CASE REPORTS

Flumazenil's Reversal of Myoclonic-like Movements Associated with Midazolam in Term Newborns

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Sedation is an important aspect of care for critically ill newborns. Proper sedation reduces stress during procedures such as mechanical ventilation. Midazolam, a short-acting benzodiazepine, is widely administered as a sedative in newborn intensive care units but is not without side effects. Three term newborns developed myoclonic-like abnormal movements after receiving midazolam. In one, flumazenil controlled the abnormal movements. Flumazenil is a potent benzodiazepine antagonist that competitively blocks the central effects of benzodiazepines. It can reverse the sedative effects of benzodiazepines occurring after diagnostic or therapeutic procedures or after benzodiazepine overdose. Flumazenil may be considered in cases of abnormal movements associated with midazolam. However, further studies are needed to provide guidelines for the administration of this drug in newborns.
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Sedative and analgesic drugs are administered to newborns experiencing pain and stress during mechanical ventilation.[1, 2] These drugs also are used as preoperative agents[3] and for various procedures where sedation is required.[4, 5] The most common drugs are benzodiazepines (midazolam, diazepam, and lorazepam), chloral hydrate, and opioids (fentanyl and morphine).[6]

Midazolam is a water-soluble benzodiazepine with sedative, amnesic, anxiolytic, muscle-relaxant, and anticonvulsant properties.[7] It has a faster onset and shorter duration of action than lorazepam.[7] However, because of adverse effects occasionally reported in children and newborns, there are concerns about its safety. Adverse effects include hypotension,[8, 9] myoclonic activity,[8, 10–12] and a paradoxical behavioral reaction.[13] In 76 premature infants, 6 (7.9%) developed myoclonic activity during a continuous infusion of midazolam.[11] In a smaller series, 3 of 10 premature infants developed myoclonic activity after an intravenous bolus of midazolam.[12]

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Case Reports

Patient No. 1

An infant weighing 2750 g was born by normal vaginal delivery at 38 weeks' gestation with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. The pregnancy was uneventful. The infant was transferred to our institution within 24 hours of birth because of episodes of apnea and bradycardia, which resolved later. At 4 days of age, a magnetic resonance imaging (MRI) scan was done to exclude intracranial abnormalities. The infant was given an intravenous bolus of midazolam 160 µg/kg for sedation before the procedure. Forty-five minutes after the bolus, he developed bicycling movements of both legs and myoclonic-like movements of the upper limbs that lasted for 90 seconds. After these episodes, the infant became very irritable and unconsolable for approximately 10 minutes before falling

Table 1. Case Reports of Abnormal Movements after Administration of Midazolam

No. of Patients	Gestational Age (wks)	Birth Weight (g)	Administration Method	Dosage	Time of Onset[a]	Duration[b]
NP[8]	< 32	NP	i.v. bolus	200 µg/kg	15–30 sec	NP
6[11]	27–34	970–2060	i.v. infusion	30–60 µg/kg/hr	2–48 hrs	A few hrs
3[12]	25–30	< 1501	i.v. bolus	100 µg/kg	Immediately	5–60 min
3[22]	24–26	671 ± 170[c]	i.v. bolus	100 µg/kg	5 min	5–10 min

NP = not provided.
[a]Time of onset of abnormal movements after administration of midazolam.
[b]Duration of abnormal movement activity after administration of midazolam.
[c]Data are mean ± SD.

asleep. Investigations showed normal glucose, calcium, and electrolytes. The MRI, an electroencephalogram (EEG), and an auditory brain stem evoked response (the latter two done the day after the MRI) showed no abnormalities. The only other drugs that the patient had received were intravenous ampicillin and gentamicin. No more midazolam was given, and no further abnormal movements were noted. At 10 days of age, the infant was well and was discharged.

Patient No. 2

A full-term infant weighing 3770 g was born at 41 weeks' gestation by spontaneous vaginal delivery after an uncomplicated pregnancy. Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. At 26 minutes of age, he was intubated for episodes of apnea and cyanosis. He then experienced generalized seizures. Diazepam 0.3 mg/kg was given intravenously. When seizures persisted, a loading dose of intravenous phenobarbital 20 mg/kg was added, with a maintenance dosage of 5 mg/kg every 12 hours. An EEG that day showed probable epileptiform discharges in the frontal, left temporal, and right midtemporal regions. Other investigations—urea, electrolytes, glucose, calcium, magnesium, cerebrospinal fluid, ammonia, amino acids, lactate, long-chain fatty acid, and computerized tomography of the head—did not reveal any cause for seizures. Phenobarbital was stopped on day 4 of age.

