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CASE REPORT

Metabolic Acidosis in a Pediatric Patient Receiving Topiramate

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Topiramate is an anticonvulsant that is labeled for the management of several seizure types in children >2 years of age. With the exception of cognitive dysfunction, nephrolithiasis, weight loss, and paresthesia, adverse effects in children are similar to other those noted with other anticonvulsants. We describe a 33-month-old child with complex partial seizures and secondary generalization who received topiramate 45 mg orally twice daily (6.2 mg/kg/d) for approximately 4 weeks before admission. He developed asymptomatic metabolic acidosis that was evidenced by a decrease in HCO_3^-, which was unresponsive to treatment with sodium bicarbonate. The child was weaned off topiramate and the metabolic acidosis resolved 48 hours after its discontinuation.

KEYWORDS: adverse effects, child, metabolic acidosis, topiramate, pediatrics,

J Pediatr Pharmacol Ther 2003;8:287-92

INTRODUCTION

Topiramate (Topamax, Ortho-McNeil Pharmaceutical, Raritan, NJ) is a sulfamate-substituted monosaccharide that is structurally different from other anticonvulsants.[1] It is currently FDA labeled for pediatric patients 2–16 years of age who have partial onset or primary generalized tonic-clonic seizures.[2] It is also approved as adjunctive therapy for the management of Lennox-Gastaut syndrome in children >2 years of age.[2] Topiramate exerts its pharmacological effect by at least four different mechanisms including blockage of voltage-dependant Na+ channels,[3] potentiation of gamma-aminobutyric acid,[4] antagonism of a kainite subtype of the glutamate receptor,[5] and inhibition of carbonic anhydrase isoenzyme II and IV.[6]

Although topiramate is structurally similar to acetazolamide and is a weak inhibitor of carbonic anhydrase, acetazolamide is significantly more potent an inhibitor of the carbonic anhydarase isoenzymes.[6] While studies in animal have supported the contention that anticonvulsant activity of topiramate is not related to it effects on carbonic anhydrase, it is likely that certain topiramate-associated adverse effects are related to the drug's ability to inhibit the carbonic anhydarase isoenzymes.[1,6]

Several cases of metabolic acidosis have been associated with the use of topiramate in pediatric[7,8] and adult patients;[9,10] however, many practitioners are unaware of this adverse effect. We report a case of a child who was taking topiramate for a few weeks before developing asymptomatic metabolic acidosis. This patient was unresponsive to treatment with sodium bicarbonate and only improved once topiramate was discontinued.

CASE REPORT

A 33-month-old Hispanic male with a history of complex partial seizures and secondary generalization was placed on topiramate for seizure control approximately one month prior to admission. The child was delivered by Cesarean section, was premature and had a birth weight of 3.8 kg. His past medical history was significant for intractable complex partial seizures with secondary generalizations. He was brought him to the Emergency Department following a seizure-associated fall that caused a lip and chin laceration. The mother reported that

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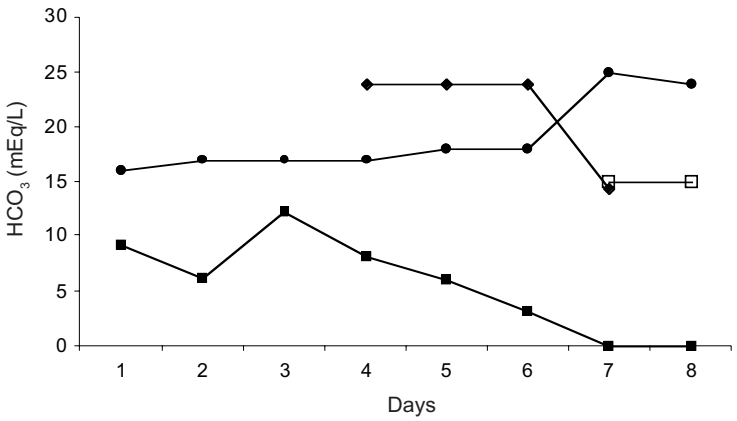
Table 1. Laboratory Results during Hospitalization

LABORATORY STUDIES	DAY 2*	2†	3	4	5	6	7	8	9
Glucose (60–100 mg/dL)	79	82	88	88	95	88	77	78	85
Sodium (137–145 mEq/L)	139	135	135	138	140	139	136	136	138
Potassium (3.5–5.3 mEq/L)	3.8	3.5	4.2	3.8	3.8	4.3	4.9	4.3	4.8
BUN (5–17 mg/dL)	7	5	2	6	5				
Creatinine (0.3–0.8 mg/dL)	0.4	0.4	0.3	0.4	0.5	0.4	0.3	0.4	0.3
CO2 (22–30 mmol/L)	16	16	16	17	17	18	18	25	24
Chloride (98–107 g/dL)	108	107	109	109	109	108	107	104	107
Calcium (8.7–9.8 g/dL)	9.5	9.3	9.7	9.8	9.3	9.7	10	9.3	9.6
Magnesium (1.6–2.3 mg/dL)		2.0							
Lactic Acid (0.7–2.1 mmol/L)		0.8							

