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The Preclinical and Therapeutic Activity of the Novel Anticonvulsant Topiramate

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INTRODUCTION

Topiramate (TPM; 2,3:4,5-bis-0-[1-methylethylidene]-β-D-fructopyranose sulfamate) is a structurally novel antiepileptic compound derived from the monosaccharide D-fructose (Fig. 1) and developed by the R. W. Johnson Pharmaceutical Research Institute. It was tested in animals for potential antiepileptic activity and toxicology in the early 1980s. Pivotal clinical trials date back to 1986 in the U.S. Since then, the efficacy and safety of TPM have been evaluated in six add-on, double-blind, controlled trials and in one controlled monotherapy trial in patients with refractory partial epilepsy. The potential benefit of TPM is currently being studied in monotherapy trials, pediatric trials as adjunctive use for refractory epilepsy (including Lennox Gastaut syndrome), and trials in idiopathic generalized epilepsy. A number of reviews devoted to TPM are now available (4,7,46,58).

TPM is already on the market in most European countries (U.K., Sweden, Norway, Finland, France, Switzerland, Austria, Portugal, Spain, Poland, Ireland, Greece), the U.S., and South Africa; it is also being licensed in many other countries worldwide.

PRECLINICAL STUDIES

Anticonvulsant Activity

In animal models, inhibition of chemically induced seizures suggests that an agent elevates seizure threshold, whereas activity in the Maximal Electroshock Seizure (MES) test is attributed to the blockade of seizure spread (111). TPM was shown to have a strong anticonvulsant activity in the MES test when given orally or parenterally to rats or mice (42,92) and, in this animal model, TPM was similar in potency to

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Fig. 1. Structural formula of topiramate.

phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB) and acetazolamide (ACZ) (92). TPM was also very effective in some animal models of kindled epilepsy (55,68,106) and ischemia-induced epilepsy (33), suggesting efficacy in blocking the spread of seizures. On the contrary, TPM was either weak or inactive in preventing seizures induced by systemic administration of pentylenetetrazole, bicuculline, or picrotoxin (42,55,92).

This profile of TPM (activity in the MES and kindled models but not in tests using chemical convulsants) seemed to predict its efficacy in human partial and secondarily generalized seizures but not in absence seizures (107). Moreover, in a sensitive model of absence epilepsy, the lethargic mouse model, TPM did not significantly affect seizure frequency (52). In contrast with these findings, however, TPM effectively raised the threshold doses at which pentylenetetrazole induces seizures in mice (92,112) and suppresses both tonic- (like PHT) and absence-like (like ethosuximide [ESM]) seizures in spontaneously epileptic rats (69). TPM was also effective in a rat model of stroke-induced epilepsy (103) and in DBA/2 mice with audiogenic seizures (69). These data justify clinical efforts to determine whether TPM has a more broad spectrum of therapeutic action.

No tolerance developed to TPM after its administration to rats for 14 d at twice the median effective dose (ED_{50}) in the MES test (42,92). The TPM anticonvulsant protective index (i.e., the ratio of the median toxic dose (TD_{50}) in tests indicative of motor impairment to ED_{50} in the MES test) was compared with that for PHT, PB, CBZ, and valproic acid (VPA) in mice and rats. In mice, the anticonvulsant protective index of TPM was similar to that of CBZ and was significantly higher than those for PB or PHT. In rats, TPM index was higher than those for PHT, PB, and CBZ (92).

Mechanism of Action

Although the mechanism of action of TPM has not been fully elucidated, several pharmacological properties have been defined that may account for, or contribute to, TPM's anticonvulsant activity.

In electrophysiological studies on cultured hippocampal cells displaying spontaneous or depolarization-induced epileptiform discharges, TPM (10 to 200 μM) induced a concentration-dependent decrease of the duration and frequency of action potentials within a burst (21). Similar inhibition of repetitive firing has been observed in cortical neurons (107). TPM also reduced voltage-activated Na currents in cultured neocortical neurons (2,120). These events are presumably related to a state-dependent inhibition of voltage sensitive sodium channels.

TPM 10 μM increased GABA-induced Cl^- fluxes across the membrane in mouse cortical neurons (110) or cerebellar granule cells (15,109). This effect was caused by an increase in the frequency of GABA-mediated channel activation (but not the channel open-time duration) (110). Although the TPM-induced potentiation of GABA activity is similar to that observed with benzodiazepines (BDZ), flumazenil fails to inhibit TPM activity. It is believed, therefore, that TPM may interact with a novel, BDZ-insensitive binding site on the $GABA_A$ receptor (110).

In other studies performed in rat cultured hippocampal neurons, TPM 1 to 200 μM caused a concentration-dependent inhibition of kainate- but not NMDA-evoked inward ionic currents suggesting that TPM has antagonistic effects on the kainate/AMPA subtype of glutamate receptor (91,108).

In an additional series of preclinical investigations, TPM inhibited some isoenzymes of carbonic anhydrase (92). This pharmacological effect is much weaker than that of ACZ (a known carbonic anhydrase inhibitor) and is considered to be more relevant to TPM's side effects than to its antiseizure activity.

Receptor binding and neurotransmitter uptake studies performed to date have not revealed any direct effect of TPM on NMDA, GABA, or monoamine receptors, or on adenosine, GABA, serotonin, dopamine, norepinephrine, or glutamate transport systems.

