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Prevalence and spot urine risk factors for renal stones in children taking topiramate

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Abstract *Introduction:* Topiramate (TPM), an anti-epileptic drug with >4 million users, increases renal stones in adults. We screened outpatient TPM-treated children without history of stones to estimate the prevalence of renal stones and to characterize urine stone-risk profiles.
Methods: Children taking TPM ≥1 month underwent an interview, renal ultrasound, and spot urine testing in this prospective study. Normal spot urine values were defined as: calcium/creatinine ratio ≤0.20 mg/mg (>12 months) or ≤0.60 mg/mg (≤12 months), citrate/creatinine ratio >0.50 mg/mg, and pH ≤ 6.7.
Results: Of 41 patients with average age of 9.2 years (range 0.5—18.7), mean TPM dose of 8.0 mg/kg/day (range 1.4—23.6), and mean treatment duration of 27 months (range 1—112), two (4.9%) had renal stones. The majority of children taking TPM had lithogenic abnormalities on spot urine testing, including 21 (51%) with hypercalciuria, 38 (93%) with hypocitraturia, and 28 (68%) with pH ≥ 6.7. Hypercalciuria and hypocitraturia were independent of TPM dose and duration; urine pH increased with dose. 24-h urine parameters improved in 1 stone-former once TPM was weaned.
Conclusions: Asymptomatic stones were found in 2/41 (4.8%) children taking TPM. Risk factors for stones were present in the spot urine of most children, including hypocitraturia (93%) and

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hypercalciuria (51%), independent of TPM dose and duration. High urine pH, found in 68%, correlated with TPM dose. Pediatric specialists should be aware of increased risks for stones, hypercalciuria, hypocitraturia, and alkaline urine in children taking TPM.
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Introduction

Topiramate (TPM) is a neuromodulatory agent increasingly used in children for a wide range of conditions including migraine prophylaxis [1], various forms of pediatric epilepsy [2–4], Tourette syndrome [5], bipolar disorder [6], and autistic disorder [7]. TPM has been shown to cause a metabolic acidosis [8–12], presumably by inhibiting carbonic anhydrase activity in the kidney [13]. Metabolic acidosis related to TPM is associated with the formation of alkaline urine, hypocitraturia and hypercalciuria in adults [14–18]. TPM use is also associated with an increased risk of calcium stones in adults, demonstrating a stone prevalence of 20% among long-term users compared to an expected prevalence of 5–8% in the general population [19,20]. Limited reports of the prevalence of kidney stones in children taking TPM have shown variable results, ranging from 0 to 54%, with minimal information about urinary risk factors for stone formation [1,3,4,20,21]. We hypothesized that children on TPM would be at increased risk for stones and might exhibit similar stone-risk urine profiles to adults taking TPM. Thus, we screened a cohort of outpatient TPM-treated children without known history of stones to estimate the prevalence of asymptomatic renal stones by ultrasound scan and to characterize spot urine stone-risk profiles.

Methods

Patients

This study was reviewed and approved by the institutional review board of Children's Medical Center at Dallas and UT Southwestern Medical Center with primary caregivers signing informed consent and children aged 10 and older giving assent. An electronic database of pediatric patients with active TPM prescriptions was obtained from the Children's Medical Center (CMC) at Dallas Department of Neurology. The parents of patients were mailed invitations to participate in this cross-sectional study or they were invited by the patient's neurologist during routine visits to the CMC outpatient Neurology clinic if they were actively receiving TPM (minimum one month). Interested parents received an interview by telephone or in clinic, which included questions regarding their child's age, demographics, height, weight, total daily dosage and duration of TPM, urinary symptoms, and any history of stones. Exclusion criteria included subjects with a preexisting history of kidney stone disease, use of other carbonic anhydrase inhibitors, antacids and/or diuretics, recurrent urinary tract infections, chronic diarrhea, and/or ketogenic diet. We did not exclude neurologically-impaired and/or immobilized children since such these children make up a substantial portion of outpatients taking TPM and may be at particularly high risk for developing stones on TPM due to their underlying condition.

Imaging

All eligible subjects were invited to undergo renal-bladder ultrasound and spot urine testing via bag or clean catch collection. Renal-bladder ultrasounds were interpreted by both a pediatric radiologist and a pediatric urologist specifically evaluating for the presence of stones. Screening computed tomography (CT) and abdominal radiographs were not performed due to unnecessary radiation risk. A suspected stone (mobile echogenic focus with shadowing on ultrasound) was confirmed with abdominal radiograph.

Urine

Urine was preserved with thymol and refrigerated, with testing performed within 48 h. Urine pH was determined by pH electrode (Radiometer Analytical SAS, Lyon, France). Urine creatinine was analyzed by kinetic alkaline picrate method and citrate by citrate lyase procedure (Roche Diagnostics, Indianapolis, IN). Urinary calcium was analyzed by atomic absorption spectroscopy (Varian Inc, Palo Alto, CA). 24-h urine testing was not performed because this was a pilot study designed to determine whether or not spot urine metabolic abnormalities were present in children taking TPM. In the absence of any known preliminary data, we could not justify invasive instrumentation with 24-h indwelling catheter placement in the subset of TPM-prescribed children who are neurologically-impaired and incontinent. Normal spot and 24-h urine values were defined as follows: calcium:creatinine (Ca/Cr) ratio $\leq$0.2 mg/mg for patients greater than 12 months and $<$0.6 mg/mg for ages 6–12 months; citrate:creatinine (Cit/Cr) ratio as $\geq$0.5 mg/mg; and pH $\leq$ 6.7 [22–25]. Patients with stones identified by renal ultrasound underwent abdominal radiograph, 24-h urine testing, and stone treatment as deemed appropriate.

Statistical analysis

The primary outcome variable was stone prevalence on ultrasound (i.e. the number of screened children with stones divided by the total number of screened children). The secondary measures were spot urine Ca/Cr ratio, Cit/Cr ratio, and urine pH. Spearman's rank correlations were performed using GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego California USA), with $p < 0.05$ considered statistically significant.

Results

Telephone or in-person interviews were completed by 87 patients, and ultrasound and spot urine testing in 41 patients (Fig. 1). All interviewed subjects had seizure disorder as the indication for TPM treatment. Demographics of interview-responders and the subset of ultrasound/spot