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Original Article

Topiramate as an adjunctive therapy in children with intractable epilepsy

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ABSTRACT

Background Epilepsy is a chronic disease that requires antiepileptic drugs (AEDs). Only 60-70% of new patients could be controlled effectively by standard AEDs and this stimulates the search for new, more effective and well-tolerated AEDs.

Objective To asses the efficacy and safety of topiramate, as an adjunctive therapy to standard AEDs for children with intractable epilepsy.

Methods This was an open label, parallel group study. Forty children with at least 4 seizures during a 4-week baseline period were randomly assigned to topiramate (n=20) or control group (n=20). In the topiramate group, the drug was given in adjunct to AEDs for 12-week titration dosage continued with a 12-week stabilization period, while the control group received only AEDs adjusted to their clinical responses.

Results Mean reduction from baseline in monthly seizures frequency was significantly greater in the topiramate group (88.6% vs. 25%; p=0.030). Other variable of efficacy was significantly different (e"50% reduction in seizures: 14/20 vs. 6/20; p=0.049). Adverse effects of topiramate, such as decreased weight, paresthesia, somnolence, diarrhea, fever, aggressive reaction and flushing, were temporary and mild.

Conclusion Results of this trial strongly suggested that topiramate is effective and well tolerated in reducing seizures of intractable epilepsy **[Paediatr Indones 2002;42:287-291].**

Keywords: *topiramate, intractable epilepsy, antiepileptic drugs, adjunctive therapy.*

The incidence of epilepsy in most developed countries is between 50 and 100 cases per 100,000 population per year, and the prevalence is about 5-8 cases per 1,000 population.[1] In the Child Health Department, Cipto Mangunkusumo Hospital, Jakarta, during 2000 and 2001, there were 408 and 472 epilepsy patients respectively showing a slight increase of cases each year. Approximately 60-70% of newly diagnosed patients will have their seizures controlled effectively by standard AEDs, the rest have a tendency for relapses or having intractable seizures.[1,2] Recurrent seizures during childhood have been associated with impaired psychosocial development, lower IQ scores, behavioral problems and difficulty in adjusting to school, creating the potential of lifetime disability.[3] The failure of standard AEDs to adequately control seizures in 30% of the epileptic population continues to stimulate the search for effective and well-tolerated AEDs. The standard AEDs have a clearly defined action in controlling seizures, while the new antiepileptic drugs have broad spectrum and multiple mechanisms of action with better tolerance than standard AEDs.[4]

Topiramate (TPM) (2,3,4,5-bis-O-(1-methyl ethylidene)-beta-D-fructopyranose sulfamate) is a new antiepileptic drug that blocks sodium channels, enhanc-

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ing GABA-induced influx of chloride. In addition, TPM inhibits some isoenzymes of carbonic anhydrase but this pharmacologic effect is not thought to be a major component of its antiepileptic activity.[4,5] The efficacy, tolerance and safety of TPM as addition to maximally tolerated dosage of standard AEDs had been evaluated in some studies. TPM significantly reduced seizure frequency and was well tolerated.[3,6] The principal measurement of efficacy was the percentage of monthly seizures reduction during the study phase compared to the baseline phase. Other measure included percentage of responders (patients experiencing e"50% seizure reduction).[7] The primary adverse effects of topiramate were CNS- related, i.e. dizziness, fatigue, ataxia, confusion, somnolence, abnormal thinking, diplopia, speech difficulties, psychomotor slowing, nystagmus, paresthesia, impaired concentration and confusion.[5] The incidence of kidney stones (1.5%) increased two to four times over that expected in the general population. This may be because topiramate is a weak inhibitor of carbonic anhydrase, which may also explain the occurrence of paresthesias in some patients.[5] Clinical experience suggests that slow titration helps decreasing adverse effects. This trial assessed the efficacy and safety of TPM, as adjunctive therapy to standard AEDs for children with intractable epilepsy.

Methods

The study group was composed of 40 outpatients aged between 1 to 15 years with refractory seizures. To be eligible for the trial, a child had to have four or more seizures during a 4-week baseline period, even though was in medication of at least two standard AEDs.

The subjects were recruited from the Pediatric Neurology Clinic of Cipto Mangunkusumo Hospital from July 2001 to July 2002. They were selected according to the following criteria: aged 12 months to 15 years old, had refractory seizures even though was treated with at least two AEDs, had at least four seizures in 4 weeks before TPM was administered, and had an informed consent from parents to participate in the study. Children were excluded from the study if they had status epilepticus within the previous 3 months even during appropriate treatment, presence of systemic, psychiatric or progressive diseases, had a history of nephrolithiasis, recent treatment with acetazolamide or triamterene, were unable to take medication routinely, were unable to maintain seizure calendars either independently or assisted by parents or guardians.

