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Refractory Metabolic Acidosis as a Complication of High-Dose Midazolam Infusion for Pediatric Status Epilepticus

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Background: The use of midazolam for the treatment of status epilepticus in children has generally been shown to be well tolerated and safe. Furthermore, encouraging efficacy has been observed when pediatric patients with status epilepticus have received continuous intravenous infusions of midazolam.

Case Presentation: A 9-year-old girl was treated with high-dose, continuous intravenous infusion of midazolam for the management of refractory status epilepticus. The patient developed a severe hyperchloremic, non–anion gap metabolic acidosis and resultant hemodynamic compromise, necessitating significant inotropic support and the initiation of a vasopressor infusion. We speculate that this complication was due to the preparation of parenteral midazolam with hydrochloric acid. The midazolam infusion was stopped, and, in less than 5 hours, the patient's metabolic acidosis resolved. The patient's inotropic and vasopressor infusions could only be weaned after discontinuing the use of high-dose midazolam.

Conclusions: Although this complication was observed in only 1 pediatric patient with cortical dysplasia, caution and close clinical and laboratory surveillance should be exercised when administering continuous intravenous infusions of midazolam to pediatric patients.

Key Words: midazolam, epilepsy, status epilepticus, metabolic acidosis

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Epilepsy is a potentially devastating neurological disorder with an incidence of 30,000 pediatric cases per year in the United States,[1] with the risk of developing status epilepticus as a complication.[2] Midazolam has been shown to be efficacious in the treatment of status epilepticus when used as a continuous intravenous infusion.[3–10] We report a potentially lethal complication of high-dose, continuous intravenous infusions of midazolam used for the treatment of refractory status epilepticus in a pediatric patient that, to our knowledge, has not been previously described.

Our institution does not require institutional review board review and approval for isolated case reports and therefore waived the need to review this report.

CASE REPORT

The patient is a 9-year-old girl with right frontal cortical dysplasia who was transferred to our tertiary care pediatric intensive care unit for management of intractable epilepsy. The patient was admitted for status epilepticus 1 week before transfer. She had been intubated on her fourth hospital day and started on a low-dose dopamine infusion for hypotension. Her multiple antiepileptic medications, including oxcarbazepine, valproic acid, phenytoin, levetiracetam, lamotrigine, and topiramate had failed. Her antiepileptic medication regimen was eventually changed to phenobarbital and pregabalin, but the patient's seizures remained uncontrolled. The patient was transferred to our institution for higher-level care and to obtain a neurosurgical evaluation for resection of her seizure focus.

Continuous electroencephalographic monitoring revealed multiple seizures correlated with buildup of rhythmic fast activity over the right frontocentral region with rapid generalization consistent with complex partial status epilepticus. The neurology team recommended oxcarbazepine, fosphenytoin, high-dose phenobarbital and, eventually, an intravenous midazolam infusion with the goal of burst suppression. The infusion was started at 15 μg/kg per minute and titrated for 27.5 hours to a maximum dosage of 200 μg/kg per minute. To maintain normal blood pressure, the patient required an increased dose of dopamine, followed by epinephrine and phenylephrine infusions. The patient's electroencephalogram then showed short periods without seizures but persistent brief seizures in clusters over the right frontal area. Burst suppression was not achieved.

After approximately 48 hours of the midazolam infusion, the patient developed a hyperchloremic, non–anion gap metabolic acidosis that worsened despite sodium bicarbonate administration. The patient's lowest arterial pH level was 7.16 (reference range, 7.37–7.41). At the maximum midazolam infusion rate (200 μg/kg per minute), the patient's osmolality, lactate, blood urea nitrogen, and creatinine levels were normal. Given the severity and refractoriness of the patient's metabolic acidosis and her vasopressor and inotropic requirements, the midazolam infusion was stopped after 81 hours. In less than 5 hours, the patient's metabolic acidosis resolved and the inotropic and vasopressor infusions were weaned. The patient continued to have frequent seizures despite maximal medical therapy, so the patient underwent resection of her right cortical dysplasia on the ninth hospital day.