Toxicology

Acute toxicity studies included TPM oral (1000 to 4500 mg/kg) and i.p. (500 to 2250 mg/kg) administration to mice (25,61) and rats (24,62) and oral (250 to 400 mg/kg) administration to dogs (115). Rodents tolerated TPM well; high acute doses were required to cause death. No death occurred among dogs, which were, however, more sensitive to the acute toxic effects of TPM than were rodents. The acute toxicity was primarily CNS related: ataxia, decreased motor activity, tremors, and clonic convulsions.

Long-term toxicity was evaluated by 3- and 12-month oral multiple-dose treatments of rats and dogs. Increased liver weights and liver cell hypertrophy, elevated serum gastrin levels and gastric mucosal hyperplasia, and renal pelvis and urinary bladder epithelium hyperplasia were seen at the highest doses of TPM in rats (23,67,97). Hyperplasia of the gastric epithelial and endothelial cells did not progress to neoplasia after lifetime exposure of rats and mice to TPM (119). Moreover, no changes in gastric histology or gastrin levels were noted in humans receiving therapeutic doses of TPM (8).

Some of these effects (e.g., liver changes) may be related to the weak induction of drug-metabolizing enzymes, whereas other effects (e.g., gastric, renal, and urinary changes) may be due to the carbonic anhydrase inhibitory properties of TPM.

Chronic toxicity studies also showed additional dose-dependent effects, including lower body weight and reduced body weight gain occasionally associated with decreased food efficiency, CNS clinical signs, shifts in fluid and electrolyte levels related to diuresis, and higher urine pH (23,96,97).

Carcinogenicity studies revealed the occurrence of urinary bladder tumors in mice (119). These tumors were considered to be morphologically unique to the mouse, without any known counterpart in other mammalian species (119).

Teratology studies demonstrated that TPM is teratogenic in mice, rats, and rabbits. In mice fetal weights and skeletal ossification were reduced by TPM at 500 mg/kg/d in conjunction with maternal toxicity (56). In rats, limb and digit defects were noted at 400 mg/kg/d and higher doses (117). In rabbits, rib and vertebral malformations occurred at 120 mg/kg/d (118). The teratogenic effects observed in rats and rabbits were similar to those seen with carbonic anhydrase inhibitors, which have not been associated with malformations in humans (90). Indeed, no abnormalities were evident in the infants of five women who received topiramate during pregnancy (58).

Pharmacokinetics and Metabolism in Animals

Studies evaluating the pharmacokinetic profile and metabolism of TPM were performed in mice, rats, rabbits, monkeys, and dogs. Absorption of oral doses of TPM was rapid; peak plasma concentrations were achieved between 0.5 and 4 h in all species (98,99,100,116). The absolute bioavailability of oral TPM was ~100% in rats (98) and ranged between 69% and 99% in other species studied (79,116). *In vitro* TPM was poorly bound (9% to 17%) to plasma proteins of mice, rats, rabbits, dogs, monkeys, and humans (75). TPM was rapidly distributed to tissues in all species; in rats, concentrations of radioactivity in the brain were less than or equivalent to those in the plasma at 1 to 48 h following administration of radiolabeled TPM (16). TPM was a weak inducer of several hepatic microsomal, drug-metabolizing enzymes in rats (37). The metabolic pathways for TPM are qualitatively similar in animals and man and involve hydroxylation or hydrolysis of the isopropylidene groups (113). Eight metabolites have been identified, of which six have been found in humans (114). Two metabolites, which retained much of the structure of TPM, were tested and found to have little or no anticonvulsant activity (22). The major route of elimination for unchanged topiramate and metabolites was via the kidney in all species (79,116).

CLINICAL STUDIES

Pharmacokinetics

Absorption

TPM is rapidly absorbed after oral administration, with peak plasma concentrations (C_{max}) of 1.73 to 28.7 mg/l being achieved between 1.4 and 4.3 h (T_{max}) at TPM

Fig. 2. Mean topiramate plasma concentrations after a single oral dose (100 to 1200 mg) in healthy volunteers (n = 4 to 6 in each group). From ref. 73.

doses of 100 to 1200 mg in healthy volunteers (31,32). The mean half-life of TPM across the doses tested was 21.5 h. In single-dose pharmacokinetic studies, the increase in peak plasma concentrations was linear, but not proportional, with respect to topiramate dose (31,32) (Fig. 2).

In a multiple dosage pharmacokinetic study in healthy volunteers, plasma TPM concentrations increased in a linear and dose-proportional manner following doses of 50 to 200 mg (26). Steady-state parameters for TPM after multiple oral dosing in patients receiving concomitant CBZ were also linear and proportional (87). In two separate trials, the effect of food on oral bioavailability of TPM at single 100- and 400-mg oral doses was determined. In these studies, the rate but not the extent of TPM absorption was slightly decreased with a high-fat meal (27,31). The absolute oral bioavailability of this drug was estimated to be ~80% (114) but values of up to 95% have been documented (70). The relative bioavailability for a 100-mg tablet of TPM was 82% when compared with a 100-mg solution dosage form (28).

Distribution

TPM volume of distribution ranges from 0.6 to 0.8 l/kg, a finding consistent with distribution into total body water (32). The extent of protein binding is approximately 15% (9 to 17%). However, TPM is extensively bound to erythrocytes until binding sites are saturated (53,73).

