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ORIGINAL ARTICLES

An open-label study of topiramate as add-on therapy for epilepsy using slow titration

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Abstract

Objective: To find the appropriate dose and titration method for using topiramate (TPM) as add-on therapy in patients with refractory epilepsy. *Methods*: Fifty patients (30 adults and 20 children) were recruited in this open-label, observational study with lower initial and target dose and slower dose escalation schedule followed by a 24-weeks stabilization phase. A pause or small decrease of dose was also allowed in titration. The efficacy and safety of TPM, and its relationship with dosage and titration process was evaluated. *Results:* Seizure frequency reduction by >50% was found in 58% of all patients. Eleven patients (22%) became seizure-free. The average dose in responders was 124±48 mg/day for adults and 3.6±1.2 mg/kg/day for children, which were much lower than that reported previously. Better seizure control was achieved in 9 patients after decreasing the dose from their maximally achieved dosage. Adverse events were observed in 18 (36%) patients, 23% for adults and 11 patients (55%) for children. The most frequent symptom was anorexia, which occurred in 28%. Weight loss and language disturbance were the other symptoms reported. In patients taking more than one antiepileptic drugs, there was significantly lower responder rate and higher incidence of adverse events.
Conclusions: TPM was effective and safe as add-on therapy for refractory epilepsy among Chinese patients, with lower dose when used in slow titration. Anorexia was the most frequent adverse event.

INTRODUCTION

Topiramate (TPM) is a broad-spectrum antiepileptic drug (AED) with multiple mechanisms of action. The efficacy and safety of TPM as add-on therapy in adults with refractory epilepsies, especially partial epilepsies, have been extensively evaluated.[1-5] It has also been reported that TPM was effective for childhood epilepsies[6,7], including Lennox-Gastaut syndrome and infantile spasms.[8,9] There were a number of studies on dose (concentration)-response relationship, from multiple dose-ranging studies[2,3] to trials focusing on specific target doses[4,5], in which high doses of TPM were usually used. Recent studies showed that low dose at 100 mg/day or even lower may be effective for adult patients with epilepsy.[10,11] Large individual variability was also seen within the same study, in which blood concentration monitoring of TPM failed to find the traditional "therapy range".[11-13] There are limited data on dose of TPM based on practical designed study to guide daily clinical use of the drug. This open-label study was designed to adopt a slower dose escalation schedule with lower initial and target dose of TPM, as well as allowing for pause of titration or decreasing dose, to find the most appropriate dosage for each individual. The efficacy and safety, as well as the relationships between concomitantly used AEDs and effectiveness of TPM were also studied.

METHODS

Patients

The study subjects consisted of adult and pediatric patients from Guangdong province, southern China, who were in-patients or out-patients of the Second Affiliated Hospital, Guangzhou. The inclusion criteria were: 1) Adults and children with partial seizures with or without secondarily

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generalization; Lennox-Gastaut syndrome or infantile spasms; 2) Received a fixed regimen of 1-3 following AEDs, phenytoin, carbamazepine, valproate, phenobarbital, or clonazepam; 3) More than 8 seizures during an 8-week baseline phase, while the AEDs were maintained in therapeutic range. Women of childbearing age were permitted to enroll in the trial if they were not pregnant or breast-feeding and were using birth-control measures. Patients were excluded from the study if they had: 1) History of pseudoseizures, 2) Active systemic or progressive neurological disease; 3) Currently receiving >3 AEDs listed above; 4) History of drug or alcohol abuse, nephrolithiasis, hypersensitive to carbonic anhydrase inhibitors or sulfonamides. Written informed consent was obtained from the patients or their guardians. All patients had EEGs, CT or MRI brain.

Study design

At the initial 4 weeks *screening* and *recruitment* phase, AEDs were adjusted to therapeutic range. The patients then entered an 8 weeks *baseline* phase with 4-weekly visits to determine the seizure frequency. For adults, during *titration* phase, the patients were given a starting dose TPM of 25 mg/day and increased by 25 mg every week until 200 mg/day. For children, the starting dose was 1 mg/kg/day, and increased by 1 mg/kg every week until 6 mg/kg/day. If the dose for a child was higher than that for adult based on body weight, the dosage schedule of adult was used. Thereafter the dose may increase to maximally tolerated dose at weekly interval. The titration would be paused when: 1) Seizure free for >1 week for patients with a baseline seizure frequency of >1/day, or seizure free duration 4 times longer than the baseline interval in patients with a baseline seizure frequency of <1/day; 2) Intolerable adverse events (AEs); 3) Seizure frequency increased by 50% from the baseline, even though the seizure increase occurred after a period of improvement. In (2) and (3), the TPM dose was adjusted downward by 12.5 mg or 25 mg (0.5-1 mg/kg for children). This was followed by a 24-weeks *stabilization* phase.

