Review Article

A Review on Topiramate and Available Analytical Methods

Raval Kashyap*, Subrahmanyam EVS and Sharbaraya AR

Department of quality assurance, Srinivas College of pharmacy, Mangalore, Karnataka, India.

ABSTRACT

The present review describes information regarding newer drug topiramate, an antiepileptic and anti-migraine drug. Antiepileptic drugs suppress seizures, but do not cure the disorder so lifelong treatment is required. Topiramate is presently gaining interest in the treatment of epilepsy. The present review includes all available information like pharmacokinetics, pharmacological action and side effects. Moreover sometimes it is necessary to monitor the therapeutic concentration of Topiramate. Review also contains various available analytical methods for determining plasma concentration briefly.

INTRODUCTION

Topiramate is also known as Topamax,Topiragen,Topamax Sprinkle. Topiramate (brand name Topamax) is an anticonvulsantandanti-migraine drug. It was originally produced by Ortho-McNeil Neurologics and Noramco, Inc., both divisions of Johnson & Johnson. It was discovered in 1979 by Bruce E. Maryanoff and Joseph F. Gardocki during their research work at McNeil Pharmaceutical.[1, 2, 3] Generic versions are available in Canada and were FDA approved in September 2006. Mylan Pharmaceuticals was recently granted final approval for generic topiramate 25, 100, and 200 mg tablets and sprinkle capsules by the FDA for sale in the US. 50 mg tablets were granted tentative approval.[4]the last patent for topiramate in the U.S. was for pediatric use; this patent expired on February 28, 2009.[5] On May 21, 2010, Ortho-McNeil plead guilty and was fined US$6.14 million by the FDA for promoting Topamax to treat psychiatric disorders, without applying for any approval and there was no data from any well-controlled clinical trial to demonstrate that Topamax was safe and effective to treat any psychiatric conditions.[6]

Topiramate is a sulfamate-substituted monosaccharide. TOPAMAX® (topiramate) Tablets are available as 25 mg, 50 mg, 100 mg, and 200 mg round tablets for oral administration. TOPAMAX® (topiramate capsules) Sprinkle Capsules are available as 15 mg and 25 mg sprinkle capsules for oral administration as whole capsules or opened and sprinkled onto soft food.

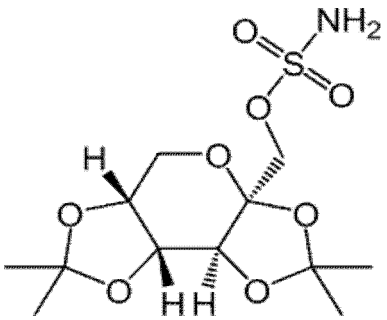
SYNONYMS

- Tipiramate [French]
- Tipiramato [Spanish]
- Topiramate tablet
- Topiramatum [INN-Latin]
- Topiramic acid [7]

HETEROCYCLIC CHEMISTRY

Topiramate is a sulphamate-substituted monosaccharide with a structure distinct from other AEDS. Its chemical formula is 2, 3:4, 5-di-O-(l-isopropylidene)-ß-D-fructopyranosesulphamateIt is a derivative of the naturally-occurring monosaccharide D-fructose.[8]

Topiramate has the molecular formula $C_{12}H_{21}NO_8S$. Topiramate is designated chemically as 2, 3:4, 5-Di-*O*-isopropylidene-β-D-fructopyranosesulfamate and has the following structural formula. It is of Synthetic origin and belongs to SulphamateMonosaccharides. . The Molecular Weight of Topiramate is 339.40.[9]



PHARMACEUTICAL ASPECTS

Solubility

Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3 [10]

Pharmacodynamics

It appears as though Topiramate enhances GABA through interfering with calcium and sodium channels. It is also a weak inhibitor of carbonic anhydrase. Mood Stabilizations seems to occur before anticonvulsant qualities at lower dosages. [11]

Pharmacokinetics

Volume of distribution is found to be 0.7(0.6-0.8)l/kg and plasma protien binding is 13 - 17 %. Renal Excretion accounts for ~ 70 % and plasma half life is 21 hr. [12]

PHARMACOLOGICAL ACTION:

The exact mechanism of action is unknown, [13] but four properties that may contribute to topiramate's antiepileptic and antimigraine efficacy include a blockage of voltage-dependent sodium channels, an augmentation of gamma-aminobutyrate acid activity at some subtypes of the GABA- A receptors, antagonism of AMPA/kainate subtype of the glutamate receptor, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV.