Metabolism and Excretion

In healthy male subjects given a single 100-mg oral dose of [^{14}C]TPM, unchanged TPM represented more than 85% of plasma radioactivity at 24 h, indicating that the drug is not extensively metabolized (114). After 10 d, 80.6% of the total dose was recovered in the urine and only 0.7% in the feces, suggesting that renal excretion is the major route of elimination. Six trace metabolites of TPM, resulting from three metabolic pathways (hydroxylation or hydrolysis of the isopropylidene groups and

subsequent conjugation) have been identified and characterized (114). All these metabolites account for < 5% of the total radioactivity and show no significant pharmacological activity. In healthy volunteers who received a single dose of TPM 100 to 1200 mg, oral plasma clearance (CL_P) and renal clearance (CL_R) ranged from 1.3 to 2.2 l/h and 0.65 to 0.79 l/h, respectively (32). No changes in CL_P or CL_R were evident after multiple dosing (73) (Table 1).

TPM pharmacokinetics was studied in 18 non-epileptic adult subjects with mild to severe renal insufficiency and in 14 healthy controls (44). Renal failure resulted in a significant increase in TPM concentrations and half-life, which paralleled the decrease in CL_P and CL_R. On the contrary, C_{max} and T_{max} values were not significantly affected. In non-epileptic subjects with end-stage renal disease receiving a single oral dose of TPM 100 mg, TPM plasma concentrations decreased an average of 50% during a 3-h hemodialysis, and a mean of 19 mg of TPM was removed from the body (43). A supplemental dose of TPM is recommended on the day of hemodialysis.

TPM pharmacokinetics was also studied in five adult non-epileptic subjects with mild to severe hepatic impairment and in six healthy controls. A moderate increase (~29%) in TPM plasma concentrations due to decreased TPM CL_P (~26%) was observed (29).

The pharmacokinetic characteristics of TPM in the pediatric age group were studied in 18 epileptic subjects (aged 4 to 17 years) following 4 weeks of add-on, once-daily administration, in escalating doses ranging from 1 to 9 mg/kg/d (81). As observed in adults, TPM pharmacokinetics was linear in children, with steady-state plasma concentrations increasing in proportion to the dose. The mean TPM CL_P in pediatric subjects receiving concomitant enzyme inducing or non-inducing antiepileptic drugs (AEDs) was ~50% higher than historical data from adults receiving the same types of concomitant AEDs. Steady-state TPM plasma concentrations for the same dose would therefore be expected to be ~33% lower in children than in adults.

TABLE 1. TPM: Mean pharmacokinetic parameters of TPM in healthy subjects after single and multiple dosing

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Drug Interactions

Potential interactions between TPM and the concomitantly administered AEDs CBZ, PHT, PB, and VPA were assessed in a number of open-label, pharmacokinetic studies in patients with partial epilepsy (13). In general, TPM did not affect the pharmacokinetic profile of CBZ (or CBZ 10-11 epoxide) (87), PB or primidone (30), or VPA (84). A small decrease in PHT clearance may occur in some patients due to the addition of TPM, causing an increase (of ~25%) in PHT plasma concentrations (45).

On the other hand, enzyme-inducing agents (e.g., CBZ and PHT) significantly lowered the plasma clearance of TPM by 48 and 59%, respectively (45,87). These effects resulted in a two-fold increase in TPM plasma levels after removal of PHT or CBZ. In contrast, VPA has little effect on TPM plasma clearance. On discontinuation of VPA to achieve TPM monotherapy a slight increase (~17%) in TPM peak plasma concentration was observed, probably resulting from either VPA-induced increase in the metabolic clearance of TPM or reduction in TPM absorption (84).

A potential pharmacokinetic interaction between TPM and digoxin was evaluated in a cross-over study in 12 normal subjects (59). Mean digoxin C_{max} and the area under the plasma concentration–time curve (AUC) were slightly decreased in the presence of TPM (~16 and 12%, respectively).

Similarly, the effect of TPM on the pharmacokinetics of an oral contraceptive was studied in 12 adult women with partial epilepsy receiving a combination norethindrone 1.0 mg/ethinyl estradiol 35-μg tablet daily for 21 d (83). Concomitant administration of TPM (100 to 800 mg/d) appeared to have no significant effect on norethindrone pharmacokinetics, while ethinyl estradiol serum levels were reduced by approximately 30%.

Relationship between Serum Levels and Clinical Effects

There are no available reports describing drug levels, dose-response serum levels, or relation of serum levels to adverse events. In a post-marketing study in 62 adult patients receiving doses ranging from 75 to 1000 mg/d, TPM levels > 4 μg/ml appeared to be necessary for effectiveness but no clear level-efficacy or level-adverse events relation was seen (72).

Efficacy

Partial Seizures

Add-on placebo-controlled trials in adults: Five randomized, double-blind, placebo-controlled, parallel trials have evaluated the efficacy of add-on TPM in adult patients with refractory partial-onset seizures (10,39,76,93,102). Two of these trials were conducted in the U.S. (39,76) and three in Europe (10,93,102). The studies shared similar design, entry criteria, and efficacy measures.