Evaluation

Efficacy evaluations were based on the diaries with records of the time, date, and description of each seizure. During the titration phase, the patients were reviewed every 2 weeks. The patients were reviewed 4-weekly during stabilization phase. At the end of the study, the investigators and patients conducted a global evaluation of the treatment trial. Efficacy was evaluated by comparing seizure frequency of the last 8 weeks with baseline.

Weight, hematological studies, blood chemistry, urinalysis, ECG, and serum AED levels were repeated at the recruitment, titration and conclusion of study. Patients were interviewed with a checklist at each visit to document adverse events.

RESULTS

Demography

A total of 52 patients were initially recruited, 2 patients were lost to follow-up at the beginning of titration phase. The other 50 patients who completed the study were analyzed in this report. The baseline characteristics of the study patients are summarized in Table 1.

Efficacy

The treatment response is summarized in Table 2. As shown, 29 patients (58%) had a >50% seizure reduction, while 11 patients (22%) were seizure-free. Adults had significantly better response than children. The treatment response in different types of seizure is showed in Table 3. Patients with complex partial seizure and secondary generalized tonic clonic seizure responded better to TPM, but these were not statistically significant.

Dosage

There was marked individual difference in the initial dose at onset of efficacy. Some adult patients showed response at the dose as low as 25 mg/day. The dose of TPM at different stages and in different groups is summarized in Table 4. As shown, the mean dose at stabilization phase in responders was 124 mg/day for adults and 3.6 mg/kg/day for children. In seizure-free patients, the mean doses of TPM at stabilization phase were only 111 mg/day for adults and 2.7 mg/kg/day for children.

Among the 29 responders, 9 patients (36%) experienced an increase in seizure frequency in the later period of treatment after some improvement in the early stage of titration. With the decrement of dosage (12.5 mg or 25 mg, or 0.5-1 mg/kg for children), seizure became better controlled again. Two of the patients became seizure-free.

Table 1: Baseline characteristics of the patients (n=50)

	Adults (n=30)	Children (n=20)
Mean age in years, range in parenthesis	27±10 (15-55)	7±4 (1-14)
Male : Female	3 : 1	3 : 1
Body weight in kg	56±9	27±14
Duration of illness in years	13.5±8.0	4.1±3.0
Seizure types and epilepsy syndrome		
Simple partial seizure	4	6
Complex partial seizure	25	11
Secondary generalized tonic clonic seizure	18	7
West syndrome	0	2
Lennox-Gastaut syndrome	1	3
Seizure frequency per 4 weeks		
Mean	22±55	88±114
Median	6	20*
Number of AEDs		
One drug	15	6
Two drugs	11	9
Three drugs	4	5

*Signed rank test, $P<0.05$, compared with adults

Table 2: Seizure response to TPM

	n	>50% reduction	>75% reduction	Seizure-free
Adults	30	21 (70%)	16 (53%)	7 (23%)
Children	20	8 (40%)*	6 (30%)	4 (20%)
Total	50	29 (58%)	22 (44%)	11 (22%)

*χ^2 test, $P<0.05$, compared with adults.

