Case Series
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Midazolam Induced Abnormal Movements in Preterm Newborns: Case Series

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Abstract

Objectives – The aim of our article is to highlight the adverse effects of midazolam, which causes abnormal behavior and a paradoxical behavioral reaction, although it is used for sedation and seizure control, as well as preoperative and procedure-related sedation in neonates. **Case Presentation** – We report myoclonic seizure-like abnormal activity in four preterm neonates, who received intravenous midazolam for sedation before laser photocoagulation for retinopathy of prematurity and seizures. All neonates had a long NICU stay, but were clinically well before undergoing the procedure. Cases 1, 2 and 3 developed multifocal seizure-like abnormal movements after receiving a midazolam injection for photocoagulation therapy for retinopathy of prematurity. Case 4 developed multifocal seizure-like abnormal movements after receiving an injection of midazolam for seizures. In all the cases the seizure-like abnormal movements were controlled by phenobarbitone. **Conclusion** – Midazolam is increasingly being used in NICUs, but caution must be exercised while administering it in preterm neonates with comorbidities. It is difficult to identify the neonates at risk, but it is necessary to be aware of and cautious about the adverse effects of midazolam when administering the drug.

Key Words: Midazolam ▪ Multifocal Myoclonic Seizures ▪ Adverse Effects ▪ Prematurity ▪ Newborn.

Introduction

Midazolam is widely used nowadays in the pediatric age group for sedation and seizure control. Although its safety has been established in children and adults, some concerns still remain regarding neonates, especially preterm newborns, who have other significant co-morbidities. Reports of the adverse effects of midazolam have been published and include hypotension, abnormal movements, and paradoxical behavioral reaction. Midazolam, belongs to the benzodiazepine group of drugs, which are used preoperatively and in procedures related sedation in neonates (1). However paradoxical reactions, such as arrhythmic myoclonic jerking or myoclonic movements, have been reported after midazolam administration in preterm infants (2, 3). The mechanism is unclear but it is probably due to an imbalance of GABA subunit (agonist) and benzodiazepine subunit (modulators) where the longer half-life of midazolam causes an excitatory effect, causing seizure-like activity (4). A recent Cochrane review raised concerns regarding the safety of midazolam infusion in neonates (5).

Here, we report paradoxical events observed in four preterm neonates who received a midazolam bolus for procedural sedation and seizures.

Case 1

A male preterm neonate was delivered at 30 weeks' gestation by vaginal delivery, with a birth weight of 1.43 kg and an APGAR score of 3 and 7 at 1 and 5 minutes respectively. The baby needed active

resuscitation and mechanical support for 48 hours, and intra-tracheal surfactant was administered. Gradually the baby was weaned off this treatment and discharged on spoon feeding on day 30 of life. Neurological examination and cranial ultrasound were normal on discharge. During his NICU stay, all laboratory parameters were in the normal range. Retinopathy of prematurity (ROP) screening during follow up was suggestive of ROP, for which he was readmitted for laser photocoagulation. The procedure was planned to be performed under midazolam sedation and topical anaesthesia. Tropicamide 0.8% was used as a mydriatic agent before the procedure. An injection of midazolam was administered intravenously at a dose of 0.1 mg/kg, diluted in 1 ml of 5% dextrose solution, slowly over 2-3 minutes. Immediately after the injection, baby developed multifocal convulsions. Blood glucose was 76 mg/dL. The baby received another dose of midazolam at 0.1 mg/kg, as the seizures were not initially attributed to midazolam. The seizures did not stop but continued. The baby was administered an injection of phenytoin at 20 mg/kg, but the seizure-like movements persisted. The seizure-like abnormal movements were finally controlled by a loading dose of phenobarbitone 20 mg/kg intravenously. Sepsis and metabolic screening, and a cranial ultrasonogram were normal. The procedure was performed after 72 hours, but this time child was given oral trichlofos and topical anaesthesia. EEG was performed after 3 months of the event and was found to be normal, so anti-epileptics were tapered off. On follow-up, the baby was neuro-developmentally normal.

