Published in final edited form as:

Pediatr Neurol. 2011 June ; 44(6): 439–442. doi:10.1016/j.pediatrneurol.2011.01.006.

Topiramate for the Treatment of Neonatal Seizures

Hannah C. Glass, MDCM^{*}, Chantal Poulin, MD[†], and Michael I. Shevell, MDCM[†]

^{*} Departments of Neurology and Pediatrics, University of California, San Francisco, CA, United States of America

[†] Departments of Neurology/Neurosurgery and Pediatrics, McGill University, and the Division of Pediatric Neurology, Montreal Children's Hospital-McGill University Health Centre, Montreal, PQ, Canada

Abstract

Current therapeutic options for treatment of neonatal seizures, such as phenobarbital and phenytoin lack efficacy, and are potentially harmful to the developing brain. Topiramate appears to be effective as both an anti-seizure and neuroprotective agent in animal models of newborn brain injury. Though topiramate is commonly used as an add-on agent in newborns, its use in this population has not yet been reported. We performed a retrospective cohort study of clinical topiramate use in newborns with acute symptomatic seizures that were refractory to standard agents. In four of six identified newborns, there was apparent reduction or no further seizures, and none of the children experienced side effects that resulted in discontinuation of the drug, either during the hospital admission or after discharge home. Prospective studies evaluating the safety and efficacy of topiramate for both seizures and neuroprotection will be important to determine whether this medication deserves widespread use in clinical practice.

Keywords

Infant, newborn; Seizures; Electroencephalography; Magnetic resonance imaging

Introduction

Neonatal seizures occur in approximately 1–3.5 per 1,000 live births [1–7], and are the most common acute sign of serious underlying newborn brain injury [8]. Treatment for neonatal seizures has gained increasing attention in light of accumulating evidence that seizures, in and of themselves, may harm the developing brain [9–11]. However, anti-seizure therapy for newborns has remained largely unchanged for decades, with phenobarbital as the preferred first line agent in both the North America and abroad [12–14]. This is despite good evidence demonstrating that phenobarbital and phenytoin (a commonly-used second line agent) are effective in less than 50% of newborns with seizures [15]. Furthermore, there is increasing evidence from animal models that these agents have intrinsic potentially neurotoxic effects, though their effect on human newborns with seizures is not known [16,17].

Correspondence: Hannah C. Glass, Department of Neurology Box 0663, 521 Parnassus Avenue, C-215, San Francisco, CA 94143-0663, Phone: 415-514-3277; Fax: 415-502-5821, Hannah.Glass@ucsf.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Topiramate is approved by the US Food and Drug Administration for children older than age two. In animal models of newborn brain injury, topiramate appears to be an effective anti-seizure medication with evident neuroprotective properties [18–22]. Furthermore, animal models show no evidence of harmful effects of topiramate on the developing brain [23].

In spite of survey results suggesting that topiramate is commonly used as an add-on agent for neonatal seizures [24], its use has not yet been reported. We examined medical records to identify and report six children who were treated with topiramate for neonatal seizures.

Study Design and Methods

This is a retrospective cohort study of clinical use of topiramate in newborns treated for seizures at the Montreal Children's Hospital, after January 1, 2009. The Montreal Children's Hospital neonatal intensive care unit is an outborn Level III nursery serving newborns delivered in hospitals in Montreal and the province of Québec. We identified newborns treated with topiramate for acute symptomatic seizures that were refractory to initial medications, and who were followed in the Neonatal Neurology clinic at the Montreal Children's Hospital. Seizure therapy (including drug dosing), measurement of phenobarbital levels, timing and duration of electroencephalogram (EEG) monitoring, and imaging were at the discretion of the attending neonatologist and neurologist. Topiramate drug levels were not clinically available and were not performed.

The hospital charts were systematically reviewed for clinical features of interest, including perinatal history, clinical course, seizure etiology, neurophysiology, imaging, and follow-up data. Clinical seizures were diagnosed when the medical records indicated events that were considered to be and treated as seizures. Semiology was classified according to Mizrahi et al [25]. Electrographic seizures were diagnosed based on the clinical neurophysiology reports. Seizure control was considered when there was no further mention of clinical seizures, or electrographic seizures when EEG was available. Potential side effects of topiramate (including anorexia, weight loss, vomiting, diarrhea, acidosis leading to discontinuation of medication, glaucoma and renal calculi) were noted by reviewing the medical records. The children were evaluated in the Neonatal Neurology follow-up clinic by a neurologist who is familiar with the use of topiramate in children (MS or CP). Routine blood work was not performed as part of the follow-up evaluation. The Director of Professional Services at the Montreal Children's Hospital approved the chart review as per standard local protocol.

