Giornale Italiano di Nefrologia

Efficacy of sustained low-efficiency dialysis in the management of topiramate intoxication: case report

Nefrologo in corsia

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ABSTRACT

Guidelines on the use of dialysis treatment in patients with chronic kidney disease (CKD) and TPM (Topiramate) intoxication are controversial. A 51-year-old man with epilepsy and CKD was carried to our emergency department for dysuria and sickness. He chronically assumed TPM 100 mg 3/day. Creatinine level was 2.1 mg/dL, blood urea nitrogen 70 mg/dL, and inflammation indexes were increased.
We started empirical antibiotic therapy and rehydration. The day two he had diarrhea and an acute insurgence of dizziness, confusion, and bicarbonate levels reduction. Brain CT resulted negative for acute events. During the night his mental status worsened, and urinary output results were about 200 mL in 12h. EEG showed desynchronized brain bioelectric activity. Thereafter, there was an episode of seizure and then anuria, hemodynamic instability, and loss of consciousness. Creatinine value was 5.39 mg/dL with a serious metabolic acidosis non-anion gap. We decided to start 6-hours Sustained Low Efficiency Hemo-Dia-Filtration (SLE-HDF). We assisted in the recovery of consciousness and later in the improvement of kidney function after 4 hours of treatment. TPM levels before SLE-HDF resulted in 123.1 µg/mL. At the end of treatment resulted in 30 µg/mL. To our knowledge, this is the first report of TPM involuntary intoxication in a patient affected by CKD who survived such a high TPM concentration treated with renal replacement therapy. SLE-HDF resulted in moderate elimination of TPM and acidemia resolution, continuous monitoring patient's vital parameters in relation to his hemodynamic instability, since blood flow and dialysate flow are lower than conventional hemodialysis.

KEYWORDS: Intoxication, Sustained Low-efficiency dialysis, hemodialysis, metabolic acidosis, continuous venovenous haemofiltration

Introduction

Topiramate (TPM) is an anticonvulsant agent indicated according to American Academy of Neurology (AAN) guidelines as an adjunct therapy for the treatment of focal and mixed seizures, Lennox-Gastaut syndrome, and as monotherapy for refractory generalized tonic-clonic seizures in adults and children. At steady-state concentration, renal clearance of this drug is 1.02 L/h and its elimination half-life (T1/2) varies from 20 to 30 h. In all species, TPM is predominantly excreted unchanged in the urine [1].

Guidelines on the use of dialysis treatment in patients with chronic kidney disease and topiramate intoxication are controversial. We describe a case of topiramate overdose treated with sustained low-efficiency dialysis (SLED).

Case report

A 51-year-old, 93-kg caucasian man with a history of head trauma following a motor vehicle accident with residual aphasia, short-term memory impairment, and epilepsy was carried to our emergency department for dysuria and sickness, arising three days ago. He was also affected by chronic kidney disease (CKD) but he didn't have any documentation to stage CKD itself, dyslipidemia, and hypothyroidism. He chronically assumed Levothyroxine, Oxcarbazepine, Topiramate 100 mg 3 times a day, and Clobazam. The patient was asymptomatic, alert, and oriented in all spheres. His vital signs were stable, with a temperature of 37° C, blood pressure was 133/70 mmHg, pulse of 90 bpm, and respiratory rate of 18 breaths per minute.

Laboratory tests drawn in the emergency room revealed a creatinine level of 2,1 mg/dL, blood urea nitrogen 70 mg/dL; increased inflammation indexes and white blood cell count. Serum electrolytes and liver function tests were within normal range. The blood gas test revealed metabolic acidosis with pH 7.31; HCO3 21 mEq/L and pCO2 level 40 mmHg. We started at the time of admission empirical therapy with Piperacillin/Tazobactam and rehydration therapy. The day after admission (day 1) he had three episodes of diarrhea and acute insurgence of dizziness, fatigue, nervousness, confusion, and depression associated with a reduction of bicarbonate levels. Urinary output was about 1200 mL/24h. Brain CT without contrast was performed and resulted negative for hemorrhage or ischemic areas.

