Midazolam-induced acute dystonia reversed by diazepam

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Abstract

Midazolam can induce acute dystonia in childhood. We report the development of acute dystonia in a 6-year-old girl after receiving midazolam as a sedative. Dystonic contractions persisted despite flumazenil and biperiden lactate injections and the patient was treated with diazepam. Acute dystonia was rapidly abolished after the administration of diazepam intravenously. Diazepam may be an effective treatment option in patients who are unresponsive to flumazenil.

Key words: Acute dystonia, diazepam, midazolam

Introduction

Dystonia is a neurologic disorder characterized by sustained muscle contractions producing torsional and repetitive movements or abnormal postures. It can be classified as focal, multifocal, segmental, hemi-dystonia, or generalized. In children generalized dystonia is observed frequently.[1,2] Midazolam is a short-acting benzodiazepine used for induction and maintenance of general anesthesia and for sedation in palliative care. Several adverse reactions have been reported after midazolam use, which include agitated excitement, mental confusion, and extrapyramidal reactions, such as dystonia, athetoid movements, and tremor.[3] Midazolam-induced acute dystonia was rarely reported in the literature.[3-5]

We report midazolam-induced acute dystonia in a 6-year-old girl reversed by diazepam. This is possibly the youngest case reported in the literature that developed acute dystonic reaction after midazolam injection and the first case reversed by diazepam.

Case Report

A previously healthy 6-year-old girl was given intravenous (IV) midazolam (0.2 mg/kg) as a sedative prior to removing foreign body from external ear canal, without any other premedication. Five minutes after midazolam injection the patient has developed dystonic contractions. The dystonic contractions persisted despite administration of flumazenil (0.01 mg/kg) and biperiden lactate (2.5 mg) IV twice. There were no history of consanguinity, psychiatric disorder or neurological disorders, including dystonia, in the family. The vital signs of the patient were in normal ranges and she was alert and oriented. She was in opisthotonus posture and there were dystonic contractions in lower and upper extremities.

The complete blood count, liver and renal function tests, electrolytes and glucose concentrations were normal. Serum creatine phosphokinase (CK) was raised to 700 U/L. The patient was given diazepam 0.2 mg/kg IV, since dystonic contractions persisted despite flumazenil (0.01 mg/kg) and biperiden lactate (2.5 mg) administration two times. Acute dystonia rapidly abolished within 4 minutes after the administration of diazepam. Diazepam was repeated at 4 hours intervals, because dystonic contractions relapsed 4 hours after the first diazepam administration. Two days after the recovery from the dystonic contractions diazepam was stopped.

By the fourth day of the hospitalisation serum CK decreased to normal range. Brain magnetic resonance imaging (MRI) and electroencephalography (EEG) were normal. Secondary dystonia was excluded with the normal images at basal ganglia on MRI [Figure 1]. Tandem mass and urine organic acid analyzes were normal. The patient was discharged to home on the fifth day of hospitalization.
A prolonged (5.6 hours) in older men. 
Extrapyramidal side effects have been reported to disappear completely in a few days after the cessation of midazolam treatment. 
Dystonic reactions persisted longer than the estimated half life of midazolam in our patient. The half-life of midazolam may have been prolonged in our patient due to an unestablished factor. 
Facilitation of the inhibitory effects of gama-aminobutyric acid (GABA) or anticholinergic effects in the central nervous system may be the underlying mechanisms of the extrapyramidal reactions induced by midazolam. 
GABA is a major inhibitory neurotransmitter. 
Midazolam facilitates the inhibitory effects of GABA at the presynaptic junction through GABA\(_A\) receptors. GABA\(_A\) has many subunits, which indicate the structural heterogeneity of the GABA\(_A\) receptors. 
Flumazenil is a potent GABA antagonist, and is used to antagonize the midazolam-induced extrapyramidal side effects. We used diazepam in our patient since acute dystonic reaction persisted despite flumazenil administration. Many cases of antidyskinetic effect of diazepam have been reported. Although diazepam does not act directly on the GABA\(_A\) receptor, benzodiazepine receptor is part of the same ionophore as the GABA\(_A\) receptor and facilitates the opening of the chloride channel. The antidyskinetic effect of diazepam may be explained by the structural heterogeneity of GABA\(_A\) receptors. 
In conclusion, midazolam can induce acute dystonia in childhood. Although it remains to be shown how diazepam successfully treated, diazepam may be an effective treatment option in patients who are unresponsive to flumazenil.

**References**

1. Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Adv Neurol 1998;78:1-10.
2. Bressman SB. Dystonia genotypes, phenotypes, and classification. Adv Neurol 2004;94:101-7.
3. Prommer EE. Midazolam-Induced Extrapyramidal Side Effects. J Pain Symptom Manage 2008;36:65-6.
4. Stolarek IH, Ford MJ. Acute dystonia induced by midazolam and abolished by flumazenil. BMJ 1990;300:614.
5. Brown DJ, McArthur D, Mouldske H. Subcutaneous midazolam as a cause of extrapyramidal side effects in a patient with prostate cancer. J Pain Symptom Manage 2007;34:111-3.
6. Weinbroum AA, Szold O, Ogorek D, Flaishon R. The midazolam-induced paradox phenomenon is reversible by flumazenil. Epidemiology, patient characteristics and review of the literature. Eur J Anaesthesiol 2001;18:789-97.
7. Thurston TA, Williams CG, Foshee SL. Reversal of a paradoxical reaction to midazolam with flumazenil. Anesth Analg 1996;83:192.
8. Guo T, Mao GF, Xia DY, Su XY, Zhao LS. Pharmacokinetics of midazolam tablet in different Chinese ethnic groups. J Clin Pharm Ther 2011;36:406-11.
9. Fragen RJ. Pharmacokinetics and pharmacodynamics of midazolam given via continuous intravenous infusion in intensive care units. Clin Ther 1997;19:405-19.
10. Cassady SL, Thaker GK, Tamminga CA. GABAergic Treatment for Tardive Dyskinesia. In: Yassa R, Nair NPV, Jeste DV, editors. Neuroleptic-induced movement disorders. New York: Cambridge University Press; 1997. p. 454-70.
11. Mohler H. GABA(A) receptor diversity and pharmacology. Cell
Tissue Res 2006;326:505-16.

12. Fritschy JM, Mohler H. GABAA-receptor heterogeneity in the adult rat brain: Differential regional and cellular distribution of seven major subunits. J Comp Neurol 1995;359:154-94.

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