Each trial consisted of two phases, an 8- to 12-week prospective baseline phase during which patients continued on their concomitant antiepileptic drugs (AEDs), and a double-blind phase during which subjects were first titrated to their assigned (or maximally tolerated) dosage and then maintained on this dose for a period of 8 or 12

TABLE 2. Efficacy of add-on TPM in five double-blind, placebo-controlled, randomized trials in patients with refractory partial seizures

Ref.	Drug target (achieved) Dose mg/d	No.	Median baseline monthly seizure rate	Median % reduction from baseline	Overall treatment responders (% of patients)[b]		Withdrawals due to adverse events	
					≥ 50%	75 to 100%	No.	%
39	Placebo	45	10	13	18	9	7	15
	TPM 200 (200)	45	11.5	30	27	9	4	9
	TPM 400 (391)	45	11	48	47	22	9	20
	TPM 600 (556)	46	11.2	45	46	22	13	28
76	Placebo	47	9.3	1	9	0	2	4
	TPM 600 (544)	48	10.0	41	44	23	21	44
	TPM 800 (739)	48	16.2	41	40	13	10	21
	TPM 1000 (799)	47	11.7	38	38	13	17	36
10	Placebo	28	11.4	–18[a]	0	0	0	0
	TPM 800 (568)	28	14.2	36	43	36	6	21
102	Placebo	30	15.0	–12[a]	10	3	1	3
	TPM 600 (519)	30	16.8	46	47	23	4	13
93	Placebo	24	10	1	8	4	1	4
	TPM 400 (387)	23	18	41	35	31	6	26

[a] Negative numbers indicate an increase in seizure rate.
[b] Responders defined as those patients achieving at least a 50% reduction of seizure rate compared to baseline.

weeks. The two U.S. studies were dose-response trials; the European studies were single dosage trials. In these studies, eligible patients were 18 to 65 years of age, experienced four or more seizures per month and received one or two standard AEDs. In all trials, the primary efficacy measure was median percent reduction in overall seizure rate from the baseline to the double-blind phase. Secondary measures included percent responders (percent of patients experiencing a ≥ 50% reduction in seizures), percent reduction in secondarily generalized tonic-clonic (SGTC) seizures, and physician and patient global evaluations at the conclusion of the treatment. All analyses were on an intent-to-treat basis, i.e., every patient randomized was included in the analysis regardless of whether the patient completed the study. Table 2 summarizes the characteristics and results of each study.

Overall, the five trials included 534 patients randomized to double-blind, add-on treatment with TPM (360 patients) or placebo (174 patients). The median age of the population was 34 years, the median duration of epilepsy was 22 years, and the median baseline frequency was eleven seizures per month. Most patients (62%) were taking two AEDs; 71% of patients were being treated with CBZ alone or in combination. Almost all patients (92%) were having complex partial seizures with almost two-thirds (64%) reporting SGTC seizures.

In the U.S. studies, patients randomized to the 200, 400, 600, 800, or 1000 mg/d treatment groups actually achieved mean daily dosages of 200, 391, 550, 739, and

Fig. 3. Relationship between TPM dosage and percent of responders. The values were obtained by pooling the data across five double-blind studies (refs. 10,39,76,93,102).

799 mg/d, respectively (39,76). In the European studies, patients randomized to the 400, 600, or 800 mg/d treatment groups received mean daily dosages of 387, 519, and 568 mg, respectively (10,93,102).

TPM consistently reduced baseline seizure rates more than placebo. Mean percent seizure reduction in TPM-treated patients ranged from 30 to 48% across the various doses used (200 to 1000 mg/d). In comparison, placebo-treated patients demonstrated a range of responsiveness from an 18% median increase to a 13% median reduction in seizures. At target doses of ≥ 400 mg/d improvement over placebo in the average monthly seizure rate was statistically significant in four (8,38,73,99) of the five trials and showed a strong trend in the fifth trial ($p = 0.065$) (90). The 200-mg/d group also showed borderline statistical significance ($p = 0.051$) in seizure rate in favor of TPM (39).

The similarity in study design and efficacy parameters for all five studies allowed pooling of data to assess changes in seizure frequency within specific subsets of the patient population (6,38,78). TPM treatment produced statistically significant median percent reductions versus placebo for all seizure types: simple partial, complex partial, and SGTC seizures. Greater reductions in seizure rate were produced with TPM treatment than with placebo for both men and women and across all age groups. Patients with low (4 to < 9/month), mid (9 to 20/month), and high (≥ 20/month) baseline seizure rates all had greater reductions in seizure rates with TPM treatment than with placebo.

Across the five trials, 41% of TPM-treated patients (146 of 360) responded to treatment with at least a 50% reduction in seizure rate while 10% of placebo-treated patients showed the same level of response. Within the responders, 47% (68 of 146) had a ≥ 75% reduction in seizures and 10% (14 of 146) became seizure free during the

trial. Differences between TPM and placebo were statistically significant ($p < 0.01$) for any level of change in seizure frequency.

The relationship between TPM dosage and percent of responders is illustrated in Fig. 3. It appears that the lowest improvement (27% of responders) was obtained with the 200-mg/d dose. However, at doses ≥ 400 mg/d, there was no definite dose-response pattern, since increases in dose did not produce a parallel increase in the number of responders.

Consistent with the therapeutic effects measured by reduction in seizures, investigators' and patients' global ratings were consistently higher with TPM treatment at any of the doses used than with placebo. Importantly, no significant changes in the plasma concentrations of concomitantly administered AEDs were detected during the active treatment phase, which suggested that improvement in seizure control was due to TPM and not to changes in the concentrations of other agents.

