

Paradoxical Reaction With Midazolam

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Citation

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Abstract

We report 4 cases of paradoxical reaction to midazolam after being used for sedation. The picture was characterized by a marked aggressiveness. In one case the reaction was treated with general anesthesia, whereas in the other two patients the clinical picture was rapidly reversed by administration of fentanyl. We describe the possible causative mechanisms of this reaction as well as their treatment.

INTRODUCTION

Midazolam has sedative, anxiolytic, and anesthetic effects with proper doses. However even with normal doses excitation, aggression, disorientation, tachycardia, uncomfortable feeling can be seen. This phenomenon is called as paradoxical disinhibitory reaction. (1).

We report 4 cases of paradoxical reaction to midazolam after being used for sedation in our clinic during past 10 years. The picture was characterized by a marked aggressiveness. In one case the reaction was treated with general anesthesia, whereas in the other two patients the clinical picture was rapidly reversed by administration of fentanyl. We describe the possible causative mechanisms of this reaction as well as their treatment.

CASE REPORTS

CASE 1

A 82 years old male was diagnosed with inguinal hernia. In preanesthetic examination signs of pulmonary infection was determined and expiratory time was longer than normal. He was consulted by respiratory diseases department. He had diagnosis of mixed type respiratory disease. Following three weeks treatment including antibiotics, corticosteroids, aminophylline, mucolytic and antitussive medication his respiratory tests were normal. Blood gas analysis was normal. In his medical history several antiulcer drug use was noted. Epidural anesthesia was chosen for the operation. In the operation room under standard monitorization 0.015 mg/kg iv midazolam was given the patient for sedative purpose. When we applied local anesthesia for epidural procedure we observed agitation. The patient calmed down

and sedated with fentanyl 1 µg/kg. The patient became stable and general anesthesia preferred for the operation under new circumstances. There were no extra problems during and after surgery. The patient was sent to his ward after the operation.

CASE 2

A 60 years old female patient was diagnosed with cholelithiasis when she came to the emergency room with vomiting and abdominal distention. Laparoscopic cholecystectomy was planned. In the patient's medical history there was digoxin use over a year due to the heart failure and also H₂ receptor antagonist (ranitidine). Her blood pressure was 160/60 mmHg and heart rate was 60 min⁻¹. She was consulted by cardiologist and no additional treatment was suggested. All other laboratory tests were normal. In the operation room addition to standard monitorization for invasive blood pressure measurement placement of arterial cannula was planned. Local anesthetic applied for cannulation and 0.015 mg/kg iv midazolam was given for sedation. The patient showed agitation after midazolam administration. Fentanyl 1 µg/kg iv was given for sedation. Later on, general anesthesia induction was started and she was successfully operated.

CASE 3

A 38 years old female patient was planned to have operation for breast cancer. All preanesthetic examinations and laboratory tests were normal. Midazolam 0.01 mg/kg iv was given for preoperative sedation. Agitation was observed after midazolam administration. General anesthesia induction was immediately started. She was operated without any problem.

CASE 4

A 35 years old female patient was planned to have operation for breast cancer. All preanesthetic examinations and laboratory tests were normal. Midazolam 0.01 mg/kg iv was given for preoperative sedation. Agitation was observed after midazolam administration. General anesthesia induction was immediately started. She was operated without any problem.

DISCUSSION

Midazolam is a frequently used drug which belongs to benzodiazepines. Imidazole chain group provides water solubility and short acting time. Its effects like sedation, dizziness, sleep and anesthesia are dose dependent effects. Its first effects limbic system and it supplies muscle relaxation by central nervous system. Midazolam is an anticonvulsant drug also decreases intracranial and intraocular pressures.⁽²⁾

However even with proper doses excitation, aggression, tachycardia, uncomfortable feeling and disorientation can be seen. This phenomenon is called as disinhibitory reaction or paradox reaction.^(3,4)

Massanari et al reported that incidence of this phenomenon is (4) % 1.4. In a study by Pena and Krauss⁽⁵⁾ in 7 children among 1180 showed this phenomenon after sedation with midazolam. In another study with dogs showed that ataxia and agitation can reverse in two our following midazolam administration⁽⁶⁾. Oral midazolam intake can cause delirium in children⁽⁷⁾.

It is not well understood what causes the paradoxical reaction. It is believed that some people who has personality problems and genetic characteristics shows this phenomenon. Hypoventilation, hypoxia, hypotension and other drugs can start or worsen the situation. Midazolam mainly effects benzodiazepine receptors in GABA receptor complex and it can also effect acetylcholine, serotonin or catecholamine mediator functions. Existing pain, fever and constipation can cause the phenomenon. Lorazepam or clonazepam can be used for agitation⁽⁸⁾.

