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Review Article

Extended Release Topiramate Formulations in Epilepsy

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Abstract

Topiramate is a novel antiepileptic medication with multiple mechanisms of actions. It is a broad spectrum antiepileptic drug and it is indicated for adjunctive treatment, conversion to monotherapy and initial monotherapy of partial onset and primary generalized epilepsies, the Lennox-Gastaut syndrome as well as for treatment of migraine headaches. It is also used clinically for a variety of neurologic and psychiatric disorders as well as for obesity. Recently, two extended release formulations of topiramate were approved by the FDA for treatment of epilepsy. We review these two formulations in this paper.

Keywords: Topiramate; Extended release formulations; Epilepsy

Introduction

Topiramate (2,3:4,5-bis-O-(1-methylethylidende)-beta-D-fructopyranose-sulfamate) is a novel antiepileptic drug (AED) derived from the naturally occurring monosaccharide D-fructose. It is not structurally related to other antiepileptic drugs and was originally synthesized as part of a search for fructose-related compounds with hypoglycemic activity [1]. Its anticonvulsant activity was discovered in animal experimental seizure models in the 1980's [2]. Topiramate (TPM) has since been shown to be effective in the rodent maximal electroshock model [3], in the amygdala kindling model [4] and in genetic models of epileptogenicity [5].

Topiramate has multiple mechanisms of action [6,7]. These include: 1) Sodium channel blockade/modulation: Topiramate inhibits sustained repetitive firing in a use and concentration-dependent manner in cultured hippocampal neurons and reduces voltage-activated sodium currents in cultured neocortical neurons. 2) Calcium channel blockade: Topiramate inhibits N-, P- and L-type calcium currents [8]. 3) Potassium channel activation: Topiramate activates potassium currents which may contribute to membrane hyperpolarization. 4) Glutamate receptor antagonism (Kainate/AMPA): Topiramate also has inhibitory effects on the Kainate/AMPA subtype (GluR5) of the glutamate receptor. It reduces kainate-evoked inward currents, blocks kainate-evoked cobalt influx, and blocks kainate acid receptor-mediated postsynaptic currents. The effects of topiramate on kainate-evoked currents are unique to this compound among the AEDs. 5) GABA potentiation: Topiramate enhances GABA-evoked single-channel chloride currents by increasing the frequency of opening and burst frequency, without affecting the open channel duration or burst duration. Although the enhancement of GABA-A by topiramate is similar to that of the benzodiazepines, it is not reversed by flumazenil. 6) Carbonic anhydrase inhibition: Topiramate inhibits certain carbonic anhydrase isoforms and results in alteration of bicarbonate homeostasis.

Immediate-release Topiramate was FDA-approved for prescription use in the United States in December 1996 under the brand name Topamax (Janssen pharmaceuticals, Titusville NJ USA). Perhaps as a result of its multiple mechanisms of action, Topiramate is effective against many seizure types. It is currently indicated for adjunctive treatment of partial onset epilepsy, primary generalized epilepsy, and the Lennox-Gastaut syndrome in adults and children ages 2 to 16 years, as well as for conversion to monotherapy and initial monotherapy. It is efficacious as an add-on treatment for drug resistant partial onset epilepsy [9] and is three times more effective compared to placebo in reducing seizures [10]. It is also indicated for the prophylaxis of migraine headache in adults [11]. Topiramate has also been used for the treatment of hyperkinetic movement disorders[12], trigeminal neuralgia [13], obesity [14], antipsychotic medication-induced weight gain [15], eating disorders [16], a variety of psychiatric and mood disorders [17-19] as well as drug and alcohol addiction [20,21].

Immediate-release Topiramate is dosed twice daily. It is rapidly absorbed from the gastrointestinal tract, and its absorption is not significantly affected by food. It is characterized by a plasma elimination half-life ranging from 21-42hrs and by dose-proportional pharmacokinetics from 200-800mg. Ninety percent of the maximal plasma concentration (Cmax) is achieved within 2 hours after oral administration [22].

The most significant dose-limiting adverse effects of immediate-release TPM are its effects on cognition, particularly language function [23]. The serious side effects of topiramate include acute myopia and secondary angle closure glaucoma, reversible visual field defects (independent of elevated intraocular pressure), oligo/anhydrosis and hyperthermia, kidney stones, acute pancreatitis, non-anion gap metabolic acidosis and fetal toxicity (Pregnancy Category D). Other serious side effects include hyperammonemia and encephalopathy with or without concomitant valproic acid (VPA) therapy, hypothermia with concomitant VPA use, paresthesias, suicidal behavior and ideation [11].

