

Topiramate induced metabolic acidosis and kidney stones – a case study

Tomas Salek^{*1,2}, Ivan Andel³, Irena Kurfurstova²

¹Medical Faculty of the University of Ostrava in Ostrava, Ostrava – Zábřeh, Czech Republic

²Department of Clinical Biochemistry, Tomas Bata Hospital in Zlín a. s., Zlín, Czech Republic

³Department of Urology, Tomas Bata Hospital in Zlín a. s., Zlín, Czech Republic

*Corresponding author: tsalek@seznam.cz

Abstract

Introduction: The aim of this study is to present a case of 44 years old woman with topiramate induced metabolic acidosis and kidney stones.

Materials and methods: The laboratory features of topiramate caused renal tubular acidosis in blood and urine during topiramate treatment, with correction of metabolic acidosis by potassium citrate, and after topiramate withdrawal are presented. Differential diagnosis of all possible causes of metabolic acidosis is discussed.

Results: The results revealed negative base excess in extracellular fluid of - 9.2 mmol/L, low serum HCO₃⁻ concentration (18.6 mmol/L), trend to alkaline urine (pH 6.39) and low urine citrate concentration (0.3 mmol/24h). After topiramate withdrawal, all parameters of the internal environment normalized.

Conclusions: This study has shown that long-term topiramate administration could induce metabolic acidosis and consequently urolithiasis. Thus, we could recommend testing blood acid base balance, urinary pH and citrates in patients taking topiramate and suffering from kidney stones.

Key words: urolithiasis; acidosis; renal tubular acidosis; topiramate; glomerular filtration rate

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Introduction

Kidney stones affect approximately 10% of the European population. It means that medical doctors frequently encounter this disease. It is a metabolic disease with urological complications. Kidney stone analysis and identification of risk factors for kidney stone formation are the first steps in the diagnostic procedure in patients with urolithiasis. Risk factors for kidney stone formation include family history of kidney stones, low fluid intake, some types of diets, certain pharmacotherapy, some diseases, increased concentration of stone forming substances and decreased concentration of inhibitors of stone formation. Laboratory medicine plays key role in identification of risk factors. European guidelines on urolithiasis recommend many laboratory blood and urine tests for metabolic evaluation of patients with kidney stones of

known and unknown composition. Clear algorithms with treatment decision points are defined for each type of kidney stones for prevention of kidney stone recurrence (1).

The acid base balance plays a very important role mainly in calcium phosphate, uric acid and cystine stone formation. The phosphoric acid system is one of the most important urinary buffers. At the pH level above the second acid dissociation constant of phosphoric acid (> 6.8) the monohydrogen phosphate (HPO₄²⁻) predominates in urine and is able to accept calcium ions. It increases the probability of crystals and stones formation. The systemic metabolic acidosis causes hypercalciuria and hypocitraturia, which also contribute to calcium nephrolithiasis formation.

Some drugs may also contribute to kidney stones formation. They may crystallize in urine or disturb urine composition. More than 20 drugs which contribute to kidney stone formation are listed in European guidelines (1).

Topiramate is an antiepileptic drug which leads to mixed renal tubular acidosis by the inhibition of carbonic anhydrase in renal tubules, which leads to systemic metabolic acidosis with low plasma bicarbonate concentration and alkaline urine pH with low urine citrate concentration. These metabolic changes result in calcium phosphate stone formation (2).

The aim of this study is to present a case of a 44 years old woman with topiramate induced metabolic acidosis and kidney stones.

Material and methods

A 44-year old woman, nonsmoker, presents at urology clinic for right low back pain in April 2012. She did not have signs of renal colic or fever. Her previous medical history included only chronic bronchitis and migraine headaches for years. Since 2007 she was taking topiramate at the daily dose of 200 mg for migraine headache prophylaxis, which greatly improved her headaches. She was also taking sumatriptan in the dose of 50 mg during migraine attack. It was prescribed by pain specialist.

Her body mass index (BMI) was 25.6 kg/m². It indicates the range of overweight. Other physical examination did not find any abnormality.

After careful physician examination by urologist in April 2012, plane X-ray of the patient's abdomen was performed, following by computer tomography. She visited urologist regularly every 6 months.

In May 2012, on admission to metabolic clinic arterial blood gas analysis was performed. At the same time blood sample and spot urine sample were obtained in fasting state at 7:00 am. Three weeks later a 24-hour urine sample was obtained. The 24-hour urine specimen was collected in a container with 15 mL of 6 molar HCl.

In November 2012 morning fasting venous blood sample and spot urine sample was obtained. Fasting venous blood sample and spot urine sample at metabolic clinic were obtained every six months.

