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Safety of Topiramate for Treating Migraines

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Abstract:

Introduction: Topiramate is an effective, popular prophylactic migraine treatment that is approved for use in adults and adolescents. Due to its multiple mechanisms of action, topiramate has multiple potential safety issues, including systemic and central nervous system adverse events, that may complicate therapy. These include weight loss, metabolic acidosis, renal calculi, acute angle closure glaucoma, visual distortions, and cognitive slowing. This review highlights both common and unusual safety issues associated with topiramate use, including use in pregnancy or lactation and important drug interactions.

Keywords:

Topiramate, migraine, preventive treatment, metabolic acidosis, pallinopsia

Introduction:

Topiramate is approved by the Food and Drug Administration (FDA) for the prevention of migraine in adults [1,2] and adolescents [3,4]. The usual dose of topiramate for migraine is 100 mg, because this dose has the best balance of efficacy and low adverse events (AEs) [5]. The doses used in clinical practice, however, may vary considerably for individual patients and disorders and may be higher for some off-label uses, such as chronic migraine or idiopathic intracranial hypertension [6].

Although topiramate was originally investigated for its potential to treat gluconeogenesis, it was subsequently found to be effective in animal models of epilepsy, and found to be effective in humans. [7] Topiramate is FDA-approved for the adjunctive treatment of partial-onset seizures, primary generalized tonic-clonic seizures, and Lennox-Gastaut syndrome in adults and children 2 years old or greater [8,9]. Recently the FDA approved a combination of phentermine and topiramate for the treatment of obesity in association with hypertension, type 2 diabetes, or dyslipidemia [10]. Off-label uses of topiramate in headache disorders include chronic migraine [11], trigeminal neuralgia [12], cluster headache [13], and idiopathic intracranial hypertension [14].

Mechanism of Action

Topiramate has numerous pharmacologic actions including (1) increasing gamma-aminobutyric acid (GABA) activity at GABA-A receptors; (2) inhibiting carbonic anhydrase isoenzymes II and IV; (3) blocking voltage-dependent sodium and calcium channels; (4) antagonism of the of AMPA/kainate subtype of the glutamate receptor; and (5) antagonism of 5-HT_{2C} receptors [15]. Compared to acetazolamide, tolerance to the anticonvulsant effects of topiramate is significantly longer. (Anderson RE, Chiu P, Woodbury DM, *Epilepsia* 1989) The exact mechanism of action that allows topiramate to be effective in migraine prophylaxis is unclear but

may relate to inhibition of cortical spreading depression [16]. These actions contribute to multiple potential AEs with topiramate use, including both systemic and central nervous system (CNS) events. In some cases, such as antagonism of 5-HT_{2C} receptors causing anorexia or carbonic anhydrase inhibition triggering metabolic acidosis and paresthesias, the cause of these AEs is fairly well understood. The cause of CNS AEs is less clear. In many cases the AEs are related to the dose used.

Topiramate is renally excreted, has peak levels at 2 hours and a half-life of 21 hours. Blood plasma concentration increases linearly as a function of dose. [17] Topiramate binds poorly to plasma proteins (about 15%), meaning the drug should be dosed after dialysis in patients with renal failure.

This review will focus on common, serious, and unusual AEs associated with topiramate use, utilizing data from large clinical trials, case series, and case reports. Systemic and CNS AEs will be considered separately, as will the use of topiramate in pregnancy and lactation and drug interactions.

Safety Evaluation in clinical studies and postmarketing data

Systemic AEs

Weight loss and anorexia

Anorexia and weight loss were common AEs in topiramate clinical trials. In some cases, weight loss is desirable, and obesity is among the indications for topiramate. In the original 26-week trials, anorexia rates were 11%, 13% and 14%, respectively, in patients taking the 50, 100 and 200 mg doses, respectively [18,19], while weight loss occurred in 5%, 10% and 12% of patients. Those with a higher baseline weight were more likely to lose weight. Many patients reported disturbance in food taste, such as causing carbonated beverages to taste “flat” (19% on 50 mg,

10% on 100 mg, and 14% on 200 mg compared with 2% on placebo). This is also seen with other anticonvulsant drugs (i.e., acetazolamide and zonisamide).