Results

We identified six term newborns treated with topiramate for acute symptomatic seizures that were refractory to phenobarbital (30–60mg/kg, level 34–42µg/mL), and who were followed in the Neonatal Neurology clinic at the Montreal Children's Hospital. In all cases, the topiramate was administered as a suspension of the crushed tablet via a nasogastric tube. The dose used was 10mg/kg in five subjects and 3mg/kg in one subject. No seizures were detected on follow-up EEG in three subjects and frequency was reduced in one subject. No side effects of topiramate therapy were noted during the admission or at follow-up, though three subjects had a weight <5th percentile. The case histories are summarized in Table 1.

Discussion

We report six children who were treated with topiramate for neonatal seizures that were refractory to standard doses of phenobarbital and/or phenytoin. In five of the children, topiramate was administered as an enteric loading dose of 10mg/kg, and in one child,

maintenance therapy was initiated at 3mg/kg/day. In four of five children who received a loading dose of topiramate, there was apparent reduction or absence of further seizures, whereas one child who received only a maintenance dose continued to have seizures without evident change in frequency. None of the children experienced side effects that resulted in discontinuation of the drug, either during the hospital admission or after discharge home, although three with neurological impairment had weight at or below the 5th percentile at follow-up.

Animal model data suggest that topiramate is effective as both an anti-seizure and a neuroprotective agent, and, unlike phenobarbital and phenytoin, does not enhance apoptosis [18–23,26]. Human data from open label studies suggest that topiramate may be a safe and effective anti-seizure therapy for infants greater than one month. Topiramate has been used for refractory status epilepticus with reported effect in at least two infants ([27,28]), as well as for many more infants as initial monotherapy or for refractory epilepsy ([29–32]), and for infantile spasms ([33–37]). However, a recent randomized controlled trial suggested that topiramate in doses up to 25mg/kg/day may not be an efficacious add-on agent for infants aged one month to two years with refractory epilepsy [38].

Though this is a novel series of newborns treated with topiramate for refractory neonatal seizures, our case series is not without limitations. We report a small series of patients who were evaluated retrospectively. Like many centers, the Montreal Children's Hospital does not have the capacity for long term video-EEG monitoring, and so seizures were identified based on clinical diagnosis and intermittent EEG evaluations. Neonatal seizures are best evaluated with continuous video-EEG monitoring: clinical diagnosis is uncertain and there is a high rate of electroclinical dissociation in newborns (with ongoing electrographic seizures following resolution of clinical seizures) [39,40]. For this reason, there is consensus among experts that video-EEG is the “gold standard” for confirmation of neonatal seizures, and we agree that future studies must evaluate the immediate effect of topiramate on electrographic seizures [41]. Neonatal seizures are often self-limited over 48–72 hours, making any add-on agent appear more effective than the initial therapy. Fourth, clinical testing for serum topiramate levels was not possible, so it is uncertain how much of the drug was absorbed via the enteric route, especially in the setting of hypoxic-ischemic encephalopathy. This is especially important considering that hypoxic-ischemic encephalopathy was the most common diagnosis, and ischemia to the gut may have limited absorption. Evaluation of the side effects of topiramate was limited by documentation by the treating physician. Due to this limitation, as well as small sample size, we cannot exclude medication side effects from topiramate. Finally, the small size of the cohort and lack of pharmacokinetic evaluation makes any speculation about optimal doses, timing and treatment population impossible.

Conclusions

There is an urgent need for well-designed clinical trials to test newer seizure treatments for newborns. Topiramate is an attractive candidate, since it is neuroprotective in animal models of hypoxic-ischemic injury, the most common etiology of seizures in the newborn and a common cause of developmental disability. Furthermore, a stable intravenous formulation has been tested in adults with epilepsy and healthy volunteers, and the results show that IV and oral bioavailability are equivalent, and that the IV formulation is well tolerated [42].

Prospective studies evaluating topiramate safety and efficacy for both seizures and neuroprotection will be important to determine whether this medication deserves widespread use in clinical practice.

