After Intravenous Sedation During Cesarean Section

Sivakumar Sengottaian 1, Roni Mendonca 1, Don Demeterio 2, Michael Girshin 2

1. Anesthesiology, Metropolitan Hospitals, New York, USA 2. Anesthesiology and Perioperative Medicine, Metropolitan Hospitals, New York, USA

Corresponding author: Sengottaian Sivakumar, sengottaian@yahoo.com

Abstract

Propofol and midazolam are commonly used drugs in procedural sedation. Midazolam is widely used for its five principal pharmacologic effects: anxiolysis, sedation and hypnotic, anticonvulsant actions, spinal cord-mediated skeletal muscle relaxation, and anterograde amnesia. Increased talkativeness, emotional release, excitement, and excessive movement are the common paradoxical reactions to all kinds of benzodiazepines, which are reported since the introduction of chlordiazepoxide (Librium), the first benzodiazepine in 1955. In the United States, sedation with a combination of midazolam with opioids accounts for approximately 75% of routine procedural sedations. Most cases are distinctive. However, some data indicate that these reactions are due to serotonin imbalance, a central cholinergic effect, or a reflection of genetically determined variability in benzodiazepine receptor density or affinity (isoreceptors) throughout the brain. The idea of isoreceptors is comparable to that of isoenzymes like genetic variants of pseudocholinesterase. We report a case in which midazolam administration resulted in paradoxical reactions, which manifested as profound delirium with extrapyramidal symptoms after cessation of propofol sedation in a term parturient during cesarean section. This case report describes paradoxical reactions to benzodiazepines in a term parturient promptly reversed with a small dose of flumazenil. Even though paradoxical reactions to benzodiazepines have low prevalence and are not life-threatening, they have to be treated promptly with flumazenil. Therefore, anesthesiologists performing procedural sedation should be aware of untoward reactions and be prepared to manage them promptly.

Keywords: Anesthesiology, Neurology, Obstetrics/Gynecology

Introduction

Propofol and midazolam are commonly used drugs in procedural sedation. Midazolam is widely used for its five principal pharmacologic effects: anxiolysis, sedation and hypnotic, anticonvulsant actions, spinal cord-mediated skeletal muscle relaxation, and anterograde amnesia. Increased talkativeness, emotional release, excitement, and excessive movement are common paradoxical reactions to all kinds of benzodiazepines, which have been reported since the introduction of chlordiazepoxide (Librium), the first benzodiazepine in 1955. In the United States, sedation with a combination of midazolam with opioids accounts for approximately 75% of routine procedural sedation for esophagogastroduodenoscopies and colonoscopies [1]. Most cases are distinctive. However, some data indicate that these reactions are due to a genetic link [2]. We report a case in which midazolam administration resulted in paradoxical reactions, which manifested as profound delirium with extrapyramidal symptoms after cessation of propofol sedation in a term parturient.

Case Presentation

A 37-year-old Gravida 3 Para 0 Hispanic female parturient at 40 weeks of gestation presented with lower abdominal pain and regular contractions. Her past medical history was significant for cystic fibrosis carrier state and gestational diabetes mellitus. The patient had no history of psychiatric illness, substance abuse, or seizure disorder. Throughout her antenatal period, she did not take any medications except for prenatal vitamins. As her labor pains progressed, she requested labor epidural analgesia. Preprocedural examination revealed body mass index (BMI) 29.49 kg/m², pulse rate 90/minute, blood pressure 96/66 mmHg, oxygen saturation 99%, and respiratory rate 14/minute. With the patient in a sitting position, the L3-4 interspace was identified, and the procedure was carried out with standard sterile precautions. With an 18G Tuohy needle, the epidural space was reached at 4 centimeters from the skin by the loss of resistance to saline technique. A 20 G multi-orifice epidural catheter threaded up to a length of 10 centimeters at the skin level. After a negative test dose, ropivacaine 2 mg/ml epidural infusion started at the rate of 10 ml/hour. Her pain relief was excellent, and she continued to be in labor for 29 hours post epidural placement. Due to arrest of descent, an emergent cesarean section was called, the patient was moved to the operating room, and standard American Society of Anesthesiologists (ASA) monitors were connected. Epidural fentanyl 100 mcg bolus along with three separate doses of 5 ml 2% lidocaine with epinephrine 1: 100,000...
The management of these reactions should be done systematically. Soothing and comforting of the patient
CYP3A4 enzymes was not studied in cystic fibrosis carriers. intestinal CYP3A4 activity, affecting the metabolism of orally administered midazolam inactive metabolites. Cystic fibrosis carriers have one copy of the mutated cystic fibrosis gene and increased Midazolam is metabolized by hepatic and small intestine cytochrome CYP3A4 enzymes to active and isoenzymes like genetic variants of pseudocholinesterase. serotonin imbalance or a reflection of genetically determined variability in benzodiazepine receptor density mechanism of paradoxical reactions is unknown, it may be related to the central cholinergic effect or cause bodily harm from physical injuries due to agitation and aggressive behavior. Although the exact patient. However, it creates an unpleasant memory for the caregivers surrounding the patient and can also
Nearly all these reactions are preceded by a short period of apparent sedation, after which the patient is seen in a state of intense agitation. Reactions do not affect the vital signs and are usually not recalled by the patient. During cesarean section, it is commonly given for anxiolysis after delivery of the fetus. Unfortunately, some patients experience paradoxical reactions to benzodiazepines. These may include agitation, hallucinations, restlessness, disorientation, uncontrollable crying or verbalization, involuntary movements, self-injury, and aggressive or violent behavior, which sometimes requires restraints. Usually, they manifest in five minutes after administration, and these reactions are termed paradoxical or disinhibitory reactions. These reactions include drug reactions, intractable pain, acute pathological states such as cerebrovascular events causing changes in brain perfusion or oxygenation, exacerbation of preexisting neurologic or psychiatric illness, and psychological stress related to surgery itself.