VACUETTE® red top 6 mL tubes (Greiner Bio-One GmbH, Kremsmünster, Austria) with clot activator and without gel separator were used for venous blood collection. The separation of cells from serum was performed within 1 hour. Transport on ice was used for parathormone testing. Capillaries with balanced heparin (Radiometer, Brønshøj, Denmark) were used for arterial blood gas analysis. Transportation of samples was on ice and samples were analyzed within 15 minutes.

Whole blood pH, whole blood pCO₂, whole blood pO₂ were performed on Radiometer ABL 800 FLEX blood gas analyzer (Radiometer, Brønshøj, Denmark) by electrochemistry methods. Serum glucose, electrolytes, urea, enzymatic creatinine standardized to NIST SRM 967 reference material, uric acid, total bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total cholesterol, triacylglycerols, total protein, albumin, C-reactive protein, serum HCO₃⁻ (enzymatic test), cystatin C traceable to reference material DA ERM 472, parathyroid hormone, urine citrate were measured on ci16200 Abbott Architect analyzer (Abbott Laboratories, Illinois, USA).

Estimation of glomerular filtration rate was calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from serum creatinine. pH in urine was measured on pH meter PerpHecT Meter 330 (Thermo Scientific, Beverly, USA).

Oxalate in urine is measured on Analytik Jena AG Specord 40 analyzer (Analytik Jena, Jena, Germany). Oxalate is precipitated with calcium sulfate and ethanol, re-dissolved and then oxidized by oxalate oxidase. Reagents are from Instruchemie (Instruchemie, Delfzijl, The Netherlands). Urinary sediment was performed on Arkray analyzer IRIS IQ 200 (Arkray, Kyoto, Japan). Urinary cystin and dibasic aminoacids were measured on amino acid analyzer AAA 400 (Ingos, Prague, Czech Republic) by

medium pressure liquid ionex chromatography with postcolumn ninhydrin derivatization and detection at 440 and 570 nm. Polarized light microscopy was used for determination of stone composition.

The patient signed informed consent regarding publication of this article and the case study was approved for publication by the Tomas Bata hospital ethics committee.

Results

In April 2012, plane X-ray of the abdomen showed presence of the kidney stones. Urolithiasis was confirmed in medium right calyx and inferior left calyx (both in diameter of 3 mm) by computed tomography. The composition of the stone was unknown, but the stone was X-ray contrastive. We thought it could be a calcium phosphate stone.

On admission (May 2012), during only topiramate treatment, results of patient arterial blood gas analysis revealed metabolic acidosis (negative base excess of -9.2 mmol/L was calculated from pH and $p\text{CO}_2$), serum bicarbonate concentration by enzymatic test was 18.6 mmol/L, urine analysis showed trend to alkaline urine (pH 6.39) and low urine citrate concentration (0.3 mmol/24h) and all other parameters were normal. Results are presented in Table 1. According to results topiramate induced urolithiasis was suspected and patient was advised to discontinue topiramate treatment, but she did not want to as it improves her headaches.

In order to correct metabolic acidosis, since June 2012 potassium citrate was administered to patient. Following therapy, HCO_3^- concentration was partially corrected to 21 mmol/L. Results are presented in Table 2.

TABLE 1. Results of basic biochemistry analysis, arterial blood gas analysis and urine analysis in patient on admission in May 2012, during topiramate treatment only.

Test	Unit	Result	Reference range
Basic biochemistry analysis (9th May 2012)			
Serum glucose	mmol/L	6.5	3.9–5.5
Serum sodium	mmol/L	139	136–144
Serum potassium	mmol/L	4.4	3.8–5.1
Serum chloride	mmol/L	111	95–107
Serum urea	mmol/L	4.1	2.0–6.7
Serum creatinine	$\mu\text{mol/L}$	71	49–90
eGFR (CKD-EPI equation)	mL/min/1.73m^2	90	90–150
Serum uric acid	$\mu\text{mol/L}$	219	140–340
Serum total bilirubin	$\mu\text{mol/L}$	6	< 17
Serum ALT	U/L 37 °C	30.6	< 43.8
Serum AST	U/L 37 °C	16.2	< 40.2
Serum GGT	U/L 37 °C	24.6	< 106.2
Serum AP	U/L 37 °C	51.6	< 150
Serum cholesterol	mmol/L	6.45	< 5
Serum triacylglycerides	mmol/L	1.71	< 1.7
Serum total protein	g/L	69.4	64.0 – 83.0
Serum albumin	g/L	43.9	35.0 – 52.0
Serum C-reactive protein	mg/L	< 1	< 3
Serum HCO_3^-	mmol/L	18.6	22.0 – 28.0

