Topiramate for Seizures in Preterm Infants and the Development of Necrotizing Enterocolitis

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abstract

Neonatal seizures represent a significant health burden on the term and preterm neonatal population and are linked to poor long-term neurodevelopmental outcomes. Currently, there are no US Food and Drug Administration–approved antiepileptic drugs for neonates, and authors of the medical literature have yet to reach a consensus on the most adequate approach to neonatal seizures. Topiramate is readily used in the adult and older pediatric population for the management of migraines and partial-onset seizures. Topiramate continues to gain favor among pediatric neurologists who often recommend this medication as a third-line treatment of neonatal seizures. We report our recent experience with 4 preterm neonates, born between 2015 and 2017, who developed radiographic signs of necrotizing enterocolitis after receiving topiramate for seizures. Each was given oral topiramate for the treatment of electrographic and clinical seizures and developed the subsequent diagnosis of necrotizing enterocolitis, with abdominal distention, hemoccult-positive stools, and radiographic signs of intestinal distention and pneumatosis. More research regarding the risk factors of topiramate use in premature infants is needed.

CASE SERIES

Seizures represent a significant health burden on the term and preterm neonatal population and are strongly associated with poor neurodevelopmental outcomes.[1,2] The management of neonatal seizures is riddled with issues pertaining to diagnosis, monitoring, and treatment. The etiology of seizures in premature and term neonates is multifactorial, including perinatal asphyxia, intracranial bleeding, cerebrovascular lesions, central nervous system malformations, infections, metabolic disturbances, and drug withdrawal. At present, there are no medications for the treatment of seizures in preterm or term infants <1 month of age that are approved by the US Food and Drug Administration. The broad spectrum of pathologies and the relative paucity of treatment options make for difficult medical management of neonatal seizures.

Since the early 1980s, phenobarbital has been the most commonly used medication for neonatal seizures. Negative long-term neurodevelopmental outcomes of phenobarbital compared with newer antiepileptic drugs (AEDs) such as levetiracetam have shifted the pharmacotherapy for neonatal seizures.[3,4] In cases of uncontrolled seizures with dual AED therapy, the addition of topiramate as a third agent is controversial. Topiramate was first isolated in 1978 and has been approved for the treatment of epilepsy and migraines in the adult population since the late 1990s. Recently, the compound has received US Food and Drug Administration approval as

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TABLE 1 Clinical Characteristics of the Patients Who Received Topiramate for Neonatal Seizures

Case	Race and/or Ethnicity	Sex	GA, weeks	Birth Weight, kg	Birth Weight, %	Apgar Score 1 Min	Apgar Score 5 Min	Wt at Topiramate, kg	Wt at Topiramate, Percentile	PCA at Topiramate
1[a]	African American	Female	24	0.44	3	3	6	0.55	4	27
2[a]	Hispanic	Male	23	0.58	55	2	5	0.70	6	28
3[a]	African American	Female	23	0.54	51	2	4	0.77	73	25
4[a]	White	Female	36	2.21	18	2	3	2.24	3	38
5	African American	Male	32	1.76	47	9	9	2.88	27	38
6	African American	Male	25	0.61	16	8	8	1.82	2	38
7	African American	Female	25	0.89	94	8	8	6.50	27	59
8	African American	Male	25	0.77	59	1	4	1.24	31	30
9	African American	Male	27	1.19	94	1	1	1.21	59	29
10	African American	Female	24	0.72	87	7	9	0.72	32	26

GA, gestational age.

[a] Patients who displayed radiographic signs of NEC after topiramate administration.

monotherapy for the management of epilepsy in children >10 years of age and as an adjunctive therapy for the treatment of seizures in children >2 years of age. Fifty percent of pediatric neurologists recommend topiramate as a tertiary medication in neonates.[5]

Despite several animal studies, the evidence and potential consequences of the use of topiramate in neonatal seizures is unknown. The literature has limited information on the neonatal side effects of topiramate and the neurodevelopmental implications of this treatment in neonatal seizures.[6] We reviewed 10 cases of preterm infants treated with topiramate for neonatal seizures, 4 of whom developed necrotizing enterocolitis (NEC).

METHODS

This is a case series of 10 preterm infants (born before 37 weeks of gestation) who received oral topiramate for neonatal seizures in the level III NICU at Holtz Children's Hospital between September 2015 and September 2017. The diagnosis of seizures was made by using continuous video electroencephalography. Seizures were monitored electrographically and clinically, and a seizure-free state was considered as achieved after an EEG demonstrated the resolution of seizures. The length and frequency of EEG monitoring was based on the discretion of the pediatric neurologists and by the clinical fragility of the patient. Treatment with topiramate was initiated at the following dosages: 10 mg/kg per day per os on day 1, followed by 5 mg/kg per day on day 2 (with the exception of case 1, in which a patient received 2 mg/kg of topiramate daily).[7,8] Topiramate drug levels were not clinically available. The diagnosis of NEC was made on the basis of clinical signs (abdominal distention, bloody stools, etc) and radiographic findings of intestinal distention and pneumatosis intestinalis.