Table 3: Response to TPM in different seizure types and epilepsy syndromes

	n	>50% reduction	>75% reduction	Seizure-free
Simple partial seizure	10	3 (30%)	3 (30%)	
Complex partial seizure	36	25 (69%)	18 (50%)	9 (25%)
Secondary generalized tonic clonic seizure	25	14 (56%)	11 (44%)	6 (24%)
West syndrome	2	1 (50%)	1 (50%)	
Lennox-Gastaut syndrome	4	1 (25%)	1 (25%)	

Table 4: Dose of TPM at different stages and in different patient groups

	Adults (mg/day) (mean±SD)	Children (mg/kg/day) (mean±SD)
Dose at onset of efficacy	102±57 (n=21)	3.1±1.9 (n=8)
Dose at stabilization phase	124±48 (n=21)	3.6±1.2 (n=8)
Dose of seizure-free patients	111±20 (n=7)	2.7±0.6 (n=4)
Dose of non-responders	195±97 (n=9)	3.6±2.2 (n=12)
Maximal dose	300	6.3

Adverse events

AEs were observed in 18 patients (36%), 7 patients (23%) for adults and 11 patients (55%) for children. A significant difference in AE was found between adults and children. As shown in Table 5, the most frequent symptom was anorexia, especially in children. Weight loss, language disturbance and other CNS-related events were the other common symptoms. One adult had paranoia. Language problems appeared to be more prominent in children. AEs often appeared around the middle of titration phase. But the time of onset of AEs differed from patient to patient. So was the dose of TPM inducing the AEs. Some patients experienced more than one AEs. None of the patients had changes in their laboratory investigations.

Concomitant AEDs, response and adverse events

The relationships between number of concomitant AEDs and response rate or incidence of AEs are shown in Table 6. Patients with more than one concomitant AEDs had significantly lower response rate and a higher incidence of AEs.

DISCUSSION

It has been 16 years since the first report of TPM for treatment of epilepsy in 1988.[14] The efficacy and safety of TPM as add-on therapy, and monotherapy[10,15,16] in refractory epilepsy and newly diagnosed epilepsy, have been extensively evaluated by controlled trials conducted in many countries. However, there were conflicting reports on the dose and titration of the drug. Early reports from U.S. indicated that 200 mg daily dose was not significantly different in efficacy from placebo.[2] Other studies showed that dose >200 mg had a definite effect whereas no significant difference in efficacy was found in different doses greater than 200 mg.[17] More recent studies confirmed that lower dose of TPM may be effective.[10,11,18] These differences may reflect greater inter-individual variability for TPM than other AEDs. Racial differences and body weight may be the other variables affecting the dose of efficacy. On the other hand, incidence of AEs increases with the dose increment.[10,19,20]

In the present open-label study, with slow titration, seizure frequency reduction by >50% was found in 58%, and seizure free in 22% of

Table 5: Incidence of AEs

	Adults (n=30)	Children (n=20)	Total (n=50)
Anorexia	5 (17%)	9 (45%)	14 (28%)
Weight loss*	2 (7%)	4 (20%)	6 (12%)
Language decrease		2 (10%)	2 (4%)
Word-finding difficulty		1 (5%)	1 (2%)
Psychiatric symptoms	1 (3%)	1 (5%)	2 (4%)
Dizziness	2 (7%)		2 (4%)
Somnolence	2 (7%)		2 (4%)
Rash	1 (3%)		1 (2%)
Total	7 (23%)	11 (55%)**	
Time in weeks AE developed	4.1±4	4.7±2.3	
Dose of TPM when AE developed	128±98 mg/day	4.0±1.4 mg/kg/day	

*defined as more than 10% of baseline weight at any time during the treatment phase
** χ^2 test, P<0.05, compared with adults

Table 6: Relationships between number of concomitant AEDs, response rate and adverse events

AEDs	>50% reduction	>75% reduction	seizure-free	Adverse event rate
1 drug (n=21)	16 (76%)	13 (62%)	9 (43%)	3 (14%)
2 drugs (n=20)	11 (55%)	7 (35%)	1 (5%)	10 (50%)*
3 drugs (n=9)	3 (33%)*	2 (22%)	1 (11%)	5 (56%)*

*χ^2 test, P<0.05, compared with 1 drug group.

patients. This is higher compare with some previous reports, but comparable to the results of similarly designed study[11] and data from Asia.[21-24] As shown in the report from Korea[21], it might be related to the different patient characteristics and more gradual introduction of TPM. In our study, a significantly better efficacy was found in adults as compared to children. TPM has been shown to be effective and safe in children.[6-9,13,23,25] Difference in the type of epilepsies and a more drug resistant group among our children may partially explain the difference in response. TPM is usually regarded as a broad-spectrum AED. Some studies suggested that it has equal efficacy for all types of seizures.[26] In the present study, the efficacy of TPM on complex partial seizure and secondary generalized tonic clonic seizure seemed superior to other seizure types, but these were not statistically significant.

