

CASE REPORT

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A Case of Nephrolithiasis and Metabolic Acidosis induced by Topiramate

Akram Askar

Division of Nephrology, King Khalid Medical University Hospital, King Saud University Medical City, Saudi Arabia

Introduction: This case reports the relationship between the treatment with topiramate and the propensity for metabolic acidosis and stone formation in the kidneys in a pediatric patient.

Case Presentation: The patient is a 14 years old girl known to have cerebral palsy and hydrocephalus for which she was treated with ventriculoperitoneal shunt; along with congenital brain atrophy and epilepsy, presented with vomiting, anorexia, right loin pain. She had a past medical history of several anti-epileptic drugs including Phenobarbitone, Phenytoin, Carbamazepine, Levetiracetam. She was started on Topiramate for past 8 years. She looked unwell and hypovolemic but on examination was afebrile with stable vital signs. There was, however, tenderness at right loin and suprapubic area. Midstream urine analysis showed urinary tract infection with many pus cells. Laboratory showed leukocytosis, along with high anion gap metabolic acidosis. The final diagnosis was made for metabolic acidosis and nephrolithiasis precipitating urinary tract infection.

Conclusion: Topiramate has been reported to cause metabolic acidosis and nephrolithiasis which is more pronounced in pediatric patients than adult patients. Evidence-based on literature indicates a higher risk in children: 30-50% of adults and 70% of children using topiramate develop metabolic acidosis, while 1.5% of adults and 5% of children develop kidney stones.

Keywords: Renal calculi, topiramate, acidosis

Introduction

Topiramate is a neuronal stabilizing agent approved by the Food and Drug Administration (FDA) for the treatment of generalized and partial seizures, as well as for the prevention of a headache and migraine. This drug affects the body metabolism by lowering serum bicarbonate level, while increasing urinary bicarbonate levels, resulting in elevated urine pH level. It decreases the urine citrate level,

resulting in increased blood acidity level. Overall acid-base balance is shifted favoring conditions to form calcium phosphate stones (1). It was originally synthesized as a structural analog of fructose- 1,6-diphosphate – hoping it would inhibit fructose 1,6- bisphosphatase and thereby block gluconeogenesis. It has, however, no significant effect on this enzyme. It is also structurally similar to acetazolamide and is found to inhibit carbonic anhydrase II & IV and

Corresponding Author: Akram ASKAR, MD; Division of Nephrology, King Khalid Medical University Hospital, King Saud University Medical City, Saudi Arabia

E-mail: askakram@yahoo.com

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reduce seizure frequency in experimental animal models. It is this structural resemblance that makes Topiramate prone to causing Renal Tubular Acidosis (RTA) and Normal Anion Gap (AG) MA (50-70%).

It's indicated as initial Monotherapy for epileptic patients more than 10 years old with partial onset or primary generalized tonic-clonic seizures. It's also indicated as Adjunctive-therapy for epileptic adults and children more than 2 years with partial onset or primary generalized tonic-clonic seizures. Topamax® (topiramate) is used Off-Label for conditions like: adjunctive treatment for bipolar disorder, cluster headaches, eating disorders, vanity dieting, fibromyalgia, depression, posttraumatic stress disorder, alcoholism, sleep disorders and in healing scars.

Nephrolithiasis (Ca-phosphate) is relatively frequent in patients using Topiramate, and 30-50% of adults and 70% of children develop metabolic acidosis.

