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Clinical Experience of Topiramate Use in Children with Refractory Epilepsy

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Abstract A retrospective review was done on 22 children who were put on Topiramate as adjunctive therapy for the treatment of refractory epilepsy from 1998 to 2001. The patients' response during the initial six months of therapy was evaluated. Treatment response was defined as ≥50% reduction in seizure frequency from baseline while the patient was on maximum drug dose for at least 2 weeks. Five patients (23%) responded while they were on a mean maximum dose of 4.5±2.3 mg/kg/day. The response rate of patients with refractory complex partial seizures was higher (31%). Adverse effects including anorexia, somnolence, hyperactivity, and aggressiveness were observed in some patients, but many of them were transient and trivial. This study shows that Topiramate is probably an effective new adjunctive therapy for the treatment of refractory complex partial seizures in the local paediatric population, and it appears to be well tolerated.

Key words Children; Refractory epilepsy; Topiramate

Introduction

Refractory epilepsy has long been a headache of paediatric neurologists who have a limited number of new anticonvulsants to choose when treating their patients. Some of the new drugs, although proven to be effective, were reported to have post approval idiosyncratic reactions, which limited their use. Out of this group of new anticonvulsants, Topiramate is increasingly used in our clinic for the treatment of children with refractory epilepsy whose seisures are not well controlled with first line anticonvulsants (Carbamazepine, Sodium Valproate, Phenytoin and Phenobarbitone) and/or combination of other various anticonvulsants.

Topiramate (TPM) is a new, chemically novel anticonvulsant. It has multiple mechanisms of action including: 1) Reduces the duration of epileptiform discharges and the number of action potentials generated within each discharge, most likely by inhibition of voltage-sensitive sodium channels;[1] 2) Enhances the activity of γ-aminobutyric acid (GABA) at a nonbenzodiazepine site on the $GABA_A$ receptor;[2] and 3) Antagonizes the kainite/AMP A-glutamate receptor.[3] The multiple mechanisms of action implied that Topiramate should be broadly active in a number of seizure types, and tolerance to this drug is less likely.

Clinical evidence is emerging that Topiramate is effective as adjunctive therapy in a broad range of seizure disorders in both adults and children. The recent studies and results are summarised in Table 1. In a current review on the usage of Topiramate in catastrophic epilepsies of childhood, Glauser concluded that Topiramate is an effective agent for the treatment of a variety of seizure types in children, with the added advantage of very favourable safety margin. Overall, it is a valuable new antiepileptic medication for this group of patients. [4]

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Table 1 Summary of clinical evidences of Topiramate as adjunct therapy in different types of seizure (1996-2003)

Author	Study	Age (year)	No.	Dose	Duration (month)	Result (% of patient with ≥50% reduction in seizure attack)
Partial-onset seizure						
Ben-Menachem et al, Faught et al, Privitera et al, Sharief et al, Tassinari et al, 1996[5-9]	Five controlled trials	Adult	600	200-1000 mg/d	~ 2-6	TPM 41% Placebo 10%
Elterman et al, 1999[10]	Controlled trial	2-16	86	6 mg/kg/d	4	TPM 39% Placebo 20%
Ritter et al, 2000[11]	Open label phase of above trial	2-16	83	9 mg/kg/d	15	TPM 57%
Coppola et al, 2001[12]	Prospective open trial	2-30	55	Max 12 mg/kg/d	9	TPM 65%
Generalised tonic clonic seizure						
Crawford, 1998[13]	Review	12-75	-	350 mg/d	-	TPM 33%
Biton et al, 1999[14]	Controlled trial	3-59	80	175-400 mg/kg/d	5	TPM 56% Placebo 20%
Montouris et al, 2000[15]	Open label phase of above trial	3-59	131	7 mg/kg/d	24	TPM 63%
Lennox-Gastaut syndrome						
Sachdeo et al, 1999[16]	Controlled trial	2-29	98	6 mg/kg/d	2-3	TPM 33% Placebo 8%
Glauser et al, 2000[17]	Open label phase of the above trial	2-29	97	10 mg/kg/d	1.5-44	TPM 45%
Coppola et al, 2002[18]	Prospective open label study	4-34	45	1.4-12 mg/kg/d	3-98	TPM 40%
Infantile spasms						
Glauser, 1998[19]	Pilot study	3-48 mth	11	8-24 mg/kg/d	3-6	TPM 82%
Glauser, 2000[20]	Extension phase of above study	As above	11	29 mg/kg/d	18	TPM 64%
Herranz, 2000[21]	Open label review	Infant	13	Max 16 mg/kg/d	-	TPM 69%
Watemberg et al, 2003[22]	Open label chart review	0-2	8	6-12 mg/kg/d	14	TPM 88%