TABLE 1. continued

Test	Unit	Result	Reference range
Serum calcium	mmol/L	2.25	2.10 – 2.55
Serum parathyroid hormone	pmol/L	3.6	1.6 – 7.2
Serum cystatin C	mg/L	0.93	0.40 – 0.96
Arterial Blood gas analysis (9th May 2012)			
Whole blood pH	pH units	7.386	7.36 – 7.44
Whole blood pCO ₂	kPa	3.61	4.6 – 6.0
Whole blood pO ₂	kPa	11.75	10.67 – 14.40
Actual HCO ₃ ⁻ (calculated)	mmol/L	15.9	22.0 – 28.0
Base excess (calculated)	mmol/L	- 9.2	- 2.5 – 2.5
Saturation of hemoglobin (measured)	%	96.8	95.0–99.0
Spot urine analysis (9th May 2012)			
Urine pH	pH units	6.39	
Urine calcium/creatinine	mol/mol	0.38	< 0.60
Urine uric acid/creatinine	mol/mol	0.18	< 0.30
Urine magnesium/creatinine	mol/mol	0.27	0.2-0.5
Urine oxalate/creatinine	mol/mol	0.011	< 0.04
Urine citrate/creatinine	mol/mol	0.03	> 0.15
Urine sediment (9th May 2012)			
Erythrocytes in urine sediment	x 10 ⁶ /L	9	< 10
Leukocytes in urine sediment	x 10 ⁶ /L	13	< 15
Biochemistry analysis of 24h urine (31th May 2012)			
Urine volume/24h	L	2.95	1.5 – 3.0
Sodium/24h	mmol/24h	145	100 – 260
Potassium/24h	mmol/24h	71	35 – 80
Calcium/24h	mmol/24h	6.8	2.5 – 7.5
Inorganic phosphate/24h	mmol/24h	27	13 – 35
Magnesium/24h	mmol/24h	3.4	3 – 5
Oxalate/24h	mmol/24h	0.325	0 – 0.5
Citrate/24h	mmol/24h	0.3	2.5 – 5.0

eGFR - estimated glomerular filtration rate; CKD-EPI - Chronic Kidney Disease – Epidemiology Collaboration; ALT - alanine aminotransferase; AST - aspartate aminotransferase; GGT - gamma-glutamyl transferase; AP - alkaline phosphatase.

From May 2013 to July 2014 repeated spot urine samples yielded citrate to creatinine ratio 0.04, 0.04, 0.05 and 0.05 (reference range is over 0.15 mol/mol). Spot urine pH ranged from 6.54 to 7.52.

In December 2014, a regular urologic visit ultrasonography revealed that her stones enlarged. Following these results she stopped taking both topiramate and potassium citrate. After this withdraw-

al serum bicarbonate concentration and urine citrates normalized. Results are presented in Table 3. The extracorporeal shock wave lithotripsy was performed on right kidney three times. Urography showed that the patient's calyx neck was narrow but the last lithotripsy, in January 2016, was successful. The stone was composed of calcium phosphate (80%) and calcium oxalate (20%). It consist-

TABLE 2. Results of basic biochemistry analysis and urine analysis in patient in November 2012, during topiramate and potassium citrate treatment

Test	Unit	Results	Reference range
Basic biochemistry analysis (14th November 2012)			
Serum sodium	mmol/L	138	136 - 144
Serum potassium	mmol/L	4.2	3.8 – 5.1
Serum chloride	mmol/L	110	95 - 107
Serum HCO ₃ ⁻	mmol/L	21	22.0 – 28.0
Spot urine analysis (14th November 2012)			
Urine pH	pH units	6.79	
Urine calcium/creatinine	mol/mol	0.44	< 0.60
Urine citrate/creatinine	mol/mol	0.04	> 0.15

TABLE 3. Results of basic biochemistry analysis and urine analysis in patient in December 2014, after both topiramate and potassium citrate withdrawal

Test	Unit	Results	Reference range
Basic biochemistry analysis (10th December 2014)			
Serum HCO ₃ ⁻	mmol/l	27	22.0 – 28.0
Spot urine analysis (15th December 2014)			
Urine pH	pH units	6.28	
Urine calcium/creatinine	mol/mol	0.28	< 0.60
Urine uric acid/creatinine	mol/mol	0.28	< 0.30
Urine inorganic phosphate/creatinine	mol/mol	1.72	< 2.8
Urine magnesium/creatinine	mol/mol	0.3	0.2 - 0.5
Urine oxalate/creatinine	mol/mol	0.004	< 0.04
Urine citrate/creatinine	mol/mol	0.21	> 0.15

ed of Brushite (60%), Apatite (20%), and Whedelit (20%) according to mineralogical terminology.

Discussion

In the present study we presented a case of the woman with topiramate induced urolithiasis.