Nausea and other gastrointestinal AEs

In clinical trials for migraine, nausea was more common in those using topiramate than in those on placebo (9% 50 mg, 13% 100 mg, and 14% 200 mg vs. 8% placebo). Timing of drug use may affect rates of nausea: although food does not affect topiramate's effectiveness, taking it with a meal may reduce nausea [18,19]. Diarrhea is another common AE, with 9%, 11% and 11% of those in the 50 mg, 100 mg and 200 mg groups, respectively, suffering from this condition, compared to 4% with placebo.

Paresthesias, metabolic acidosis and hypokalemia

Paresthesias are an extremely common AE in those taking topiramate. In migraine trials, topiramate users were much more likely to experience them, even at low doses (35% 50 mg, 51% 100 mg, 49% 200 mg compared to 6% placebo). The cause of these paresthesias may be related to underlying metabolic acidosis. In clinical trials, lowering of bicarbonate levels occurred in 44% of those taking 200 mg/day, 39% taking 100 mg/day, 23% taking 50 mg/day, and 7% taking placebo. The incidence of abnormally low serum bicarbonate (either below 17 mEq/L or a decrease greater than 5 mEq/L) was 11% at 200 mg, 9% at 100 mg and 2% at 50 mg, compared with <1% of placebo. This may cause hyperventilation, fatigue, or anorexia and in rare cases, renal failure, cardiac arrhythmias, or stupor [20]. Chronic metabolic acidosis may also decrease growth rate in children. Treatment duration does not appear to affect the prevalence of metabolic acidosis, but polymorphisms in the carbonic anhydrase type XII gene may influence the risk of its development [21]. Hypokalemia is also common, with about 7% to 10% of patients taking topiramate having low serum potassium levels [22]. In another pediatric study, potassium

levels were significantly lower in those using topiramate (3.7 versus 4.0 mmol/L; $P < 0.03$) [23]. Supplemental potassium may alleviate paresthesias in patients using topiramate [24]. The package insert by Janssen Pharmaceuticals, Inc. 2009 recommends monitoring serum bicarbonate at baseline and periodically after that, although no timeframe for repeat testing is specified [25]. Patients with severe respiratory disorders or those on a ketogenic diet may be particularly susceptible; bicarbonate supplements may be useful in symptomatic patients [26].

Renal calculi

The incidence of renal calculi in migraine clinical trials was 1% at 100 mg and 2% at 200 mg, compared with 0% for 50 mg and placebo. The increased rate of kidney stone formation is related to the fact that topiramate causes metabolic acidosis, hypokalaemia, hyperuricemia, and hypocitraturia (a promoter of renal stone formation) [22]. Topiramate causes increased urinary pH, bicarbonate excretion, fractional excretion of bicarbonate, and decreased urinary citrate. Those using topiramate are particularly more likely to develop calcium phosphate stones. Since the development of renal calculi takes months or years, this may be a delayed AE in topiramate users. Hydration, dietary changes, and a lower dose of topiramate may reduce this risk.

Glaucoma, including angle closure glaucoma

Topiramate may rarely cause acute angle closure glaucoma as an idiosyncratic reaction. Signs and symptoms include uveal effusion, lens forward displacement, conjunctival injection, corneal edema, and increased intraocular pressure leading to vision loss. The risk of this serious reaction is highest in the first month after therapy is initiated, [27] and can cause sudden vision loss that requires urgent ophthalmologic attention. Topiramate-induced glaucoma may be unilateral or bilateral, [28] and intraocular pressure may range from mildly to very highly elevated [29]. Treatment includes not covering the eye (which causes pupillary dilation), supine positioning,

medications, and, in refractory cases, surgical procedures, such as laser peripheral iridotomy.

These patients should not continue on Topiramate.

Rash and Stevens-Johnson syndrome

An erythematous rash occurred in 2% of pediatric patients in clinical trials (compared with 0% placebo) but was not reported in adult migraine trials. More severe reactions, such as erythema multiforme or Stevens-Johnson syndrome, are rare, but they are more common in patients taking multiple anti-convulsants [30].