Acknowledgments

The authors would like to thank Ms. Alba Rinaldi and Ms. Jessica Kan, as well as the physicians from the Montreal Children's Hospital neonatal follow-up clinic for their kind assistance.

Financial Support

NINDS/NCRR/OD UCSF-CTSI Grant Numbers KL2 RR024130 and K23NS066137 (HCG) supported this project. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. MCH Foundation provided salary support for MS during this study.

References

1. Lanska MJ, Lanska DJ, Baumann RJ, Kryscio RJ. A population-based study of neonatal seizures in Fayette County, Kentucky. *Neurology*. 1995; 45:724–32. [PubMed: 7723962]
2. Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. *J Pediatr*. 1999; 134:71–5. [PubMed: 9880452]
3. Lanska MJ, Lanska DJ. Neonatal seizures in the United States: results of the National Hospital Discharge Survey, 1980–1991. *Neuroepidemiology*. 1996; 15:117–25. [PubMed: 8700303]
4. Saliba RM, Annegers JF, Waller DK, Tyson JE, Mizrahi EM. Incidence of neonatal seizures in Harris County, Texas, 1992–1994. *Am J Epidemiol*. 1999; 150:763–9. [PubMed: 10512430]
5. Minchom P, Niswander K, Chalmers I, Dauncey M, Newcombe R, Elbourne D, Mutch L, Andrews J, Williams G. Antecedents and outcome of very early neonatal seizures in infants born at or after term. *Br J Obstet Gynaecol*. 1987; 94:431–9. [PubMed: 3580326]
6. Patterson CA, Graves WL, Bugg G, Sasso SC, Brann AW Jr. Antenatal and intrapartum factors associated with the occurrence of seizures in term infant. *Obstet Gynecol*. 1989; 74:361–5. [PubMed: 2761911]
7. Glass HC, Pham TN, Danielsen B, Towner D, Glidden D, Wu YW. Antenatal and Intrapartum Risk Factors for Seizures in Term Newborns: A Population-Based Study, California 1998–2002. *J Pediatr*. 2008
8. Volpe, JJ. Neonatal Seizures. In: Volpe, JJ., editor. *Neonatal Neurology*. WB Saunders; Philadelphia: 2008. p. 203–244.
9. Glass HC, Pham TN, Danielsen B, Towner D, Glidden D, Wu YW. Antenatal and intrapartum risk factors for seizures in term newborns: a population-based study, California 1998–2002. *J Pediatr*. 2009; 154:24–28. e1. [PubMed: 18760807]
10. Miller SP, Newton N, Ferriero DM, Partridge JC, Glidden DV, Barnwell A, Chuang NA, Vigneron DB, Barkovich AJ. Predictors of 30-month outcome after perinatal depression: role of proton MRS and socioeconomic factors. *Pediatr Res*. 2002; 52:71–7. [PubMed: 12084850]
11. Holmes GL. The long-term effects of neonatal seizures. *Clin Perinatol*. 2009; 36:901–14. vii–viii. [PubMed: 19944841]
12. Barth A, Shen J, Katz KH, Mischel RE, Yap KR, Ivacko JA, Andrews EM, Ferriero DM, Ment LR, Silverstein FS. Neonatal seizures: multicenter variability in current treatment practices. *Pediatr Neurol*. 2007; 37:85–90. [PubMed: 17675022]
13. Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. *Epileptic Disord*. 2007; 9:353–412. [PubMed: 18077226]
14. Bassan H, Bental Y, Shany E, Berger I, Froom P, Levi L, Shiff Y. Neonatal seizures: dilemmas in workup and management. *Pediatr Neurol*. 2008; 38:415–21. [PubMed: 18486824]
15. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, Paneth N, Minnigh B, Alvin J. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med*. 1999; 341:485–9. [PubMed: 10441604]
16. Bittigau P, Siffringer M, Genz K, Reith E, Pospischil D, Govindarajulu S, Dzietko M, Pesditschek S, Mai I, Dikranian K, Olney JW, Ikonomidou C. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci U S A*. 2002; 99:15089–94. [PubMed: 12417760]