He had taken routine therapy. During the night between day 1 and day 2 his mental status worsened, he began to have blunted mental reactions, slow responses, and disorientation; urinary output resulted in about 200 mL from evening to morning. We performed an electroencephalogram (EEG) that showed desynchronized brain bioelectric activity. In the following hours, there was an episode of seizure and subsequent rapid deterioration of clinical condition with anuria, hemodynamic instability (BP 85/40 mmHg), despite hydration therapy, and loss of consciousness. The blood test revealed creatinine value 5.39 mg/dL, blood urea nitrogen 220 mg/dL, normal serum electrolytes but a serious metabolic acidosis non-anion gap with pH 7.1 and HCO3 10 mmol/L, Lac 1.5. Urine toxicology screening (on day 2) for amphetamines, barbiturates, tetrahydrocannabinol (THC), cocaine, opiates, and alcohol was negative.

We were waiting for topiramate serum values, assuming intoxication, but in view of the rapid deterioration and loss of consciousness, we decided to start 6-hour Sustained Low-Efficiency Hemo-Dia-Filtration (SLE-HDF). The basic dialysis schedule was 10 hours, with 2 L/hour of dialysate for our patient based on his weight, half in post-convention and half in diffusion, for a total of 20 L per session. The replacement fluid had the following composition: calcium 1.75 mmol/L, magnesium 0.5, sodium 140, chlorine 111.5, lactate 3, bicarbonate 32, glucose 6.1. The K content was changed from

2 to 4 mmol/L, depending on the serum potassium value. The monitor was Prysma Gambro-Baxter with semipermeable hollow fiber dialyzer with high biocompatibility. As anticoagulant, low molecular weight heparin in bolus was used as first choice. After 4 hours of treatment, we assisted in the recovery of consciousness without new seizure episodes and in the following days a complete recovery of urinary output and improvement of kidney function without other hemodialysis sessions. Topiramate serum concentration before SLE-HDF resulted in 123.1 µg/mL (measured by liquid chromatography-mass spectrometry). Topiramate blood level was repeated at the end of treatment, after the patient's stabilization, and resulted in 30 µg/mL. At discharge, the patient was awake, alert, and fully oriented and he followed his therapy with Topiramate 100 mg 2 tablets a day. The patient after six months has eGFR 53.1 mL/min per 1.73m^2 and has had no further seizures.

Discussion

Topiramate, a second-generation broad-spectrum antiepileptic drug (AED) is approved as monotherapy or adjunctive therapy for the prevention of different types of epileptic seizures in both adults and children. It 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 [2].

There were few cases in the literature about topiramate intoxications. Five cases were reported during clinical trials and adverse reactions included mental status changes, ataxia, memory lapses, seizures, and hyperreflexia. In literature were reported accidental TPM overdoses in children, a case of intentional overdoses in an adolescent, and another for suicide purposes [3].

Lofton et al., have described cases, due to the data provided in the Toxic Exposure Surveillance System in the United States in 2000-2001. The 567 patients described who had no prior treatment with topiramate were significantly more likely to present toxicity [4]. Also, in the therapeutic clinical trials, adverse events such as anorexia, fatigue, nervousness, concentration difficulties, aggression, psychomotor slowing, and paresthesia occurred more often during initiation of therapy and after rapid dose escalation. Chung et al. have described a patient who ingested 800 mg of topiramate and developed coma, followed by agitation, confusion, speech perseveration, and mood lability [5]. On the other hand, Smith et al. have described a case of a 24-year-old woman, treated with topiramate 200 mg/day, who had ingested 4000 mg and presented no symptoms [6].

To our knowledge, this is the first report of topiramate involuntary intoxication in a patient affected by CKD, who survived such a high TPM concentration treated with renal replacement therapy. TPM concentrations were mostly considerably lower in data provided by Smith et al. or not measured or not reported, respectively.