Its possible effect as a mood stabilizer seems to occur before anticonvulsant qualities at lower dosages. Topiramate inhibits maximal electroshock andpentylenetetrazol-induced seizures as well as partial and secondarily generalized tonic-clonic seizures in the kindling model, findings predictive of a broad spectrum of activities clinically. Its action onmitochondrial permeability transition pores has been proposed as a mechanism. [14]

1.Gamma-aminobutyric-acid receptor subunit alpha-1 Pharmacological action: yes
Actions: agonist
2. Sodium channel protein type 1 subunit alpha Pharmacological action: yes
Actions: inhibitor
3. Glutamate receptor, ionotropickainate 1 Pharmacological action: yes
Actions: antagonist
4. Carbonic anhydrase 2 Pharmacological action: yes
Actions: inhibitor
5. Carbonic anhydrase 4 Pharmacological action: yes
Actions: inhibitor
6. Cytochrome P450 2C19
Actions: inhibitor[15]

SIDE EFFECT

A GlaxoSmithKline-sponsored Phase IV study suggested that cognitive side effects may be more common with topiramate than with lamotrigine. In studies of healthy volunteers, therapeutic doses of topiramate for bipolar disorder produced greater cognitive deficits than lamotrigine, including short term memory loss and word-finding difficulty.The side-effects reported by > 10% of subjects in at least 1 clinical study [16, 17]

The inhibition of carbonic anhydrase may be strong enough to cause metabolic acidosis of clinical importance. Topiramate has been associated with a statistically significant increase in suicidality

They also cause effect like numbness, burning, or tingling in the hands or feet, slowed reactions, difficulty concentrating, speech problems, especially difficulty thinking of specific words, memory problems, lack of coordination, confusion,nervousness,and aggressivebehavior. irritability , mood

swings ,depression, headache, drowsiness , weakness , excessive movement , uncontrollable shaking of a part of the body , uncontrollable eye movements , extreme thirst , weight loss , constipation , diarrhea , gas , heartburn , , change in ability to taste food , swelling of the tongue , overgrowth of the gums , dry mouth.
Some side effects can be serious. blurred vision , double vision , eye pain ,worsening of seizures , slow heart rate , pounding or irregular heartbeat , chest pain , trouble breathing , fast, shallow breathing , inability to respond to things around you , excessive tiredness , nausea , vomiting , stomach pain , loss of appetite , intense back or side pain , bloody, cloudy, or foul-smelling urine[18]

DOSE: Topiramate's dosage details are as follows

Dose	Single dose	Frequency	Route	instruction
Adult dosage (>12years)				
200.000 mg	200 (200)	12 hr	PO	
Paedriatic dosage (20kg)				
1.660 mg/kg	33(33.2)	24 hr	oral	Initial, at night . Not recommended under 2 yrs. of child
3.500 mg/kg	70(70)	12 hr	oral	Maintenance.Gradually increase the dose

Neonatal dosage

No data regarding the Neonatal dosage details of Topiramate is available. [19]

USE

Topiramate (Topamax®) is a prescription medication used to treat various conditions related to the nervous system. Specific topiramate uses include:
Epilepsy treatment (either used alone or in combination with otherepilepsy medication)

Migraine prevention

Topiramate is a prescription medication that is licensed to treat epilepsy and to prevent migraine headaches. By slowing electrical signals in the brain and calming overly excited nerve cells, the medicine can help prevent seizures and migraines. Topiramate, which is available in the form of tablets or "sprinkle" capsules, is usually taken twice a day. Potential side effects of this drug may include dizziness, burning or tingling sensations, and fatigue.[20] Topiramate Use in Obese Patients with Binge Eating Disorder. [21] It also use in a general neurology clinic. [22] Topiramate: a new antiepileptic drug for refractory epilepsy.Use of Topiramate in Treatment-Resistant Bipolar Spectrum Disorders.[23]