Recently, two extended release formulations of topiramate were approved by the FDA for the treatment of epilepsy with once daily dosing: Trokendi XR (Supernus Pharmaceuticals) in August 2013, followed by Qudexy XR (Upsher-Smith Laboratories, Inc) in March 2014. An authorized generic of Qudexy XR was launched in July 2014 by Upsher-Smith Laboratories. Table one summarizes all the brand formulations of topiramate.

In order to gain FDA approval, Supernus pharmaceuticals conducted pharmacokinetic studies on Trokendi XR, to prove that

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Table 1: Brand formulations of topiramate.

Brand	Company	Formulation	Dosage
Topamax	Brand: Janssen Multiple generics	Tablets: 25mg, 50mg, 100mg, 200mg Sprinkle Capsules: 15mg, 25mg	BID
Trokendi XR	Brand: Supernus pharmaceuticals	Capsules: 25 mg, 50 mg, 100 mg, 200 mg	Once per day
Qudexy XR	Brand, Generic: Upsher Smith	Capsules: 25 mg, 50 mg, 100 mg, 150 mg 200 mg	Once per day
Qsyma (phenteramine/topiramate ER)	Brand: Vivus Inc	3.75/23, 7.5/46, 15/92	Once per day

the difference in pharmacokinetics profiles of the immediate-release and extended-release formulations of topiramate is sufficiently small, that no difference in clinical response is anticipated; thus meeting the FDA bioequivalent standards [24]. In the case of Qudexy XR, clinical trials in addition to pharmacokinetic profiles were conducted. In this paper, we review the available data on these two new, extended release formulations of Topiramate used in treatment of epilepsy.

Trokendi XR

Trokendi XR uses the Microtrol delivery technology as its drug delivery system [25]. The Microtol technology is propriety of Supernus pharmaceuticals [25,26]. The same technology had been used in another commonly used extended-release formulation AED, the Carbatrol formulation of carbamazepine [27]. In the Carbatrol formulation there are fixed ratio of 3 bead types: immediate release (25%), enteric coated (35%) and extended release (40%) [28]. However, while the Carbatrol formulation can be used as an intact capsule or by opening the capsule and sprinkling its contents on food (not crushed or chewed) [28], the Trokendi XR capsules have to be taken as a whole. Currently there is no published data about the number and/or ratio of the beads in Trokendi XR.

According to the package insert [26], the basis for approval of Trokendi XR included the demonstration of the pharmacokinetic bioequivalence of Trokendi XR and immediate-release topiramate. A bioequivalence study was conducted in thirty-three healthy subjects who were titrated to 200mg daily dosage of Trokendi XR versus immediate-release topiramate and were maintained for 10 days in a cross over manner. Pharmacokinetic samples were collected at steady state. There was no clinically significant difference between the two formulations and the 90% CI for the ratios of AUC 0-24, Cmax, Cmin, and partial AUC (from zero to each time point post dose) were within the 80-125% bioequivalence limits required by the FDA. Partial AUC represent the average exposure within the defined time intervals. Equivalence of partial AUCs between times zero and all subsequent time points suggest equivalence in the average exposures within any time points of interest and thus no clinically meaningful difference was anticipated between the two formulations.

Based on the bioequivalence studies, Trokendi XR was approved by the FDA for adjunctive treatment of partial onset seizures, primary generalized seizures and the Lennox-Gastaut syndrome in patients of 6 years of age and older. The recommended dosage for adjunctive therapy in adults with partial onset epilepsy is 200-400 mg once per day, and for adults with primary generalized tonic-clonic seizures is 400 mg once per day. The dosage for pediatric patients is 5-9 mg/kg once per day [26]. Trokendi XR was also approved for initial monotherapy in patients with partial onset or primary generalized epilepsy of 10 years of age or older [26]. The recommended dosage for monotherapy is 400 mg once per day. Trokendi XR absorption is not affected by food. Trokendi is contraindicated in patients with metabolic acidosis and patients with recent alcohol use, i.e. within 6 hours of administration (before or after) [26]. Trokendi capsules should be swallowed whole and intact. It cannot be sprinkled on food, chewed or crushed [26]. Trokendi XR has not been studies in randomized clinical trials in the epilepsy population.