Objectives

In this retrospective review, we attempted to: 1) summarise our clinical experience using Topiramate in paediatric patients; 2) assess its effectiveness as an adjunctive therapy for the treatment of refractory seizures; 3) compare with the foreign studies regarding efficacy and safety; and 4) make recommendations for effective use of Topiramate in clinical practice.

Methods

A retrospective longitudinal review was conducted to

evaluate the efficacy and safety of Topiramate as adjunctive therapy in the treatment of refractory epilepsy in our paediatric neurology clinic patients.

Patient population: All patients who have been on Topiramate since it was available in our clinic in 1998, up to 2001, were evaluated. The neurology clinic records were reviewed, and their condition was updated during the study period from September 2000 to September 2001.

Exclusion criteria: If the patients had: 1) seizures due to acute progressive disease; 2) poor compliance with drug treatment; 3) increases in dose of concomitant anticonvulsants, or use of other epilepsy treatment regimes during the initial 6 months of Topiramate treatment, which made their response difficult to interpret.

Efficacy: The primary determinant of efficacy was based on the self-reported reduction in average monthly rate of major seizures within the initial 6 months of Topiramate treatment. Patients' epileptic diaries were checked to confirm their response. Treatment responders were defined as those who experienced ≥50% reduction from baseline seizure attack rates while on the maximum Topiramate dose for at least 2 weeks. Patients who showed some response, but <50% reduction in seizure rate, were also discussed.

Antiepileptic medication: Topiramate was prescribed to our patients as adjunctive therapy due to their poor clinical response to first line anticonvulsants and/or combination of various anticonvulsants. The dose of Topiramate was stepped up gradually, based on the clinical response of the patient and tolerability of adverse effects. It was stepped down, as necessary if the efficacy of treatment was poor or significant adverse effects occurred. The maximum drug dose used during initial 6 months of Topiramate therapy, the duration on that dose, and the titration period were noted.

Safety data: Treatment emergent adverse events were defined as adverse events, which were either new in onset or aggravated in severity or frequency during the study treatment period. The data was collected by retrospective review of the clinic records. For those patients who had follow up visits during the study period, they were directly questioned regarding common adverse reactions, and any other specific individual reactions. A detailed physical examination was also done. Since anorexia/weight loss was one of the most commonly reported adverse effects, the patient's body weight was noted before and 6 months after starting on Topiramate treatment (or when the treatment was terminated before 6 months). The patients were considered to have significant weight loss if they had lost 5% of their initial body weight, or failed to have appropriate weight gain (BW dropped below the initial growth percentile line) during the initial 6 months of treatment, in the absence of other systemic illness.

Statistical method: Statistics on the patient characteristics, treatment response and adverse events were calculated, and this pattern was compared with the data from foreign studies.

Results

Patient Characteristics

A total of 30 patients had been put on Topiramate treatment in our center from 1998 to 2001. Eight patients were excluded from the study: one patient was lost to follow up shortly after starting on Topiramate, and seven patients had increases in the dose of concomitant anticonvulsants during the initial 6 months of Topiramate treatment, which made their responses difficult to interpret. Thus, only 22 patients were included in the data analysis. Their demographic data and baseline characteristics are summarised in Table 2.

Dosage and Duration of Treatment

The mean maximum Topiramate dose during the initial 6 months of treatment was 4.5±2.3 mg/kg/day (range: 0.9 -8.4 mg/kg/day) for a mean duration of 8.1±5.4 weeks (range: 2-24 weeks). The majority of patients had a titration period of >9 weeks.