**=collected at 0600 am*
†=collected at 0930 am

over the past month, the child had experienced 10 seizures despite the initiation and dosage escalation of topiramate. Current medications included topiramate 45 mg orally twice daily (6.2 mg/kg/d). Computed tomography and magnetic resonance imaging of the head were normal. The physical examination was within normal limits. The patient was afebrile (36.6° C) and had an oxygen saturation greater than 97% on room air. The patient was admitted to a pediatric floor and a pediatric neurology consult was ordered. Although the serum sodium was slightly below the reference range (i.e.,135 mEq/L), a basic metabolic panel, lactic acid, magnesium, alkaline phosphatase, albumin, and calcium were all normal. The child's carbon dioxide level was 16 mEq/L, which is well below the normal reference range (i.e., 22-30 mEq/L). A urine culture was negative. On days 2–5 of hospitalization the child continued to have frequent seizures and his topiramate dosage was progressively increased. The patient oxygen saturation on room air was always above 97% and he was afebrile during the hospital stay. A scalp electro-

Figure.



= HCO3- (mEq/L); = Topiramate (mg/kg/d);
= Sodium bicarbonate (mEq/d); = Citrate/Citric Acid (mL/d)

Table 2. Review of topiramate dosing and other medical therapies

Day	Medication	Intravenous Fluids
1	None	D5W NS with 20 mEq/L KCL at 50 mL/hr
2	Topiramate 45 mg x 1 Topiramate 45 mg q 12 hr (6.2 mg/kg/d)	D5W NS with 20 mEq/L KCL at 50 mL/hr
3	Topiramate 45 mg q 12 hr (6.2 mg/kg/d)	D5W NS with 20 mEq/L KCL at 50 mL/hr
4	Topiramate 60 mg x 1 Topiramate 60 mg q 12 hr (8.2 mg/kg/d)	D5W NS with 20 mEq/L KCL at 50 mL/hr
5	Topiramate 60 mg q 12 hr (8.2 mg/kg/d)	1/4 NS with 20 mEq/L KCL and 20 mEq/L of NaHCO3 at 60 mL/h
6	Topiramate 45 mg q 12 hr (6.2 mg/kg/d); IV valproate 200 mg now (13.2 mg/kg); Valproic acid 50 mg po x 1 followed by 75 mg po x 2 doses	1/4 NS with 20 mEq/L KCL and 20 mEq/L of NaHCO3 at 60 mL/hr
7	Topiramate 45 mg x 1; Valproic acid 50 mg po followed by 75 mg TID	1/4 NS with 20 mEq/L KCL and 20 mEq/L of NaHCO3 at 60 mL/hr
8	Valproic acid 75 mg po x 2 doses, 100 mg po TID (1 dose); and sodium citrate and citric acid 5 mL TID	1/4 NS with 20 mEq/L KCL and 20 mEq/L of NaHCO3 at 30 mL/hr
9	Valproic acid 100 mg po TID (21 mg/kg/d); Valproic acid 50 mg po x 1 Carnitine 400 mg orally TID Sodium citrate and citric acid 5 mL TID	D/C IVF
10	Valproic acid 100 mg po x 1 dose; Valproic acid 125 mg po TID (only received 2 doses); valproic acid 100 mg orally now; carnitine 400 mg orally BID	
11	Valproic acid 125 mg po TID; Carnitine 400 mg po BID; Sodium citrate and citric acid 2.5 mL po TID	

encephalogram revelaed sharp and spike wave discharges from the right frontal, bifrontal, and bianterior regions of the brain. The neurologist and attending physician ordered an additional dose of topiramate on day-2 and increased the dosage on day 4 (Table 1).

Despite adequate hydration (100 mL/kg/day), the carbon dioxide level remained below the reference range (Table 2). All other electrolytes were within the normal range. A lactic acid level obtained on day 2 was normal (0.8 mmol/L). A capillary blood gas on day 5 confirmed metabolic acidosis. On day 5, the physician began to treat the resistant metabolic acidosis by adding 20 mEq/L of sodium bicarbonate to the patient's maintenance intravenous fluids. The following day, the child's HCO_3- level remained unchanged (Table 2), despite continuing sodium bicarbonate therapy. A prior medical record from one year ago revealed that the patient had a normal carbon dioxide level.