Case Presentation

A 14 years old girl known to have Cerebral Palsy and Hydrocephalus for which she was treated with VP shunt; along with congenital Brain atrophy and Epilepsy, presented now with vomiting, anorexia, & right loin pain. She had a past medical history of several antiepileptic drugs including, Phenytoin, Phenobarbitone, Carbamazepine, Levetiracetam (Keppra). She was started on Topiramate (Topamax) for past 8 years. On presentation, she was on Keppra & Topamax. She looked unwell and hypovolemic but on examination was afebrile with stable vital signs. There was, however, tenderness at right loin & suprapubic area. MSU analysis showed Urinary Tract Infection (UTI) with many pus cells. Labs showed Leukocytosis ($22 \times 10^9/L$), while

Serum Chemistry was as follows: Cr=43 mcm/L; Na= 141; Cl=110, $HCO_3=17$ mEq/L; $K^+=3.4/3.7$; Urea=1.2. Arterial Blood Gases (ABG) showed: pH=7.35; $PaCO_2=30$; $HCO_3=17$. Anion Gap (AG) turned out to be higher: $Na-(Cl+HCO_3) = 14$. Utilizing the Delta/Delta equation, a higher AG metabolic acidosis, in this case, was associated with a normal anion gap.

Δ/Δ Ratio was calculated as follows: $\Delta AG = \text{measured AG} - \text{normal AG}$ ($14 - 10 = 4$); $\Delta HCO_3 = \text{normal } HCO_3 - \text{measured } HCO_3$ ($24 - 17 = 7$); $\Delta/\Delta = 4/7 = 0.57$ (where <1 suggests a combined normal and high AG metabolic acidosis).

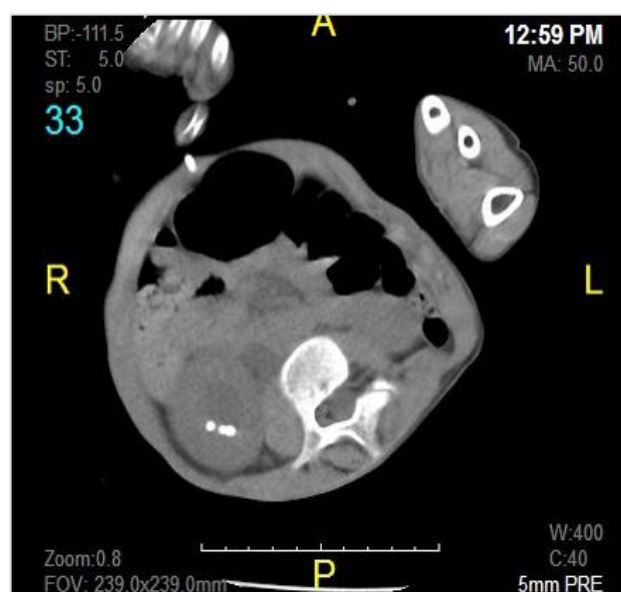


Figure 1. The axial section at the level of mid- portion of the right kidney, showing multiple small renal stones with mild hydronephrotic changes.

An abdominal CT was carried out showing Right sided Nephrolithiasis, along with resulting Right Hydronephrosis. The final diagnosis was made for Metabolic Acidosis and Nephrolithiasis precipitating UTI. The patient has managed accordingly, and Topiramate was discontinued. The high AG metabolic acidosis in our patient was owing to UTI and ensuing sepsis, while normal AG was due to Topamax use.

Discussion

Topiramate is mainly used to treat epilepsy and migraine prophylaxis but is also used a wide range of other indications. Topiramate-induced metabolic acidosis has been reported as its use increased over past years. The drug impairs the function of both: proximal renal tube, in normal reabsorption of filtered HCO_3^- ; and distal renal tubule, in excretion of H^+ . This renal defect is termed mixed renal tubular acidosis (RTA). Topiramate-induced RTA can cause acute illness, and in a long-term lead to nephrolithiasis, osteoporosis, and growth retardation in children.

Two large-scale cohort studies; one done in 1996 in UK (2), while other in 2015 in Taiwan (3) reported the occurrence of kidney stone formation to be insignificant with Topiramate. The first study was done on 1809 individuals; most of them were under treatment for more than 1 year. This study reported Nephrolithiasis in 1.5% of the patients. The second cohort included 1377 individuals with a gender-matched control group with the same number of subjects. Urolithiasis was found in 2.9% of the total of 2754 subjects (3). This study similar to the one done by Shorvon SD et al. ruled out the risk of urolithiasis related to Topiramate. It is important to note, however, that we did not find study of similar size on pediatric patients.