On day 6 of age, the infant was given midazolam 500 µg/kg orally for sedation before an MRI. Thirty minutes later, he became increasingly agitated. He then displayed myoclonic-like movements of both upper and lower extremities. These abnormal movements were controlled successfully with intravenous phenobarbital 20 mg/kg. An EEG failed to show seizure activity, with the exception of intermittent bitemporal spikes of uncertain significance. The patient did not receive any other drugs. No more midazolam was given, and no further abnormal movements were noted.

Patient No. 3

A baby girl weighing 2045 g was delivered by spontaneous vaginal delivery at 38 weeks' gestation. Before birth, a left-sided diaphragmatic hernia and abnormal karyotype with terminal deletion in the short arm of chromosome 8 had been diagnosed. At birth, the infant's Apgar scores were 5 and 7 at 1 and 5 minutes, respectively. The infant was intubated at 2 minutes of age and kept on a high frequency oscillator. Initially, she was paralyzed with a vecuronium infusion for 10 days and sedated with a morphine infusion. Primary repair was done successfully on day 7 with a silastic patch.

On day 12, a continuous intravenous infusion of midazolam 60 µg/kg/hour was started in addition to the ongoing morphine infusion. Within an hour, the infant developed myoclonic jerks of the extremities. The midazolam infusion was stopped, and an intravenous bolus of flumazenil 7.8 µg/kg was given. Abnormal movements ceased within 5 minutes. Other drugs at that time were morphine infusion 40 µg/kg/hour, heparinized saline (heparin 1 U/ml in 0.9% sodium chloride), and total parenteral nutrition. Arterial blood gases, serum electrolytes, glucose, calcium, and magnesium were within normal limits.

Discussion

These three cases highlight the paradoxical effects of midazolam in term newborns. Benzodiazepines are known to cause paradoxical stimulation of the central nervous system and thus may increase the frequency of nightmares, euphoria, restlessness, hallucinations, and

hypomanic behavior in adults[14] and children.[13, 15] Anticonvulsant benzodiazepines can also increase the frequency of seizures in patients with epilepsy.[16] In fact, lorazepam has caused seizures in newborns.[17–21]

Abnormal movements after midazolam administration in preterm infants (Table 1)[8, 11, 12, 22] and adults have been reported.[23] Involuntary epileptiform movements lasting 15–30 seconds in premature newborns with gestational ages under 32 weeks appeared after intravenous boluses of midazolam 200 µg/kg.[8] Myoclonus in six premature infants (gestational ages 27–34 weeks) was observed after intravenous infusions of midazolam in dosages ranging from 30–60 µg/kg/hour.[11] In these infants, myoclonus was noticed 2–48 hours after beginning the midazolam infusion, ceased a few hours after discontinuing the infusion, and never recurred.

Three infants with very low birth weights (average 671 ± 170 g) experienced accentuated myoclonic jerks resembling clonic seizures within 5 minutes of receiving slow bolus administration of midazolam 100 µg/kg for sedation.[22] In another study, 3 of 10 preterm newborns (25–30 weeks' gestation) with birth weights under 1500 g developed myoclonus after midazolam administration.[12]

Myoclonus was observed after the use of midazolam in 11 neonatal intensive care units in France.[24] In these units a loading dose of 100–200 µg/kg was administered followed by a continuous infusion of 30–200 µg/kg/hr. No subsequent neurologic abnormality was seen in any of the infants.

Another study[11] recorded EEG patterns in six preterm infants who developed myoclonus after midazolam infusion. Investigators did not observe ictal activity in these infants. Five of the six displayed excessive discontinuity on their EEGs. Disappearance of physiologic fluctuation and excessive theta waves were evident in three patients. An EEG performed on our second patient during the episode of abnormal movements showed no ictal activity.

The mechanism responsible for abnormal movements after midazolam administration is unclear. Adverse reactions may result from inadequate or excessive dosages, improper administration, cerebral hypoxia, or they may be simply paradoxical reactions.[25]

Dosages used in our patients were within the recommended range, and the drug was properly administered. Among newborns, however, large interpatient variability exists in pharmacokinetic parameters after intravenous infusion of midazolam.[24, 26–28] Mean clearance rate is lower in newborns younger than 39 weeks' gestation (1.17 ml/kg/min) than in those older than 39 weeks (1.84 ml/kg/min).[24] Moreover, infants weighing less than 1000 g at birth have significantly lower clearances than those weighing more.[28] The low clearance rate is probably related to immature hepatic enzyme activity rather than differences in renal function.[24] Therefore, individual dosage adjustment may be required.[27]