Among the drugs given to this patient, intravenous propofol, intravenous and epidural fentanyl [4-7], and ondansetron [8] are all capable of producing delirium and excitatory symptoms. Paradoxical reactions are common in patients with alcohol abuse disorder or mental health condition that causes extreme mood swings [7]. Our patient had no prior psychiatric or neurological illness. Her intraoperative glucose levels were also within normal limits. No hypoxic or hypotensive episodes were noted during the perioperative period, resulting in cerebral hypoxia. As the patient had a working epidural block supplemented at regular intervals, intractable pain may not be the reason for her delirium. These paradoxical reactions can also be attributed to propofol [9], but it was readily reversed with flumazenil, which quickly points towards the diagnosis of midazolam-induced paradoxical reactions.

As midazolam readily crosses the placenta, it is associated with severe respiratory depression in newborns. During cesarean section, it is commonly given for anxiolysis after delivery of the fetus. Unfortunately, some patients experience paradoxical reactions to benzodiazepines. These may include agitation, hallucinations, restlessness, disorientation, uncontrollable crying or verbalization, involuntary movements, self-injury, and aggressive or violent behavior, which sometimes requires restraints. Usually, they manifest in five minutes after administration, and these reactions are termed paradoxical or disinhibitory reactions. These reactions are more common in the pediatric population [10].

Nearly all these reactions are preceded by a short period of apparent sedation, after which the patient is seen in a state of intense agitation. Reactions do not affect the vital signs and are usually not recalled by the patient. However, it creates an unpleasant memory for the caregivers surrounding the patient and can also cause bodily harm from physical injuries due to agitation and aggressive behavior. Although the exact mechanism of paradoxical reactions is unknown, it may be related to the central cholinergic effect or serotonin imbalance or a reflection of genetically determined variability in benzodiazepine receptor density or affinity (isoceptors) throughout the brain [2,7]. The idea of isoceptors is comparable to that of isoenzymes like genetic variants of pseudocholinesterase.

Midazolam is metabolized by hepatic and small intestine cytochrome CYP3A4 enzymes to active and inactive metabolites. Cystic fibrosis carriers have one copy of the mutated cystic fibrosis gene and increased incidence risk of a wide range of cystic fibrosis-related conditions. Cystic fibrosis patients have increased intestinal CYP3A4 activity, affecting the metabolism of orally administered midazolam [11]. The activity of CYP3A4 enzymes was not studied in cystic fibrosis carriers.