DISCUSSION

The use of midazolam for the treatment of status epilepticus in children has generally been shown to be well tolerated and safe, and encouraging results have been observed when pediatric patients with status epilepticus have received continuous intravenous infusions of midazolam.[3,5,6,9–11] Other benzodiazepine medications for refractory status epilepticus include lorazepam and diazepam. The use of these medications is limited, however, by the potential for propylene glycol toxicity.[12]

Midazolam, an imidazobenzodiazepine with a benzepine ring, does not require propylene glycol for solvency.[13] In an acidic environment, the benzepine ring opens, facilitating solvency in water. Once midazolam, in its parenteral form, encounters a

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relatively neutral pH, the benzepine ring closes, and the drug assumes a lipid-soluble form. Parenteral midazolam is prepared with hydrochloric acid to achieve appropriate solubility. In addition, benzyl alcohol is added as a preservative. Benzyl alcohol toxicity, however, has been associated with anion gap metabolic acidosis,[14] which we did not observe. We speculate, therefore, that the non–anion gap metabolic acidosis we encountered was due to the hydrochloric acid solvent exposure. Furthermore, we speculate that others have not reported the severe toxicity we observed because our patient's dosage of hydrochloric acid was higher. The maximum dosage of midazolam use in this patient was 200 μg/kg per minute, whereas previous studies generally report dosages in the range of 1 to 50 μg/kg per minute.[5,7,10]

The toxicity of hydrochloric acid may be a cumulative effect. Hyperchloremia and a low serum bicarbonate level were discovered 58 hours after starting our infusion, despite normal serum electrolyte levels at approximately 15 and 36 hours. Two published series have also reported early (12 and 24 hours) normal serum electrolyte levels during midazolam infusions.[5,7] Metabolic acidosis has been reported, however, in some patients receiving midazolam. One retrospective study comparing propofol to other sedative agents in children showed 14 of 61 patients who received midazolam developed some degree of metabolic acidosis.[15] However, the occurrence of the acidosis did not seem to be related to either the duration or dose of the infusion. By comparison, our patient demonstrated normal serum chloride and bicarbonate levels at 36 hours, despite reaching her maximum midazolam infusion rate (200 μg/kg per minute) at 27.5 hours. We speculate, therefore, that the toxicity of midazolam's hydrochloric acid solvent becomes clinically relevant after a significant, cumulative exposure has occurred.

Despite midazolam's solubility advantage and the manufacturing ability to avoid propylene glycol, we hypothesize that high-dose, continuous intravenous infusions of midazolam may be limited by the toxicity of its solvent, hydrochloric acid. We speculate that the patient developed her metabolic acidosis and hemodynamic compromise as a result of significant hydrochloric acid exposure. This mechanism is supported by the resolution of her metabolic acidosis less than 5 hours after the cessation of the midazolam infusion. The patient's hemodynamic compromise was unlikely due to midazolam itself, given that its elimination half-life is 1.8 to 6.4 hours (Bedford Laboratories, Bedford, Ohio). Prolongation of the half-life of midazolam has been reported in 2 patients who received midazolam for 68 and 148 hours. In these patients, the half-life of midazolam was prolonged to 53 and 20 hours.[16] Our patient, however, showed hemodynamic instability after only 48 hours of midazolam infusion, and her hemodynamic instability improved 5 hours after discontinuing the midazolam, which is not consistent with half-life prolongation.

CONCLUSIONS

In summary, we report a potentially lethal complication of high-dose, continuous intravenous infusions of midazolam used for the treatment of refractory status epilepticus in a pediatric patient that, to our knowledge, has not been previously described. We speculate that this complication is due to parenteral midazolam's preparation with hydrochloric acid, which causes a hyperchloremic, non–anion gap metabolic acidosis and resultant hemodynamic compromise. Although this complication was observed in only 1 pediatric patient with cortical dysplasia, we believe caution and close clinical and laboratory surveillance should be exercised when administering continuous intravenous infusions of midazolam to pediatric patients.

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