A sixth double-blind, placebo-controlled, parallel study of add-on TPM in 209 adult patients with refractory epilepsy has recently been published in abstract form (82). In this study, patients received either CBZ (~75%) or PHT (~25%) as concomitant therapy and were titrated up to 1000 mg/d TPM (mean dose achieved: 832 mg/d). The median percent seizure reduction was 51% in the TPM group and 1% in the placebo group ($p < 0.001$). The percentage of patients with a $\geq 50\%$ reduction in seizure rate during the double-blind phase was 52% in the TPM group and 19% in the placebo group ($p < 0.001$). Unfortunately, the percentage of patients achieving a $\geq 75\%$ reduction in seizures or complete disappearance of seizures was not mentioned.

Add-on open trials in adults: Several scattered, open-label trials, mostly published in abstract form only, have described the short- and long-term efficacy of TPM as adjunctive therapy in the treatment of refractory partial seizures (1,3,5,11,18,40,49,50,60,65,66,74,77,85,101). Some of these studies are non-blinded extensions of double-blind, placebo-controlled, add-on trials in patients who had responded to TPM or had received placebo.

Overall, responders to TPM (defined as those achieving $\geq 50\%$ reduction in seizures) ranged between 27% (74) and 86% (60) after 3 to 6 months of treatment, with a median value of about 50%.

The long-term efficacy was more difficult to assess because of wide variability in lengths of treatment, TPM dosages, and efficacy parameters across the studies. In the largest series (reporting > 200 patients) (1,3,74,85) the percentage of patients still on TPM after a mean period of 2 y ranged between 32% (1) and 64% (85), with 2% to 10% of patients being seizure free.

Monotherapy trials in adults: In a double-blind, parallel study, 48 patients with refractory partial epilepsy currently treated with one or two conventional AEDs were randomized to receive TPM 100 or 1000 mg/d in a 5-week conversion and an 11-week monotherapy period (88). Time until exit from the study was significantly longer ($p = 0.002$) with TPM 1000 mg/d than with 100 mg/d. Seizure-rate reductions of $\geq 50\%$, $\geq 75\%$, or 100% were achieved by 46, 25, and 13% of the 1000 mg/d group, respectively, as compared with 13, 8, and 0% of the 100 mg/d group, respectively. Rosenfeld et al. (85) also reported that out of 136 patients with refractory partial seizures being improved by add-on TPM on a long-term basis, 45 (33%) were

successfully converted to TPM monotherapy and 62% of those converted were seizures free for at least 3 months.

Add-on trials in children: In a double-blind, parallel study in 86 children with refractory partial epilepsy, add-on TPM at a mean target dose of 6 mg/kg induced a median seizure rate reduction of 33% compared to 11% in placebo-treated patients (36). Patients achieving ≥ 50%, ≥ 75%, or 100% reductions in seizure rate were 39, 17, and 5% in the TPM group, but only 20, 2, and 0% in the placebo group, respectively. In this study, no patient discontinued therapy due to adverse events. This observation, along with the pharmacokinetic characteristics of TPM in children, may warrant evaluation of higher TPM doses in the pediatric group. Eighty-three patients from this double-blind trial entered a long-term, open-label extension study (48). In this trial, the mean TPM dosage was 9 mg/kg and the duration of treatment ranged between 96 and 923 d (mean = 440 d). Fifty-seven percent of these patients achieved ≥ 50% seizure reduction from baseline and 14% were seizure free for at least 6 months. Only five patients were discontinued due to adverse events.

Generalized Seizures

Add-on placebo controlled trials in generalized seizures: So far, 2 double-blind, placebo-controlled trials have evaluated the potential efficacy of TPM in the treatment of non-focal generalized tonic-clonic seizures (GTCS) (9,12). Both studies, published in abstract form only, shared the same design, inclusion criteria, and efficacy parameters, allowing a pooled analysis of the results. A total of 160 patients (both children and adults) with at least three GTCS during an 8-week baseline period despite medication with one or two standard AEDs, were randomized to either TPM ($n = 79$) or placebo ($n = 81$). During the 8-week titration period, the TPM-treated patients were titrated to a mean TPM target dosage of 6 mg/kg/d and then maintained on a constant TPM dose for the 12-week stabilization period. Overall, the median percent reduction in GTCS frequency was 57% with TPM and 27% with placebo ($p < 0.005$). In addition, a reduction in GTCS ≥ 50% was documented in 55% of TPM-treated and 28% of placebo-treated patients ($p < 0.005$).

In the same trials, the patients also suffered from other seizure types, including absences, tonic, myoclonic, or atonic seizures. When the generalized seizures were considered as a whole, the median percent reduction in seizure rate was 38% with TPM compared with 7% with placebo; a > 50% reduction of all seizures was observed in 43% of TPM-treated patients and in 19% of placebo-treated patients. These differences significantly favored TPM for both comparisons. The efficacy of TPM in specific seizures types other than GTCS was also studied: median percent reductions in seizure rate were 49% and 40% for tonic and myoclonic seizures, respectively, whereas absences did not change from baseline.

The long-term efficacy of TPM in GTCS has recently been described. In a preliminary study reporting the non-blinded extension phases of double-blind trials in 131 patients, TPM retained its efficacy over a mean period of 387 d (range: 14 to 909 d), with 15% and 7% of patients being free of GTCS and/or all generalized seizures, respectively, for at least 6 months at last visit (14).