17. Forcelli PA, Janssen MJ, Stamps LA, Sweeney C, Vicini S, Gale K. Therapeutic strategies to avoid long-term adverse outcomes of neonatal antiepileptic drug exposure. *Epilepsia*. 51(Suppl 3):18–23. [PubMed: 20618394]
18. Schubert S, Brandl U, Brodhun M, Ulrich C, Spaltmann J, Fiedler N, Bauer R. Neuroprotective effects of topiramate after hypoxia-ischemia in newborn piglets. *Brain Res*. 2005; 1058:129–36. [PubMed: 16139822]
19. Liu Y, Barks JD, Xu G, Silverstein FS. Topiramate extends the therapeutic window for hypothermia-mediated neuroprotection after stroke in neonatal rats. *Stroke*. 2004; 35:1460–5. [PubMed: 15105511]
20. Koh S, Tibayan FD, Simpson JN, Jensen FE. NBQX or topiramate treatment after perinatal hypoxia-induced seizures prevents later increases in seizure-induced neuronal injury. *Epilepsia*. 2004; 45:569–75. [PubMed: 15144420]
21. Zhao Q, Hu Y, Holmes GL. Effect of topiramate on cognitive function and activity level following neonatal seizures. *Epilepsy Behav*. 2005; 6:529–36. [PubMed: 15878305]
22. Cha BH, Silveira DC, Liu X, Hu Y, Holmes GL. Effect of topiramate following recurrent and prolonged seizures during early development. *Epilepsy Res*. 2002; 51:217–32. [PubMed: 12399072]
23. Glier C, Dzietko M, Bittigau P, Jarosz B, Korobowicz E, Ikonomidou C. Therapeutic doses of topiramate are not toxic to the developing rat brain. *Exp Neurol*. 2004; 187:403–9. [PubMed: 15144866]
24. Silverstein FS, Ferriero DM. Off-label use of antiepileptic drugs for the treatment of neonatal seizures. *Pediatr Neurol*. 2008; 39:77–9. [PubMed: 18639748]
25. Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. *Neurology*. 1987; 37:1837–44. [PubMed: 3683874]
26. Alaverdashvili M, Kubova H, Mares P. Motor performance and behavior of immature rats are not compromised by a high dose of topiramate. *Epilepsy Behav*. 2005; 7:222–30. [PubMed: 15996529]
27. Perry MS, Holt PJ, Sladky JT. Topiramate loading for refractory status epilepticus in children. *Epilepsia*. 2006; 47:1070–1. [PubMed: 16822255]
28. Kahriman M, Minecan D, Kutluay E, Selwa L, Beydoun A. Efficacy of topiramate in children with refractory status epilepticus. *Epilepsia*. 2003; 44:1353–6. [PubMed: 14510830]
29. Veggianti P, Longaretti F, Signorini S, Cardinali S, Lanzi G. Topiramate efficacy in an infant with partial seizures refractory to conventional antiepileptic drugs. *Seizure*. 2004; 13:241–3. [PubMed: 15121132]
30. Valencia I, Fons C, Kothare SV, Khurana DS, Yum S, Hardison HH, Legido A. Efficacy and tolerability of topiramate in children younger than 2 years old. *J Child Neurol*. 2005; 20:667–9. [PubMed: 16225812]
31. Kim JM, Kwon S, Seo HE, Choe BH, Cho MH, Park SP. Long-term effectiveness and tolerability of topiramate in children with epilepsy under the age of 2 years: 4-year follow-up. *J Korean Med Sci*. 2009; 24:1078–82. [PubMed: 19949663]
32. Grosso S, Galimberti D, Farnetani MA, Cioni M, Mostardini R, Vivarelli R, Di Bartolo RM, Bernardoni E, Berardi R, Morgese G, Balestri P. Efficacy and safety of topiramate in infants according to epilepsy syndromes. *Seizure*. 2005; 14:183–9. [PubMed: 15797353]
33. Hsieh MY, Lin KL, Wang HS, Chou ML, Hung PC, Chang MY. Low-dose topiramate is effective in the treatment of infantile spasms. *Chang Gung Med J*. 2006; 29:291–6. [PubMed: 16924891]
34. Peltzer B, Alonso WD, Porter BE. Topiramate and adrenocorticotrophic hormone (ACTH) as initial treatment for infantile spasms. *J Child Neurol*. 2009; 24:400–5. [PubMed: 19225138]
35. Kwon YS, Jun YH, Hong YJ, Son BK. Topiramate monotherapy in infantile spasm. *Yonsei Med J*. 2006; 47:498–504. [PubMed: 16941739]
36. Zou LP, Lin Q, Qin J, Cai FC, Liu ZS, Mix E. Evaluation of open-label topiramate as primary or adjunctive therapy in infantile spasms. *Clin Neuropharmacol*. 2008; 31:86–92. [PubMed: 18382180]

