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Case Report

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Hallucinations in a Toddler Following Topiramate Intoxication

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Abstract

Topiramate is a common anticonvulsant medication used to treat seizures. We describe a 3-year-old boy who unintentionally ingested an unknown amount of topiramate tablets and soon after, was found to have strange behavior. He experienced visual hallucinations with evolving neurologic abnormalities including incoherence, confusion, and delirium. After 1 day from the suspected time of ingestion, the child had completely recovered without medical intervention and experienced no permanent neurologic sequelae. Topiramate ingestion is a rare cause of hallucinations in children and should be suspected in children who present with altered mental status and mild metabolic acidosis.

Keywords: Pediatrics; Topiramate intoxication; Altered mental status; Hallucinations

Introduction

Topiramate is a potent anticonvulsant medication that is used as monotherapy or as an adjunct to other medications to treat patients 2 years and older with generalized and partial seizures [1, 2]. The exact mechanism of action is unknown, but it is believed the drug interferes with conductance through voltage-sensitive sodium and T-type calcium channels, augments the activity of gamma-aminobutyric acid (GABA) at the GABA-A receptor, and weakly inhibits carbonic anhydrase enzyme in the brain and kidneys [2, 3]. It has also been found to block select glutamate receptors, thus decreasing inward (excitatory) currents [2]. In adults, topiramate is indicated for treatment of focal epilepsy and can be used to manage other conditions including bipolar disorder, cluster headaches, and neuropathic pain [4]. To our knowledge, there is only one previous report of hallucinations in a child with topiramate toxicity [5]. Most children with topiramate toxicity present with neurologic abnormalities and altered mental status [5, 6]. We present a 3-year-old boy who developed neurologic symptoms that persisted for 1 day after suspected ingestion of topiramate.

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Case Report

Investigations

A 3-year-old boy presented to the emergency department with his parents for altered mental status. The parents found the patient shaking and drooling in bed while waking him up in the morning 1 h prior to arrival, and he has behaved strangely since then. He was not responsive to parents' questions, appeared confused, and had intelligible speech. When his parents asked him what was wrong, the child stared blankly and pointed at the ceiling. He did not have any medications nearby in his bed. Parents reported neither of them take daily medications. He had no prior illnesses and had not received any vaccines within the previous month. He had no prior medical history and took no medications daily. He was born at full term without complication. There was a family history of epilepsy in his aunt and febrile seizure in the mother. He had no history of developmental delay.

On physical examination, his vital signs revealed an oral temperature of 37 °C, pulse of 86 beats per minute, respiratory rate of 24 breaths per minute, blood pressure of 97/42 mm Hg, and oxygen saturation of 100% on room air. He was awake and disoriented to location, person, or time. He was sitting in the bed, confused, and occasionally turned his head quickly to each side. He was not responsive to verbal stimuli and unable to follow commands. His pupils were 4 mm bilaterally and reactive to 2 mm with direct and indirect light bilaterally. There was no nystagmus. He stared upward at the ceiling and glanced around in the bed as if he was seeing objects that were not real. He occasionally pointed upwards at the ceiling and said, "Look, up there!" and yelled "Daddy!". He had no facial weakness and startled with a loud clap to each ear. His tongue was midline, and his face was symmetric. He had no dysarthria. He had normal motor tone. He withdrew to pain in his extremities. He had normal brachioradialis and patellar reflexes. We were unable to formally assess strength or sensation because he did not follow commands, but he moved all extremities against full resistance. He was unable to walk and regressed to crawl in the bed as if looking for objects. While lying in exam bed, he intermittently would roll around while hyperextending at the spine in a "barrel roll" fashion. His oral mucosa was dry. He had no meningismal signs. His cardiac sounds were regular

without a murmur and his lungs were clear bilaterally. His abdomen was soft with normal active bowel sounds. The rest of his physical examination was unremarkable.

Diagnosis

Laboratory tests in the emergency department revealed normal serum electrolytes and complete blood cell count besides a carbon dioxide level of 16 mmol/L (normal 18 - 28 mmol/L). Liver function tests were normal. Serum ethanol, salicylate, and acetaminophen were undetectable. A noncontrast computed tomography of the head revealed no cerebral hemorrhage, mass, or hydrocephalus. The patient had a dose of lorazepam with minimal improvement in mental status. A lumbar puncture was performed, and cerebrospinal fluid studies were not concerning for bacterial or viral meningitis. He was placed on electroencephalogram monitoring. Urine drug screen returned negative for amphetamine, benzodiazepine, barbiturate, cannabinoid, cocaine, opiate, and oxycodone.

The patient was admitted to the medical ward and his neurological status was closely monitored. His urine gas chromatography was found to be positive for topiramate. After further investigation, the parents identified a relative who lives in the home who is prescribed topiramate for epilepsy.