Efficacy

During the initial six months of Topiramate treatment, 10 out of the 22 patients reported reduction in seizure rate (45%), with 5 of them reported ≥50% reduction from baseline seizure rate (23%) (Figure 1).

Four of the five patients who showed ≥50% reduction in seizure rate suffered from complex partial seizures with/ without secondary generalisation. They were treated with a mean maximum dose of 3.7±1.8 mg/kg/day for a mean duration of 8±4.7 weeks.

For the remaining 17 patients, 5 showed <50% reduction in seizure rate, 10 showed no change in their seizure frequency, and 2 reported worsening of their symptoms. They were treated with a mean maximum dose of 4.5±2.3 mg/kg/day for a mean duration of 8.2±5.7 weeks. These figures showed no significant difference from the responder group. For the 2 patients who reported worsening of symptoms, their maximum drug dose was 3.3 and 4.8 mg/ kg/day respectively for duration of 4 weeks. Both of them

Table 2 Demographic data and baseline characteristic

Variable	Patients (n=22)
Sex, male/female	8/14
Age, year, mean±SD	11.7±6.2
Range	4-21.5
Weight, kg, mean±SD	33.5±16.3
Range	13.7-64
Ethnicity, Chinese/Others	21/1
Baseline seizure type	
Complex partial±secondary generalisation	13
Myoclonic	3
Generalized tonic clonic	2
Lennox Gastaut syndrome	2
Infantile spasm	2
Median baseline monthly seizure frequency	33.4
Range	1-110
Number of background anticonvulsants (AED)	
One AED	4
Two AEDs	10
More then two AEDs	8
Background AEDs	
Valproic acid	12
Carbamazepine	11
Clobazem/Vigabatrin/Lamotrigine	7/6/5
Others (Clonazepam, Trileptal, Lorazepam, Phenytoin, Luminal, Gabapentin)	8
Underlying disease/structural lesion identified	
Cerebral atrophy/Cerebella brainstem atrophy	3/1
Tuberous sclerosis	2
Porencephalic cyst/Cerebello-pontine angle cyst	1/1
MELAS	1
Smith lenti opitz syndrome (suspected)	1
Mesial temporal sclerosis	1
Schizencephaly	1
Epilepsy without cause identified	10
- Temporal lobe epilepsy	6
- Frontal lobe epilepsy	1
- Myoclonic epilepsy	1
- Lennox Gastaut syndrome	1
- Prematurity without brain lesion identified	1

suffered from complex partial seizures with or without secondary generalisation.

When the analysis of treatment responders (n=5) was extended to 7 to 12 months of Topiramate treatment, 3 of them persistently experienced reduction in seizure attacks, but the other 2 had increases in the dose of concomitant anticonvulsants which made their response difficult to interpret. For the initial non-responders (n=17), 2 of them responded after their drug dose were stepped up from 4/4.7 to 6.5/7.4 mg/kg/day, and they suffered from complex partial seizures and myoclonic epilepsy respectively.

Analysis of the type of seizure and treatment response:

- Complex partial seizures – 13 patients suffered from complex partial seizures in our series, 4 showed ≥50% reduction of seizure rate, 3 showed <50% reduction, 4 showed no change and 2 reported worsening of their seizure rate during the initial 6 months of treatment. This gave a response rate of 31% (i.e. 4/13). No statistically significant association was found between clinical response and other variables, including: age of patients, frequency of seizure attack, presence of brain lesions, dose of drug and duration of treatment.
- Other types of seizures/epileptic syndromes – the number of patient treated was too small to give any meaningful result.

