Pediatric Case Report of Topiramate Toxicity

Pediatrik Olgu Sunumu; Topiramat Entoksikasyonu

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Geliş Tarihi/*Received:* 16.12.2008
Kabul Tarihi/*Accepted:* 20.02.2009

This study was previously presented as a poster at Xth National Pediatric Neurology Congress, 28-31 May 2008, Trabzon

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ABSTRACT Topiramate is a FDA-approved anticonvulsant with multiple efficacy mechanisms and suggest a broad spectrum of activity. Published literature on the toxicity of a topiramate in children is limited. We report an 8-year-old boy admitted to the emergency department after 3 days post - ingestion of this medication with neurological symptoms. It was learned from the anamnesis who had taken 4500 mg of topiramate within six days. He was lethargic with increased deep tendon reflexes at lower extremities, and positive signs of meningeal irritation in physical examination. All laboratory investigations, viral serological tests, cerebrospinal fluid, cranial MR imaging, and EEG showed no abnormalities. The topiramate level on day of admission was low, although could be studied at 6th day post-ingestion. Patient began walking with a severe ataxia on the fourth day, and able to walk on the seventh day. There are limited case reports in children of topiramate toxicity in the medical literature. The patient was reported for persisting neurological symptoms and signs of meningeal irritation after overdose topiramate ingestion.

Key Words: Child; topiramate; overdose; neurologic manifestations

ÖZET Topiramat, FDA onaylı, çok yönlü etki mekanizması olan, geniş spektrumlu antiepileptik bir ilaçtır. Çocuklarda topiramat toksisitesi ile ilgili bilgiler sınırlıdır. Sekiz yaşında erkek olgu, topiramat alımından 3 gün sonra nörolojik semptomlarla acil servise getirildi. Öyküsünden 6 günde 4500 mg topiramat aldığı öğrenildi. Fizik muayenesinde uykuya eğilimli, meninks irritasyon bulguları pozitif, derin tendon refleksleri alt ekstremitelerde artmış olarak alınıyordu. Rutin biyokimyasal tetkikleri, kraniyal görüntüleme, lomber ponksiyon sonuçları, viral serolojik tetkikleri ve EEG'si normaldi. Başvurusu sırasında alınan topiramat kan düzeyi seviyesi son alımından sonraki 6. gün incelenebildi ve düşük bulundu. Olgu izleminin 4. gününde belirgin ataksik olarak yürümeye başladı. Yedinci gün normal yürüyebildi. Literatürde çocuklarda topiramat intoksikasyonu az sayıda olguda bildirilmiştir. Bu olgu, akut yüksek doz topiramat alımından sonra gelişen uzun süren nörolojik semptomları ve pozitif meninks irritasyon bulguları nedeniyle sunulmuştur.

Anahtar Kelimeler: Çocuk; topiramat; aşırı doz; nörolojik bulgular

Turkiye Klinikleri J Pediatr 2010;19(3):227-30

Topiramate is a second generation antiepileptic drug approved by FDA. Its mechanism of action is block voltage-dependent sodium and calcium channels potentiate the effects of GABA inhibitory neurotransmission, and antagonism of kainate subtype of the glutamate AMPA receptor (except NMDA). It is also a weak carbonic anhidrase inbitor.[1,2] Approximately 80% to 90% of orally ingested topiramate is reaches peak plasma concentration within 1 to 4 hours. It is minimally metabolized by

the liver in the absence of enzyme inducers. The majority is excreted unchanged via the kidneys. Topiramate clearance is higher in children than in adults.[1,3,4] Topiramate is used in the prophylaxis of migraine headaches, essential tremor, obesity, acute mania, Tourette's syndrome, bipolar disease, alcohol dependence, neuropathic pain, and for adjunctive/mono therapy in generalized and partial onset seizures with and without secondary generalization in adults and children (age ≥2 years), Lennox-Gastaut syndrome.[3,5-8] In children, the dose is divided, and initial dosing begins at 1-3 mg/kg per day, increasing by 1-3 mg/kg/day in increments of 1-2- week intervals. The effective, usual maintenance dose is 5-9 mg/kg/per day as tolerated.[9,10] In published literature on the toxicity of a topiramate overdose in children is limited to case reports. We report here an 8-year-old boy presenting with neurological symptoms including lethargy, ataxia, and prolonged positive signs of meningeal irritation after overdose topiramate ingestion.

CASE REPORT

An 8-year-old boy admitted to emergency department with nausea, vomiting, walking inability and sleepness. Anamnesis revealed that topiramate treatment was started ten days ago for seizures control. Seizures had partial onset with secondary generalization and 5-6 times daily in the last month, and his interictal EEG showed epileptiform discharges located at the temporo-occipital regions. The topiramate treatment schema had been arrenged with an initial dose at 1 mg/kg/per day, titrating the doses up to 3 mg/kg/per day as tolerated. Nevertheless, he had ingested 2 x 10 tablets of 25 mg (17, 2 mg/kg) for first 3 days, and 2 x 10 tablets of 50 mg (34.4 mg/kg) for 3 days and discontinued for the last 3 days. Patient was full term, vaginally delivered with prolonged difficulty on labor. His motor-mental developmental stage was retarded, and he was still not speaking. Family history was not notable.