Validating Methods for Topiramate

Various methods were recently developed for assaying of Topiramate

Capillary electrophoresis with indirect UV detection[24]

In this method a rapid capillary zone electrophoresis method with indirect UV detection was used for the determination of topiramate in human plasma. The analysis was carried out with a background electrolyte composed of 10mM sulfamethoxazole as chromophore in phosphate buffer (25 mM, pH 12.0) and gabapentin was selected as the internal standard.Application of a voltage of +15 kV leads to an analysis time shorter than 5 min; indirect UV detection is operated at 256 nm. Isolation of topiramate from plasma is accomplished by a carefully implemented solid-phase extraction procedure on C18 cartridges. The method provided a linear response over the concentration range of 2-60 ug/mL of plasma.

By HPLC with pre-column fluorescent derivatization[25]

This quantitative analytical method involves fluorescent derivatization technique for determination of topiramate in human serum.Topiramate is extracted from human serum by dichloromethane and derivatize by reaction with 9-fluorenylmethyl chloroformate (FMOC-Cl) in the presence of borate buffer.Analysis was performed on a CN column with sodium phosphate buffer (pH 2.2) containing 1 ml/l triethylamine and methanol (52:48 (v/v)) as mobile phase.The accuracy of the method is 96.5–107.5% (intra-day) and 98.4–105% (inter-day). The limit of quantification is 20 ng/ml of serum.

By HPLC with a chemiluminescent nitrogen detector[26]

This method is developed for determination of topiramate and its degradation product in liquid orals.The HPLC part of the method consists of a reversed-phase phenyl column and a methanol/water mobile phase. Chemiluminescent nitrogen detector (CLND) is extensively used for detection of nitrogen containing compounds. The method has a validated linearity range of 32–4800 ng of topiramate. It is accurate and sensitive method for determination of toperamate.

By HPLC using UV detectors[27]

Though topiramate has no ultra violet, fluorescence or visible absorbance, this analysis was performed by subjecting to derivatization with 9-fluorenylmethyl chloroformate.Analysis was performed on a phenyl column using of spectrophotometer detection operated at wavelength of 264 nm. A mixture of phosphate buffer (0.05 M) containing triethylamine (1 ml/l, v/v; pH 2.3) and methanol (28:72, v/v) at a flow rate of 2.5 ml/min was used as mobile phase. This method gives high degree of accuracy with a linearity range from 40 ng/ml to 40ug/ml.

By a new liquid chromatography-tandem mass spectrometric method[28]

This method was developed for the determination of topiramate level by assaying dry blood spots.The sensitivity and specificity of tandem mass spectrometry allow high throughput topiramate analysis. The linearity was seen in concentration range 0.0166-1.66 mg/L. Accuracy of this method is 93.93% to 110.67%.

By HPLC with using 4-chloro-7-nitrobenzofurazan as pre-column fluorescence derivatizing agent[29]

It is a simple and sensitive high-performance liquid chromatographic method for analysis of topiramate by using 4-chloro-7-nitrobenzofurazan as a derivatizing agent. Derivatization was performed by the labeling agent in the presence of dichloromethane, methanol, acetonitrile and borate buffer (0.05 M; pH 10.6). The procedure was validated over the concentration range of 0.01 to 12.8 µg/mL. No interferences were found from commonly co-administrated antiepileptic drugs including phenytoin, phenobarbital carbamazepine, lamotrigine, zonisamide, primidone, gabapentin, vigabatrin, and ethosuximide.