RESULTS

Ten infants received topiramate for the diagnosis of neonatal seizures at our institution between 2015 and 2017. The patients were all born prematurely (23–36 weeks), with birth weights between 440 and 2100 g, and were equally divided between boys and girls (Table 1). There were no profound differences in neonatal comorbidities between the 10 infants.

Case 1

A girl 22 days old, 24 weeks' postconceptual age (PCA), was born via cesarean delivery with Apgar scores of 3 and 6 at 1 and 5 minutes. She developed respiratory distress syndrome and a dependence on mechanical ventilation. The patient had a large patent ductus arteriosus (PDA) that remained untreated and systemic hypotension with chronic vasopressor dependence. An abdominal abscess was diagnosed at a PCA of 25 weeks, requiring Penrose drainage. The patient had no intraventricular hemorrhage (IVH) but was diagnosed with seizure disorder at 25 weeks' PCA. EEG showed frequent epileptiform discharges originating from the central brain regions and seizure activity. She was started on levetiracetam with no improvements in seizure activity on EEG; phenobarbital and fosphenytoin were then added. When the patient then failed to have seizure control after a pyridoxine challenge, topiramate was started at 27 weeks' PCA. At that time, the patient was tolerating 40 mL/kg per day of expressed breast milk (EBM) and weighed 550 g. After 2 days on topiramate, she developed abdominal distention, bloody stools, leukocytosis of 33 000/μL, acidosis (pH of 7.15), C-reactive protein elevation to 12.9 mg/dL, and radiographic evidence of NEC (Fig 1). Despite this strong temporal association between the administration of topiramate and the infant's diagnosis of NEC, it is important to entertain the possibility of a recurrence of the patient's previous intra-abdominal infection.

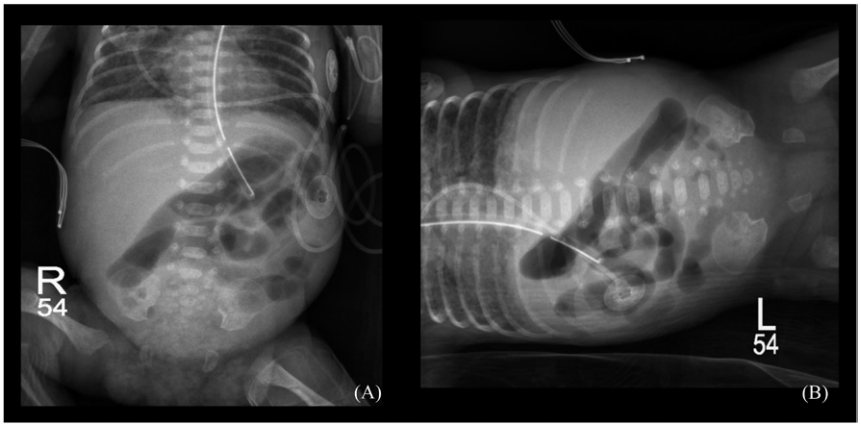

FIGURE 1
Anterior posterior (A) and left lateral decubitus (B) views of case 1 taken after two days of topiramate administration. This film shows asymmetric, distended, and featureless loops of bowel; air-fluid levels are seen on the lateral radiograph (B). These films are suggestive of NEC.