Patient's medical history, physical examination and neurological findings were recorded at the baseline period of the study. Laboratory findings including hematology, chemistry (serum alanin aminotransferase, aspartat aminotransferase, glucose, ureum, creatinine, electrolyte) and electroencephalogram (biologic digital EEG), were also collected during the baseline period.

Seizures were classified according to the International League Against Epilepsy (ILAE) classification of epileptic seizures.[8] Epilepsy and epileptic syndromes were classified according to the revised ILAE classification.[9]

After a baseline observation period of 4 weeks, the topiramate group received TPM in adjunct to the previous standard AEDs. Topiramate was initiated at a daily dose of 1 mg/kg, followed by a 2-week titration at increments of 1 mg/kg/day, up to a maximum daily dose of 9 mg/kg/day, unless the patient was unable to tolerate the drug. The dose was then maintained until 24 weeks. Children in the control-group continued at least 2 concomitant AEDs without receiving TPM. The doses and combination of AEDs were adjusted by their clinical response to seizures.

The number and type of seizures, also any adverse effects, were recorded in a seizure diary usually by parents or guardians. At a frequency of 4-week intervals, seizures were evaluated by the investigators.

The response to treatment was rated as follows: complete cessation of seizures (100% seizure control), decrease in seizure rate by 75%-99% (very good), decrease in seizure rate by 50%-74% (good), less than 50% (minimal), no change or increase in seizures rates. The efficacy of TPM was evaluated by percent of patients experiencing a greater than 50% reduction in seizures.

Statistical evaluation was performed by the X^2, Fisher exact test for nominal variables and Kolmogorov Smirnov, Whitney rank test for nominal and ordinal variables with abnormal distribution.

Results

Overall, 40 patients participated in the trial (20 patients each in the topiramate group and the control group). Patient characteristics are summarized in **Table 1**.

Median baseline seizure frequencies were 35 seizures/4-weeks in the topiramate group and 60 seizures/4-weeks in the control group. Approximately over half of the patients in both groups were treated with two AEDs.

The response during long-term TPM adjunctive therapy compared with continued standard AEDs is summarized in **Figure 1**.

Mean percentage reduction was 88.6% from baseline study (the topiramate group) during the last 6 months of TPM adjunctive titrated therapy. In the control group, mean percentage seizure reduction was 25%. Compared to standard AEDs polytherapy, TPM adjunctive therapy produced statistically significant (p=0.030) reduction of seizures

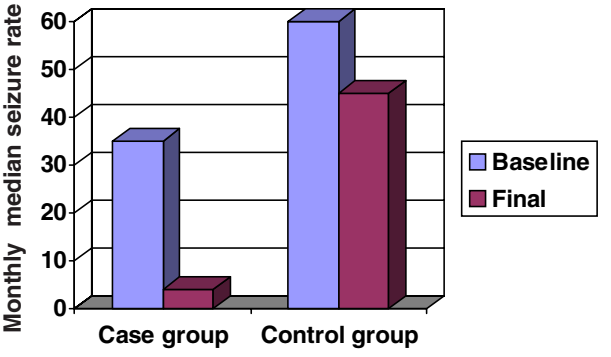
The percentages of patients demonstrating seizure reductions are shown in **Figure 2**.

In the topiramate group, 5 out of 20 patients experienced a 100% reduction in seizures, two of them continued TPM as monotherapy. Six of 20 experienced a 75%-99% reduction, 3/20 experienced a 50-74% and 3/20 had <50% reduction. In the control

TABLE 1. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patient characteristics	Topiramate group(n=20)	Control group(n=20)
Sex		
Male	9	15
Female	11	5
EEG		
Normal	3	5
Abnormal	17	15
Neurological abnormalities		
Present	11	15
Absent	9	5
Number of background AEDs		
Two AEDs	11	15
More than two AEDs	9	5
Age (years)		
Mean (SD)	6.7 (3.8)	8.2 (4.4)
Weight (kg)		
Mean (SD)	22.2 (15.7)	22.3 (12.2)
Baseline average monthly seizure rate#		
Median	35	60

Monthly = rate/4 weeks (28 days)



p=0.030
* Monthly rate = number of seizures every 28 days (4 weeks)

Figure 1. Seizure rates of the topiramate and the control group at baseline and after 24 weeks