Case 2

A male neonate, with a birth weight of 1.18 kg, was born by normal delivery at the gestational age of 28 weeks, with an APGAR score of 5 and 7 at 1 and 5 minutes respectively. The baby developed respiratory distress soon after birth for which one dose of intra-tracheal surfactant was administered, and he was ventilated mechanically for 17 days. On day 3 of life, the baby had neonatal seizures, for which a loading dose of phenobarbitone 20 mg/kg was given. Sepsis and metabolic screening were normal. The cranial ultrasound was normal. During his stay, ROP screening was performed, which was suggestive of Grade II ROP. The baby stayed in the NICU for 72 days and had no further seizures. He was discharged in a healthy condition. The baby was readmitted for laser photocoagulation 10 days after discharge. The procedure was planned to be performed under midazolam sedation and topical anaesthesia. Tropicamide 0.8% was used as a mydriatic agent before the procedure. An injection of midazolam was administered intravenously at a dose of 0.1 mg/kg in 1 ml of 5% glucose solution, slowly over 3 minutes. Immediately after the injection, the infant started having abnormal multifocal seizure-likemovements. Serum electrolytes, blood glucose, and cranial ultrasound were normal. The seizure-like abnormal movements lasted for 20 minutes and were controlled with phenobarbitone. The procedure was performed after 48 hours, and this time the child was given oral trichlofos and topical anaesthesia. The baby tolerated the procedure well. EEG performed 3 months after the event was found to be normal so antiepileptics were tapered off. On follow up at 6 months after discharge baby was normal on neuro-developmental examination

Case 3

A female neonate was born by normal delivery to a primigravida mother at 32 weeks' gestation, weighing 1.32kg. The baby developed respiratory distress, for which she was mechanically ventilated for 2 days. On day 3 of life, the baby had neonatal seizures for which a loading dose of 20 mg/kg phenobarbitone was given. Sepsis and metabolic screening were normal. Cranial ultrasound was normal. During her stay, ROP screening was done which was suggestive of Grade 3 ROP. The baby stayed for 14 days and had no further seizures, so was discharged in a healthy condition. The baby was readmitted for laser photocoagulation 10 days after discharge. The procedure was planned to be performed under midazolam at 0.1 mg/kg, diluted

with 1ml of dextrose 5% solution, gradually over 3 min, and topical tropcamide 0.8% and local anaesthesia, but unfortunately the baby developed abnormal rhythmic myoclonic seizure-like movements after sedation. The procedure was deferred, and EEG and cranial ultrasound were carried out, which were normal. The procedure was performed using another sedative agent after 2days. The baby tolerated the procedure well with no adverse events, and was neurologically normal on further follow-up.

Case 4

A male neonate, with a birth weight of 920 grams, was born by caesarian delivery at a gestational age of 26 weeks, with an APGAR score of 5 and 7 at 1 and 5 minutes respectively. The baby developed respiratory distress soon after birth, and was intubated and mechanically ventilated, followed by intra-tracheal surfactant therapy. He was gradually weaned off ventilator support and kept on Bubble CPAP. Feeding was gradually started. On day 10 of life, the baby had neonatal seizures, for which an injection of midazolam was administered intravenously at a dose of0.1mg/kg in 1 ml of 5% glucose solution, slowly over 3 minutes. Immediately after the injection, the infant started having abnormal multifocal seizure-like movements. The seizure-like abnormal movements lasted for 10 minutes, and were controlled with phenobarbitone. Sepsis and metabolic screening were normal. Cranial ultrasound was normal. The baby stayed in the NICU for 40 days and had no further seizures. He was discharged against medical advice due to financial issues, and could not be followed up later.

Discussion

Midazolam is a short-acting benzodiazepine, with rapid onset of action. It has multiple actions, including anxiolysis, sedative, anticonvulsant, muscle-relaxant and anterograde amnesic effects. Midazolam acts via $GABA_A$ receptors in the central nervous system. The binding of midazolam to the $GABA_A$ receptor complex leads to the opening of chloride channels in the cell membrane, causing hyper polarization, making it difficult for excitatory neurotransmitters to depolarize the neuron (2). Although its safety has been reasonably well established in children and adults, doubts still remain about its safety in neonates and infants, especially in the NICU. We have highlighted the occurrence of abnormal movements in the form of myoclonus-like abnormal movements in four premature neonates.