Senninger and Laxenaire⁽⁶⁾ claimed that paradoxical reaction is dose dependant. Many different kind of drugs are used for treatment and flumazenil can reverse the signs of this phenomenon without blocking the sedation.^(3,4,10). Opioids or haloperidol use can be another choice to treat the reaction⁽¹¹⁾. General anesthesia can be used for persisting reactions⁽³⁾.

Massanari et al reported that paradoxical reaction⁽⁴⁾ can be seen in 17 minutes after midazolam administration and can reverse in 14 minutes after flumazenil administration.

In our clinic, we use midazolam mostly for preoperative sedation in the operation room and we start anesthesia induction in very short time after drug use.

In our two cases, one had heart problems and other had respiratory problems. The patient with respiratory problems had proper treatment in preoperative period and his SpO₂ value could raise till %94. The patient with diagnosis of heart failure was using digoxin. As we described above, both of this respiratory and cardiac problems can cause paradoxical reaction.

In our two cases, even there were no possible causes leading paradoxical reaction in patients' medical background we observed agitation in both patient after midazolam administration.

Midazolam is mainly eliminated in liver so that all changes in liver blood flow can effect its elimination time and influence. H₂ receptor antagonists can change liver blood flow and also cause enzyme induction resulting in alteration of drug metabolism. Cytochrome p 450 is one of the enzymes playing role of elimination of midazolam. The drugs inhibiting cytochrome p 450 can effect midazolam's metabolism and influence.⁽¹²⁾ In our first case the patient was using anti ulcer drugs and in our second case she was using H₂ antagonist.

Midazolam is a water-soluble drug however in physiologic pH value it behaves like lipophilic drugs and it can pass through the blood brain barrier⁽¹³⁾. This gives drug anterograde amnesia properties, which is a desired effect of midazolam, but also can cause agitation and aggression.

Midazolam is sedative, anesthetic and anxiolytic drug but it has no analgesic effects. In our two cases although we used the local anesthetics agitation was observed after painful procedures. We observed sedation after use of narcotic analgesics which possibly resulted in pain relief.

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References

1. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology* 1985; 62: 310-2.
2. Collins VJ, Intravenous anesthesia: nonbarbiturates-non narcotics In *Principles of Anesthesiology*, Collins VJ(ed) Lea & Febiger, Philadelphia, 1993; 734-86.
3. Martínez Tellería A, Cano ME, Carlos R. Paradoxical reaction to midazolam after its use as a sedative in regional anesthesia. *Rev Esp Anestesiol Reanim* 1992; 39:379-80.
4. Massanari M, Novitsky J, Reinstein LJ. Paradoxical reactions in children associated with midazolam use during endoscopy (abstract). *Clin Pediatr (Phila)*, 1997; 36:681-4.
5. Peña BM, Krauss B. Adverse events of procedural sedation and analgesia in a pediatric emergency department. *Ann Emerg Med* 1999; 34: 483-91.
6. Court MH, Greenblatt DJ: Pharmacokinetics and preliminary observations of behavioral changes following administration of midazolam to dogs (abstract). *J Vet Pharmacol Ther* 1992;15: 343-50.
7. Doyle WL, Perrin L. Emergence delirium in a child given oral midazolam for conscious sedation. *Ann Emerg Med* 1994 ; 24: 1173-5.
8. Jakobsson M, Strang P. Midazolam(dormicum) in terminal anxiety and agitation. The last choice alternative in palliative care (abstract). *Lakartidningen* 1999;96:17;2079-81.
9. Senninger JL, Laxenaire M. Violent paradoxal reactions secondary to the use of benzodiazepines. *Ann Med Psychol (Paris)* 1995;153: 278-81.
10. Thurnstonp TA. Reversal of paradoxical reaction to midazolam with flumazenil. *Anesth Analg* 1996; 83:192.
11. Lubna C. Treatment of a paradoxical reaction to midazolam with haloperidol. *Anesth Analg* 1997; 85: 213-5.
12. Atkinson RS, Rushman GB, Davies NJH .Intravenous anesthetics In Lee's synopsis of anaesthesia. Atkinson RS, Rushman GB, Davies NJH (eds): Butterworth-Heinemann ltd. Kent, England. 1993; 157-88.
13. Trevor AJ, Miller RD, General Anesthetics In *Basic & Clinical pharmacology*. Katzung BG (ed) Mc Graw Hill, New York 2001; 419-35.

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