The management of these reactions should be done systematically. Soothing and comforting of the patient
is instituted. If the patient is unconstrained, combative, and confused, a diagnosis of paradoxical reaction should be weighed consistently. An initial dose of flumazenil (0.1-0.2 mg) should then be administered intravenously [7]. Furthermore, the same dose can be repeated after 60 seconds to a maximum dose of 1 mg. The onset of flumazenil’s effect is two to three minutes, and its peak effect occurs at five to six minutes. Flumazenil should be used judiciously if the patient has a history of seizures controlled with benzodiazepines. Postoperative monitoring of the patient is crucial because paradoxical reaction might reappear as flumazenil has a shorter half-life than midazolam [7]. In such cases, a continuous infusion may be required at the dose is 0.1-0.4 mg per hour. For pediatric cases, reversal with flumazenil has been attained with doses of 0.01 mg/kg [12]. Flumazenil can cause seizures and cardiac arrhythmias, and it has to be used with caution in preexisting seizure disorder and cardiac arrhythmia patients [13]. Even though there are concerns for breastfeeding for few hours after the last dose of flumazenil [14], in this case, breastfeeding was withheld for five hours after birth due to the mother’s mental instability.

Conclusions
In summary, this case report describes paradoxical reactions to benzodiazepines in a term parturient promptly reversed with a small dose of flumazenil. Even though paradoxical reactions to benzodiazepines have low prevalence and are not life-threatening, treatment with flumazenil should be strongly considered. Therefore, anesthesiologists performing procedural sedation should be aware of the untoward reactions and should be prepared to manage them promptly.

Additional Information
Disclosures
Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References
1. Cohen LB, Wescler JS, Gaetano JN, Benson AA, Miller KM, Durkalski V, Aisenberg J: Endoscopic sedation in the United States: results from a nationwide survey. Am J Gastroenterol. 2006, 101:967-74.
2. Short TG, Forrest P, Galletly DC: Paradoxical reactions to benzodiazepines – a genetically determined phenomenon?. Anesth Intensive Care. 1987, 15:330-1. 10.1111/j.1744-8517.1987.tb00314.x
3. Dehring DJ, Gupta B, Peruzzi WT: Postoperative opisthotonus and torticollis after fentanyl, enflurane, and nitrous oxide. Can J Anaesth. 1991, 38:919-25. 10.1007/BF03056975
4. Tae CH, Kang KJ, Min BH, et al.: Paradoxical reaction to midazolam in patients undergoing endoscopy under sedation: Incidence, risk factors and the effect of flumazenil. Dig Liver Dis. 2014, 46:710-5. 10.1016/j.dld.2014.04.007
5. McConnell MM, Gundy JT, Karon SB, Lindenmuth DM: Adverse drug reaction: midazolam-induced extrapyramidal symptoms: a case report. A A Pract. 2020, 14:e01248. 10.1215/AAX.00000000001248
6. Robin C, Trieger N: Paradoxical reactions to benzodiazepines in intravenous sedation: a report of 2 cases and review of the literature. Anesth Prog. 2002, 49:128-32.
7. van der Bijl P, Roelofse JA: Disinhibitory reactions to benzodiazepines: a review. J Oral Maxillofac Surg. 1999, 49:519-23. 10.1016/S0278-2749(91)90180-T
8. Tolan MM, Fuhrman TM, Tsueda K, Lippmann SB: Perioperative extrapyramidal reactions associated with ondansetron. Anesthesiology. 1999, 90:540-1. 10.1097/00000542-199901000-00073
9. Lee SH, Lee GM, Lee DR, Lee IU: Factors related to paradoxical reactions during propofol-induced sedated endoscopy. Scand J Gastroenterol. 2019, 54:371-6. 10.1080/00365521.2019.1585958
10. Moon YE: Paradoxical reaction to midazolam in children. Korean J Anesthesiol. 2013, 65:2-5.
11. Johnson TN, Tanner MS, Taylor CJ, Tucker GF: Enteroctylic CYP3A4 in a paediatric population: developmental changes and the effect of coeliac disease and cystic fibrosis. Br J Clin Pharmacol. 2001, 51:451-6. 10.1046/j.1365-2125.2001.01370.x
12. Massanari M, Novitsky J, Reinstein LJ: Paradoxical reactions to benzodiazepines during endoscopy. Clin Pediatr (Phila). 1997, 36:880-4. 10.1177/000992289703601302
13. Penninga EI, Graudal N, Ladekarl MB, Jürgens G: Adverse events associated with flumazenil treatment for the management of suspected benzodiazepine intoxication - a systematic review with meta-analyses of randomised trials. Basic Clin Pharmacol Toxicol. 2016, 118:37-44. 10.1111/bcpt.12454
14. Briggs G, Freeman RK, Yaffe SI: Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 7th Edn. Lippincott, Williams & Wilkins, Philadelphia, Pennsylvania; 2005.