37. Watemberg N, Goldberg-Stern H, Ben-Zeev B, Berger I, Straussberg R, Kivity S, Kramer U, Brand N, Lerman-Sagie T. Clinical experience with open-label topiramate use in infants younger than 2 years of age. *J Child Neurol.* 2003; 18:258–62. [PubMed: 12760428]
38. Novotny E, Renfroe B, Yardi N, Nordli D, Ness S, Wang S, Weber T, Kurland CL, Yuen E, Eerdekens M, Venkatraman L, Nye JS, Ford L. Randomized trial of adjunctive topiramate therapy in infants with refractory partial seizures. *Neurology.* 74:714–20. [PubMed: 20089937]
39. Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP, Connolly S. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed.* 2008; 93:F187–91. [PubMed: 17626147]
40. Malone A, Ryan CA, Fitzgerald A, Burgoyne L, Connolly S, Boylan GB. Interobserver agreement in neonatal seizure identification. *Epilepsia.* 2009; 50:2097–101. [PubMed: 19490044]
41. Silverstein FS, Jensen FE, Inder T, Hellstrom-Westas L, Hirtz D, Ferriero DM. Improving the treatment of neonatal seizures: national institute of neurological disorders and stroke workshop report. *J Pediatr.* 2008; 153:12–5. [PubMed: 18571526]
42. Kriel, R.; Clark, A.; Leppik, I.; Marino, S.; Brundage, R.; Cloyd, J. *Epilepsia* (American Epilepsy Society Abstract #1.285). 2010. Pharmacokinetics and Safety of Oral and Intravenous Topiramate in Adult Volunteers.

Table 1

Use of topiramate in six newborns with seizures.

	Clinical History	Seizure Etiology	Clinical Seizure Semiology	EEG Confirmation of Seizure	Medications	Response to Topiramate	Follow-up	Side Effects
1	41 2/7 week Male	Perinatal asphyxia with HIE and hemorrhagic infarct	Generalized tonic	Yes	Pb 45mg/kg TPM 10mg/kg	No further clinical or EEG seizures	11.5 months - Seizure-free on TPM monotherapy - Evolving spastic quadripareisis - NG dependent for 50% of intake	Weight 10–25 th %ile
2	39 6/7 week Female	Temporal lobe hemorrhage	Apnea	Yes	Pb 30mg/kg TPM 3mg/kg	Ongoing EEG seizures	8 months - Seizure-free on TPM monotherapy - Normal exam	Nil
3	38 6/7 week Male	Presumed prenatal HI injury	Focal clonic	Yes	Pb 40mg/kg TPM 10mg/kg	No further clinical or EEG seizures	11 months - Seizure-free on TPM monotherapy - Normal exam	Nil
4	37 1/7 week Female	Perinatal asphyxia with HIE	Focal clonic or tonic* and motor automatisms	No	Pb 40mg/kg TPM 10mg/kg	No further clinical or EEG seizures	8.5 months - Seizure-free on TPM monotherapy - Evolving spastic quadripareisis	Weight <5 th %ile
5	Term Female	Presumed prenatal HI injury	Focal clonic and motor automatisms	Yes	Pb 60mg/kg PHT 30mg/kg TPM 10mg/kg	Reduced frequency of EEG seizures	5 months Infantile spasms	Weight <5 th %ile

	Clinical History	Seizure Etiology	Clinical Seizure Semiology	EEG Confirmation of Seizure	Medications	Response to Topiramate	Follow-up	Side Effects
6	40 2/7 week Female	Perinatal asphyxia with HIE	Unavailable	Yes	Pb 30mg/kg TPM 10mg/kg	Ongoing clinical seizures	<i>6 months</i> - while on Pb and TPM - Evolving spastic quadriparesis - Seizure-free on TPM - Mild increased tone	Weight <5 th %ile

HIE hypoxic-ischemic encephalopathy; **Pb** Phenobarbital; **TPM** topiramate; **EEG** electroencephalogram

* Clonic vs tonic semiology cannot be determined based on available documentation