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Effectiveness, Tolerability, and Safety of Topiramate in Children with Partial-Onset Seizures

Frank Ritter, *Tracy A. Glauser, †Roy D. Elterman, ‡Elaine Wyllie, and the Topiramate YP Study Group*

*Minnesota Epilepsy Group, P.A. St. Paul, Minnesota; *Children's Hospital Medical Center, Cincinnati, Ohio; †Dallas Pediatric Neurology Associates, Dallas, Texas; and ‡Pediatric Epilepsy Program, Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.*

Summary: *Purpose:* Children with partial-onset seizures, with or without secondary generalization, participating in a double-blind, placebo-controlled trial of topiramate (TPM) as adjunctive therapy were eligible to participate in an open-label, long-term extension study.

Methods: A total of 83 children (mean age, 9 years) continued long-term open-label TPM therapy in which the dosages of TPM and concomitant antiepileptic drugs (AEDs) were adjusted according to clinical response (mean TPM dosage, 9 mg/kg/day).

Results: Seizure frequency over the last 3 months of therapy was reduced ≥50% in 57% of children; 14% of children were seizure-free ≥6 months at the last visit. During treatment periods up to 2½ years (mean, 15 months), 6% of children discontinued because of treatment-emergent adverse events; 13% discontinued because of inadequate seizure control.

Conclusions: From these findings, TPM is well tolerated and provides long-term seizure control in children with partial-onset seizures. **Key Words:** Topiramate—Antiepileptic—Children.

Recurrent seizures during childhood have been associated with impaired psychosocial development (1), lower IQ scores (2), behavioral problems and difficulty adjusting to school (3), creating the potential for a lifetime of disability. As in adults, seizures in children also represent recurrent episodes of increased risk of injury (4,5) and even death (6).

In long-term studies of children with partial-onset seizures receiving traditional antiepileptic drug (AED) monotherapy, half or fewer were seizure free for ≥2 years (3,7–9). AEDs effective against partial-onset seizures in adults are generally effective in children. However, drug clearance and therefore dosing is much more variable in children than in adults. With certain AEDs, children may be at higher risk of serious, even life-threatening, adverse reactions such as hepatic failure and skin rashes. Thus clinical studies are needed in children with partial-onset seizures to evaluate the tolerability and safety profile specific to children as well as the appropriate dosage.

As a monosaccharide, topiramate (TPM) is a structurally novel AED with robust effect in partial-onset seizures in adults. In randomized controlled trials, seizures were reduced ≥50% in 43% with TPM treatment and in 12% with placebo ($p \leq 0.001$) (10). Because such studies are of short duration and not designed to optimize therapeutic response, seizure freedom is not an expected outcome. Nonetheless, in placebo-controlled trials, 4% of adults with partial-onset seizures were seizure free for the duration of double-blind (11–19 weeks) TPM treatment; no placebo-treated patients were seizure free ($p \leq 0.001$) (10). A long-term, open-label study in a medically refractory population similar to that in the randomized controlled studies (median baseline seizure frequency, 12 seizures/month) found that 9% of TPM-treated patients had been seizure free ≥6 months at the last visit (11).

The efficacy, tolerability, and safety of TPM added to maximally tolerated dosages of AEDs was evaluated in a double-blind, placebo-controlled trial of 86 children with partial-onset seizures (12). TPM (mean dosage, 6 mg/kg/day) significantly reduced seizure frequency and severity and was very well-tolerated in these children. Children completing double-blind treatment were eligible for a long-term, open-label extension study in which the dosages of TPM and concomitant AEDs could be adjusted according to clinical response. The findings from this open-label extension study are reported here.

*The participating investigators in the Topiramate YP Study Group are listed in the Appendix.

Address correspondence and reprint requests to Dr. J. Ritter at Pediatric Services, The Minnesota Epilepsy Group, P.A., 310 North Smith Avenue, Suite 300, St. Paul, MN 55102, U.S.A.

METHODS

Subjects

Children (1–16 years) could enter long-term, open-label TPM therapy after completing a double-blind, placebo-controlled trial of TPM as adjunctive therapy for partial-onset seizures with or without secondary generalization. Key entry criteria for the children in the controlled trial included minimum age of 1 year, minimum weight of 16 kg, maintenance on one or two traditional AEDs, prior EEG demonstrating an epileptiform pattern consistent with partial epilepsy, and computed tomography (CT) or magnetic resonance imaging (MRI) excluding progressive neurologic disease. During an 8-week baseline period, patients must have had at least six partial-onset seizures classified according to the International Classification of Epileptic Seizures (13). Postmenarcheal girls had to be practicing adequate methods of contraception.

Reasons for exclusion from the study included treatable cause of seizures; status epilepticus within the previous 3 months during appropriate treatment; clinically diagnosed Lennox–Gastaut syndrome; drug or alcohol abuse; significant confounding acute or chronic disease; nephrolithiasis; history of serious psychiatric disorder; recent treatment with an experimental drug or use of an experimental device; recent use of felbamate, acetazolamide, zonisamide, or triamterene; prolonged use of antacids, calcium supplements, or vitamin C; and noncompliance with prior therapy. Patients who were unable to take medication and/or maintain seizure calendars independently or with assistance from their parent or guardian also were excluded.