Benzodiazepines, including midazolam, exert a clinical effect by binding to γ-aminobutyric acid A ($GABA_A$) receptors in the nervous system. The $GABA_A$ receptors are a family of ligand-gated ion channels that mediate the principal actions of GABA, the principal inhibitory neurotransmitter. Benzodiazepine-binding regions may be homologous to agonist-binding regions but are situated at different subunit interfaces.[29] In a hypothetical model of the $GABA_A$ receptor, there are agonist (for GABA) and modulatory (for benzodiazepine-type ligands) binding sites.[30] The receptor is composed of five subunits (2_{-1}, $2_{\beta 1}$ and $1_{\gamma 2}$ peptides), which are arranged around a central chloride ion-selective pore that opens as a consequence of agonist (GABA) binding. These receptors are found in the greatest density in the olfactory bulbs, cerebral cortex, cerebellum, hippocampus, substantia nigra, and inferior colliculus.[31]

Benzodiazepines and GABA together regulate the opening of chloride channels in the cell membrane.[32] Stimulation of this ionophore has the effect of hyperpolarizing postsynaptic neurons. These hyperpolarized cells are more difficult to depolarize in response to excitatory neurotransmitters.[7]

γ-Aminobutyric acid synthesis in experimental animals is low during the neonatal period. The activity of the synthetic enzyme for GABA, L-glutamate decarboxylase, in the cortex of a newborn rodent is low but rises rapidly to adult levels by 3 weeks of age.[33] Also, binding sites for GABA are present at relatively low concentrations at birth and increase slowly in the postnatal period.[34] Therefore, there may be less neuronal inhibition in children than would be expected in adults. In contrast, benzodiazepine receptors are found at relatively high levels in newborns.[32] It is unclear if this imbalance between relatively low numbers of GABA receptors (agonist) and relatively high levels of benzodiazepine receptors (modulators) create an

excitatory, rather than inhibitory, influence.

Midazolam is highly protein bound (96%). Low serum albumin predisposes newborns to potentially elevated serum concentrations of free midazolam. Neurologic sequelae after prolonged intravenous administration of midazolam in infants were significantly associated with low serum albumin concentrations.[35] Therefore, the uninhibited movement of free, unbound drug across the blood-brain barrier may be related to the paradoxic stimulation of neural synapses in newborns who already have decreased GABA levels.

It also was suggested that myoclonus-like abnormal movements may be related to hemodynamic changes that may affect cerebral blood flow.[8, 22] Hypotension is a well-known side effect of midazolam, particularly in premature infants. The mechanisms responsible for hypotension are not clear, but they might involve peripheral vasodilatation, a sudden decrease in circulating catecholamines, or direct myocardial depression.[36] In ventilated newborns, midcerebral blood flow velocity decreased by 12–43% after transient drops in systemic blood pressure after midazolam administration.[10, 12, 37] However, as in an earlier study,[22] we did not observe clinically significant changes in blood pressure.

In our first case, the infant fell asleep within approximately 10 minutes of the onset of myoclonic-like movements. Intravenous phenobarbital was used successfully to treat the abnormal movements in our second patient. Flumazenil was used successfully in our third patient to reverse the myoclonic effects of midazolam. There was no clinical or pharmacologic preference between the two agents. We are not suggesting that flumazenil be used based on one case report; we are simply reporting our initial experience with this drug in a newborn. Further studies will provide guidance as to whether phenobarbital, flumazenil, or, possibly, no pharmacologic intervention is best in specific clinical situations.

Flumazenil was approved by the United States Food and Drug Administration in 1991 for use in adults for complete or partial reversal of the sedative effects of benzodiazepines occurring after diagnostic or therapeutic procedures or after benzodiazepine overdose.[38] It was administered in children to reverse the sedative action of midazolam.[38–40] Flumazenil also reversed diazepam-induced neonatal apnea and hypotonia,[41, 42] midazolam-induced laryngospasm in adults,[43] and midazolam-induced paradoxical behavioral reactions in children.[13]

Flumazenil is a potent antagonist that displaces benzodiazepines linked to receptors and blocks their central effects.[44] We observed that abnormal movements stopped within 5 minutes of flumazenil injection. One study[13] reported that the amount of time to reverse the paradoxical behavior reaction in children with flumazenil was variable (3–50 min) and was dependent on the dosage of midazolam. One case report noted that the paradoxical reaction improved within 1 minute of flumazenil administration in an adult.[45] Although these are anecdotal case reports, they suggest a role for flumazenil in the control of myoclonus induced by midazolam. It should be emphasized that flumazenil can cause seizures in children,[46, 47] therefore, caution needs to be exercised in its use. We used an intravenous bolus of flumazenil 7.8 µg/kg arbitrarily based on the dose recommended for managing benzodiazepine overdose in children (10 µg/kg).[48]

In summary, we have described three cases of midazolam-induced, myoclonic-like abnormal movements in term infants. Flumazenil was effective in reversing these abnormal movements in one infant, indicating that flumazenil may be considered in cases of abnormal movements associated with midazolam. However, further studies are needed to provide guidelines for the administration of this drug to newborns.

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