CASE REPORT

Topiramate, a concealed cause of severe metabolic acidosis

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Severe metabolic acidosis is common among critically ill patients, and topiramate is a rare cause that may fail recognition. We report a lady with acute encephalopathy who had severe non-anion gap metabolic acidosis that served as the clue leading to suspicion and diagnosis of topiramate toxicity and was confirmed by elevated blood topiramate levels. Additionally, we provide a review of literature on all reported cases of topiramate toxicity.

Keywords**:** Topiramate, metabolic acidosis, migraine, altered mental status, carbonic anhydrase

BACKGROUND:

Topiramate, used for epilepsy and migraine prophylaxis, acts by blocking neuronal voltage-dependent sodium channels, enhancing gamma-aminobutyric acid (GABA) A activity and antagonizing alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite glutamate receptors [1]. It also inhibits carbonic anhydrase (CA) causing a non-anion gap metabolic acidosis (NAGMA). In clinical studies, 32% of patients consuming topiramate 400 mg had a serum bicarbonate decline to <20 mEq/L with a mean decline ~ 5.1 mEq/L [2]. Dose reduction or discontinuation may be required for persistent, symptomatic or severe acidosis. We discuss a young lady with topiramate toxicity where a severe NAGMA was the key finding leading to the diagnosis. We also provide a brief review of literature pertaining to metabolic acidosis from topiramate toxicity.

CASE:

A 29-year-old Caucasian female presented to a referring facility with altered mental status. Her symptoms began the previous night with migraines for which she took her usual pills. Her home medications included sumatriptan, bupropion, topiramate and clonazepam. At 11:30 PM, while walking downstairs, she sustained a fall without loss of consciousness or injuries. By 5:30 AM the next day, her husband noticed abnormal twitching movements of her upper and lower extremities. Since he believed it to be a symptom of restless leg syndrome, he did

not wake her up. An hour later, she was found to be unresponsive to verbal or physical stimuli, her eyes were rolled up and a she had a rapid pulse. The husband called emergency services and she was transported to the referring facility. Per husband, she was more depressed over the previous 3 days, and recently her physician increased her dose of clonazepam. At the referring facility, the patient was intubated using paralytics due to shallow breathing and for airway protection. She received two liters of 0.9% saline to resolve hypotension. Labs were significant for a white blood cell counts (WBC) of 14.7 x 10^{-3}/µL, sodium of 140 mEq/L, potassium of 3.2 mEq/L, chloride of 103 mEq/L, and a bicarbonate of 19.7 mEq/L. Serum total protein was 7.5 g/dL, albumin was 3.6 g/dL, glucose was 114 mg/dL, blood urea nitrogen was 17 mg/dL, serum creatinine was 1.0 mg/dL, and osmolality was 282 mosm/L. Urinalysis was normal, urine drug screen and pregnancy test were negative, and chest x-ray had no abnormalities. The echocardiogram showed a hyperdynamic left ventricle, but was otherwise unremarkable. The patient was air lifted to our university hospital for further evaluation, with a concern for anoxic brain injury.

At arrival to our medical intensive care unit (MICU), vitals were normal, she was unresponsive with periodic spontaneous eye opening and non-purposeful movements in all extremities. Bilateral pupils were dilated and reacted minimally to light. Deep tendon reflexes were normal. Rest of the exam was unremarkable. Blood tests results were as follows: WBC of 13.27 x 10^{-3}/µL, serum sodium of 140 mmol/L, potassium of 3.8 mmol/L, chloride of 111 mmol/L, bicarbonate of 16 mmol/L, lactic acid of 2.8 mmol/L, creatinine of 0.76 mg/dL, and blood urea nitrogen of 15 mg/dL. Liver functions tests were also normal. Arterial blood gas revealed a pH of 7.166, pCO_2 of 40.0 mmHg, pO_2 of 316 mmHg, HCO_3 of 13.9 mmol/L, and serum osmolality of 292 mOsm/kg (Osmolar gap 3 mOsm/kg). Urine pH was 5 and urine electrolytes showed: sodium of 82 mmol/L, potassium of 26.7 mmol/L, chloride of 96 mmol/L (urine anion gap 12.7 mmol/L) and creatinine of 59 mg/dL. She was empirically started on vancomycin, ceftriaxone and acyclovir. Lumbar puncture was done and cerebrospinal fluid (CSF) results were normal (colorless, protein of 43 mg/dL, glucose of 60 mg/dL, no white or red blood cells). Subsequently, the antibiotics were stopped. Computerized tomography (CT) scan of the head and neck was also normal. Electroencephalography was reported to be consistent with moderate to severe encephalopathy of no specific etiology. Comprehensive drug screen was positive for naproxen and bupropion.

