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CASE REPORT

# Topiramate as a rare cause of reversible Fanconi syndrome and acute kidney injury: a case report and literature review

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Topiramate (TPM) is a sulfa-derivative monosaccharide that has been used for multiple indications in the last several years. We describe a 53-year-old woman with known chronic kidney disease stage 2 and baseline creatinine of 1 mg/dL who developed acute kidney injury and proximal renal tubular dysfunction while on TPM for depression. The Naranjo Adverse Drug Reaction Probability Scale indicated a probable relationship (score of 6) between TPM and acute kidney injury as well as proximal tubular dysfunction; these renal conditions resolved on withdrawal of TPM. To our knowledge, this is the first report of such a scenario. Patients receiving TPM therapy should be closely monitored for evidence of kidney dysfunction and electrolyte abnormalities.

Keywords: *acute kidney injury*; *drug-related side effects*; *topiramate*; *proximal renal tubular dysfunction*

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Topiramate (TPM) has been proven efficacious for a variety of medical conditions, so that its use has increased considerably since it was first approved by the United States Food and Drug Administration for the treatment of epilepsy in 1996 (1–4). The spectrum of adverse effects of TPM has likewise expanded, as illustrated below.

## Case report

A 53-year-old woman with a history of chronic kidney disease stage 2 presented with a serum creatinine of 2.9 mg/dL on blood work that was done as a part of preoperative workup for spinal stenosis. Laboratory data from a visit to another facility 2 months prior to this presentation were reportedly normal; her known baseline creatinine was 1 mg/dL. The patient reported unintentional weight loss of 7 pounds in less than 3 months. Review of systems was positive for chronic low back pain only.

She had taken 800 mg of ibuprofen daily for just over a month but stopped it several months prior to this presentation. She had no history of use of herbal medications or intravenous contrast. Her other comorbidities included asthma, restless leg syndrome, hypertension, chronic low back pain, depression, and anxiety. Her medications included aspirin 81 mg daily, pramipexole 0.5 mg at bedtime, albuterol inhaler as needed, buspirone 50 mg/day, risperidone 1 mg at bedtime, and topiramate (TPM) 100 mg twice a day for depression. The patient had remote smoking history of 1 pack per day from the age of 14 to 18 and no alcohol use. Her family history was non-contributory.

Physical examination showed an obese patient with blood pressure of 121/59, pulse 100 beats/minute, temperature 98.2°F (36.8°C), respiratory rate 16, and oxygen saturation 98% on room air. She was alert, oriented, and in no distress. Cardiopulmonary examination revealed clear breath sounds bilaterally without wheezes or rhonchi, and normal heart sounds with no murmurs, gallops, or rubs. Abdominal examination showed no tenderness, masses, or organomegaly. She had neither focal neurologic deficit nor edema of the lower extremities.

Her laboratory data (Table 1) showed normal anion gap (hyperchloremic) metabolic acidosis, with glucosuria in the setting of normal serum glucose and hemoglobin A1C of 5.8. She also had hypouricemia and hypokalemia. However, serum phosphorus level was normal. In this setting of metabolic acidosis, urine pH was noted to





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*Table 1.* Serial serum chemistries

| | 2 months prior to presentation | At time of initial evaluation | 1 week after (topiramate was withdrawn after this test) | 3 months after stopping drug | 13 months after stopping drug |
|---|---|---|---|---|---|
| Sodium | 141 | 142 | 138 | 139 | 138 |
| Potassium | 4.0 | 3.2 | 2.9 | 3.9 | 4.4 |
| Chloride | 104 | 114 | 106 | 102 | 100 |
| Bicarbonate | 28 | 18 | 14 | 26 | 30 |
| BUN | 10 | 17 | 21 | 15 | 24 |
| Creatinine | 0.9 | 2.9 | 3.4 | 1.6 | 1 |
| Glucose | 94 | 110 | 131 | 118 | 104 |
| Calcium | 9.6 | 9.2 | 9.1 | 9.2 | 9.2 |
| Phosphorus | NA | 3.9 | 2.9 | 3.7 | 3.6 |
| Uric acid | NA | 1.9 | 2.8 | 2.3 | 3.7 |
| Total protein | 8.0 | 7.9 | 7.9 | 7.3 | 7.2 |
| Albumin | 4.2 | 4.1 | 4.1 | 3.9 | 3.9 |

NA, not assayed.

be 6.5. Urine analysis at initial evaluation showed also proteinuria without evidence of infection (Table 2); it had been normal 9 months before.

Urine electrolytes are shown in Table 3; her fractional excretion of sodium was 3. Urine anion gap was 30.7 (urine sodium added to urine potassium minus urine chloride).

The foregoing suggested proximal tubular dysfunction. Given her elevated creatinine, proteinuria, and anemia, paraproteinemia was strongly considered. However, serum and urine protein electrophoresis as well as free kappa/lambda ratio were negative. Bone marrow biopsy was also negative for multiple myeloma. Thus, a diagnosis of generalized proximal renal tubular dysfunction (Fanconi syndrome) with acute kidney injury secondary to TPM was entertained. By then, the patient had been on the same dose of TPM for 38 months and on lower doses for 20 months prior. Creatinine levels checked 2 to 4 times a year ranged from 0.9 to 1.2 mg/dL. The Naranjo Adverse Drug Reaction Probability Scale (5) indicated a probable relationship (score of 6) between TPM use and development of acute kidney injury and Fanconi syndrome. TPM was therefore tapered and discontinued by 1 week after the initial evaluation; by this time, her creatinine, bicarbonate, and potassium levels had worsened. Her laboratory function continued to improve consistently after stoppage of TPM until she had normal serum bicarbonate, potassium, and uric acid levels. These changes occurred over a few weeks and were accompanied by slower gradual improvement of her creatinine, which reached her baseline of 1.0 mg/dL 13 months after withdrawal of TPM (Table 1, Fig. 1).