On initial presentation to the emergency department, the child was afebrile with an axillary temperature 36.6 °C. His respiratory rate was 24/min, pulse rate was 124/min, and blood pressure was 90/60 mmHg. His weight was 29 kg, height, and head circumference percentile's were 50th. On neurological exam, the patient appeared lethargic. The signs of meningeal irritation (neck stiffness, Kernig's and Brudzinsky's signs) were positive, deep tendon reflexes increased at lower extremities, and inability to walk was noted. The other systems and fundoscopic examination were normal. The patient was monitorized with presumptive diagnoses of central nervous system infection and intoxication. Laboratory studies showed normal arterial blood gas, complete blood count, urine specimen, serum electrolytes, liver and kidney function tests, thyroid function tests, acute-phase reactant. Serologic tests for Ebstein Barr, Cytomegalovirus and Herpes virus have been found to be negative. His lumbar puncture was clear with normal opening pressure, and no cells were seen. The CSF protein was 21 mg/dL, and glucose was 66 mg/dL (spontaneously blood glucose was 114 mg/dL), and not be produced in CSF culture. His cranial MRI showed no abnormalities. His EEG showed normal waking and sleep patterns. The topiramate level on day admission was low (2 mcg/mL), although could be studied at 6th day post-ingestion in an outside laboratory three days after his admission to the emergency department (In theuropathic use, the topiramate level: 5-20 mcg/mL). Patient became more oriented, and agitated in the second day of clinical observation. He was able to walk with ataxia in the 4th day, and walk with a normal gait short distance by the 7th days. After he had discharged, only neck stiffness persisted until the 18th day of post-ingestion. No further follow-up was available.

DISCUSSION

The most commonly reported adverse effect of topiramate is CNS-related such as drowsiness, dizziness, agitation, ataxia, confusion, memory, behavioral and language problems. Other uncommon adverse effects related to carbonic anhydrase inhibition include weight loss, nephrolithiasis (1.5%), angle-closure glaucoma, possibly hepatotoxicity, hyperchloremic metabolic asidosis, and parestesia. None of these were reported in the children.[1,2,4,10] In placebo controlled trials involving

children receiving a topiramate approximately 6 mg /kg/day, adverse effects that occurred at a 5% greater frequency in topiramate-treated children than in placebo–treated children were fatıgue, nervousness, eating disorder, attention deficit-hyperactivity disorder, difficulty with memory, sleepiness, and weight loss. The slower rate of topiramate titration used in some of pediatric studies may have resulted in a lower frequency adverse effects.[3,5,10] In some studies, consistent relationships between serum concentration and adverse events have not found.[11]

Lofton and Klein-Schwartz reevaluated data concerning the topiramate exposure which obtained from American Association of Poison Control Centers Toxic Exposure Surveillance System's. They had been reported that in 567 cases, 65% of the cases were younger than 15 years of age, no toxic effect was present in %62.1, therapeutic error was the most frequent reason in patients aged 5-9, and symptomatic patients demonstrated drowsiness/lethargy, dizziness/vertigo, agitation, and confusion. They had established major effect in five cases. One of them, a 2 –year-old boy with a coded outcome major effect who had denoted agitation and tremor after ingesting 200 mg of topiramate.[10]

There are more reports concerning the topiramate toxicity in adults than in children. A 24-year-old girl remained asymptomatic after ingestion of 4000 mg topiramate, two patients presented with coma, status epilepticus, and hyperchloremic metabolic asidosis that recovered within 6-7 days after ingestion of 20 g and 40 g topiramate, and one patient was found dead result of cardiopulmonary arrest.[10,12] Available information on the toxicity of topiramate overdose in children limited to case reports. One of them, a 33-month-old girl with acute ingestion of topiramate appeared neurological symptoms as slurred speech, delirium, hallucination, and regression to crawling lasting 5 days. The serum topiramate level was 9.4 mcg/mL, after 3 days post-ingestion. The patient became more oriented after 4 days post-ingestion, and her slurry speech persisted until the 6th day after ingestion.[9] The second patient, a 5-year-old girl presented with neurological symptoms as agitation "not being able to feel anything", perseveration upon questioning, and abnormal motor movements, after acute ingestion of topiramate. Her symptoms resolved over 24 hours. The patient's serum topiramate level which was taken emergency department was 10.5 mcg/mL. For this reason, it was there for unclear if the patient's symptoms represented an idiosyncratic reaction or true drug toxicity.[7]

We report here an 8-year-old boy presented with neurological symptoms as lethargy, agitation, ataxia, and positive signs of meningeal irritation persisting 14 days, 3 days after 4500 mg of topiramate ingestion for 6 days. The serum topiramate level was lower than normal theurapathic level. Similarly other cases, it was there for unclear if the patient's symptoms represented an idiosyncratic reaction or true drug toxicity. Although, to our knowledge, there has been no prior pediatric case report of positive signs of meningeal irritation and prolonged neurological symptoms with overdose topiramate ingestion.

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