Reviewing the literature reveals almost all large population-based cohort studies being done on adults (2, 3). Case report and retrospective studies, however, include both pediatric and adult patients (4-13). The case reports and retrospective studies, specifically those with pediatric patients, report strong causality of nephrolithiasis due to Topiramate. The study reporting calcium phosphate-based lithiasis due to Topiramate was published in 2002 (8).

Two cases were then presented reporting on Topiramate-induced nephrolithiasis. After that initial report, many case reports followed publishing Topiramate-induced nephrolithiasis. In 2004, Lamb EJ et al. (9) profiled patients being treated with Topiramate for stone formation risk-based on their biochemical analysis. Their findings concluded metabolic imbalance induced by Topiramate increased urolithiasis risk. The study reported 3 cases in which calcium phosphate stones were treated. Similarly, a stone risk-profiling was done on 32 patients being treated with Topiramate. A cross-sectional study was done which also included 50 normal subjects. Biochemical analysis of the subjects indicated a significant increase in stone forming risk factors in patients being treated compared to normal subjects (1).

Following several case-reports on the risk of Topiramate-induced stone formation, Vega D et al. (13) called for further case-controlled studies in the US. A study of 4 women treated for chronic pain and mood stabilization using Topiramate reports development of calcium phosphate and oxalate based lithiasis (11). The treatment plan was devised by discontinuing drug in two patients, reducing in third, while maintaining in fourth. Increased fluid intake and use of potassium citrate were advised for patients on the drug. A case report of 53 years old women with chronic kidney disease was prescribed Topiramate for depression. During treatment, she developed proximal renal tube dysfunction and kidney injury. The report states Naranjo Adverse Drug Reaction Probability scale of 6, indicating that the complications were developed due to the prescribed drug. Discontinuity of the treatment resulted in the disappearance of the complications, which confirmed the causality (12). Goyal M et al. (7)

reported the risk of kidney stone formation due to anti-epileptic drugs in children. The clinical evidence of urolithiasis in 24 children under investigation was much higher (54%) than for the adult population (1.5%). In a study done on 96 children, Mahmoud AA et al. reported kidney stone formation in five (5.2%) children taking Topiramate for at least 1 year (10). In another study, among 41 children taking Topiramate, 4.8% developed kidney stones, whereas, the acid-base imbalance was reported in more than 50% of patients (4). A systematic review done on studies between 1996 to 2013 reports increased risk towards drug-induced stone due to metabolic disturbance owing to Topiramate treatment (5).

The patient in this case report had normal vital signs on presentation. She, however, looked unwell and dehydrated. Urine analysis revealed a urinary tract infection and elevated pus cells. The test results revealed MA when Delta-Delta ratio was computed. An abdominal CT showed right-sided Nephrolithiasis, along with resulting right Hydronephrosis. The final diagnosis was Metabolic Acidosis and Nephrolithiasis precipitating UTI. UTI caused high Anion Gap metabolic acidosis in our patient, while normal AG was due to Topamax use. Topiramate was discontinued to manage the patient.

Conclusion

Topiramate has been reported to cause nephrolithiasis and metabolic disorder, which is more significant in pediatric patients than adult patients. Evidence-based on case reports indicate a higher risk factor in children (70~% MA, 5%) than being in adults (50% MA, 1.5%). Further and larger pediatric cohort studies are required to establish these findings. Since Topiramate is used as long-term therapy, a

proper management scheme against its side effects must be devised.

Conflict of Interests

The author declare that he has no conflict of interest in the current study.

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Abbreviations

Food and Drug Administration (FDA), Metabolic Acidosis (MA), Ventriculo peritoneal (VP), Urinary Tract Infection (UTI), Chlorine (Cl), Midstream urine (MSU), Sodium (Na), Creatinine (Cr), Bicarbonate (HCO_3^-), K^+ (Potassium), Arterial Blood Gases (ABG), Anion Gap (AG), Potential Hydrogen (pH), Computed Tomography (CT)

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