CNS AEs

Cognitive Impairment and Fatigue

Topiramate may cause multiple cognitive AEs, which may limit therapy. In a study of topiramate for the treatment of epilepsy, treated patients had deficits of fluency, attention/concentration, processing speed, language skills, and working memory [31]. Persons with a history of psychiatric disorder are more likely to experience cognitive difficulties [32]. Verbal fluency is also impaired in persons with migraine and aura may be a risk factor for greater effects [33]. In clinical trials for migraine, memory difficulties (7% 50 mg, 7% 100 mg and 11% 200 mg compared with 2% placebo), attention difficulties (3% 50 mg, 6% 100 mg and 10% 200 mg compared with 2% placebo), language problems (7% 50 mg, 6% 100 mg and 7% 200 mg compared with 2% placebo) and psychomotor slowing (3% 50 mg, 2% 100 mg and 4% 200 mg compared with 1% placebo) were all greater in those using topiramate. Topiramate also is noted to increase incidence of fatigue (14% 50 mg, 15% 100 mg and 19% 200 mg compared with 11% placebo) and somnolence (8% 50 mg, 7% 100 mg and 10% 200 mg compared with 5% placebo). [18,19]

Pallinopsia

Topiramate may cause visual disturbances such as pallinopsia, meaning an afterimage that persists after the visual stimulus has left. [34-36]. The effects were describing after drug approval in a series of case reports. Patients may describe visual "trails" or afterimages to describe this. The cause of pallinopsia in this case is likely related to cortical dysfunction rather than retinal pathology [37]. Topiramate may also cause other visual perceptual abnormalities, such as "Alice-in-Wonderland" syndrome [34]. Visual disturbances related to topiramate appear dose-related [34]and may occur with similar medications, such as zonisamide [36]. Reducing the dose is usually necessary for symptoms to resolve.

Topiramate in Pregnancy and Lactation

The FDA recently categorized topiramate as pregnancy category D (positive evidence of human fetal risk) based on studies that demonstrate a two-fold increased risk of cleft lip, and less commonly cleft palate, in mothers using topiramate during pregnancy [38,39]. Breast feeding infants have plasma levels that are about 10% to 20% of maternal levels. No particular AEs have been noted in the infants of breastfeeding mothers using topiramate [40], but experience has been limited.

Drug Interactions

Many anticonvulsants have significant interactions with topiramate. Phenytoin, carbamazepine, valproic acid, and lamotrigine may all increase topiramate clearance and decrease levels [41]. Concomitant valproic acid use may increase the risk of hyperammonemia and encephalopathy, especially in those with mitochondrial disease [42]. Hydrochlorothiazide may increase drug levels. Topiramate should be used with caution in those taking other carbonic anhydrase inhibitors, such as zonisamide or acetazolamide, as well as metformin, which is contraindicated in those with metabolic acidosis. Topiramate may increase levels of amitriptyline and decrease

levels of lithium, digoxin, and valproic acid. Higher doses of topiramate (over 200 mg/day) may decrease plasma concentrations of estrogens and progestins in patients taking oral contraceptives, leading to lower efficacy rates. Topiramate can interact with CNS depressants, such as alcohol, especially in terms of cognition.

Comparison of safety with other drugs

Topiramate is one of four oral medications approved for treatment of migraine. The other medications are propranolol, timolol and divalproex sodium. Propranolol and timolol are both non-selective beta-blockers used for hypertension in addition to migraine, with fairly similar AE profiles. Divalproex sodium is approved for multiple forms of epilepsy and acute mania in bipolar disorder. Methysergide is also approved for migraine but is not currently available in the United States. A supraorbital transcranial stimulator (Cefaly) was recently approved for treatment of migraine [43] as well. In addition Onabotulinumtoxin A, given in a series of injections, is approved for the treatment of chronic migraine. Table 1 provides a comparison of significant AEs for these medications [44].