Study design

Children participating in the double-blind study could elect to continue with TPM open-label therapy. Patients who elected to continue with open-label TPM therapy first entered a 6-week blinded transition period. Patients who had received placebo during the controlled trial were titrated to the target dosage (6 mg/kg/day TPM), whereas those who had received TPM during double-blind treatment were maintained at the dosage achieved during double-blind treatment. The transition period was followed by a long-term, open-label phase in which the dosages of TPM and concomitant AEDs were adjusted to optimize clinical response. During the first 6 months of open-label therapy, patients were seen monthly, and then every 3 months thereafter.

Data collection and analysis

Patients' medical histories and findings from neurologic and physical examinations were recorded at the baseline visit to the double-blind phase of the study. Clinical laboratory findings (hematology, chemistry, and urinalysis), vital signs, weight, and electrocardiogram (ECG) also were collected at baseline. The number and type of seizures and any adverse events were recorded, usually by the parent or guardian, in seizure diaries.

Monthly seizure counts were recorded at each visit based on a review of seizure diaries. Seizure reductions were calculated from seizure counts during the last 3 and the last 6 months of open-label TPM therapy compared with baseline. Reasons for discontinuation of TPM therapy were also recorded.

RESULTS

A total of 83 children (2–16 years) with partial-onset seizures continued long-term, open-label TPM therapy after completing the double-blind phase. Patient characteristics are summarized in Table 1. Median baseline seizure frequency was 22 partial-onset seizures/month. Approximately half of patients were receiving two or more AEDs when TPM was added. At the cutoff for data analysis, the mean duration of TPM treatment was 441 days (range, 96–923 days); the mean TPM dosage was 9 mg/kg/day (range, 4–22 mg/kg/day).

Reductions in partial-onset seizures were calculated for (a) patients completing 3 months of TPM therapy (n = 83); and (b) patients completing 6 months of TPM therapy (n = 73). The response during long-term TPM therapy is summarized in Table 2.

Median percentage seizure reduction was 65% from study baseline during the last 3 months of open-label therapy when TPM could be titrated to optimal response. Seizure frequency was reduced ≥50% and ≥75% in 57% and 42% of children, respectively; 14% of children were seizure free for ≥3 months at the last visit. For children completing ≥6 months of TPM therapy, seizures were reduced ≥50% and ≥75% in 64 and 40% of children, respectively. Even though children had 22 seizures per month (median) before TPM treatment, 14% of children were seizure free for ≥6 months at the last visit.

Adverse events during long-term, open-label TPM therapy were similar to those observed during the double-blind phase. No clinically significant changes in clinical laboratory tests, vital signs, or neurologic and physical examinations were noted. The treatment-emergent adverse events (TEAEs) reported most frequently (≥10% incidence) over the last 6 months of open-label TPM therapy were primarily common child-

TABLE 1. *Topiramate open-label therapy: patient characteristics*

Number	83
Age, mean (range)	9 (2–16) yr
Gender, male	54%
Weight, mean (range)	35 (15–90) kg
Median baseline seizure rate	22/mo
Treatment duration mean (range)	441 (96–923) days
Topiramate dosage mean (range)	9 (4–22) mg/kg/day

TABLE 2. *Seizure reduction during open-label topiramate therapy*

	≥3 mo (n = 83)	≥6 mo (n = 73)
Median percentage reduction	65	71
Seizure reduction (% patients)		
≥50	57	64
≥75	42	40
100	14	14

Seizure-reduction calculations are derived from partial-onset seizure counts during the last 3 or last 6 months of TPM therapy versus baseline.

TABLE 3. *Incidence of most common adverse events during open-label topiramate therapy*[a]

	% (n)
Upper respiratory infection	30 (25)
Otitis media	11 (9)
Anorexia	10 (8)
Sinusitis	10 (8)
Diarrhea	10 (8)
Fever	10 (8)

[a] ≥10% incidence over the last 6 months of TPM therapy (duration of TPM therapy, ≤2.5 years).

hood illnesses [i.e., upper respiratory infections, otitis media, sinusitis, diarrhea, and fever (Table 3)]. Anorexia was reported in 10% of children during long-term therapy. The incidence of central nervous system (CNS)-related adverse events in children tended to decline over time.

Long-term TPM treatment also was well tolerated, with therapy being successfully maintained for periods ≤2.5 years in most children (75%) (Table 4). Discontinuations from TPM were due to inadequate seizure control in (13%) children, and to TEAEs in five (6%) children.

DISCUSSION

Epilepsy in children has been associated with cognitive, social, behavioral, and educational impairments, particularly when seizures are frequent and refractory to treatment (2,14). Furthermore, among adult patients with complex partial seizures, half had initially developed seizures in childhood (3).

As in adults, long-term control of partial-onset seizures in children can be difficult to achieve with traditional AED monotherapy. Only 25–50% of children with partial epilepsy remained seizure-free for ≥2 years after initiating therapy (3,7–9).