Qudexy XR

Qudexy XR uses a proprietary multi-particulate (beads in a capsule) formulation technology to deliver consistent release of topiramate in a 24 hour period [29]. The bioequivalence between swallowed intact capsules and capsules opened and sprinkled on food have been established and therefore Qudexy XR capsules can be opened and sprinkled on food [30,31].

The pharmacokinetic equivalence and tolerability of Qudexy XR in relation to immediate release topiramate was assessed with two single dose, phase I studies [32,33]. When switching between Qudexy XR and topiramate immediate-release, similar concentrations were maintained immediately after the switch and there were no significant differences in AUC 0-24, Cmax and Cmin, and the 90% CI for ratios were contained within the 80-125% equivalence limits. The fluctuation index (mean peak-to trough fluctuation) in plasma topiramate concentration was 26% lower with Qudexy XR compared to topiramate immediate-release.

The efficacy of Qudexy XR as an adjunctive treatment for partial onset epilepsy with and without secondary generalization in 249 adult patients were evaluated with a single randomized phase III study (PREVAIL trial) [34]. After 8 weeks of baseline period (during which patients experienced at least 8 seizures with no more than 21 consecutive seizure-free days), patients were randomized into Qudexy XR and placebo in 1:1 ratio. The study had an 11-week treatment phase (3 weeks of titration and 8 weeks of maintenance), during which median percent reduction in weekly seizure frequency (primary efficacy end point) and responder rate (secondary end point: proportion of patients with more than 50% reduction from baseline in weekly seizure frequency) were assessed. There was a significantly greater reduction in weekly seizure frequency in patients on Qudexy XR versus placebo (39.5% versus 21.6%, $p<0.001$) and the ≥50% responder rate was significantly greater in patients on Qudexy XR versus placebo (37.9% versus 23.2%, $p<0.013$). About 3.2 % of patient on Qudexy XR became seizure free (i.e. 100% reduction in seizure frequency) versus 1.6% on placebo.

A post-hoc analysis of PREVAIL data [35] according to patient level of treatment resistance did not show any significant difference in both groups. Therefore it was concluded that Qudexy XR was efficacious across multiple outcome groups compared to placebo.

Qudexy XR was approved by the FDA for adjunctive treatment

of partial onset seizures, primary generalized seizures and the Lennox-Gastaut syndrome in patients of 2 years of age and older. The recommended dosage for adjunctive therapy of adults with partial onset epilepsy is 200-400mg once per day, and for adults with primary generalized tonic-clonic seizures is 400mg once per day. The dosage for pediatric patients is 5-9mg/kg once per day. It was also approved for initial monotherapy in patients with partial onset or primary generalized epilepsy of 10 years of age or older. The recommended dosage for monotherapy is 400mg once per day.

Conclusion

Extended-release formulations are designed to reduce dose frequency and maintain relatively constant drug plasma concentrations with reduced fluctuations during the dosing interval, when compared to immediate-release formulations. This appears to be true for the two new extended- release formulations of topiramate. For example, in a phase one study, Qudexy displayed equivalent drug exposure to immediate release TPM; with a smoother concentration-time curve and an improved steady-state pharmacokinetic profile and reduced fluctuation index [33].

Qudexy XR has a slower rate of absorption than immediate-release topiramate, as reflected by its later tmax and longer t1/2 values. Its peak plasma exposure and plasma peak-trough fluctuations are less than those with immediate-release Topiramate [31]. These pharmacokinetic properties of the extended-release formulations of Topiramate provide scientific basis for once daily dosing, and may decrease the frequency and severity of concentration-related and peak–effect side effects. This may allow the use of increased doses of topiramate, potentially leading to improved efficacy in epilepsy patients. Additionally in the clinical study of Qudexy XR (compared to clinical trials with immediate release topiramate), lower incidences of subjective neurocognitive or neuropsychiatric side effects were reported [36]. Since objective neuropsychological assessments were not done, this only suggests that extended release formulation of topiramate may cause less cognitive side effects than immediate release topiramate. The once daily dosage for extended-release Topiramate may lead to improved patient compliance, as compliance is known to improve with reduced dosing frequency and increased tolerability [37]. The two new extended-release formulations of topiramate are a welcome addition to the epileptologist's armamentarium of extended-release AEDs (which include carbamazepine, valproic acid, lamotrigine, levetiracetam, phenytoin and oxcarbazepine) [28] for the management of patients with epilepsy.

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