Case Report

Early Post-operative Hemodynamic Perturbation Associated with Topiramate-induced Metabolic Acidosis: A Case Report

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ABSTRACT

Topiramate is a potent antiepileptic drug with multiple modes of action including inhibition of carbonic anhydrase activity. Inhibition of this enzyme predisposes to non-anion gap metabolic acidosis which has been amply described in the literature. However, the severity is yet to be well defined. We encountered a case of topiramate-induced non-anion gap metabolic acidosis associated with hemodynamic perturbations in an 8-year-old child in the postoperative period.

KEYWORDS: Acidosis, perioperative, seizures, topiramate

INTRODUCTION

Topiramate, a novel antiepileptic drug (AED) is known to induce non-anion gap (AG) metabolic acidosis and has been extensively quoted in literature.[1-7] The most likely explanation for this complication is due to urinary bicarbonate loss secondary to inhibition of renal cortical carbonic anhydrase (CA) isoenzymes.[8] The nature of acidosis is usually benign and reverts after the cessation of drug therapy. However, it has potential to cause florid symptoms even to the extent of intervention. We encountered a case of topiramate-induced severe metabolic acidosis in which the patient developed unstable hemodynamics in the early post-operative period following decompressive craniectomy.

CASE REPORT

An 8-year-old child (25 kg) was admitted in our intensive care unit (ICU) for elective ventilation following decompressive craniectomy for acute right fronto-temporo-parietal subdural hematoma. On ICU admission (Day 0), the Glasgow coma scale (GCS) was E3VTM4, blood pressure (BP) was 102–106/58–60 mm Hg, heart rate (HR) was 108–122 beats/min, and oxygen saturation (SpO2) of 99–100% at FiO2 was 0.4. Arterial blood gas (ABG) analysis showed non-AG mild metabolic acidosis with normal lactate levels [Table 1]. The patient had history of generalized tonic-clonic seizure (GTCS) for last 2 years and had been regularly taking tablet lacosamide 100 mg twice daily, topiramate 100 mg twice daily, and clobazam 10 mg once daily.

All AEDs were restarted in the postoperative period (Day 1) through a nasogastric tube. Day 1 hemodynamic parameters were also stable (BP was 98–104 mm Hg, HR was 100–104 beats/min). ABG yet again showed non-AG mild metabolic acidosis [Table 1]. Thinking it to be normal saline (0.9% NS) induced hyperchloremic metabolic acidosis (serum chloride-110 mmol/l), it was stopped and substituted with plasma-lyte A (low chloride content: 95 mmol/l). However, on day 2 and day 3 the acidosis worsened progressively with associated hypotension on day 3 (BP was 80–82/45–47 mm Hg and HR was 108–110/min). Volume status, body temperature, serum lactate levels, blood sugar levels, and urine output (average 15 ml/hour) were within normal limits. Serum electrolytes were also within normal limits except slight fall in serum sodium (129 mmol/l). Total leucocytic count (TLC) was raised marginally on day 1 (12,200/mm3) and day 2 (12,550/mm3) but remained within normal limits thereafter. Chest radiograph did not reveal any pathology. A computed tomogram (CT) scan of the brain was done, which did not reveal any new onset of ischemia, hemorrhage or worsening of edema. Low-dose noradrenaline (1.25 mcg/min)

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infusion was initiated to correct hypotension. Speculating topiramate to be the cause of this acidosis, we stopped it and started tab levetiracetam 250 mg twice daily. ABG on day 4 and day 5 still showed non-AG metabolic acidosis [Table 1], however, improved. Meanwhile, on day 5, noradrenaline was stopped following stabilization of BP. On day 6, the ABG showed normal acid-base status [Table 1]. The patient was also stable hemodynamically. However, there was no further improvement in neurological status. As such, tracheostomy was done on day 7. The patient was gradually weaned off the ventilator (room air) and discharged on day 13 with GCS-E4VTM5.

