



Topiramate

Updated: December 16, 2013.

OVERVIEW

Introduction

Topiramate is a unique antiseizure medication that is used in treatment of partial and generalized seizures. Topiramate has been rarely associated with hepatic injury and largely when used in combination with other anticonvulsant medications.

Background

Topiramate (toe pyre' a mate) is a sulfamate-substituted monosaccharide and belongs to an anticonvulsant class of its own. Topiramate is believed to act by reducing sodium channel currents and enhancing gamma aminobutyric acid (GABAA) receptor activity. Topiramate was approved for use in epilepsy in the United States in 1996 and it is still widely used. Its current indications are for prevention and management of partial and generalized seizures used either as monotherapy or in combination with other anticonvulsants. Topiramate is also used for migraine and for bipolar disorder. The recommended starting dose in adults is 25 mg twice daily, escalating at weekly intervals to a maximum of 200 mg twice daily. Topiramate is available in 25, 100 and 200 mg tablets in multiple generic forms and under the brand name Topromax. Pediatric formulations as sprinkle capsules are available in doses of 15 and 25 mg. Common side effects include dizziness, somnolence, paresthesias, change in taste, anorexia, weight loss, itching, difficulty concentrating and nervousness.

Hepatotoxicity

Prospective studies suggest that less than 1% of subjects develop elevations in serum aminotransferase levels during long term topiramate therapy. Clinically apparent hepatotoxicity from topiramate is quite rare and usually arises in patients receiving multiple other anticonvulsants. Topiramate is metabolized by CYP 3A4 and may increase risk of valproate or other anticonvulsant hepatotoxicity. A distinctive syndrome is the development of lethargy, weakness with marked serum aminotransferase elevations and hyperammonemia arising within 2 to 3 weeks of the addition (or dose increase) of topiramate to long term valproate therapy. While valproate alone can cause a similar syndrome, it appears much more common (~1%) with the combination than with valproate alone (~0.1%). This syndrome has several features suggestive of Reye syndrome (hyperammonemia, hypoglycemia, rapid reversal of injury) and in many instances is preceded by an acute viral illness. Topiramate by itself has only rarely been linked to clinically apparent liver injury and the clinical features and course of injury have not been well defined. Topiramate has not been linked to cases of the anticonvulsant hypersensitivity syndrome and is considered a safe alternative in patients with that syndrome.

Mechanism of Injury

The mechanism of topiramate hepatotoxicity is thought to be due to its effects in inducing CYP 3A4 or inhibiting CYP 2C19 and possibly through the effects of a toxic metabolic intermediate.

Outcome and Management

Topiramate hepatotoxicity is usually attributed to its effects on the metabolism of other anticonvulsants, and as such is rapidly reversible within a few days of either drug being stopped. Acute liver failure and chronic injury from topiramate therapy has not been reported.

Drug Class: Anticonvulsants

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Topiramate – Generic, Topamax®

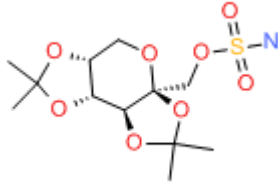
DRUG CLASS

Anticonvulsants

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Topiramate	97240-79-4	C ₁₂ H ₂₁ N-O ₈ S	

ANNOTATED BIBLIOGRAPHY

References updated: 16 December 2013

Zimmerman HJ. Anticonvulsants. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 498-516.

(Expert review of anticonvulsants and liver injury published in 1999; topiramate is not discussed).

Pirmohamed M, Leeder SJ. Anticonvulsant agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013: pp 423-42.

(Review of anticonvulsant induced liver injury; topiramate is not discussed).

McNamara JO. Pharmacology of the epilepsies. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 583-607.

(Textbook of pharmacology and therapeutics).

Wallace SJ. A comparative review of the adverse effects of anticonvulsants in children with epilepsy. *Drug Saf* 1996; 15: 378-93. PubMed PMID: 8968693.

(Systematic review; ALT elevations occur in 4% of children on phenytoin, 6% on valproate, 1% on carbamazepine, but none reported on tiagabine or gabapentin; no mention of hepatotoxicity of topiramate).

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: 752-73. PubMed PMID: 9360061.

(Summary of prelicensure studies of pharmacokinetics, efficacy and safety of topiramate; shown to be effective in doses of 400-1000 mg alone and in lower doses as adjunctive therapy; major side effects are central nervous system, including dizziness, somnolence, nervousness, paresthesia, ataxia and confusion; also causes renal stones, anorexia and weight loss; no mention of ALT abnormalities or hepatotoxicity).