Treatment

The patient received intravenous fluids. His long-term electroencephalogram revealed no epileptiform abnormalities. A serum topiramate level was not obtained given the patient's improved mental status during the following day. There were no autoantibodies identified in the patient's cerebrospinal fluid to suggest autoimmune encephalitis.

Follow-up and outcomes

The patient did not have any cardiorespiratory complications. Approximately 18 h after presentation, the patient became coherent, answered questions appropriately. and ambulated without difficulty. The patient admitted to waking up earlier in the morning prior to his parents to eat food in the kitchen. There was a guest residing briefly at the family's house who was prescribed topiramate for epilepsy and had accidentally left an open bottle of 200 mg tablets on the dining table. This was not brought to the attention of the medical staff during the initial history taking with the parents. Upon questioning the parents and guest, it was unclear how many tablets were missing from the bottle. Social work provided education to the family regarding medication safety. The incident was reported to child protective services who facilitated the patient to be discharged home with parents.

Discussion

To our knowledge, there are few prior pediatric case reports of topiramate overdose. In our case, a toddler presented soon after ingestion to the emergency department with visual hallucinations, altered mental status, and ataxia. Laboratory testing revealed a mild non-anion-gap metabolic acidosis, and electroencephalogram revealed no abnormal waveforms. Although our patient experienced severe neurologic symptoms including hallucinations, our case is unique because our patient's symptoms resolved within only 1 day, which is significantly shorter than those highlighted in previous literature [5]. Our case also highlights the short elimination half-life of topiramate in children.

Topiramate, regardless of the sprinkle capsule or tablet formulation, is absorbed rapidly from the gastrointestinal tract with peak plasma concentration occurring between 2 - 4 h after ingestion [7]. In an overdose situation, side effects are seen sooner as serum concentrations rise above therapeutic levels. Severe symptoms may manifest later as it takes longer to achieve maximum concentration. Topiramate is not extensively metabolized and 75-80% of the drug is excreted unchanged in urine [2, 7]. In children, the elimination half-life is approximately 8 h in children below 7 years old and 12 h for those between 7 and 17 years old [8]. The elimination half-life of topiramate in adults with normal renal function ranges between 20 and 30 h [9].

Like other anti-epileptic agents, adverse effects of topiramate are secondary to the medication's effect on the central nervous system. The cognitive effects appear more frequently with higher doses of topiramate and increasing the dose too quickly when starting the medication for treatment of seizures [3]. In pediatric patients, initial doses of 1 - 3 mg/kg/day divided twice daily are recommended, with an increase of 1 - 3 mg/kg/day every 1 to 2 weeks until clinical effect is achieved [10, 11]. If using extended-release medication, the recommended initial dose is 25 mg once daily with maximum doses as high as 400 mg daily rarely required in children [10]. Adverse effects are typically seen in doses above 200 mg daily and may include somnolence, dizziness, nystagmus, nervousness, and paresthesias [6, 9]. Severe cognitive adverse effects of overdose include confusion, impaired concentration, slower reactions, and word-finding difficulties [3, 6, 12]. Some children may also cycle between periods of calmness, crying, and combativeness in cases of overdose [8]. The psychotropic effects of topiramate are believed to be rare. One previous report describes a 33-month-old child with prolonged neurologic symptoms including confusion, slurred speech, and visual hallucinations for 6 days [5]. During slow titration of topiramate for migraine prevention, a 17-year-old girl described intermittent nocturnal distortions of her body image consistent with "Alice in Wonderland Syndrome" [11]. During these episodes, the patient described her head would grow bigger and the rest of her body would shrink [11]. Other adverse effects including rash, hepatotoxicity, glaucoma, and nephrotoxicity have not been reported in the pediatric population [12].

Information regarding the type, time, and dose of medication is essential in formulating a plan of action. Unfortunately, this knowledge is not always available due to lack of parental supervision, inadequate intake of history related to the illness, or failure of the patient to disclose the information. Topira-

mate intoxication may be associated with mild non-anion-gap metabolic acidosis or renal tubular acidosis due to reduced bicarbonate reabsorption in the proximal tubule due to the drug's inhibitory activity on the carbonic anhydrase enzyme [12, 13]. If an overdose is suspected, obtaining an initial plasma drug concentration is useful in confirming ingestion, although the result often does not return until several days later. Furthermore, previous studies have not found a consistent relationship between serum levels and adverse effects [14]. Evaluation for coingestion of other substances should be performed. An electrocardiogram, even though topiramate is not classically associated with cardiac rhythm abnormalities, should be performed to assess for coingestion [12].