The physician consulted the pharmacy department for assistance in determing if there was an association between topiramate and the metabolic acidosis. A search of the medical literature revealed several case reports of metabolic acidosis in individuals'receiving topiramate. Following consultation with neurology, topiramate was tapered and valproate (Depakene; Abbott) was added the patient's drug regimen (Table 1) and bicarbonate therapy was continued. On day 7, the topiramate was discontinued when the valproic acid serum concentration was within the reference range (50–100 μg/mL). The next day sodium citrate and citric acid was added and the rate of fluid administration was decreased. On days 9 and 10, the valproate dose was adjusted to maintain the serum concentration within the

reference range. On day 10, the sodium citrate and citric acid doses were decreased by 50%. The child's carbon dioxide level normalized, sodium bicarbonate or sodium citrate and citric acid were discontinued (Figure) and the child was discharged following 11 days of hospitalization on valproic acid 125 mg TID (26 mg/kg/day) and carnitine 500 mg TID (103 mg/kg/d).

DISCUSSION

Carbonic anhydrase exists in the glial cells of the brain and where it maintains pH by catalyzing hydration and dehydration of carbonic dioxide. Although topiramate's ability to inhibit carbonic anhydrase in weak, neuronal excitability is decreased when carbonic dioxide is retained.[6] Carbonic anhydrase is also located in the kidney where its inhibition causes an increase in urinary HCO_{3^-} excretion, which leads to an increase in urinary pH and serum chloride and a decrease in serum HCO_{3^-}, potassium and sodium.[3]

Several reports have noted the occurrence of metabolic acidosis in individuals receiving topiramate.[9,10,11] While the manufacture does not provide information regarding the incidence of metabolic acidosis it is listed as an infrequent adverse event.[2]

There have been several case reports of topiramate-associated metabolic acidosis in post market-surveillance. Only two cases of topiramate-associated metabolic acidosis have been reported in adults.[9,10] The first case reported a 52-year-old-male who developed asymptomatic hyperchloremic acidosis after receiving topiramate 200 mg/day for 2 months.[9] Three days before temporal lobectomy his chloride was 190 mEq/L and his bicarbonate was 24 mEq/L. Laboratory studies following surgery revealed a chloride of 115 mEq/L and a bicarbonate of 16 mEq/L. His metabolic status normalized after adminsitration of sodium bicarbonate and a 50% reduction in topiramate dosage.

The second report described symptomatic changes in a 20-year-old male who had been receiving 5 mg/kg/day (200 mg twice daily) for the previous 9 months. He presented with acute mental status changes (i.e., disorientation, somnolence, headache, and combativeness). Laboratory studies on admission were within the normal reference range with the exception of chloride (120 mEq/L) and bicarbonate (12 mEq/L). The anion gap was 13. The patient's mental status changes were contributed to the metabolic acidosis. His mental status return to normal following administration of sodium bicarbonate 2 mEq/kg/hour and the tapering and discontinuation of topiramate. Sethi et al. described three patients who developed unexplained metabolic acidosis after beginning topiramate. These patients were not on any other medications known to cause metabolic acidosis.[12]

The only study of topiramate-associated metabolic acidosis in a large number of pediatric patients was performed by Takeoka and colleagues.[7] This was a retrospective review that included 27 pediatric patients that ranged in age from 1–19 years. HCO_{3^-} levels were performed before and during topiramate therapy in 18 children and an additional nine patients also had levels obtained following discontinuation of topiramate. The mean±SD topiramate dosage was 9.3±7.4 mg/kg/day and ranged from 2–32 mg/kg/day. The authors compared the percentage decrease in pre- and post-treatment HCO_{3^-} levels and reported that 70% of patients had greater than a 10% decrease serum HCO_{3^-}. Although the mean±SD decrease in serum HCO_{3^-} was small (4.7±1.8 mEq/L) the response was variable with a maximal change in one patients of 10 mEq/L. While no baseline HCO_{3^-} level was available in our patient, a review of the child's prior medical record from one year ago revealed that the patient had a normal carbon dioxide level. His admission value was 6 mEg/L below the lower end of the reference range for age. Following discontinuation of topiramate the HCO_{3^-} level had returned to normal and had increased by 8 mEq/L.

The majority of patients who develop topiramate-associated metabolic acidosis are asymptomatic and experience a returned to baseline serum HCO_{3^-} after topiramate is discontinued. This finding was similar to that noted in our patient who developed asymptomatic metabolic acidosis that resolved after discontinuation of topiramate. Although Takeoka et al. described one child who developed symptomatic tachypnea, which required HCO_{3^-} supplementation, the authors contributed the worsening metabolic acidosis to prolonged status epilepticus during a suspected viral illness.[7] Although our patient was admitted for uncontrolled seizures, a lactic

acid level obtained to determine if the patient had developed postical lactic acidosis was normal.

