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Topiramate for the Management of Seizures in Children **Marcia L. Buck, Pharm.D., FCCP**

Topiramate was approved by the Food and Drug Administration (FDA) on December 24, 1996.¹ While studies of topiramate use in children appeared in the medical literature as early as 1995,² the drug has only recently been approved for children as young as 2 years of age. There are now a number of studies of this drug in the pediatric population, highlighting both its efficacy and the growing concern over its adverse effect profile.

Mechanism of Action

Topiramate is structurally unrelated to the other anticonvulsants. It is a sulfamate-substituted monosaccharide, 2,3:4,5-bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate. Although the precise mechanism of action is not fully understood, it is thought that topiramate reduces epileptiform activity by 1) blocking sodium channels, 2) potentiating the inhibitory effects of gamma-aminobutyrate (GABA), and 3) antagonizing the ability of kainate to activate the kainate/AMPA (non-NMDA) subtype of glutamate receptors. It has also recently been suggested that topiramate may also inhibit block calcium channels at higher concentrations.^{1,3}

Use in Children

Topiramate currently has FDA-approved indications as adjunctive therapy for partial onset and primary generalized tonic-clonic seizures. Several trials have recently been published to establish the efficacy of topiramate in children with these seizure types.⁴⁻⁷ In 1999, Elterman and colleagues, publishing for the Topiramate YP Study Group, reported the results of a double-blind, randomized trial of topiramate as adjunctive therapy in children with partial onset seizures.⁴ Eighty-six children between the ages of 2 to 16 years were enrolled for a 16 week trial.

Patients were randomized to receive either topiramate at a dose up to 6 mg/kg/day or placebo. At the end of the study period, the topiramate patients had a significantly greater reduction in seizure frequency compared to baseline than the placebo group (33.1% versus 10.5%). Parental evaluation of improvement in seizure severity was also significantly better in the topiramate group. Adverse effects such as emotional lability, fatigue, and difficulty concentrating were more common in the patients receiving topiramate, but no patients withdrew because of adverse effects.

This same research group later evaluated 83 of the original 86 children in a long-term open-label topiramate study.⁵ The average dose used during this period was 9 mg/kg/day. Treatment lasted up to 2.5 years for some patients, with a mean of 15 months on the study. In the last three month evaluation period, 57% of the children had experienced at least a 50% reduction in seizure frequency. Fourteen percent of the children became seizure-free. Six percent withdrew because of adverse effect; 13% discontinued therapy because of lack of efficacy.

A second group of researchers, the Topiramate YTC Study Group, evaluated topiramate in children and adults with primary generalized tonic-clonic seizures.^{6,7} In their initial randomized, placebo-controlled trial, the authors enrolled 80 patients between 3 and 59 years of age.⁶ As in the Elterman study, patients received topiramate, titrated to 6 mg/kg/day, or placebo. The study was conducted over a 20 week period. The median reduction in seizure frequency compared to baseline was 56.7% in the topiramate group versus 9.0% in the placebo group (p=0.019). The proportion of patients

experiencing a 50% or greater reduction in seizure frequency was also significantly higher in the treatment arm (46% versus 17%, $p=0.003$). One patient withdrew from each group.

These authors continued to follow a total of 131 patients who had been enrolled in previous topiramate studies over a period of 2.5 years.⁷ The average dose used during the open-label study follow-up was 7 mg/kg/day (range 1-16 mg/kg/day). At the time of the last study visit, the number of patients experiencing at least a 50% reduction in seizure frequency was 63%. Sixteen percent were seizure-free. Eight percent discontinued treatment because of adverse effects; 5% because of continued seizures.

In addition to these trials, topiramate has been used in the management of infantile spasms, including those associated with West syndrome.^{8,9} It has also been effective in reducing seizure frequency in patients with refractory or mixed seizure disorders, such as Lennox-Gastaut syndrome and Angelman's syndrome.¹⁰⁻¹²

Pharmacokinetics

Topiramate is rapidly absorbed from the gastrointestinal tract, with peak concentrations occurring approximately 2 hours following a dose. Bioavailability is not affected by administration with food. Topiramate is minimally bound to serum proteins and is excreted primarily as unchanged drug; approximately 20 to 30% of a dose is metabolized. Six metabolites have been identified, but none have significant pharmacologic effects. The average elimination half-life in adults is between 18 and 25 hours.^{1,13}