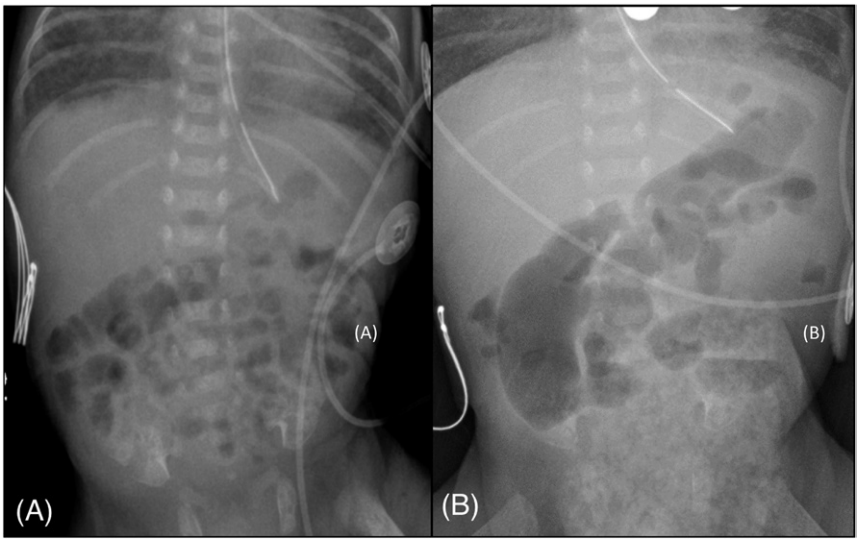

FIGURE 2
Abdominal radiograph, (A) anterior posterior view and (B) left lateral decubitus, 24 hours after the administration of one dose of topiramate showing fixed asymmetric moderately dilated loops of bowel concerning for developing NEC.

Case 2

A 23-week premature neonate was born after clinical chorioamnionitis, with Apgar scores of 2 and 5 at 1 and 5 minutes. Antibiotics were administered for 48 hours for empirical early-onset sepsis coverage with negative cultures. Hospital course was complicated by IVH grade 3, septicemia, Gram-positive cocci in both eyes, and respiratory failure with mechanical ventilation dependence. At 4 weeks of age, an EEG was obtained secondary to jerky movements of the arms and legs and showed electrographic correlation with associated multifocal sharp waves. Levetiracetam was started, followed by phenobarbital because of inadequate clinical and electrographic response. Because of further seizure activity and respiratory depression, phenobarbital was switched to fosphenytoin. When the EEG continued to show frequent seizures, he was loaded with topiramate at 27 weeks' PCA. At that time, the infant was tolerating 100 mL/kg per day of EBM and weighed 700 g. The following day, the infant was found to have abdominal distention, and NEC was confirmed on abdominal radiograph (Fig 2).

Case 3

A 4-week-old infant was born at 22 6/7 weeks of gestation, with an early hospital course remarkable for sepsis, PDA, and bilateral grade 4 IVH. At 27 weeks' PCA, the infant developed multifocal myoclonic status epilepticus and was loaded with levetiracetam and phenobarbital. Continuous video EEG monitoring demonstrated improvement of myoclonic seizures after several loading doses of phenobarbital and the initiation of topiramate. At that time, the infant was tolerating 110 mL/kg per day of EBM and weighed 770 g. Seven days later, this infant developed abdominal distension with NEC changes on abdominal radiograph, necessitating small bowel resection with a right hemicolectomy and ileostomy (Fig 3).

Case 4

A premature neonate was born with intrauterine growth restriction at 36 weeks, initially requiring mechanical ventilation and was found by echocardiography to have a PDA with mitral and tricuspid regurgitation. The patient had multiple congenital malformations, including hypotonia, microcephaly with hypoplastic vermis, and thinning of the corpus callosum, congenital cataracts, dysmorphic facies, and pancytopenia. A microarray revealed some regions of homozygosity, without any other findings of clinical relevance.

At 39 weeks' PCA, the patient developed seizures, and levetiracetam was started. Despite the addition and increase in fosphenytoin dosing, seizure activity continued, and topiramate was begun at 40 weeks' PCA, at which time the infant was tolerating 160 mL/kg per day of EBM and weighed

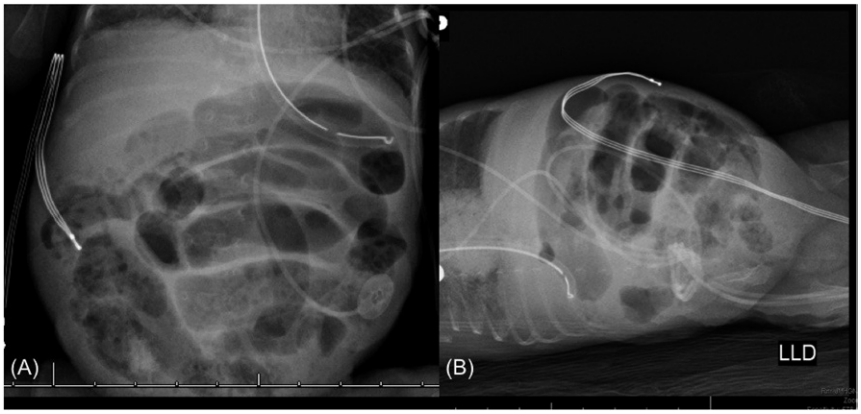

FIGURE 3
Abdominal radiograph, (A) anterior posterior view and (B) left lateral decubitus, 24 hours after the discontinuation of 12 days of topiramate showing moderate to severely distended and elongated bowel loops with pneumatosis, diagnostic of NEC. LLD, left lateral decubitus.