By spectrofluorometric and spectrophotometric method[30]

Micelle-enhanced spectrofluorometric assay is based on reaction between topiramate and fluorescamine to give highly fluorescent derivative which was then measured at 470 nm using an excitation wavelength 388 nm. The linearity range was found to be 0.01-0.10 ug/ml. spectrophotometric method is based on reaction of primary amino group of topiramate with ninhydrin reagent in ethanolic medium in the presence of 50mM sodium bicarbonate. The linearity range was found to be 4-40 ug/ml.

Determination of Sulfamate and Sulfate as Degradation Products Using Ion Chromatography and Indirect UV Detection[31]

Topiramate is a potent antiepileptic drug currently in phase III clinical trials.

Sulfamate and sulfate have been found to be two stoichiometrically formed degradation products in topiramate. An ion chromatographic method with indirect UV detection has been developed to assay sulfamate and/or sulfate in topiramate drug substance and formulated products. When used in combination with an HPLC assay method, this method is stability-indicating and can be used as a regulatory method.

Stability indicating HPLC method for analysis of Topiramate[32]

A isocratic seperaion was achieved by using phenyl colum with flow rate of 1 ml/min at uv detection at 264 nm.It was derivatization with 9-fluorenyl-methyl chloroformate. The mobile phase for separation consist of acetonitrile; 50mM sodium dihydrogen phosphate contain 3 % v/v triethylamine in 48:52 v/v ratio. Topiramate subjected to oxidation, hydrolysis, photolysis and heat for purpose of stress testing. This method was linear over the concentration range of 1-100 µg/ml with limits of quantitation and detection of 1 and 0.3 µg/ml respectively.

Colorimetry method for estimation of Topiramate by using Ammonium molybdate[33]

Here Method was based on oxidation-reduction reaction involving the formation of blue colored complex between Topiramate and Ammonium molybdate in the presence of 2M hydrochloric acid, which showed a linearity range of 10 to 50 µg/ml at a λmax of 750nm. The method was validated based on ICH guidelines. It is simple, sensitive, and reliable and results are reproducible. The high recovery and low relative standard deviation confirms the suitability of the method for determination Topiramate in pharmaceutical dosage forms.

REFERENCES

1. Maryanoff ,Nortey, Gardocki, JF Shank and Dodgson. Anticonvulsant O-alkyl sulfamates. 2, 3:4, 5-Bis-O-(1-methylethylidene)-beta-D-fructopyranosesulfamate and related compounds. Journal of medicinal chemistry.30 (5): 880–7.
2. Maryanoff, Costanzo, Nortey, Greco, Shank ET AL. Structure-activity studies on anticonvulsant sugar sulfamates related to topiramate. Enhanced potency with cyclic sulfate derivatives. Journal of medicinal chemistry.1998; 41(8): 1315–43.
3. B. E. Maryanoff and J. F. Gardocki. Anticonvulsant sulfamate derivatives, U.S. Patent 4,513,006 (1985)
4. http://www.medscape.com/viewarticle/544994
5. U.S.FDA http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=020844&Product_No=002&table1=OB_Rx
6. Ortho-McNeil Pharmaceutical: LLC Pleads Guilty to Illegal Promotion of Topamax.
7. Blum D, Meador K, Biton V, Fakhoury T, Shneker B, Chung S, Mills K, Hammer A, Isojarvi J. Cognitive effects of lamotrigine compared with topiramate in patients with epilepsy. Neurology. 2006; 67(3):400-6.
8. Faught E , Wilder BJ, Ramsay RE, et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages Neurologyv.1996 ;46:1684-1690.
9. Primary Characteristics http://www.druginfosys.com/Drug.aspx?drugCode=1079&drugName=Topiramate&type=0
10. Topamax Drug Description http://www.rxlist.com/topamax-drug.htm
11. TOPIRAMATE CHEMISTRY http://www.chemistrydaily.com/chemistry/Topiramate
12. PharmacoKinetics
13. http://www.druginfosys.com/Drug.aspx?drugCode=1079&drugName=Topiramate&type=2
14. Topamax Drug Description http://www.rxlist.com/topamax-drug.htm
15. Kudin, AP, Debska-Vielhaber, et al. The mechanism of neuroprotection by topiramate in an animal model of