Side Effects

Adverse events that were reported by the patients or found during follow up are summarised in Table 3. The most common side effects were anorexia (45%), central nervous system (CNS) effects (36%) and weight loss (23%). Among CNS effects, somnolence was most frequently reported, and three patients had multiple CNS complaints. However, most of these side effects were trivial and

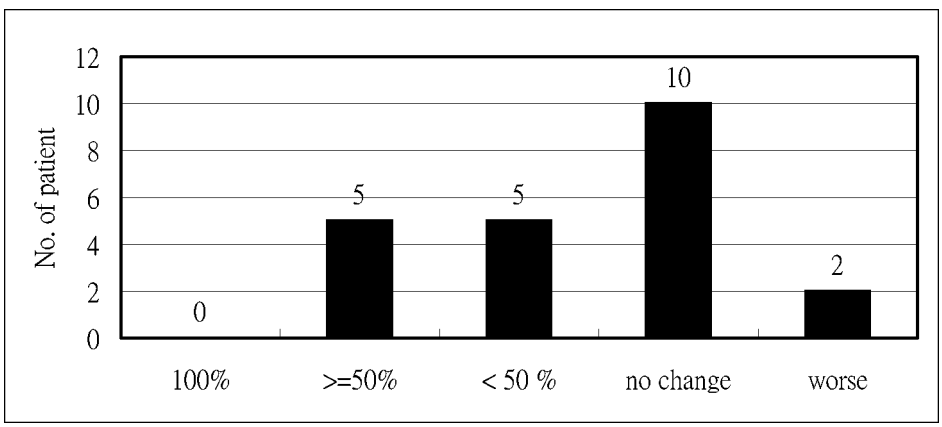

Figure 1 Initial response to Topiramate (n=22).

Table 3 Incidence of the treatment emergent adverse events

Adverse event	No. of patients (percentage)
Anorexia	10 (45%)
Central nervous system effects	8 (36%)
	(3 have multiple complaints)
Somnolence	5
Euphoria/hyperactive	2
Aggressive	1
Insomnia	1
Hypotonia	1
Difficulty with concentration	1
Decreased speech	1
Weight loss	5 (23%)
Rash	1 (4%)

transient. Only three patients stopped drug treatment because of lack of efficacy of treatment and/or adverse events (including anorexia, CNS side effects and skin rash). However, all of them had just started on low dose of Topiramate treatment (1.9 to 2.8 mg/kg/day) for a short time (2 to 6 weeks).

Discussion

This is an empirical local retrospective study on the response of paediatric patients to Topiramate therapy. The results of this study showed that Topiramate improved seizure control in about one fourth (23%) of our patients with refractory epilepsy. This figure is slightly lower than those reported by foreign studies on different types of epilepsy (see Table 1), which ranged from 33% to 88% versus 8 to 20% of placebo effect. This can be explained by several possible factors.

One factor could be due to our lower mean drug dose (4.5±2.3 mg/kg/day) when compared to the studies, which showed effective target dose ranging from 6-24 mg/kg/day. Our use of a lower drug dose was due to the following reasons: 1) we have adopted a conservative approach in the titration of a new anticonvulsant in which we have limited experience and research data; 2) in order to avoid poor drug compliance due to adverse events, a slower titration rate was adopted, and hence lower maximum dose was reached during the initial 6 months of treatment; 3) clinical response of the patients determined the drug dose rather then a preset protocol; 4) frequent clinic visit and hence adjustment of drug dose was not prescribed to those patients with severe disability. Nevertheless, when we compared the mean maximum drug dose between the initial responder and non-responder groups, there is no significant difference (3.7 versus 4.5 mg/kg/day). This may imply that some factors other than the drug dose are affecting our treatment response.

For instance, the type of epilepsy may affect the treatment response. In our initial-responder group, four out of the five patients suffered from complex partial seizures with or without secondary generalisation, and another subsequent responder during the 7 to 12 months of treatment also suffered from the same seizure type. This is consistent with the pharmaceutical companies' reported major indication for Topiramate, and also prior research data reporting effectiveness of this drug in children and adults with partial-onset seizures. The response rate of our patients with complex partial seizures is 31% (4 out of 13 treated), which is only slightly lower than the reported figures in Table 1 (39 to 65 % in the treatment group, 10-20% in the placebo group).