Bjørø K, Gjerstad L, Bentsdal O, Osnes S, Schrumpf E. Topiramate and fulminant liver failure. *Lancet* 1998; 352: 1119. PubMed PMID: 9798593.

(39 year old woman on chronic carbamazepine therapy developed progressive stupor 4 months after starting topiramate and shortly after a dose increase [300 mg/day], with hypoglycemia and acidosis [bilirubin not given, ALT 1350 rising to 10,000 U/L], coagulopathy and coma, requiring liver transplantation, explant showed massive centrilobular necrosis).

Sachdeo RC. Topiramate. Clinical profile in epilepsy. *Clin Pharmacokinet* 1998; 34: 335-46. PubMed PMID: 959261.

(Review of pharmacology, clinical efficacy and safety of topiramate; common side effects are dizziness, slowed thinking, somnolence, ataxia, fatigue, confusion and paresthesias; long term therapy may cause weight change and nephrolithiasis; no mention of ALT elevations or hepatotoxicity).

Hamer HM, Morris HH. Hypersensitivity syndrome to antiepileptic drugs: a review including new anticonvulsants. *Cleveland Clin J Med* 1999; 66: 239-45. PubMed PMID: 10199060.

(Clinical review of anticonvulsant hypersensitivity syndrome which occurs in 1-5 per 10,000 users, higher risk in African Americans and affected siblings; liver involvement common, but most cases anicteric; other manifestations include facial edema, lymphadenopathy, bone marrow aplasia, pseudolymphoma, thyroiditis, interstitial nephritis).

Faught E. Clinical studies of topiramate. *Drugs Today (Barc)* 1999; 35: 49-57. PubMed PMID: 1297340.

(Review of results of clinical trials of topiramate; most common side effects were CNS symptoms such as dizziness and somnolence; "There have been no cases of severe liver dysfunction or damage from topiramate").

Doan RJ, Clendenning M. Topiramate and hepatotoxicity. *Can J Psychiatry* 2000; 45: 937-8. PubMed PMID: 11190367.

(21 year old woman with bipolar disorder was found to have liver test abnormalities two months after adding topiramate to chronic therapy with valproate, benzotropine, and risperidone [bilirubin not mentioned; ALT 627 rising to 1909 U/L, Alk P 81 U/L, INR normal, valproate levels normal], resolving within 1 month and no recurrence on restarting valproate without topiramate).

Longin E, Teich M, Koelfen W, König S. Topiramate enhances the risk of valproate-associated side effects in three children. *Epilepsia* 2002; 43: 451-4. PubMed PMID: 11952778.

(3 children, ages 1-9 years on valproate for few months to 5 years developed apathy and hypothermia 4-8 weeks after adding topiramate with ammonia elevations [one with ALT elevation to 400 U/L as well], rapidly reversed by stopping either agent, positive rechallenge in one. Topiramate appears to enhance risk of hyperammonemia due to valproate).

Langman LJ, Kaliciak HA, Boone SA. Fatal acute topiramate toxicity. *J Anal Toxicol* 2003; 27: 323-4. PubMed PMID: 12908948.

(44 year old woman was found dead with high levels of topiramate in blood and liver; death ascribed to acute topiramate overdose; no mention of liver injury).

Bumb A, Diederich N, Beyenburg S. Adding topiramate to valproate therapy may cause reversible hepatic failure. *Epileptic Disord* 2003; 5: 157-9. PubMed PMID: 14684351.

(51 year old woman with resistant epilepsy developed confusion and liver injury after addition of topiramate to chronic valproate therapy [bilirubin not given, ALT 464 U/L, GGT 569 U/L, ammonia 88 µg/dL], resolving upon stopping valproate: topiramate likely changed pharmacokinetics of valproate).

Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDavid C, Mason A, et al. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. *Health Technol Assess* 2005; 9: 1-157, iii-iv. PubMed PMID: 15842952.

(Systematic review of anticonvulsant medications including assessment of serious, rare and long term adverse events, serious adverse events from topiramate were limited to neurological effects; no mention of hepatotoxicity).

Topal F, Ozaslan E, Akbulut S, Küçükazman M, Yüksel O, Altiparmak E. Methylprednisolone-induced toxic hepatitis. *Ann Pharmacother* 2006 40:1868-71. PubMed PMID: 16926305.

