Abstract

High-dose continuous midazolam therapy has been used successfully for control of refractory status epilepticus. However, normal anion gap (AG) metabolic acidosis, a deleterious complication of this therapy is underrecognized. Even though previously reported in an isolated case report in a pediatric patient, we observed similar complication in an adult patient. Stereotyped normal AG metabolic acidosis along with hypotension developed on two occasions during high-dose continuous midazolam hydrochloride infusion that reverted rapidly following cessation of the infusion.

Keywords: Acidosis, hydrochloric acid, midazolam, seizures

INTRODUCTION

Different antiepileptic drugs (AEDs) have been employed alone or in combinations to achieve adequate control for refractory seizure. Midazolam, because of its versatile pharmacologic profile has been used successfully in high dose as continuous infusion for treatment of refractory status epilepticus.[1,2] However, the association of high-dose midazolam infusion and metabolic acidosis is often belittled. Failure to recognize this complication heralds fatal prognosis. We encountered a similar scenario, in which stereotyped severe metabolic acidosis developed on two occasions during high-dose midazolam infusion.

CASE REPORT

A 21-year-old (61 kg, 175 cm) male patient arrived in the emergency department in altered sensorium following an episode of status epilepticus. Glasgow Coma Scale score on admission was 8 (E2V1M5). Initial resuscitation involved intubation of trachea, maintenance of ventilatory and circulatory parameters. The patient was a known case of epilepsy for the past 8 years and had been on multiple AED (phenytoin, levetiracetam, and clonazepam). The patient also had a history of uneventful surgery of intracranial electrode implantation a year ago.

Due to ongoing seizure even after starting intravenous (IV) phenytoin, levetiracetam, clonazepam, and phenobarbitone, IV sodium thiopental infusion (0.5–4 mg/kg/h) was commenced as per the guideline. Continuous electroencephalographic (EEG) monitoring was also done. On the 3rd day of hospital admission, the patient underwent craniotomy surgery for resection of epileptogenic foci. All the drugs which the patient had been taking preoperatively were started again in the postoperative period. However, clinical seizure (5–6 episodes/day) continued in the postoperative period along with continuous EEG evidence of ictal activity. As such, due to refractory status epilepticus, IV midazolam (midazolam hydrochloride 1% + benzyl alcohol 1%) was started as continuous infusion at a rate of 120 mg/h on the 12th day of admission. However, after 24 h, the patient developed severe hyperchloremic normal anion gap (AG) metabolic acidosis (nonresponsive to IV sodium bicarbonate). It was associated with hypotension (more than 20% of baseline) which required low-dose norepinephrine IV infusion (1 mcg/min). Plasma levels of AED came to be normal. All other causes of normal AG metabolic acidosis were excluded. Suspecting midazolam to be the cause of this severe...
metabolic acidosis, it was stopped, and IV ketamine (2 mg/kg/h) was started. In next 24 h, the acidosis resolved and sodium bicarbonate level assumed near normal levels. [Table 1]. Norepinephrine was tapered and stopped after achieving desired hemodynamics. Since the clinical seizure frequency increased (10–12 episodes/day) as compared to before, the patient eventually underwent right hemispherectomy surgery under general anesthesia.

Next 8 days following hemispherectomy, the patient continued to be asymptomatic. However, yet again, the patient developed intractable seizures on the 9th day after hemispherectomy. IV midazolam 100 mg/h infusion was started again along with the continuation of other AED. In next 24 h, the patient again developed severe normal AG metabolic acidosis along with fall in blood pressure within 20% of baseline. Midazolam infusion was stopped and replaced again with ketamine infusion. Yet again, the metabolic acidosis resolved in the next 12 h following cessation of midazolam infusion [Table 1]. The patient underwent percutaneous tracheostomy due to prolonged ventilation on the 12th day and weaning done in few days with no complication and rest of the patient’s hospital stay was uneventful. This time too, high-dose midazolam infusion was linked to metabolic acidosis as a diagnosis of exclusion of other causes of normal AG metabolic acidosis.