Discontinuation of topiramate and normalization of acid base status in our patient confirmed the cause of metabolic acidosis and probably its contribution to kidney stone formation. It was previously described that topiramate can induce systemic metabolic acidosis by multiple mechanisms and lead to calcium phosphate kidney stones,

which is consistent with stone composition of our patient. This drug induces renal tubular acidosis. It is combined proximal and distal tubular disorder (3). Low urine citrate excretion, urine pH over 6 and increased urine HCO₃⁻ ion are typical urine profile of topiramate treatment (4).

Her overweight might also have contributed to stone formation, because it is the risk factor for kidney stones formation. It was demonstrated in a study by Shavit *et al.*, that overweight kidney stones formers show clear alterations in metabolic urinary profiles that are associated with increased overall risk of stone formation. This greater risk is primarily due to raised urinary uric acid and sodi-

um, lower urine pH and higher prevalence of hypercalciuria (5).

Normalization of metabolic acidosis due to topiramate treatment after its withdrawal was reported in a case study of a 75 year old male (6). It is consistent with our results.

Some cases of metabolic acidosis due to topiramate treatment may be severe with highly negative base excess of -14.1 mmol/L (7). We have observed lower degree of metabolic acidosis.

The study by Maalouf *et al.* showed that the prevalence of symptomatic nephrolithiasis among long-term topiramate users was 10.7% (8). According to a review of clinical trials provided by Faught *et al.* of another antiepileptic drug zonisamide (carbonic anhydrase inhibitor), the incidence of clinically symptomatic kidney stones increased with long-term treatment. Among all studies, 15 of 549 patients (2.7%) had kidney stones (9).

The study by Jhagroo *et al.* found that urinary citrate excretion declined after starting topiramate therapy. Urinary citrate excretion increased after adding potassium citrate (10). It supports our results.

Kidney stones are the metabolic disease which usually presents as urologic complications mainly as renal colic. The differential diagnosis is broad and includes many internal diseases. The systemic metabolic acidosis can lead to formation of kidney stones. We should consider all potential causes of chronic metabolic acidosis.

Metabolic acidosis may develop during progression of chronic kidney disease (11). The patient had estimated glomerular filtration rate (eGFR) always over 1.0 ml/s/1.73m². Patient did not meet the GFR criteria for chronic kidney disease. Urine albumin to creatinine ratio was repeatedly within reference ranges. The patient did not suffer from diabetes mellitus. Her serum glucose concentration did not meet the criterion for diabetes mellitus. Ketoacidosis or biguanide lactic acidosis induced by this disease was not likely. Ethanol induced ketoacidosis was not probable. Very low level of patient's gamma-glutamyl transferase did not indicate alcohol abuse.

She denied chronic diarrhea. Pancreatic and intestinal diseases with diarrhea lead to loss of bicarbonates and metabolic acidosis. Increased absorption of oxalates in malabsorptive states can lead to calcium oxalate stones. Patient had oxaluria within reference ranges.

The combination of metabolic acidosis, low urine citrate and alkaline urine pH is the typical feature of renal tubular acidosis. Hypocitraturia and trend to alkaline pH were main features in patient's urine.

Primary hyperparathyroidism causes renal tubular disorder, which is a type of acquired renal tubular acidosis. This endocrine disease is characterized by high serum calcium and parathyroid hormone. It causes metabolic acidosis with formation of calcium oxalate and calcium phosphate stones (12). Elevated chloride concentration is typical for hyperparathyreosis, but normal patient's serum calcium and parathormon level excluded this diagnosis.

The appropriate treatment of patients with calcium kidney stones due to renal tubular acidosis includes alkalization therapy with potassium citrate. The target of treatment is correction of metabolic acidosis with extracellular fluid base excess ± 2 mmol/L. Gastrointestinal tolerability of citrates is the clinical issue. The alkali therapy reduces tubular reabsorption of citrates, which increases citrate excretion. If calcium excretion is over 8 mmol/24 hours after restoration of acid base balance, treatment with thiazide is also recommended. General life style changes are also important. Target life-style factors include daily fluid intake over 2.5 liters, urine daily volume over 2.5 liters, balanced diet rich in vegetables and fibers, limited NaCl and animal proteins content in diet, retaining a normal BMI level and adequate physical activity (1).

The study is novel in its detailed description of a complex set of both blood and urine tests during treatment and after it. Possibly the biggest limitation of this study is the fact that it was only performed on a single patient.

We can conclude that we should be aware of topiramate induced metabolic side effects, which include metabolic acidosis and kidney stones. We recommend testing blood acid base balance, uri-

nary pH and citrates in patients taking topiramate and suffering from kidney stones.

Potential conflict of interest

None declared.

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