Supuran et al. reported that Topiramate is a potent inhibitor especially against carbonic anhydrase-II, but also Carbonic anhydrase-XIII, and a medium potency inhibitor of Carbonic anhydrase-IV. Because of its activity, it can impair H+ excretion and HCO3- absorption in the proximal convoluted tubule, leading to increased delivery of HCO3- in the distal portion of the nephron, and can result in the development of type 2 renal tubular acidosis, normal anion gap metabolic acidosis, and nephrolithiasis as side effects from its use [7]. Our patient on admission had metabolic acidosis non-anion gap, probably related to topiramate assumption. In our report, we show a rapid metabolic acidosis worsening, probably related to increased topiramate circulating levels associated with the worsening of renal function. Metabolic acidosis observed in other described cases was usually mild to moderate and did not influence the clinical outcome [8].

The 2022 core curriculum on the management of poisonings and intoxications does not specifically

address topiramate, but experts say that delayed treatment of intoxication or poisoning inevitably results in worse outcomes. Therefore, some experts recommend early treatment when there is a strong suspicion or there is unexplained metabolic acidosis [9]. However, in the literature, there is no strong evidence recommending renal replacement therapy in topiramate intoxication. In many cases, osmotic agents such as sorbitol and activated charcoal can enhance drug removal. However, activated charcoal has not been shown to absorb topiramate in vitro, and therefore, is not recommended for use in topiramate overdose [10].

The data in literature based on pharmacokinetic studies suggest that clearance of topiramate is reduced by 42% in patients with moderate renal impairment (CLCr=30-69 mL/min) and 54% in patients with severe renal impairment (CLCr < 30 mL/min). In fact, in patients with clearance < 70 mL/min, the prescribed dose is half of that of a patient without renal failure. The elimination half-life for topiramate in individuals with normal renal capacity ranges between 20-30 h [11]. As expected, decreased renal function can alter the pharmacokinetics of topiramate elimination. Plasma concentrations are significantly affected by hemodialysis with clearance rates 4-6 times faster.

During a 3 h hemodialysis, plasma topiramate concentrations dropped by approximately 50%. The amount of topiramate removed by dialysis over 3 h (18.7 mg) represents a substantial fraction of the amount remaining in the body at the beginning of the hemodialysis procedure [12].

Plasma topiramate concentrations declined rapidly and substantially during the hemodialysis procedure. These rapid changes in plasma concentrations should be avoided in patients with epilepsy as described by Manitpisitkul et al [13].

To overcome this, and also in order to replace the amount of topiramate removed during the hemodialysis procedure, a supplemental dose (or doses) of topiramate at the time of hemodialysis is necessary.

Our patient presented with hemodynamic instability, typical deficit symptomatology as “thinking abnormal”. Moreover, the worsening of symptoms occurred within less than 24 hours of hospital admission, and in view of the fact that topiramate has a small molecular size (molecular weight 339.4 Da), a volume distribution reflecting the distribution of total body water (0.6-0.8 L/kg), very low protein binding (9-17%), and is mainly eliminated renally (~60%), we opted for 6 hours Sustained Low-Efficiency Hemo-Dia-Filtration treatment.

SLED resulted in moderate elimination of topiramate and resolution of acidemia. It was assumed that the clearance of topiramate in this case was greater than that reported for continuous renal replacement therapy (CRRT), but lower than that of intermittent hemodialysis (IHD). SLED was chosen to ensure better and continuous monitoring of the patient’s vital parameters in relation to his hemodynamic instability, since blood flow and dialysate flow are lower. In addition, our patient did not require drug additional doses after treatment with complete consciousness and renal function recovery.

Conclusion

To our knowledge, this is the first case of a patient affected by CKD who survived topiramate intoxication, with rapidly worsening renal function, metabolic acidosis, and hemodynamic instability. We propose sustained low-efficiency hemodiafiltration (SLE-HDF) which has assured us of subsequent recovery of renal function and improvement of consciousness.

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