Anticonvulsants exacerbating pre-existent seizures or triggering seizures is uncommon but not unheard of (6). However, the mechanisms underlying this are unclear. The possible mechanisms might include alterations in cerebral perfusion, excessive dosage, interactions with the neurotransmitter/receptor balance, favouring stimulatory action, cortical inhibition or unfavorable pharmacokinetics (6-7). Midazolam administration (either as an infusion or a bolus) has been shown to decrease the mean cerebral blood flow velocity and systemic blood pressure (7–8). A sudden decrease in cerebral blood flow (because of peripheral vasodilatation, a decrease in catecholamines, and myocardial depression) may be a cause of the abnormal myoclonic seizure-like movements observed immediately after midazolam bolus.

The adverse effects of midazolam in neonates and infants reported in the literature are hypotension, respiratory depression, abnormal behavior, a transient decrease in mean cerebral blood flow, and abnormal movements (3, 5, 8, 9). A few reports of abnormal midazolam-induced myoclonic seizure-like movements have been published in the literature (2, 3, 8, 9). Most of these newborns are preterm babies needing midazolam for sedation for ventilation or a procedure, either as a bolus or continuous infusion. From these reports, we found a gestational age at birth ranging from 24 to 41 weeks, and birth weight ranging from 671 grams to 3773 grams. The time of onset of abnormal seizure-like movements ranged from almost instantaneously to up to 42 hours. The duration of the abnormal seizure-like movements ranged from 5

minutes to up to a few hours. One of these reports is a retrospective study of Japanese NICU infants, which found abnormal myoclonus-like movements in nine out of 94 (9.6%) infants (11).

The average gestational age and birth weight of the newborns that developed abnormal myoclonic seizure-like movements was 30.1 (±5.8) weeks and 1492 (±1045) grams, respectively, in this study. They had significantly low gestational age at birth, post-conceptional age, and birth weight. Logistic regression analysis suggested birth asphyxia as a risk factor associated with abnormal seizure-like movements. Concern has been expressed regarding the altered pharmacokinetics in very low birth weight preterm neonates. The half life of midazolam in neonates is longer (around 4–6 hours), and often variable (upto 22 hours), especially in preterm babies (12), which creates an excitatory influence, thereby causing the seizure-like activity. This low clearance is probably due to immature hepatic cytochrome P450 activity in preterm and low birth weight newborns, resulting in high plasma levels. As midazolam is predominantly protein bound, and most critically ill neonates are hypoalbuminic, the free levels may reach fairly high levels, causing adverse effects.

These pharmacokinetic variations must be borne in mind when midazolam is used either as an infusion or bolus. In our cases, all the neonates developed abnormal seizure-like movements within minutes of midazolam administration. We concluded that these abnormal seizure-like movements were attributed to the midazolam injection, which is a type A class of adverse drug reaction according to the Naranjo algorithm. Multi-focal abnormal myoclonic seizure-like movements in four preterm neonates were seen after slow bolus administration of midazolam for sedation (13), while Zaw et al. (10) reported about three term neonates. Altered cerebral hemodynamics or a neurotransmitter/receptor imbalance due to midazolam might be the possible cause of the abnormal seizure-like movements in our cases. One more theory is that mydriatric (tropicamide) medicines are associated with systemic absorption following ocular administration, which can cause life-threatening adverse events, such as seizures (14). Our report highlights the safety concerns of midazolam use in preterm babies. More prospective studies are needed in newborns, especially preterm babies in neonatal units, before midazolam can be recommended for routine use in the NICU.

Conclusion

Although midazolam is increasingly being used in NICUs, caution must be exercised while administering it in preterm neonates with comorbidities. It is difficult to identify the neonates at risk, but it is necessary to be aware of and cautious about the adverse effects of midazolam while administering the drug. Further studies are needed for documentation of the safety, efficacy and adverse effects of midazolam in newborns.

What Is Already Known on this Topic:
Midazolam is widely used in the pediatric age group for sedation and seizure control.

What this Case Series Adds:
We report the adverse effects of midazolam, causing abnormal behavior and a paradoxical behavioral reaction, although it is used for sedation and seizure control, as well as preoperative and procedure related sedation in neonates. It is necessary to be aware of and cautious about the adverse effects of midazolam while administering the drug, as it sometimes results in a paradoxical behavioral reaction.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Consent: Informed consent was given by the patients' guardians for publication purposes.

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