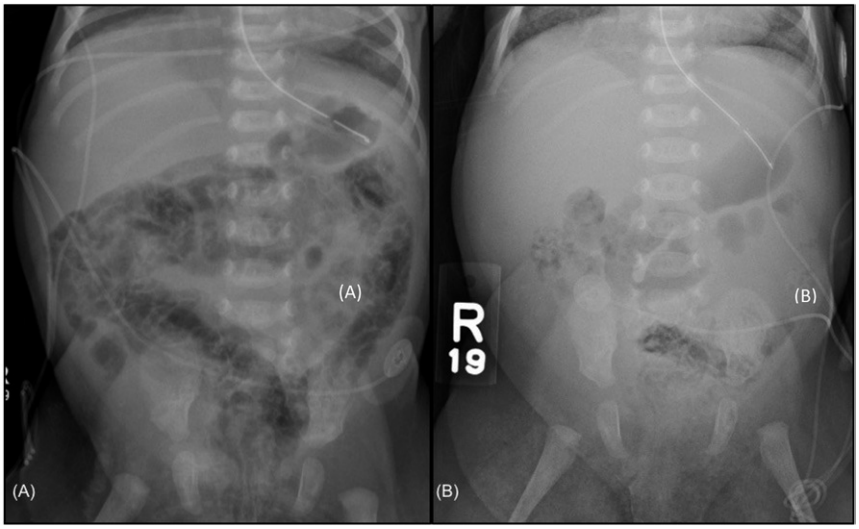

FIGURE 4
A, Abdominal radiograph on the 7th day of this infant's first course of topiramate showing mottled lucencies and pneumatosis, consistent with NEC. B, Abdominal radiograph on the 4th day of this infant's second course of topiramate, showing pneumatosis in the ascending rectosigmoid colon.

2240 g. Six days into treatment, the infant developed bloody stools and abdominal radiograph revealed diffuse colonic distention and pneumatosis, suggestive of NEC. The infant was changed to nothing by mouth and completed 10 days of antibiotics, during which oral topiramate was held and seizures were managed with levetiracetam and phenobarbital. Feeds were restarted, and once full feeds were reached, topiramate (43 weeks' PCA) was restarted. The infant was advanced to full oral feeds, but 6 days later, developed diffuse colonic distension and pneumatosis suggestive of recurrent NEC (Fig 4).

DISCUSSION

We reviewed the cases of 10 premature infants, 40% of which, after a short time interval of treatment with topiramate for seizures, developed NEC. This contrasts with our institution's baseline rate of NEC of 5.8% for 2015–2016. The temporal association between the usage of topiramate and NEC has not been reported previously. Glass et al[7] published a case series of 6 term neonates who received topiramate for neonatal seizures; none of them developed similar gastrointestinal findings observed in our cases. In reports on the use of topiramate in older children and adolescents, authors describe adverse side effects such as anorexia, vomiting, and flu-like symptoms.[9,10]

Gastrointestinal side effects of topiramate in adults have been widely reported. In a single retrospective study from Spain, authors found a significant association between topiramate therapy and microscopic colitis.[11] Other reported adverse events include weight loss, anorexia, nausea, vomiting, and gastroenteritis. Such side effects were proposed to relate to the structure of topiramate, an intermediate molecule in the synthesis of fructose-1, 6-diphosphate (FDP). Because topiramate is a precursor of FDP, it is not unreasonable to assume that topiramate, like FDP, could increase anaerobic carbohydrate metabolism and promote the formation of lactic acid within the gastrointestinal tract. In addition, the molecular resemblance of topiramate to acetazolamide could hypothetically explain the presence of metabolic acidosis in adults, secondary to renal bicarbonate losses.[12,13] Interestingly, no infant in this cohort developed significant metabolic acidosis while on topiramate.

Unfortunately, data on neonates are not provided in the published safety profile of topiramate. This case series represents the only report of topiramate use in premature infants for the treatment of seizures and is the first study in which the clinical and radiographic findings of NEC after the administration of oral topiramate in preterm neonates is reported. Yet, in light of the patients'

multiple risk factors for NEC, topiramate may only be associated but not causal for the development of NEC.

Greater clinical data collection and analysis of infants treated with topiramate are warranted given topiramate's increased popularity and use in the NICU. From this case series, hypothesis-driven, randomized controlled trials in which researchers look at the safety and efficacy of topiramate relative to other AEDs in the management of neonatal seizures is needed.

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ABBREVIATIONS

AED: antiepileptic drug
EBM: expressed breast milk
FDP: fructose-1,6-diphosphate
IVH: intraventricular hemorrhage
NEC: necrotizing enterocolitis
PCA: postconceptual age
PDA: patent ductus arteriosus

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