Given severe NAGMA and no other abnormalities in lab and imaging studies, we explored different causes of NAGMA and they were non-revealing. Past medical history was negative for diarrhea, previous abdominal processes, hyper-alimentation, chronic kidney disease or clues to inherited disorders, such as hearing loss, osteopetrosis or mental retardation (Table 1) [3]. We suspected topiramate toxicity based on its inhibition of CA. At approximately 12:30 PM (~13 hours after the suspected ingestion) a topiramate level was drawn and sent to our reference laboratory (Mayo Medical Laboratories, Rochester, MN). She was given 0.45% normal saline with 75 mEq of sodium bicarbonate at 75 ml/hr based on evidence from our literature search on topiramate toxicity (see below in discussion). Repeat blood gas later showed a pH of 7.345. On day 2, she spontaneously opened her eyes and followed commands. She was successfully extubated on day 3. Comprehensive drug screen returned with naproxen and bupropion being positive and

Table 1. Common Causes of Non-Anion Gap Metabolic Acidosis

Low/Low-Normal Serum Potassium

- Diarrhea
- Uretero-enteric fistulas
- Pancreatic/biliary drainage
- Urinary intestinal diversion
- Proximal RTA (type 2)
- Distal RTA (type 1)
- Carbonic anhydrase inhibitor
- Toluene intoxication, D-lactic acidosis

High/High-Normal Serum Potassium

- Hyperkalemic distal RTA
- Chronic kidney disease
- Hyporeninemic hypoaldosteronism
- Gordon syndrome
- High ileostomy output
- Decreased distal sodium delivery
- Hydrochloric acid administration
- Drug related (ie, NSAIDs, triamterene, trimethoprim, amiloride, heparin, pentamidine, spironolactone, ARB, ACEi)

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Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal antiinflammatory drug; RTA, renal tubular acidosis.

topiramate level was reported as 20.5 µg/mL. By day 4, her mental status was normal and she recalled taking additional doses of a migraine medication, but she was unsure if it was topiramate. She was discharged home the same day with a plan for an outpatient follow up with her preferred neurologist to consider alternatives for migraine prophylaxis other than topiramate. After a few months, per phone conversation with husband, the patient was reported to be asymptomatic and remained off topiramate since discharge.

DISCUSSION:

Common adverse effects from topiramate are neurological, including paresthesia, somnolence, fatigue, dizziness, mood and memory impairment, lack of concentration, confusion, headache, psychomotor retardation, agitation, cognitive dysfunction, ataxia, pain, as well as sensory and speech disturbances [2, 4-6]. Less commonly a variety of gastrointestinal symptoms have also been described [6]. Several reports describe toxicity at varying doses of ingestion when used for migraine and epilepsy (Table 2) [4, 5, 7-20]. Based on a retrospective review of 567 cases of topiramate toxicity (during 2000-2001), the American Association of Poison Control revealed that: 39% were adults, mild mental status changes were common, and severe respiratory depression or persistent NAGMA were infrequent yet other reports confirm their occurrence [5, 10-12]. NAGMA was of high diagnostic value in our patient's case as history was negative for any other causes of NAGMA enumerated in Table 1 [3]. Type 1 or distal renal tubular acidosis (RTA) is characterized by an

Table 2. List of reported cases with topiramate toxicity. Literature review included only those reported in English language. Search terms in PUBMED and Google Scholar included "topiramate" and one or more of "toxicity", "metabolic acidosis" and "overdose".