Add-on trials in infantile spasms: Eleven children (aged 7 months to 3.5 y) with infantile spasms (mean: 26 spasms/d) refractory to conventional therapy received add-

on TPM at a mean dose of 15 mg/kg/d. The rate of spasms was reduced by 69% from baseline and 9 of 11 (82%) patients had ≥ 50% reduction in spasms. Seven patients were converted to TPM monotherapy and four patients were spasm free (20).

Add-on trials in Lennox Gastaut syndrome: In one double-blind, placebo-controlled, parallel study, 98 patients aged 2 to 42 years (mean: 11 years) with a diagnosis of refractory Lennox Gastaut syndrome were randomized to either TPM (n = 48) or placebo (n = 50) (47). The patients suffered from various seizure types, including drop-attacks (100%), atypical absences (71%), tonic seizures (52%), myoclonic seizures (47%), tonic-clonic seizures (38%), complex partial seizures (17%), and absences (9%). During an 8-week baseline phase, the mean monthly seizure frequency was 255 for all seizures (94 for drop-attacks only) despite concomitant therapy with one or two standard AEDs. After a 3-week period during which TPM was titrated to a target dose of 6 mg/kg/d, the patients were kept on a constant TPM dosage for 8 weeks. The median percent reduction in drop-attacks was 15% in the TPM-treated group compared with a 5% increase in the placebo-treated group, a significant difference (p = 0.04) favoring TPM. However, the difference was not statistically significant (p = 0.47) when all the seizures types were considered as a whole: the median percent seizure reduction from baseline was 21% for all seizures with TPM versus 9% with placebo.

All patients completing the double-blind phase of the trial were offered enrollment in the open-label extension of the study (80). Of the 97 patients who entered the open extension, 69 were continuing TPM for a mean duration of 539 d (range: 44 to 1225 d). The median seizure reduction from baseline for all seizures was 58% at an average TPM dose of 11 mg/kg/d. More than half of the patients (58%) had ≥ 50% reduction in drop-attacks, with 15% of patients becoming free of drop-attacks. These data seem to suggest that the improvement is maintained or even reinforced with higher TPM doses on long-term treatment in Lennox Gastaut syndrome, the drop-attacks being particularly responsive to the drug.

Promising results in Lennox Gastaut syndrome have been also observed in four open-label trials with add-on TPM (41,51,57,63). Overall, ≥ 50% seizure reduction was achieved by 54% (range: 35% to 88%) of patients who received add-on TPM for a period ranging from 3 to 32 months.

Safety

Early adverse events

The short-term safety profile of TPM was evaluated in a series of double-blind, placebo-controlled trials among patients with refractory partial epilepsy in which TPM was studied at dosages of 200 to 1000 mg/d (10,39,76,93,102). The most common treatment-emergent adverse events (TEAEs) in these studies were related to the CNS (Table 3). Clinically relevant TEAEs (defined as those adverse events for which the incidence in TPM-treated patients was ≥ 10% greater than in the placebo-treated patients) included dizziness, somnolence, abnormal thinking, fatigue, ataxia, confusion, paresthesia, impaired concentration, nervousness, amnesia, and language problems. Across all dosage groups, most TEAEs were rated as mild or moderate in severity and

transitory in duration. Several events, including dizziness, somnolence and ataxia, appeared to be drug-related but not dose-related. On the contrary, most other events, such as cognitive effects (impaired concentration and attention [17], confusion, amnesia), anorexia, or emotional reactions were reported more frequently at the assigned doses of 600 to 1000 mg/d than at the lower doses of 200 to 400 mg/d (94). Because CNS-related adverse events generally were more frequent at higher doses, the percentage of patients reaching the assigned target doses decreased proportionally with the dose; target doses of 200, 600, and 1000 mg/d were achieved by 98%, 69%, and 55% of patients, respectively, in the five double-blind studies.

When the investigators considered adverse events that were probably or definitely related to the study medication, the only events reported at a frequency of $\geq 5\%$ were ataxia, impaired concentration, confusion, dizziness, fatigue, paresthesia, somnolence, and abnormal thinking (94,95).

In the double-blind studies, 3% of patients receiving placebo and 14% of TPM-treated patients withdrew prematurely because of an adverse event. The most common reasons for discontinuation of TPM were CNS-related adverse events. Approximately three-fourths of patients dropped out within the first 2 months of therapy, frequently during the rapid titration period provided by the study protocols. Rapid titration was therefore, considered to be the main cause for early discontinuation of TPM. When rapid and slow titration of TPM dosages were compared, withdrawals of TPM due to adverse events were significantly less common when the target dose of 400 mg/d was achieved in 8 weeks (10 of 95 patients) instead of 3 weeks (20 of 93 patients) (34).

TABLE 3. Incidence of most common treatment-emergent adverse events by assigned TPM dosage in double-blind trials

	Assigned TPM dosage (mg/d)					
Event	Placebo (n = 174)%	200 (n = 45)%	400 (n = 68)%	600 (n = 124)%	800 (n = 76)%	1000 (n = 47)%
Dizziness	13	36	22	31	32	40
Somnolence	10	27	26	17	20	28
Abnormal thinking*	2	20	12	29	28	26
Fatigue	16	13	18	31	49	32
Ataxia	7	20	22	17	16	21
Confusion	5	9	15	18	14	28
Paresthesia	3	18	13	13	18	13
Impaired concentration	1	11	9	12	15	21
Agitation	5	9	10	16	18	19
Amnesia	3	13	13	10	9	19
Speech disorders	3	13	16	13	13	17
Aphasia	1	2	9	11	9	13
Anorexia	3	4	4	8	9	21

* The WHOART phrase "thinking abnormal" describes problems with cognitive processes and includes such investigator terms as "mental slowing," "can't think clearly" and "slowed calculations." It does not include psychotic symptoms.