For the treatment of epileptic syndromes of childhood such as Lennox-Gastaut Syndrome (LGS) and infantile spasms, different titration rates and target doses of Topiramate were recommended based on previous research. For instance, for LGS, a start slow (0.5 to 1.0 mg/kg/day), go slow (0.5 to 1.0 mg/kg/day every 1-2 weeks) approach was recommended, with a goal of higher target dose of 6-10 mg/kg/day in order to improve seizure control and reduced side effects.[4] In our study, two patients with LGS were treated with 0.9/6.4 mg/kg/day for 24/8 weeks respectively; both showed no change in seizure frequency. Their response might be better if a higher target dose close to 10 mg/kg/day was given as recommended.

For the treatment of infantile spasms, a high starting dose (2-3 mg/kg/day), rapid titration (2-3 mg/kg/day as frequent as every 3-4 days), and a high target dose of 10-15 mg/kg/day was recommended.[4] This could be due to the higher clearance and shorter half life of Topiramate in infants receiving concomitant enzyme-inducing anticonvulsants.[23,24] In our study, two patients with infantile spasms were treated with 2.5/7.8 mg/kg/day for 4/3 weeks respectively, and again both of them showed no response. A more robust approach, like that recommended above, might benefit some of our patients with infantile spasms.

For progressive myoclonic epilepsy, no double-blind placebo-controlled trials of Topiramate therapy have been reported before 2001. Although one case report showed a favourable response,[4] others found that patients with myoclonic seizures responded poorly to Topiramate. In our study, three patients with myoclonic epilepsy were treated

with drug dose of 1.8/4/5.8 mg/kg/day for 12/4/15 weeks respectively. Two patients showed no change and one showed <50% reduction in seizure frequency during the initial 6 months of treatment. During the 7 to 12 months of treatment, the partial responder had her drug dose stepped up gradually from 4 to 7.4 mg/kg/day, which resulted in ≥50% reduction in seizure frequency for 15 weeks of follow up. These observations indicate that a target dose approaching 6-8 mg/kg/day might benefit some of our patients with myoclonic epilepsy.

Topiramate was generally well tolerated. CNS effects and anorexia/weight loss were the most common adverse effects described in children. CNS effects include somnolence, difficulties with concentration and behaviour changes; however, tolerance to these adverse effects seems to develop in most children. Weight loss was also reported to be transient, with no long-term impact on growth. A slower titration rate was reported to be associated with lower incidence of adverse events.[25] In our review, the adverse effects of Topiramate were generally mild and transient. Three of our patients required termination of treatment because of adverse events and/or lack of efficacy. There were no significant treatment-related complications in those three patients. We can thus be reassured that Topiramate is a generally safe new drug with a very favourable safety margin.

In this retrospective review, we encountered several important limitations: 1) there was no preset protocol on the titration, maintenance and target dose of the drug, and adjustments were all based on the clinical response; 2) clinical response was obtained by self-report and confirmed by checking the epileptic diaries. This is intrinsically not a very accurate measure of clinical efficacy; 3) we arbitrarily chose the initial 6 months of Topiramate treatment for analysis because there was generally not much change in the concomitant anticonvulsants during this titration period. This allowed us to interpret the patients' response to Topiramate more accurately; 4) our sample size was small and only included patients from one local paediatric neurology clinic. All of these factors limit our ability to draw broad conclusion about the efficacy and safety of Topiramate in the treatment of refractory seizures in other paediatric population.

Summary and Conclusion

Results of this study show that Topiramate is probably an effective adjunctive therapy for the treatment of refractory complex partial seizures in the local paediatric population, but our response rate (31%) is slightly lower than that reported in the foreign studies (39-65%), and placebo effect cannot be excluded. As with other anti-epileptic drugs, individual response to Topiramate may be highly varied. Titration of the drug dose should be based on clinical response particularly when therapeutic serum drug concentration monitoring is not available. Although adverse events are common, they are mostly trivial and transient, and the drug is shown to have a very favourable safety margin. Its usefulness in the treatment of other epileptic syndromes in childhood requires further observation and study. Reports from previous studies showed that a higher target dose (at least 6 mg/kg/ day) could be given in a shorter titration period (6-9 weeks), and some fine adjustments are needed when treating different epileptic syndromes. Keeping these factors in mind, further local study on the efficacy and safety of Topiramate therapy should be conducted.

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