| Incidence | Timing of ABG | pH | PCO₂ | HCO₃⁻ | Base deficit | Lactate | Na⁺ | Cl⁻ | Anion gap | K⁺ | Urea | Creatinine |
|-----------|---------------|----|------|-------|-------------|---------|-----|-----|-----------|----|-------|------------|
| 1         | 24 h after start of midazolam infusion | 7.19 | 20   | 7.9   | -18         | 1.33    | 145 | 121 | 18.5      | 2.4 | 11    | 0.4        |
|           | 24 h after sodium bicarbonate correction | 7.20 | 21   | 8     | -18.1       | 1.22    | 147 | 122 | 19.3      | 2.3 | 12    | 0.5        |
|           | 24 h after stopping midazolam | 7.47 | 25   | 18.1  | -4.1        | 1.1     | 145 | 113 | 17.7      | 3.8 | 19    | 0.6        |
| 2         | 24 h after start of midazolam infusion | 7.21 | 18.8 | 7.5   | -18.4       | 1.15    | 141 | 119 | 18.2      | 3.7 | 18    | 0.5        |
|           | 24-36 h after stopping midazolam | 7.38 | 29.7 | 17.3  | -6.7        | 0.99    | 143 | 112 | 17.6      | 3.9 | 14    | 0.5        |

ABG: Arterial blood gas

**DISCUSSION**

Promising results have been shown with the use of high-dose IV midazolam for the treatment of refractory status epilepticus both in adults[1] and children. Its water-soluble property decreases venous irritation and its lipophilic property at physiological pH accounts for its rapid onset of action. [1] Prolonged infusion of other benzodiazepine drugs such as diazepam and lorazepam is not advisable because of the inherent risk of propylene glycol (solvent) toxicity. [4] Refractory metabolic acidosis as a complication of high-dose midazolam infusion has been previously reported in pediatric status epilepticus. [5] However, this association in adults has not been reported. Conventionally, midazolam is used in intensive care units for sedation in adults in doses ranging from 2 to 5 mg/h. [6] However, in our case, due to epilepsy syndrome, high-dose midazolam infusion (up to 2 mg/kg/h) was used. Normal AG metabolic acidosis that developed on two occasions in our patient during midazolam infusion were stereotyped and reverted after cessation of infusion. Moreover, since no other cause could be found to cause hyperchloremic acidosis in our patient, we speculated that the most probable cause was due to high-dose midazolam therapy.

Unlike diazepam or lorazepam, midazolam is prepared with hydrochloric acid (HCl) to achieve required solubility. In addition, 1% benzyl alcohol is added as a preservative. Benzyl alcohol toxicity has been associated with high AG metabolic acidosis. [7] However, in our case, the metabolic acidosis was associated with normal AG during both situations, and thus, benzyl alcohol toxicity seemed unlikely in our case. Therefore, the normal AG hyperchloremic metabolic acidosis in our case can be most commonly attributed to cumulative exposure to HCl.

During the first episode, hypotension was more than 20% of baseline and thus required vasopressor (norepinephrine) support. However, hypotension during the second episode (within 20% of baseline) did not require any vasopressor support. In both situations, blood pressures returned back to its baseline values after stopping midazolam infusion. Even though literature have found a significant association between hyperchloremic metabolic acidosis and acute kidney injury, [8,9] but in our case, neither clinical (urine output) nor laboratory parameters showed any such association. Presumably, this could be due to transient hyperchloremia and its rapid reversibility following the cessation of the offending agent.

**CONCLUSION**

Benzodiazepines are used as first-line drugs for control of acute seizures. Since midazolam is short-acting with less side effects, it is utilized as a continuous infusion for the treatment of refractory status epilepticus. However, normal AG metabolic acidosis and resulting hemodynamic perturbations that accompany high-dose midazolam infusion should always be borne in mind. Since there is no role of bicarbonate therapy, prompt cessation of infusion and maintenance of hemodynamic parameters are the only remedial measures.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
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Conflicts of interest
There are no conflicts of interest.

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