*Table 2.* Urine analysis at initial evaluation

| | |
|---|---|
| Urine specific gravity | 1.010 |
| Urine pH | 6.5 |
| Urine protein | 100 |
| Urine glucose | 250 |
| Urine blood | Small |
| Urine ketones | Negative |
| Urine nitrite | Negative |
| Urine leukocytes | Negative |

## Discussion

TPM is a sulfa-derivative monosaccharide with multiple mechanisms of action, which include blockage of voltage-gated sodium and calcium channels, enhancement of postsynaptic gamma-aminobutyric acid receptor activity, and inhibition of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainite receptors, as well as some carbonic anhydrase isoenzymes (2).

TPM is rapidly absorbed after oral intake, peak plasma levels being usually attained in 2–3 hours. The drug is negligibly (9–17%) bound to plasma proteins and is eliminated largely by renal excretion in unchanged form (6). In healthy volunteers, the half-life is about 20–30 hours. Since its initial approval by the Food and Drug Administration for the treatment of epilepsy, it has been found effective for migraine prevention (3), weight loss (4), bipolar disorder (2), and several other conditions.

*Table 3.* Urine electrolytes

| | |
|---|---|
| Urine creatinine | 40 mg/dL |
| Urine sodium | 59 mEq/L |
| Urine chloride | 59 mEq/L |
| Urine potassium | 30.7 mEq/L |
| Urine urea nitrogen | 192 mg/dL |


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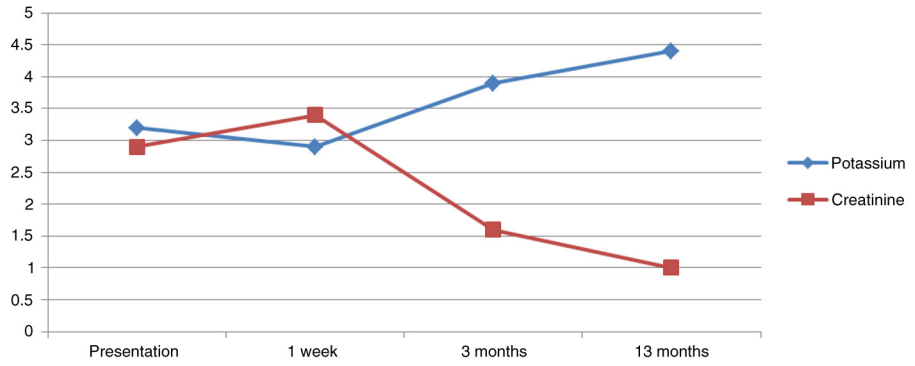


*Fig. 1.* Trends in serum potassium and creatinine.

Common systemic adverse effects include somnolence, fatigue, headaches, ataxia, diplopia, nystagmus, cognitive impairment, and dizziness, as well as rash, paresthesias, and nausea (2). A tendency toward nephrolithiasis has been reported, especially among patients on 300 mg or more of TPM per day (7). TPM use has been associated with hyperchloremic normal anion gap metabolic acidosis without regard to dose; this is attributed to mixed renal tubular acidosis (8). The higher tendency of such acidosis to appear by 5 or more years of therapy (9) was borne out in our patient. Therefore, it is imperative to identify risk factors that may predispose patients to hyperchloremic metabolic acidosis while taking TPM. Such factors include infection (10), diarrhea, ketogenic diet, underlying renal or lung disease, and surgery. In addition, patients taking TPM should be taught to recognize symptoms attributable to metabolic acidosis, which include fatigue, hyperventilation, and confusion (8).

Our case is unique as TPM not only caused normal anion gap metabolic acidosis years after initiation but was also associated with Fanconi syndrome and acute kidney injury that reverted with discontinuation of the drug. Metabolic acidosis attributed to TPM therapy has not typically been concurrent with creatinine elevation (7). To our knowledge, only one case of probable TPM-induced acute renal failure has been reported; renal failure was severe enough to warrant hemodialysis; presentation occurred 10 days after starting TPM therapy; and upon TPM discontinuation, the altered parameters became normal (11).

Use of the Naranjo Adverse Drug Reaction Probability Scale (5) in our case indicated a probable relationship between generalized proximal tubular dysfunction with acute kidney injury and TPM (score of 6). The timeline of starting and discontinuing the drug was consistent with the appearance of the adverse reaction; however, re-administration of the drug was not attempted. No placebo was given, no drug level was available, and the adverse drug reaction was confirmed by objective laboratory data. Fanconi syndrome is a generalized proximal tubular dysfunction with features that include normoglycemic glucosuria, uricosuria, and tubular proteinuria. Drug-induced Fanconi syndrome may be temporarily related to the introduction of the offending drug, but can occur years later (12).

It appeared that TPM ingestion was the most likely cause of the presentation of our patient. However, it is not clear why some people develop significant reductions of serum bicarbonate on TPM, while others do not. TPM inhibition of carbonic anhydrase type II may or may not be responsible (8). Recognition of the underlying cause is crucial so that the drug can be withdrawn while supportive care is provided.

## Conclusion

Considering that the onset of proximal tubular dysfunction and acute kidney injury during TPM therapy appears unpredictable, we recommend measuring serum bicarbonate, potassium, and creatinine before initiation of TPM therapy and at regular intervals when this drug is being administered to any patient. Future research into the most effective scheme of monitoring kidney function and electrolytes while on TPM therapy is advised.

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