One group of investigators have suggested that there maybe an association between the dosage of topiramate and the development of metabolic acidosis.[7] Fifteen patients had both HCO_{3^-} and serum topiramate concentrations. Linear regression analysis from data in these 15 patients showed no relationship between the daily dosage or serum concentration of topiramate and serum HCO_{3^-} values. Although the authors did not define "larger" doses, within patient data suggested that there was a greater decrease in serum HCO_{3^-} values in patients who were receiving larger doses of topiramate.

Although the patient described in our case had his topiramate dosage titrated appropriately to approximately 6 mg/kg/day over a four week period, the patient's topiramate had recently been increased in order to rapidly control his seizures. It was likely that the metabolic acidosis was causing a lower seizure threshold, thus exacerbating his seizures and causing a subsequent need for more topiramate. However, it is important to note that when the patient was admitted to the hospital he was already titrated appropriately to approximately 6 mg/kg/day of topiramate. It was only when topiramate dosage was decreased and sodium citrate and citric acid added that the HCO_{3^-} rise to normal, thus allowing the patient to recover from the metabolic acidosis.

Takeoka et al. also noted that patients who had a <10% change in serum HCO_{3^-} were also taking a multitude of other anticonvulsants.[7] In fact, the average number of anticonvulsants per patient was 3.3 and ranged from 1–7. Several of these medications may have increased the hepatic clearance of topiramate thereby decreasing the likelihood of developing metabolic acidosis. Although the mechanism is unknown, phenytoin and carbamazepine decrease topiramate serum concentration by about 50–70%.[13]

The child described in our case was not receiving any other medication for at least one month prior to hospitalization. Nor did he receive any other medications during the time frame when he developed metabolic acidosis. He was prescribed valproic acid, which has been reported to induce the clearance of topiramate and thereby increase the HCO_{3^-} level.[14] Given the time course and modest decrease in topiramate serum concentration (15%) caused by valproic acid, it is unlike that the drug-drug interaction was clinically important in this case.

The majority of patients that develop topiramate-associated metabolic acidosis are asymptomatic; however, symptomatic acidosis has been described.[10] Individuals with inborn errors of metabolism, those with acute metabolic changes due to systemic illness, those receiving salicylates or who are on the ketogenic diet may have a greater propensity to develop topiramate-associated acidosis. None of the above were a factor in our patient since he did not have any of the above "at risk" conditions.

There were several reasons why we feel that the metabolic acidosis was due to topiramate: The child did not have any of the above "at risk" conditions and was not on any other medications for at least one month prior to hospitalization and during the time frame when the patient developed metabolic acidosis. A review of a previous hospitalization from one year ago revealed that the patient had a normal carbon dioxide level. A lactic acid level was obtained, which was normal, and eliminated the possibility of postical lactic acidosis. The patient's oxygen saturation on room air was always above 97% and he was afebrile during the hospital stay.

Although the patient had been titrated appropriately to about 6 mg/kg/day of topiramate prior to hospitalization, his dosage of topiramate was rapidly increased during his hospital stay in an attempt to control his seizures. It was likely that the metabolic acidosis was causing a lower seizure threshold, thus causing the patient to seize more and subsequently require more topiramate. The addition of sodium bicarbonate to his intravenous fluids did not affect the HCO_{3^-} level while topiramate was still being administered. It was only when topiramate was discontinued and sodium citrate and citric acid added did the HCO_{3^-} return to normal.

SUMMARY

Although rare, practitioners should be aware that topiramate may cause profound metabolic acidosis that is resistant to correctional treatment. Monitoring serum HCO_{3^-} levels before and during topirmate therapy or following an increase in dosage may be warranted. This is especially true for individuals with inborn errors of metabo-

lism, acute metabolic changes due to systemic illness, or renal dysfunction and those receiving salicylates or who are on the ketogenic diet since they may have a higher incidence of topiramate-associated acidosis. The occurrence of metabolic acidosis may necessitate a decrease in topiramate dosage of complete discontinuation of the medication.

Because some reports have suggested a relationship between dosage and topiramate-associated acidosis it is important to initiate topiramate slowly. The normal recommended starting dose is 1–3 mg/kg/day. This dosage should be increased by 1–3 mg/kg/day at 1–2 week intervals to a normal total daily dose of 5–9 mg/kg/day given in two divided doses.[2] Practitioners should also be aware of any medication that decrease the clearance of topiramate and thereby increasing the serum topiramate concentration. Likewise, it is important to recognize medications that increase topiramate clearance since their discontinuation may also cause topiramate concentration to increase. Should metabolic acidosis occur in a patient on topiramate the drug should be discontinued since severe symptomatic acidosis or renal calculi may occur.

CONFLICTS OF INTEREST: The authors declare no conflicts of interest or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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