Special attention had been given to the low initial dose and slow titration in the design of the present study. With minimum seizure frequency of once weekly, median frequency of 6 episodes/4-weeks for adults, and 20 episodes/4-weeks for children, assessment of efficacy in the treatment period was possible. An initial dose of 25 mg and increment of 25 mg per week, an eight weeks of titration to just 200 mg/day allowed for determination of onset of efficacy as well as AEs. A pause in titration was also allowed, which avoided the missing of lowest effective dose, drop-out by intolerable AEs, and seizure worsening caused by over-dose. In this study, the average dose at onset of efficacy was about 101 mg/day (3.1 mg/kg/day for children), with a great inter-individual variability. Some adult patients showed response as low as 25 mg/day. In patients who were seizure-free, the dose of TPM was 110 mg/day (2.7 mg/kg/day for children). Although there were a number of studies concerning the therapeutic dose of TPM, few[10,11,18,24] studied doses less than 200 mg, except those using low dose TPM as control. The Korean study showed that there was no significant difference in efficacy between three groups with average dose of 176.5 mg, 345.2 mg, 582.4 mg.[21] In the report by Stephen *et al*[11] the mean dose was 250 mg in seizure free patients, and one third (13/39) of the study subjects took 100 mg or less. TPM 200 mg/day was suggested to be an appropriate target dose for adjunctive therapy in adults, whereas 100 mg/day also appeared to be effective.[18] Privitera *et al* [10] showed that 100 mg/day of TPM is as effective as 200 mg of TPM, carbamazepine and valproate acid in monotherapy. The average dose for maintenance in responders was 123.9±47.9 mg/day. Thus, despite the great inter-individual variability, a dose range of 100-200 mg (3-5 mg/kg/day for children) may be initially recommended for majority of the patients, at least among Chinese patients. Other variables such as patient response and body weight should also be considered. The average body weight was 56 kg for adults in this trial. It was 58 kg in an Asia study[22], 63.7 kg in Korean trial [21], and 75.2 kg in the Scandinavian study by Ben-Menachem *et al*.[1]

Overall, there appear to be a higher efficacy in the patients using higher doses of TPM.[16,17,27] In this trial, it is found that in 9 (31%) of 29 patients who had >50% seizure reduction, the seizure frequency increased in the later period of treatment after some improvement in the early stage of titration. The best seizure-control effect was achieved by a small decrement of TPM. This may indicate that there is a narrow "therapeutic range" for an individual patient causing this paradoxical effect.

The pattern of AEs in the present study is different from that reported in the literature, in which CNS-related events were the most frequent.[1-4,17] Anorexia was the most common AE in both adults and children in the present study, similar to the report from Korea[21], suggesting that racial difference may be a factor. Other AEs were similar to the previous reports, such as weight loss and CNS-related events. Psychiatric symptoms and language disturbance were less. The lower dose and slow escalation of TPM in this study may contribute to less CNS-related side effects in this study.

A higher incidence of AEs was found in children. Anorexia was the most intolerable events complained by the patients or parents. However, most of the AEs disappeared or became tolerable after the slowing down of titration or a small decrease of dose. Comparing the titration speed of 25mg/day (less than 0.5mg/kg/day) every week for adults, 1mg/kg/day per week may be too fast for children. An initial dose of 1mg/kg/day with 0.5mg/kg/day per week titration may be a better dose regime for children.

It is difficult to differentiate whether the AEs is related to a particular AED in an add-on trial. The incidence of AEs increased significantly in patients with more than one concomitant AEDs, suggesting drug-interaction as a factor in the occurrence of AEs. It has been reported that reduction of dosage of concomitant AEDs may decrease the drop out rate from AEs.[28] Drug-

interactions might also be responsible for the decreased efficacy in patients with more concomitant AEDs. However, the patients with greater number of AEDs were usually more refractory.

In conclusion, the efficacy of TPM as add-on therapy for refractory epilepsy was confirmed among Chinese patients in this study. The effective dose was <200mg/day for adults and <5mg/kg/day for children. A low initial dose and slow titration may partially explain the relative efficacy and low CNS-related AD in this study.

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