Table 1: FDA-approved medications for migraine and AEs

Drug(s)	Common AEs	Serious AEs
Propranolol, Timolol	Bradycardia, hypotension, weight gain, dizziness, sexual dysfunction, vertigo, fatigue, exacerbation of peripheral vascular symptoms	Bronchospasm, depression of cardiac contractility, blunting of hypoglycemia symptoms.
Divalproex sodium	Sedation, tremor, dizziness, weight gain, diplopia, thrombocytopenia.	Hepatotoxicity, pancreatitis, polycystic ovarian syndrome, neural tube defects
Onabotulinumtoxin A	Injection site pain, neck	Dysphagia, diplopia

	weakness, ptosis, cosmetic effects	
Topiramate	Weight loss, nausea, paresthesias, renal calculi	Metabolic acidosis, hypokalemia, cognitive effects

Conclusions

Topiramate is well-established as an effective treatment for migraine, and may be a first-line migraine prophylactic agent due to its lack of weight gain, effectiveness at lower doses than those used in epilepsy, and potential cost savings. When prescribing topiramate, clinicians need to be familiar with its AEs and titrate the drug appropriately. Topiramate may take weeks or months to become effective, and the recommended titration is 25 mg per week to an initial starting dose of 100 mg [2]. This is in contrast to its use in epilepsy which suggests a 50 mg/week titration up to a minimum of 200 mg/day [45]. In patients experiencing AEs, a slower titration may be useful to reduce discontinuation. For less serious AEs, such as nausea or paresthesias, reassurance is important, as these tend to resolve with time and the need to lower the dose may be temporary. The frequency and importance of monitoring serum bicarbonate and potassium is unclear, especially in those on a stable dose with no clear AEs. In general, clinicians should be aware of symptoms that suggest symptomatic metabolic acidosis and screen for it in those with symptoms or in those with systemic illness in general. For more problematic AEs, such as cognitive impairment, lowering the dose of topiramate or discontinuing it altogether should be considered. With skillful titration, patients may not perceive mental slowing or mood AEs, so clinicians should screen for these symptoms in patients taking higher doses. Patients

using topiramate for extended periods of time may develop drug tolerance leading to fewer AEs, or tachyphylaxis, which may require a higher dose or render the drug ineffective.

Expert Opinion:

Topiramate is a mainstay of migraine treatment due to its efficacy and safety. Many migraine medications contribute to weight gain such as beta-blockers and antidepressants, and migraine itself may predispose to weight gain and metabolic syndrome. [46] The potential of topiramate to reduce weight may be desirable. The other potential benefits of topiramate include less need for acute treatment especially those who overuse medications, more effective treatment with acute medications, lower attack severity and overall cost savings. Although migraine prevention remains underutilized {Lipton, Silberstein}, topiramate is among the most attractive and popular treatments. Topiramate is not specifically indicated for chronic migraine, unlike Onabotulinumtoxin A, but appears effective based on clinical trials. Advantages of topiramate compared to Onabotulinumtoxin A include cost and no need to perform injections on a regular basis; the disadvantage is increased AEs. Given the disparity in cost, many insurance providers will require a trial of other medication treatments such as topiramate before authorizing Onabotulinumtoxin A injections for migraine, even if the patient has chronic migraine. Topiramate's efficacy is well-established for migraine, but long-term data and outcomes are less clear. An observational study performed at our center [6] suggested that in a real-world setting topiramate dosing varies widely between patients. Patients with chronic migraine and intracranial hypertension were more likely to take topiramate at doses beyond 100 mg, and those with co-existing medical problems such as bipolar disorder, obesity, epilepsy received it more often. Only a minority of patients used topiramate for more than 1 year. Some patients discontinued due to lack of benefit or AEs, others due to migraine remission or plans for pregnancy. Ultimately

topiramate clinicians will continue to utilize topiramate for patients with frequent or disabling migraine until more effective treatments are found with fewer AEs.

Drug Summary Box:

Drug	Topiramate
Phase	IV
Indication	Migraine Prophylaxis
Pharmacology	Increases activity at GABA-A receptors; inhibits carbonic anhydrase; blocks voltage-dependent sodium and calcium channels; antagonist of the of AMPA/kainate subtype of the glutamate receptor 5-HT _{2C} receptors
Route of Administration	Oral
Chemical structure	2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate
Pivotal trials	Brandes et al. JAMA 2004; Silberstein et al., Arch Neurol 2004; Hershey et al. Headache 2013.

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