Late Adverse Events

Chronic adverse events were evaluated in the larger TPM database, which included more than 2000 people, 100 of them having been treated with TPM for 5 to 7 years. The late adverse effects included psychosis or depression, weight loss, and nephrolithiasis (58,94). Depression occurred in 15% (usually during the first 3 months of treatment) and psychosis in 3% (generally late in the course) of patients in non-comparative trials. Acute psychotic symptoms have been also reported soon after initiation of TPM therapy (54). These rates of occurrence are comparable to those reported in epidemiologic studies of patients with epilepsy.

Weight reduction observed during TPM therapy appeared to be dose-related, with mean decreases ranging from 1.1 kg in patients receiving 200 mg/d of TPM to 5.9 kg in patients receiving > 800 mg/d. Body weight loss (occurring in up to 78% of patients) was also more common in heavier patients, women, and those patients receiving concomitant therapy with VPA (86). Weight reduction typically began within the first 3 months of treatment and peaked approximately after 9 (71) to 15 months of therapy (94); weight loss was considered to be a "positive" adverse event by many patients (86).

Nephrolithiasis occurred in 1.5% of 1200 patients receiving TPM in non-comparative trials (104); this incidence is similar to that reported during ACZ therapy. Stones occurred only in male patients and were passed spontaneously in 67% of cases. Seventy-eight percent of subjects with TPM-induced nephrolithiasis elected to continue TPM treatment after passing the stone. Stone formation is believed to be related to an increase in urinary pH and reduced excretion of citrate associated with TPM's carbonic anhydrase-inhibitory activity (105).

No clinically important changes or consistent alterations in clinical laboratory values or other safety measurements were observed in either placebo-controlled or non-comparative studies. As for any other new AED, the number of exposures to TPM is not yet large enough to exclude rare idiosyncratic reactions.

Dosage and Administration

TPM therapy should be slowly titrated in order to minimize early adverse events (89). The initial recommended dosage is 25 or 50 mg nightly for one week. Thereafter, the dosage may be increased by 25 to 50 mg/d in two divided doses at weekly intervals. In adults, the usual total daily dosage of TPM as adjunctive therapy is 200 to 600 mg/d, given in two divided doses, but individual patients in clinical trials have required up to the maximum recommended dose of 1600 mg/d. The minimum effective dosage is considered to be 200 mg/d. In children TPM dose ranges between I and 15 mg/kg/d.

In general, the addition of TPM to the conventional AEDs (PHT, CBZ, PB, VPA) does not influence the pharmacokinetics of these drugs. The only exception is PHT, whose plasma levels may increase after adding TPM, making it necessary to decrease the PHT dosage in some patients.

On the other hand, enzyme-inducing agents such as CBZ and PHT result in reduced plasma TPM concentrations. Therefore, the addition or withdrawal of these drugs from TPM adjunctive therapy may necessitate TPM dosage adjustment. Despite

this interaction potential, TPM plasma concentrations are not usually monitored in clinical practice.

Because TPM is removed from plasma by hemodialysis, a supplemental dose equal to or approximately one-half the daily dose should be administered in divided doses at the beginning and completion of hemodialysis. Moreover, due to the predominantly renal route of excretion, TPM dosage reduction may be necessary in patients with renal insufficiency.

The Role of TPM in Antiepileptic Therapy and Comparison with Other New Antiepileptic Agents

At the present time TPM may be prescribed as add-on treatment in patients with refractory partial seizures. In these cases, TPM has proven to be effective (leading to $\geq 50\%$ seizure reduction) in almost half of the patients in controlled clinical trials. Moreover, promising results obtained from controlled and open studies in non-focal GTCS and Lennox Gastaut syndrome may contribute to widening of the indications for TPM in the near future.

As yet, no studies have directly compared the efficacy and tolerability of TPM with the newer AEDs (e.g., felbamate, gabapentin, lamotrigine, tiagabine, vigabatrin, and zonisamide). Because clinical trials of the newer AEDs have involved similar study designs, patient populations and efficacy endpoints a meta-analysis of the results of randomized controlled trials was performed to indirectly compare the newer AEDs (19,64). The outcome selected for estimation of efficacy was the proportion of patients experiencing a $\geq 50\%$ reduction in seizure frequency from baseline. Tolerability was estimated on the basis of rates of withdrawal from studies for any reason. Efficacy and tolerability odds ratios and the 95% confidence interval for each measure were calculated for each AED across all studies. The odds ratios for treatment response suggested that response rates were best with TPM and worst with gabapentin. TPM ranked midway among these agents with regard to tolerability. Although there were substantial differences in the odds ratios for treatment responders, the overlap in confidence intervals obscured differences between the drugs. A subsequent analysis of the same clinical trials determining the "number-needed-to-treat" to yield one patient with 50% seizure reduction illustrated substantial differences among the newer AEDs (35). This number-needed-to-treat analysis mirrored the odds-ratios analysis in terms of rank order of efficacy (with TPM showing the highest response and gabapentin the lowest response). The TPM 95% confidence intervals overlapped only with those of vigabatrin suggesting statistically significant differences between TPM and other agents.