First Author (Ref no)	Year	No: of cases	Dose	Clinical Features	Biochemical abnormalities at admission	Treatment	Outcomes
Chun-hung (12)	2001	2	300 mg/day for 1 weeks; unknown for second patient	Hyperventilation; Increased irritability	Case 1: pH 7.36, HCO_3 14.9 mEq/L; Case 2: pH 7.34, HCO_3 20.4 mEq/L	Sodium bicarbonate; discontinued topiramate	Full recovery
Fakhoury (5)	2002	2	Case 1: 20,000 mg Case 2: 40,000 mg	Obtundation, Seizures, myoclonic jerks	Case1: pH 7.22, HCO_3 12 mEq/L. Case 2: pH 7.41, HCO_3 12 mEq/L	Both needed intubation for airway protection, intravenous fluids, antiepileptics	Both had full recovery. Case 1: mental status normal in 24 hours, acidosis resolved at six days Case 2: mental status normal in 24 hours, acidosis resolved in 7 days.
Traub (11)	2003	1	Unknown	Agitation, Arching back movements, "can't feel anything"	pH not reported, HCO_3 20 mEq/L.	Observation	Full recovery in 24 hours.
Langman (17)	2003	1	Unknown	Found dead in bed	No data	Not applicable	Died
Chung (8)	2004	1	800 mg	Incoherence, Confusion, Disorientation, Echolalia	pH 7.38, HCO_3 18 mEq/L	Supportive	Full recovery in 24 hours
Ozer (13)	2004	1	25-50 mg daily for 7 days	Asymptomatic	pH 7.29, HCO_3 20 mEq/L	Bicarbonate	Acidosis resolved after bicarbonate.
Burmeister (14)	2005	1	100 mg/day for 3 months	Asymptomatic	pH 7.31, HCO_3 8.9 mEq/L	Discontinued topiramate	Lab abnormalities normalized at 30 days.
Lofton (3)	2005	567	12-2200 mg	Asymptomatic (62.1%), drowsiness/lethargy (15.5%), dizziness/vertigo(4.9%), agitation(4.9%), confusion (3.9%), nausea(2.6%), vomiting(2.5%	Only one case with metabolic acidosis, no data on pH or bicarbonate	Unspecified	Unspecified

Lin (7)	2008	1	Unknown	Confusion, visual hallucinations, slurred speech, ataxia.	No data reported	Observation	Full recovery in 6 days.
Mathews (19)	2008	1	200-400 mg/day	Seizures	HCO3 13 on day 9 of hospital stay (nosocomial onset of acidosis following dose increase for seizures)	Discontinued topiramate	Full recovery in 10 days
Wisniewski (2)	2009	6	Range: 750-12000 mg	Somnolence (66.7%); Vertigo, Agitation, & Mydriasis (33.4%), Seizure	Mild to moderate metabolic acidosis in 4 of 7 cases (pH range 7.23 – 7.34, HCO_3 range 15.3-17.3 mEq/L)	Four received bicarbonate, two with supportive therapy	Full recovery all patients
Beyenburg(15)	2009	1	150 mg/day	Blurred Vision	No data reported	Discontinued topiramate	Subjective improvement of vision after 6 months
Shiber (10)	2010	1	No data	Dyspnea, Tachycardia, Confusion, Respiratory Failure	pH 7.14, HCO_3 11 mEq/L	Mechanical ventilation for respiratory fatigue, Intravenous fluids and bicarbonate	Full recovery in 72 hours
Pierson (9)	2010	1	400 mg	Flushing, Anxiety, Tachycardia, Hypertension, Confusion	pH 7.34, HCO_3 13 mEq/L	Observation	Full recovery in 24 hours
Beer (24)	2010	1	Unknown	Unresponsive in bed	No data reported	Resuscitation	Died
Lynch (6)	2010	1	Unknown overdose	Coma, respiratory failure	pH 7.26, HCO_3 16 mEq/L	Intubated for airway protection, discontinued topiramate	Full recovery in 72 hours
Brandt (16)	2010	1	~20x200mg tablets	Non convulsive status epilepticus	No data reported	Discontinue topiramate, antiepileptics	Full recovery in 10 days

impaired ability to secrete acid in the collecting tubules, and type 2 or proximal RTA is characterized by a decreased reabsorption of filtered bicarbonate in the proximal tubule; both are mediated by a CA type II (major type in kidneys), which is inhibited by topiramate causing a mixed RTA [2, 21-24].