(Acute hepatic injury arising after 7 days of self prescribed methylprednisolone [32 mg/day] in a patient on long term topiramate [bilirubin 10 mg/dL, ALT 2478 U/L, Alk P 138 U/L], with rapid recovery with stopping both; no recurrence on restarting topiramate).

LaRoche SM. A new look at the second-generation antiepileptic drugs: a decade of experience. *Neurologist* 2007; 13: 133-9. PubMed PMID: 17495757.

(Review of second generation anticonvulsants approved since 1994 including felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide and pregabalin; no mention of liver toxicity from topiramate).

Nicolai J, Gunning B, Leroy PL, Ceulemans B, Vles JS. Acute hepatic injury in four children with Dravet syndrome: valproic acid, topiramate or acetaminophen? *Seizure* 2008; 17: 92-7. PubMed PMID: 17697789.

(4 children with severe infantile myoclonic epilepsy [Dravet syndrome: SCN1A+] on chronic therapy with topiramate and valproate had sudden and transient onset of marked elevations in ALT [2209, 5898, 280 and 480 U/L] and hyperammonemia or coagulopathy without jaundice shortly after febrile illness and/or use of acetaminophen; possibly Reye syndrome due to valproate and topiramate, rapid recovery despite continuing anticonvulsants).

Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K, McKay A, et al.; Topiramate for Alcoholism Advisory Board; Topiramate for Alcoholism Study Group. Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Arch Intern Med* 2008; 168: 1188-99. PubMed PMID: 18541827.

(Randomized controlled trial of topiramate vs placebo in 371 alcohol dependent patients found ALT levels decreased more in treated than placebo group; one patient in each group had de novo ALT elevations).

Chung AM, Eiland LS. Use of second-generation antiepileptic drugs in the pediatric population. *Pediatr Drugs* 2008; 10: 217-54. PubMed PMID: 18590343.

(Extensive review of antiepileptic drugs and their use in children; no mention of topiramate).

Chalasanani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, valproate accounted for 6, lamotrigine 5, phenytoin 5, gabapentin and topiramate 1 each; however, the case initially linked to topiramate was later found to be due to acute hepatitis C).

Del Val Antoñana A, Ortiz Polo I, Andrade Bellido RJ. [Topiramate-induced acute hepatitis]. *Gastroenterol Hepatol* 2010; 33: 148-9. Spanish. PubMed PMID: 19800146.

(16 year old girl developed fatigue and abdominal pain 10 weeks after starting topiramate [bilirubin 1.3 mg/dL, ALT 8030 U/L, Alk P 135 U/L, INR 2.6, glucose 52 mg/dL], resolving rapidly, within 2 weeks of stopping).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury including 11 linked to anticonvulsants, but none to topiramate).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. *Am J Gastroenterol* 2010; 105: 2396-404. PubMed PMID: 20648003.

(313 cases of drug induced liver injury were seen over a 12 year period at a large hospital in Bangalore, India; 35 were attributed to anticonvulsants, but none to topiramate).

Molleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasanani N; for the Drug-Induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN Prospective Study. *J Pediatr Gastroenterol Nutr* 2011; 53: 182-9. PubMed PMID: 21788760.

(Among 30 children with drug induced liver injury enrolled in a prospective US database between 2004 and 2008, 8 were due to anticonvulsants [lamotrigine in 3, valproate in 3, phenytoin in 1 and carbamazepine in 1], but none to topiramate).

Noh Y, Kim DW, Chu K, Lee ST, Jung KH, Moon HJ, Lee SK. Topiramate increases the risk of valproic acid-induced encephalopathy. *Epilepsia* 2013; 54: e1-4. PubMed PMID: 22691153.

(Retrospective analysis of 8,372 Korean patients with epilepsy treated with valproate at a single referral hospital between 2001 and 2009 found 1236 who also received topiramate; hyperammonemic coma developed in 0.6% of those on the combination compared to only 0.06% on valproate alone).

Gaitatzis A, Sander JW. The long-term safety of antiepileptic drugs. *CNS Drugs* 2013; 27: 435-55. PubMed PMID: 23673774.

(Review of long term safety of commonly used anticonvulsants; topiramate hepatotoxicity is not mentioned).

Drugs for epilepsy. *Treat Guidel Med Lett* 2013; 11: 9-18. PubMed PMID: 23348233.

(Concise review of indications and side effects of anticonvulsants; topiramate is used for partial and primary generalized tonic-clonic seizures, both as monotherapy and adjunctive therapy in adults and children; adverse events include drowsiness, dizziness, headache and ataxia; mentions that liver failure has been reported).