The management of drug ingestions begins in the emergency department. Airway management with intubation and mechanical ventilation should be performed if indicated clinically. Vital signs should be carefully monitored. The local poison control center should be contacted while the patient is in the emergency department. Previous reports in the adult population have highlighted gastric lavage to retrieve unabsorbed pill fragments if the patient is brought to the emergency department within 1 to 3 h of ingestion [6, 7, 9]. Activated charcoal or sorbitol has been used in previous reports but has not been shown to absorb topiramate *in vitro* and is not recommended for management of topiramate overdose [8, 10]. Induction of emesis is not recommended due to risk of aspiration secondary to quick depression of mental status. In patients with decreased renal function, hemodialysis may significantly decrease topiramate plasma concentrations four to six times faster [15]. However, hemodialysis for topiramate overdose is not routinely recommended by poison control centers and is reserved for patients with severe renal disease and critically elevated topiramate concentrations.

Children confirmed to have ingested a subtherapeutic dose (< 0.5 mg/kg) of topiramate with no other coingestion and are asymptomatic may be monitored closely at home. Otherwise, all children with suspected overdose and altered mental status should be admitted to the hospital once stabilized in the emergency department. In general, it takes between three to four half-lives for elimination of 90% of the medication [1, 4]. The child should be monitored closely for changes in neurological function including somnolence, dizziness, fatigue, and ataxia. Seizure precautions should be exercised if the patient has a previous history of seizures, as breakthrough seizures can occur as serum concentrations decline. To our knowledge, there are no reported fatalities or permanent neurological sequelae in children to date associated with topiramate only overdose.

Learning points

Ingestion of unknown substances, including anti-epileptic medications, should always be suspected in a child who presents with altered mental status. Topiramate overdose manifests with confusion, word-finding difficulties, and strange behavior. Hallucinations are a rare symptom of intoxication. A mild non-anion gap metabolic acidosis is consistent with topiramate intoxication. Supportive management is recommended for topiramate ingestion until complete resolution of symptoms occurs.

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The authors have nothing to declare.

Conflict of Interest

The authors declare no conflict of interest regarding the publication of this article.

Informed Consent

Informed consent was obtained.

Author Contributions

Dr. Shieh and Dr. Schellpfeffer contributed to the content of this study. Both authors drafted, edited, and revised the manuscript as submitted.

Data Availability

The clinical and laboratory data supporting the findings in this study are available within the article.

References

1. Elterman RD, Glauser TA, Wyllie E, Reife R, Wu SC, Pledger G. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. Topiramate YP Study Group. Neurology. 1999;52(7):1338-1344. doi pubmed
2. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia. 2000;41(S1):3-9. pubmed
3. Petroff OA, Hyder F, Rothman DL, Mattson RH. Topiramate rapidly raises brain GABA in epilepsy patients. Epilepsia. 2001;42(4):543-548. doi pubmed
4. Tremont-Lukats IW, Megeff C, Backonja MM. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. Drugs. 2000;60(5):1029-

1052. doi pubmed
5. Lin G, Lawrence R. Pediatric case report of topiramate toxicity. Clin Toxicol (Phila). 2006;44(1):67-69. doi pubmed
6. Traub SJ, Howland MA, Hoffman RS, Nelson LS. Acute topiramate toxicity. J Toxicol Clin Toxicol. 2003;41(7):987-990. doi pubmed
7. Langtry HD, Gillis JC, Davis R. Topiramate. A review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of epilepsy. Drugs. 1997;54(5):752-773. doi pubmed
8. Chung AM, Reed MD. Intentional topiramate ingestion in an adolescent female. Ann Pharmacother. 2004;38(9):1439-1442. doi pubmed
9. Privitera MD. Topiramate: a new antiepileptic drug. Ann Pharmacother. 1997;31(10):1164-1173. doi pubmed
10. Ormrod D, McClellan K. Topiramate: a review of its use in childhood epilepsy. Paediatr Drugs. 2001;3(4):293-319. doi pubmed
11. Jurgens TP, Ihle K, Stork JH, May A. "Alice in Wonderland syndrome" associated with topiramate for migraine prevention. J Neurol Neurosurg Psychiatry. 2011;82(2):228-229. doi pubmed
12. Jones MW. Topiramate—safety and tolerability. Can J Neurol Sci. 1998;25(3):S13-15. doi pubmed
13. Ko CH, Kong CK. Topiramate-induced metabolic acidosis: report of two cases. Dev Med Child Neurol. 2001;43(10):701-704. doi pubmed
14. Contin M, Riva R, Albani F, Avoni P, Baruzzi A. Topiramate therapeutic monitoring in patients with epilepsy: effect of concomitant antiepileptic drugs. Ther Drug Monit. 2002;24(3):332-337. doi pubmed
15. Garnett WR. Clinical pharmacology of topiramate: a review. Epilepsia. 2000;41(S1):61-65. doi pubmed