A Review on Topiramate and Available Analytical Methods

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ABSTRACT
The present review describes information regarding newer drug topiramate, an antiepileptic and antimigraine 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 anticonvulsant and anti-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 US was for pediatric use; this patent expired on February 28, 2009.5 On May 21, 2010, Ortho-McNeil pleaded 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 are available as 15 mg and 25 mg sprinkle capsules. TOPAMAX® 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

HETEROCYCLIC CHEMISTRY
Topiramate is a sulfamate-substituted monosaccharide with a structure distinct from other AEDS. Its chemical formula is \( \text{C}_{12} \text{H}_{21} \text{NO}_8 \) S. Topiramate is designated chemically as 2, 3:4, 5-di-O-(l-isopropylidene)-β-D-fructopyranosylsulphamate. It is a derivative of the naturally-occurring monosaccharide D-fructose.8 Topiramate has the molecular formula \( \text{C}_{12} \text{H}_{21} \text{NO}_8 \). Topiramate is designated chemically as 2, 3:4, 5-di-O-isopropylidene-β-D-fructopyranosylsulphamate and has the following structural formula. It is of Synthetic origin and belongs to Sulphamate Monosaccharides...
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.

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.

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

PHARMACOLOGICAL ACTION:
The exact mechanism of action is unknown, 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 andpentyleneterazol-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 on mitochondrial permeability transition pores has been proposed as a mechanism.

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

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

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
Some side effects can be serious.

**DOSE: Topiramate’s dosage details are as follows**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Single dose</th>
<th>Frequency</th>
<th>Route</th>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult dosage ( &gt;12 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200.000 mg</td>
<td>200 (200)</td>
<td>12 hr</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Paedriatic dosage (20kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.660 mg/kg</td>
<td>33(33.2)</td>
<td>24 hr</td>
<td>oral</td>
<td>Initial, at night. Not recommended under 2 yrs. of child</td>
</tr>
<tr>
<td>3.500 mg/kg</td>
<td>70(70)</td>
<td>12 hr</td>
<td>oral</td>
<td>Maintenance. Gradually increase the dose</td>
</tr>
<tr>
<td>Neonatal dosage</td>
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No data regarding the Neonatal dosage details of Topiramate is available.  

**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 other epilepsy medication)
- Migraine prevention

Validating Methods for Topiramate

Various methods were recently developed for assaying of Topiramate

**Capillary electrophoresis with indirect UV detection**

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 µg/mL of plasma.
By HPLC with pre-column fluorescent derivatization

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

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

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

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 fluoresence derivatizing agent

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

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

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**

A isocratic separation was achieved by using a phenyl column with a 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 consisted of acetonitrile; 50 mM 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**

Here Method was based on oxidation-reduction reaction involving the formation of blue colored complex between Topiramate and Ammonium molybdate in the presence of 2 M hydrochloric acid, which showed a linearity range of 10 to 50 µg/ml at a λmax of 750 nm. 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.

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