METABOLIC ACIDOSIS INDUCED BY TOPIRAMATE: RESPONSE TO BICARBONATE SUPPLEMENTATION*

Mark Mintz, MD

ABSTRACT

A retrospective chart review of a pediatric population receiving topiramate was conducted to explore the possible effects of carbonic anhydrase inhibition. The predominant clinical symptoms of the patients were lethargy and fatigue, although some reported poor balance, startle sensitivity, and a subjective sensation of feeling cold. The efficacy of bicarbonate supplementation on symptomatic patients was evaluated. The study suggests that bicarbonate supplementation may be indicated for use in patients at specific serum carbon dioxide thresholds or who have clinical symptoms of metabolic acidosis.

Well-controlled studies have demonstrated that topiramate, a sulfamate-substituted monosaccharide, is a very effective antiepileptic agent. One of this drug's many mechanisms of action is carbonic anhydrase inhibition. While this action may contribute to topiramate's efficacy as an antiepileptic agent, it may also contribute to the adverse effects associated with use of this drug, such as renal stone formation and paresthesias. Carbonic anhydrase inhibition causes a series of electrolyte changes. At the renal level, a net loss of bicarbonate occurs, leading to a rise in urinary pH. The renal loss of bicarbonate causes a decrease in serum bicarbonate levels, which can cause metabolic acidosis. Subsequently, as a compensatory mechanism, the level of serum sodium or potassium ions may increase or the level of serum chloride ions may decrease.

Although pediatric studies of the use of topiramate report a 10% incidence of side effects, including fatigue, somnolence, difficulty concentrating, and decreased appetite, side effects were not correlated with bicarbonate levels. A recent study reviewed 30 children on topiramate therapy, with doses ranging from 2 to 32 mg/kg/day. In 66% of these children, serum bicarbonate levels decreased by more than 10%. Two of these patients experienced a decrease from baseline of 8 to 10 mEq/L. All of these patients were considered to be asymptomatic, and 2 of this subgroup discontinued topiramate because of anorexia.

To further explore possible effects of carbonic anhydrase inhibition on a pediatric population receiving topiramate, a retrospective chart review identifying dosage, seizure type, elements of seizure control, and laboratory findings was conducted. The predominant symptoms were lethargy and fatigue, although some patients reported poor balance, startle sensitivity, and a subjective sensation of feeling cold. An attempt was made to determine whether symptoms occurred chronically or only during the time of an intercurrent illness. The efficacy of bicarbonate supplementation, which is frequently administered to symptomatic patients, was evaluated.

In a cohort of 19 patients ranging from 1.75 to 14.8 years of age, 15 had partial seizures; 4 were diagnosed with primarily generalized seizures. Within the
The mean dose of topiramate was 5.7 mg/kg/day, ranging from 4.3 to 9.0 mg/kg/day, used as an initial monotherapy in 3 patients and as an add-on medication in 16 patients. Ten of the 16 were eventually able to achieve monotherapy. Seizure control improved in 16 patients, and 6 became seizure free. No change in seizure control was seen in 2 patients, and 1 reportedly worsened.

Laboratory results showed a serum bicarbonate level of less than 20 mEq/L in 10 patients (53%). Clinical symptomatology, usually lethargy and fatigue, was reported in 6 of these patients (32% of the total cohort); all of the symptomatic patients had suppressed bicarbonate levels ranging from 13 to 19 mEq/L. One of the symptomatic patients developed symptoms only during an intercurrent illness and exhibited a fruity odor to the breath, suggesting the possibility of a ketogenic state. One patient reported less lethargy and fatigue on topiramate, but developed poor balance and startle sensitivity. An anion gap was discernible in 5 of the 6 patients, with a mean of 16.8 and a range of 14 to 23. One of the symptomatic patients discontinued topiramate.

The remaining 5 patients were given a bicarbonate supplement (Bicitra® 1 cc=1 mEq of bicarbonate); doses ranged from 5 to 15 mEq per dose 2 to 3 times daily. All patients reported improvements in symptomatology, with lethargy and fatigue reduced to a point of tolerability, allowing the continued use of topiramate therapy. One patient was able to discontinue bicarbonate therapy after 1 month; he required long-term, daily therapy. The remaining patient was prescribed bicarbonate therapy only during intercurrent illness without further episodes of clinical ketosis.

These results suggest that some of the reported side effects of topiramate may result from metabolic acidosis. In some children, the metabolic acidosis may be marginally compensated, which could predispose them to developing a clinically significant state of metabolic acidosis at times of intercurrent illness, stress, or poor oral intake. Furthermore, topiramate-associated side effects of poor concentration and cognitive impairment may also be an indirect effect of systemic metabolic acidosis.

This study suggests that bicarbonate supplementation may be indicated for use in patients at specific serum carbon dioxide thresholds or who have clinical symptoms of metabolic acidosis. Additional research is required to further define those thresholds, as well as to determine the efficacy of bicarbonate supplementation for the treatment of clinical symptoms of metabolic acidosis and the adverse effects of topiramate. Empiric use of bicarbonate supplementation in times of compromised situations, such as an intercurrent illness, is also an area for further study.

REFERENCES