Our patient probably ingested an unknown number of topiramate 100 mg immediate release tablets. One report described altered mental status in an adult following a single-dose of 400 mg of topiramate prescribed for migraine; a blood topiramate level drawn 15 hours after ingestion returned at 8.4 µg/mL, and symptoms resolved 24 hours after admission [11]. A 17 year old lady with suicidal intake of 800 mg of topiramate developed incoherence, confusion, disorientation, and speech impairments, but eventually had full resolution of symptoms within ~24 hours [10]. Most patients with topiramate toxicity recover relatively quickly with just supportive treatment [4, 5, 10, 11, 13]. In our literature search we found only two cases of fatal topiramate toxicity. The first case was a 41-year-old lady found unresponsive with bottles of topiramate, citalopram, and flunitrazepam at the scene. Autopsy and toxicology results reported a topiramate level of 49 µg/mL and citalopram level of 0.85 µg/mL, and the cause of death was stated to be topiramate intoxication in combination with citalopram. The other case was a 44-year-old lady found dead in bed, whose qualitative screening detected high concentrations of topiramate and the cause of death was attributed to it [19, 25].

Our patient's serum topiramate level was 20.5 µg/mL. The reference range for serum topiramate is 2.0-8.0 µg/mL when used for psychiatric indications and 5.0-20.0 µg/mL as an anticonvulsant. In studies conducted on topiramate for epilepsy, there were some patients who tolerated levels higher than this range and a few others who exhibited toxicity even within this therapeutic range [26]. Sampling for drug level monitoring is usually done prior to the next daily dose (trough), but definite toxic levels have not been well defined [26]. Based on the information from the family, we guessed that the last dose of topiramate was consumed 13 hours prior to drawing a sample for topiramate level. Topiramate exhibits linear pharmacokinetics (PK) over a dose range of 100 mg to 1200 mg immediate release tablets [1, 26, 27]. It is rapidly absorbed and almost completely achieves peak or maximal concentrations (Cmax) ~ 2 hour post ingestion (range 1-4 hours) which is unaffected by food. It is poorly bound to plasma proteins, has a volume of distribution of 0.6 to 0.8 L/kg, and 75-80% of unchanged drug undergoes renal elimination resulting in a half-life between 20-30 hours [1, 28]. The Cmax varies between 1.73 µg/mL to 28.7 µg/mL for the dose range of 100 mg to 1200 mg respectively. Based on these PK data, the reported level of 20.5 µg/mL at 13 hours post ingestion projects into an ingestion of at least 800 mg or higher dose of topiramate. Our patient's clinical course is reminiscent of prior reports which stated that within a relatively short period of time and with only supportive treatment to correct acidosis the patient's symptoms resolved. In summary, without a clear history, severe NAGMA was the key to the diagnosis of topiramate toxicity. Our case highlights the fact that topiramate must be suspected as a cause of severe NAGMA in those taking it when other causes are not apparent.

CONCLUSION:

Topiramate can cause severe symptomatic NAGMA and our review of literature suggests that this occurs even at therapeutic doses. Drug level testing is not widely available, but fortunately most cases recover with symptomatic treatment. It is important for physicians to be aware of such serious toxicity, because early diagnosis by high index of suspicion can improve outcomes.

Notes

Author Contributions: Lovinger made the first draft, Schroeder edited and revised first draft of case background, case description, and added details to discussion. Ludwig added data on pharmacokinetics and pharmacodynamics and aided further review of literature. Regunath then further edited the manuscript, did further review of literature and gathered all reported cases on topiramate toxicity. Lovinger and Regunath created the tables and further revised discussion. All authors have reviewed and approved the final version of manuscript.

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