CONCLUSIONS

As a sulfamate-substituted monosaccharide, TPM represents a chemically unique agent. In animal seizure models, TPM shows a strong anticonvulsant activity in the MES test and in kindled epilepsy, but had little or modest effect in chemically induced seizures. This profile suggests that TPM acts primarily by blocking seizure

spread rather than by elevating the seizure threshold. Other experimental data, however, such as TPM efficacy in suppressing absence-like seizures in spontaneously epileptic rats, indicate that TPM may have a more broad spectrum of therapeutic activity. The anticonvulsant effect of TPM may result from multiple mechanisms of action, including modulation of Na^+ and/or Ca^{2+} dependent action potentials, enhancement of GABA activity at some subtypes of GABAA receptors, and inhibition of kainate-mediated conductance. On the other hand TPM is a weak carbonic anhydrase inhibitor, and this effect seems to be more relevant to side effects associated with TPM than to its antiseizure activity.

Toxicological studies have demonstrated that short- and long-term oral exposure of animals to TPM is well tolerated, with acute toxicity being primarily CNS-related. Hyperplasia of the gastric and urothelial cells seen in short-term studies do not progress to neoplasia after lifetime exposure in rodents; moreover the TPM-induced smooth muscle tumors of the urinary bladder appear to be unique to the species. Similarly to other carbonic anhydrase inhibitors, TPM is teratogenic in rodents. As in preclinical studies, TPM has also demonstrated a favorable pharmacokinetic profile in humans. After oral administration, TPM is rapidly and well absorbed (bioavailability = 80%) with peak plasma concentrations being obtained between 1.4 and 4.3 h in volunteers. TPM bioavailability is not influenced by food. TPM exhibits a linear pharmacokinetics with dose-proportional increases in plasma concentrations, is poorly bound to plasma proteins (13% to 17%), and is excreted mostly in unchanged form via the kidney. In humans, six metabolites devoid of any pharmacological action have been observed. The elimination half-life, CL_P and CL_R range from 19 to 25 h, 1.3 to 2.2 l/h, and 0.65 to 0.79 l/h, respectively, after administration of single or multiple doses. The pharmacokinetics of TPM in children is similar to that in adults except that clearance is 50% higher, resulting in 33% lower plasma concentrations than in adults. TPM does not usually affect the pharmacokinetic profile of CBZ, PB, or VPA, but causes a small increase in PHT plasma levels in some individuals. On the other hand, enzyme-inducing agents, such as CBZ and PHT, significantly lower TPM plasma clearance, resulting in decreased TPM plasma concentrations.

TPM has been primarily used as add-on treatment in adult patients with refractory partial seizures following five double-blind, placebo-controlled, randomized clinical trials with similar design, inclusion criteria, and efficacy endpoints. The meta-analysis of these studies shows that TPM at doses of 200 to 1000 mg/d induces a median percent seizure reduction from baseline ranging from 30% to 48% compared with an 18% median increase to a 13% median reduction with placebo. Similarly, of the TPM-treated patients, 41% experienced a $\geq 50\%$ reduction of seizures compared to 10% of patients receiving placebo. While TPM doses of 400 to 1000 mg/d are statistically superior to placebo, TPM 200 mg/d shows only a borderline statistical significance. The response to TPM does not change as a function of gender, sex, seizure type, or baseline seizure frequency. In open long-term studies, the percentage of patients still on TPM after a median period of 2 y ranged between 32 and 64%, with 2% to 10% being seizure free. In a controlled study, 33% of responders to TPM were successfully converted to TPM monotherapy.

The favorable results obtained in adults have been confirmed in children with refractory partial seizures treated with a mean TPM dose of 6 mg/kg/d.

TPM has been shown to be superior to placebo-controlled also in well-controlled studies conducted in patients with non-focal generalized (tonic clonic, myoclonic, and tonic) seizures and Lennox-Gastaut syndrome.

CNS-related symptoms are the most common adverse effects induced by TPM. These events, including dizziness, somnolence, psychomotor slowing, nervousness, paresthesia, ataxia, difficulty with memory, confusion, and speech disorders, arc usually mild to moderate and may cause withdrawal of TPM in the early phase of treatment. They may be attenuated or avoided by a slow titration of TPM over several weeks in small increments (25 to 50 mg/d each week). Long-term adverse events are rare and may include psychosis or depression, loss of body weight, and nephrolithiasis.

At the present time, TPM 200 to 800 mg/d may be prescribed as add-on therapy in patients with partial seizures refractory to conventional AEDs. In these difficult cases, it shows a potent anticonvulsant effect with some chance of obtaining complete remission of the epileptic disorder. The promising results observed also in non-focal tonic-clonic seizures and Lennox Gastaut syndrome may contribute to widening of the spectrum of indications for TPM in the near future. There is indirect evidence, obtained from a meta-analysis of all controlled clinical trials with the newer AEDs, that TPM is significantly more potent than the other new compounds, with an intermediate level of tolerability.

Additional research is needed to address how TPM directly compares with other AEDs, its efficacy in well-defined epileptic syndromes, the existence of indications for use in non-epileptic neurologic conditions, and its potential for rare, idiosyncratic toxicity.

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