The pharmacokinetic profile of topiramate has also been evaluated in infants and children. In 1999, Rosenfeld and coworkers published their evaluation of topiramate pharmacokinetics in 18 children.¹⁴ Dosing was initiated at 1 mg/kg/day and titrated to a maximum of 9 mg/kg/day. As in adults, topiramate plasma concentrations were linear and proportional with the dose. As anticipated, topiramate clearance was more rapid in children receiving enzyme-inducing drugs (such as phenytoin and carbamazepine) than in those not receiving those therapies. Mean elimination half-life was 7.6 ± 2.6 hours in the enzyme-inducing drug group and 15.3 ± 2.9 in the patients not induced. Mean clearance in both groups was significantly greater than previously reported in adults. The greatest degree of difference was observed in the 4-7 year old group, with values in the 12-17 year olds

approaching those of adults. Based on their data, the authors predicted that at steady-state with the same mg/kg dose, children will have a serum concentration 33% lower than adults.

Also that year, Glauser and colleagues studied topiramate disposition in five patients with refractory infantile spasms.¹⁵ The patients were between 23.5 and 29.5 months of age. Doses ranged between 11 and 38.5 mg/kg/day. The mean plasma clearance (66.6 ± 27.4 ml/hr/kg) was significantly faster than that reported for older children and adults, resulting in a shorter half-life (median 6.7 hrs) and suggesting a need for higher doses. As in the Rosenfeld study, the concomitant administration of enzyme-inducing drugs increased clearance.

Drug Interactions

As mentioned previously, drugs which induce the cytochrome P450 enzyme system are likely to increase the clearance of topiramate. Phenytoin and carbamazepine reduce the half-life of topiramate to 12-15 hours in adults, producing a 40 to 50% reduction in topiramate serum concentrations. Valproic acid has a more modest effect, reducing topiramate concentrations by 10 to 15%. Phenobarbital does not appear to significantly alter topiramate clearance.^{1,13}

Topiramate has been shown to adversely affect other therapies. Patients taking phenytoin may experience up to an 25% decrease in serum concentrations when topiramate is initiated. Valproic acid concentrations may decrease by 10% with concomitant topiramate use. Serum concentrations of oral contraceptives, estrogen products, and digoxin also may decrease when given with topiramate. Topiramate also has weak carbonic anhydrase activity and should not be used concomitantly with acetazolamide.^{1,13}

Adverse Effects

The most frequently reported adverse effects in trials involving children include somnolence (26%), anorexia (24%), nervousness (14%), personality changes (11%), fatigue (16%), difficulty with concentration (10%), aggressive reactions (9%), gait abnormalities (8%), insomnia (8%), ataxia (6%), and dizziness, speech disorders, difficulty with memory, confusion, hyperkinesia, nausea, constipation, and increased salivation (all 4-5%). The presence and severity of many of these adverse effects appear to be dose-related and may lessen with dose reduction.

The profound effects of topiramate on cognitive function in children have received increased

attention during the past several years. In a retrospective evaluation of 87 children receiving topiramate, 41% were taken off therapy because of adverse effects, primarily cognitive dulling.¹⁶ Several investigators have attempted to identify factors which might predict or modify behavioral changes.^{17,18} In their retrospective review of 75 children, Gerber and colleagues found no correlation between dose and behavioral and cognitive abnormalities.¹⁷ The authors found only two variables that were associated with behavioral problems during topiramate therapy: a previous history of behavior problems and the concurrent use of lamotrigine, possibly signaling more difficult cases.

The relationship between topiramate dose and behavior remains controversial. A paper by Aldenkamp and colleagues suggests that dose escalation may play a role in the cognitive impairments seen in some children.¹⁸ The authors conducted a multicenter, randomized trial comparing topiramate to valproic acid as add-on therapy to carbamazepine in children with partial-onset seizures. Differences in test scores between the groups were small, except for one test measuring short-term verbal memory which demonstrated worsening of function with the initiation of topiramate. The authors suggest that, although the effect may not be dramatic, gradual dose escalation of topiramate is warranted. More research in this area is needed, particularly with long-term topiramate use.

As discussed previously, topiramate acts as a weak carbonic anhydrase inhibitor, reducing urinary citrate excretion and increasing urinary pH. Kidney stones are estimated to occur in 1-2% of adults taking topiramate, based on clinical trials, and have been reported in children.¹ Parents should be made aware of the need to maintain adequate hydration in children receiving topiramate. A case of central hyperventilation syndrome in a 15 year old girl has also been reported, presumably related to inhibition of carbonic anhydrase.¹⁹

Dosing Recommendations

The recommended starting dose for topiramate in children 2-16 years of age is 1 to 3 mg/kg/day given once daily, preferably before bedtime, for the first week. The dose may then be increased at 1 to 2 week intervals by increments of 1 to 3 mg/kg/day to achieve the optimal clinical response. The usual maintenance dose in children is 5 to 9 mg/kg/day in two divided doses.¹ Slow dose titration is recommended to reduce the incidence of somnolence and other behavioral adverse effects.