epilepsy. Epilepsia. 2004;45 (12):1478 –87.
16. DRUG DISCRIPTION http://www.rxlist.com/topamax-drug.htm
17. Roy Chengappa,Schwarzman, Hulihan, Xiang , Rosenthal. Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo-controlled trial. The Journal of clinical psychiatry 2006; 67 (11): 1698–706.
18. Mirza, Nasir ,Marson, Anthony G, Pirmohamed. Effect of topiramate on acid-base balance: extent, mechanism and effects. British Journal of Clinical Pharmacology. 2009;68 (5): 655–61.
19. MEDLINE PLUS : SIDE EFFECT http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697012.html
20. DOSAGE http://www.druginfosys.com/Drug.aspx?drugCode=1079&drugName=Topiramate&type=9
21. MEDTV : WHAT IS TOPIRAMATE http://headache.emedtv.com/topiramate/topiramate.html
22. Jose Appolinario, Leonardo FF, Marcelo P , Joao RB, WalmirCoutinho. Topiramate Use in Obese Patients With Binge Eating Disorder: An Open Study. The Canadian Journal of Psychiatry
23. Pamela Crawford. An audit of topiramate use in a general neurology clinic Seizure. 1998; 7(3): 207-11.
24. Vieta, Eduard, Garcia-Ribas et al. Use of Topiramate in Treatment-Resistant Bipolar Spectrum Disorders Journal of Clinical Psychopharmacology. 2002; 22(4): 431-35.
25. Mandrioli R, Musenga A, Kenndler E, de donno m, Amore M, Raggi MA. Determination of topiramate in human plasma by capillary electrophoresis with indirect uv detection. J pharm biomed anal. 2010; 53(5):1319-23.
26. Bahrami G, mirzaeei S, Kiani A. Sensitive analytical method for topiramate in human serum by hplc with pre-column fluorescent derivatization and its application in human pharmacokinetic studies. Journal of chromatography b. Analytical technologies in the biomedical and life science.2004; 813(1-2): 175- 80.
27. Maria styslo-zalasikand weiyong li. Determination of topiramate and its degradation product in liquid oral solutions by high performance liquid chromatography with a chemiluminescent nitrogen detector. Journal of pharmaceutical and biomedical analysis. 2005; 37 (3): 529-34.
28. Gholamreza bahrami, shahla mirzaeei, bahareh mohammadiand amir kiani. Developed high performance liquid chromatographic determination of topiramate in human serum using uv detection.Journal of chromatography b. 2005; 822 (1-2):322-25.
29. Giancarlo la marca, sabrina malvagia, luca filippi, et. Al. Rapid assay of topiramate in dried blood spots by a new liquid chromatography-tandem mass spectrometric method.Journal of pharmaceutical and biomedical analysis. 2008; 48 (5): 1392-96.
30. Gholamreza bahrami, bahareh mohammadi.A novel high sensitivity hplc assay for topiramate, using 4-chloro-7-nitrobenzofurazan as pre-column fluorescence derivatizing agent. Journal of chromatography b. 2007; 850 (1-2):400-04.
31. Nahla nour el-din ahmed salama. Development and validation of spectrofluorometric, spectrophotometric and thin layer chromatography stability indicating methodsfor the assay of topiramate. International journal of pharmacy and technology. 2010; 2(4) : 1299-1314.
32. Rossi W. Lit. M. Determination of sulfamate and sulfate as degradation products in an antiepileptic drug using ion chromatography and indirect uv detection .journal of liquid chromatography and related technologies. 1995; 18 (5): 917- 23
33. Ali, nasir R, mahadi A and Roderick BW. Development of stability indicating high performance liquid chromatographic method for the analysis of topiramate and dissolution rate testing in topiramate tablets.

Asian journal of chemistry.2010; 22(5):3856-3866.

34. Raval Kashyap,E. V. S. Subrahmanyam, A. R. Sharbaraya. Development and validation of new colorimetric method for the estimation of topiramate in bulk and dosage form. International journal of pharmacy and technology. 2012; 4(1): 3974-3989.