**Discussion**

Topiramate is an atypical newer antiepileptic used for the treatment of GTCS and is being increasingly used in refractory status epilepticus with a high response rate. Along with weak inhibitory activity on CA, it also blocks voltage-dependent sodium channels, potentiates gamma-aminobutyrate receptors, and antagonizes glutamate receptor subtype kainate receptors. Probably its anti-CA activity results in somnolence, nephrolithiasis, paresthesia and metabolic acidosis. Although symptomatic metabolic acidosis is a rare consequence of topiramate therapy, the same might manifest with hemodynamic perturbations. In our case, day 0 and day 1 ABG showed mild non-AG metabolic acidosis which could have been actually a presentation of chronic topiramate therapy. When topiramate was restarted on day 1, the acidosis worsened on day 2 and day 3 along with hypotension on day 3 probably under the effects of inflammatory, metabolic changes, and endocrine changes that accompanies severe head injury. Post-surgical stress could have been another aggravating factor. Only when the offending agent was stopped, the normal acid-base status was restored after an interval of about 72 hours. Simultaneously, the hemodynamic parameters were also stabilized leading to the cessation of inotropic support.

In our patient, continuous infusion of midazolam (1 mg/hr) and fentanyl (20 mcg/hr) were started in ICU as sedation. Although high dose midazolam (200 mcg/kg/min) has been reported to cause non-AG metabolic acidosis in pediatric status epilepticus, the midazolam infusion dose in our patient was too low to cause metabolic acidosis. Again, 0.9% NS as a possibility was also ruled out when the serum chloride levels attained normal values after replacing NS with plasma-lyte A (isotonic). Moreover, our patient did not have episodes of diarrhea and thus safely excluded as a possibility of non-AG metabolic acidosis. Again, there was no history of administration of calcium chloride, magnesium chloride or amino acid solutions.

It is a matter of curiosity as to what increases the susceptibility to topiramate-induced metabolic acidosis in only a few patients. As topiramate has a different power of inhibition over each CA isoenzyme, it seems reasonable to assume that differences between CA isoenzymes activity expression in different people could exist. Maybe this could explain the apparent diversity of susceptibility to metabolic acidosis in different persons. Ozer et al. proposed that the acidosis may be the resultant effect of an idiosyncratic reaction or rapid increment in dose. Our patient achieved normal acid-base status after 72 hours of stoppage of topiramate similar to cases reported by Stowe et al. and Fakhoury et al.

Various factors have been mentioned in literature as aggravating factors for topiramate-induced metabolic acidosis. These include concomitant CA inhibitors (acetazolamide), surgery, anesthesia, ketogenic diet, renal disease, dialysis, and diarrhea.

**Conclusion**

Since topiramate is a widely used drug, anaesthesiologists and critical care physicians should be aware of its potential complication that can be deleterious particularly during the perioperative period.

**Table 1: Showing progression of ABG values and serum urea and creatinine in the postoperative period**

| Post-op day | pH     | PCO₂ (mm Hg) | HCO₃⁻ (mmol/l) | Base deficit (mmol/l) | Lactate (mmol/l) | Na⁺ (mmol/l) | K⁺ (mmol/l) | Cl⁻ (mmol/l) | Anion gap (mmol/l) | Serum Urea (mg/dl) | Serum Creatinine (mg/dl) |
|-------------|--------|--------------|----------------|----------------------|-----------------|--------------|-------------|--------------|-------------------|---------------------|------------------------|
| 0           | 7.33   | 28           | 18.1           | 8.2                  | 1.2              | 136          | 3.4         | 111          | 10.3              | 11                  | 0.4                    |
| 1           | 7.32   | 26           | 17.2           | 11.1                 | 1.1              | 138          | 3.6         | 110          | 14.4              | 12                  | 0.6                    |
| 2           | 7.27   | 21           | 14.6           | 14.1                 | 1.4              | 131          | 3.4         | 107          | 12.8              | 19                  | 0.6                    |
| 3           | 7.20   | 18           | 11.2           | 16.6                 | 1.3              | 129          | 3.8         | 105          | 16.6              | 20                  | 0.7                    |
| 4           | 7.30   | 24           | 16.6           | 10.2                 | 1.5              | 132          | 4           | 106          | 13.4              | 15                  | 0.5                    |
| 5           | 7.32   | 27           | 19.1           | 6.4                  | 1.6              | 134          | 3.7         | 103          | 15.6              | 13                  | 0.5                    |
| 6           | 7.38   | 29           | 21.3           | 5.2                  | 1.3              | 133          | 3.3         | 100          | 15                | 14                  | 0.7                    |
Timely diagnosis and prompt intervention can prevent undue catastrophes.

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Conflicts of interest
There are no conflicts of interest.

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