The starting dose for topiramate in adults is 25 to 50 mg/day followed by a titration of 25 to 50 mg every week. The usual maintenance dose in adults is 400 mg/day in two divided doses. Doses above this amount have not been shown to significantly improve response. It is recommended that the dose of topiramate be reduced by 50% in adults with renal dysfunction. Topiramate is cleared by hemodialysis. There are currently no specific dosing recommendations for topiramate use in children with renal impairment.¹

Availability

Topiramate (Topamax®; Ortho-McNeil) is available in 25, 100, and 200 mg tablets, as well as 15 and 25 mg sprinkle capsules. The sprinkle capsule may be swallowed whole or opened and the sprinkles mixed with a small amount of a soft food. Once mixed with food, the mixture should be swallowed immediately, without chewing. Instruct parents not to mix the sprinkles with food and store for later use.¹

Summary

Topiramate appears to be a useful adjunctive therapy in children and adults with partial onset and primary generalized tonic-clonic seizures, as well as in some refractory seizure disorders. Clinical trials have shown it to be very effective in reducing seizure frequency, but slow dose titration appears to be necessary to minimize adverse effects. Recent publication of dose-ranging studies and pharmacokinetic analyses, as well as the introduction of a sprinkle dosage form, have made topiramate a promising addition to the agents available for the management of seizures in children.

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Pharmacology Literature Review

Compliance in HIV-infected children

In this report, the authors present their results with the placement of gastrostomy tubes in six HIV-infected children with severe medication noncompliance issues to facilitate medication delivery. Estimated compliance improved from a range of 15-57% before placement to 90-100%. The authors caution that this extreme measure should only be considered after all other attempts at improving compliance have been exhausted. Temple ME, Koranyi KI, Nahata MC. Gastrostomy tube placement in nonadherent HIV-infected children. ***Ann Pharmacother* 2001;35:414-8.**

Gabapentin pharmacokinetics

Single-dose pharmacokinetic parameters were evaluated in this study of 48 children from 1 to 12 years of age. Significant age-related differences were observed. The authors concluded that younger children may require doses as much as 30% higher than those used in older children and adults. Haig GM, Bockbrader HN, Wesche DL, et al. Single-dose gabapentin

pharmacokinetics and safety in healthy infants and children. ***J Clin Pharmacol* 2001;41:507-14.**

Midazolam-induced myoclonus

Three infants with midazolam-induced myoclonus are presented. In two of the cases, midazolam was given prior to a procedure. In the third case, an infusion of 60 mcg/kg/hr was being given during mechanical ventilation. The first patient's myoclonus resolved spontaneously after 90 seconds. The second infant was given a single 20 mg/kg dose of phenobarbital; and, the third was given flumazenil at a dose of 7.8 mcg/kg. None of the patients were rechallenged with midazolam and none had further episodes. Zaw W, Knoppert DC, da Silva O. Flumazenil's reversal of myoclonic-like movements associated with midazolam in term newborns. ***Pharmacotherapy* 2001;21:642-6.**

Medibottle evaluation

The Rx medibottle, a new system which incorporates an oral syringe into a baby bottle, was designed to improve medication delivery to infants. The authors of this open-label crossover study compared the medibottle to a standard oral syringe in 30 infants receiving acetaminophen. The percentage of patients receiving the whole dose without spitting or spilling was 93.3% in the medibottle group compared to 56.7% in the syringe group; however, time to administer a dose was significantly longer (70.7±66.3 versus 22.4±7.6 sec). Despite the longer time, the raters administering the doses preferred the medibottle. Kraus DM, Stohlmeyer LA, Hannon PR, et al. Effectiveness and infant acceptance of the Rx Medibottle versus the oral syringe. ***Pharmacotherapy* 2001;21:416-23.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/25/01:

1. Dexmedetomidine (Precedex®) was added to the Formulary for the sedation of non-intubated neurosurgical intensive care patients during procedures.
2. Compounded bismuth subgallate/epinephrine paste (BSE paste) was added to the Formulary for use as a hemostatic during adenotonsillectomies.

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