A number of newer AEDs have been proven effective in adults and would presumably be effective in children. Meta-analyses of randomized controlled trials of newer AEDs have confirmed the effectiveness of TPM (15,16). In calculations of the number of patients that need to be treated to expect one to have a therapeutic response (≥50% seizure reduction), TPM appeared to be particularly "efficient" (i.e., three patients would need to be treated to expect a patient with a clinically significant response) (16).

Although effectiveness of AED therapy against partial-onset seizures in children is expected to be equivalent to that in adults, provided equipotent dosages are used, children can be more susceptible to toxic effects of AEDs. For example, the risk of serious hepatotoxicity is greater in children treated with valproate (VPA) as is the risk of serious skin rash in children treated with lamotrigine (LTG) (17,18). Because the results of clinical studies in adults cannot be indiscriminately extrapolated to children, clinical studies of new therapies must be conducted in children to define effective dosages and to evaluate age-related tolerability and safety.

In the double-blind, placebo-controlled trial of TPM that preceded the open-label extension study reported here, seizures were reduced ≥50% in 39% of children receiving TPM (n = 41) and 20% of those receiving placebo (n = 45) (p = 0.080); 5% of TPM-treated, but no placebo-treated children, were seizure free during double-blind treatment (12). The mean target TPM dosage in the controlled trial was 6 mg/kg/day. Because TPM plasma clearance is ~50% higher in children than in adults (19), this dosage corresponds to an adult dosage of ~270 mg/day. However, in adults, a statistically significant reduction in partial-onset seizures was achieved with TPM, 400 mg/day (20,21). Thus the magnitude of therapeutic effect with TPM in children may have been underestimated in the double-blind, placebo-controlled phase. During open-label treatment when the dosages of TPM and concomitant AEDs were adjusted to maximize response, seizure control increased as TPM dosage was increased from 4.8 mg/kg/day (mean) during double-blind therapy to 9.9 mg/kg/day at the last open-label visit in those treated with TPM in both phases.

The open-label results reported here show that children can achieve long-term seizure control when TPM is adjusted according to clinical response. Some children may benefit from dosages ≤30 mg/kg/day. Among all patients treated with open-label TPM, 14% were seizure-

TABLE 4. *Patient disposition during open-label topiramate therapy*

	% (n)
Continuing TPM[a]	75 (62)
Discontinuations	
Inadequate seizure control	13 (11)
Adverse events	6 (5)
Patient choice	2 (2)
Lost to follow-up	1 (1)
Other	2 (2)
Total	25 (21)

[a] Up to 2.5 years at last study visit.

free for ≥6 months of TPM therapy, even though the median baseline frequency was 22 partial-onset seizures/month while receiving one or more AEDs.

TPM has a favorable safety record and is well tolerated in adults (22). This study confirms that long-term TPM therapy is also very well-tolerated in children. Aside from childhood illnesses, the most common TEAE was loss in appetite. Although adverse effects such as fatigue, somnolence, difficulties with concentration, attention, and memory, and emotional lability occurred in >10% of children during double-blind treatment (12), the incidence was 0–9% during TPM long-term therapy, even though children were treated for ≤2.5 years. No children discontinued double-blind therapy, and only five (6%) children discontinued long-term therapy because of TPM-associated TEAEs.

Because patients are highly individual in their responses to AED therapy, the availability of an expanded array of AEDs with different structures and clinical profiles improves the prospects for effective, well-tolerated treatment in children with epilepsy. As the clinical experience reported here demonstrates, TPM is well tolerated and provides long-term seizure control in children with partial-onset seizures. This may warrant its consideration early in the sequence of AEDs when initial therapy does not render children seizure free.

Appendix. Members of the Topiramate YP Study Group: D. Bettis, MD (Boise, ID); B. Bourgeois, MD, Harvard Medical School (Boston, MA); R. Clancy, MD, Children's Hospital of Philadelphia (Philadelphia, PA); S. Collins, MD, PhD, University Hospital of Cleveland (Cleveland, OH); M. Duchowny, MD, Miami Children's Hospital (Miami, FL); K. Edwards, MD, Neurology Consultants, P.C. (Bennington, VT); R. Elterman, MD, Dallas Pediatric Neurology Associates (Dallas, TX); T. Glauser, MD, Children's Hospital Medical Center (Cincinnati, OH); F. Ritter, MD, The Minnesota Epilepsy Group, P.A. (St. Paul, MN); W. Rosenfeld, MD, The Comprehensive Epilepsy Care Center for Children and Adults (St. Louis, MO); R. Sachdeo, MD, Robert Wood Johnson Medical School (New Brunswick, NJ); N. Sanchez, MD, Children's Hospital Medical Center (Cincinnati, OH); F. Sell-Salazar, MD, Hospital Nacional de Ninos (San Jose, Costa Rica); E. So, MD, Mayo Medical School (Rochester, MN); M. Tennison, MD, University of North Carolina at Chapel Hill (Chapel Hill, NC); W. Turk, MD, Nemours Children's Clinic (Jacksonville, FL): E. Wyllie, MD, Pediatric Epilepsy Program, Cleveland Clinic Foundation (Cleveland, OH).

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