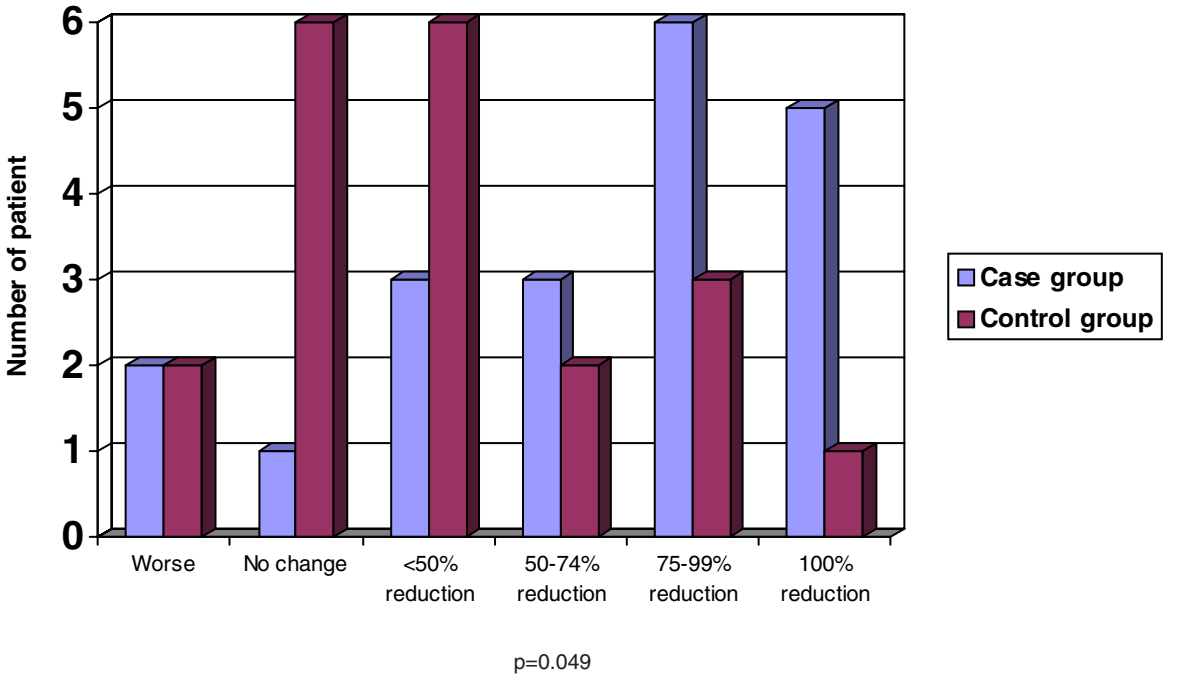


Figure 2. Seizure reduction between the topiramate and the control group after 24 weeks of treatment

group, only 1 of 20 had a 100% reduction in seizures. Three of 20 had a 75%-99% reduction, 2/20 experienced a 50-74% and 6/20 had <50% reduction. There was a significant difference between the groups in the proportion of seizure reduction (p= 0.049).

There was no clinically significant change in clinical laboratory tests during the long-term TPM-added therapy. The most common side effect was weight loss due to loss in appetite. Neurological adverse effects reported were paresthesia, aggressive reaction, and decreased awareness of surroundings.

Discussion

Most of the subjects were male aged more than 6 years, which was in accordance with the literature.[10,11] Most subjects had abnormal EEG (17/20 in the topiramate group vs. 15/20 in the control group) and neurological abnormalities (11/20 in the topiramate group vs. 14/20 in the control group). Baseline seizure rates in both groups were in the severe category (more than 20 seizures monthly). Patsalos *et al* and Elterman *et al* stated that EEG performance, neurological abnormalities and baseline seizure rates were factors that influenced the development of intractable epilepsy.[2,6]

The median percentage reduction from baseline for the TPM adjunctive therapy group was 88.6% compared to 25% in the control group. There was also significant difference in patient proportions of seizure reduction (p=0.003). Glauser reported that median percentage reduction in TPM-added therapy group was 33.1%, compared to 10.5% in the placebo group (p=0.034).[5] Elterman *et al* evaluated the efficacy of TPM (mean dose of 6 mg/kg/day) as adjunctive therapy on patients with uncontrolled partial-onset seizures with or without secondary generalized seizure, and found a median percentage reduction of 33.1% compared to 10.5% in the placebo group (p= 0.0034).[6]

In the TPM group, 100% seizure reduction was found in 5 out of 20 patients. Seizure reduction of <50% was found in 3 of 20 patients. Seizure frequency remained unchanged in 1 of 20 and in-

creased in 2 of 20 patients treated with TPM. In the control group, seizure reduction of 100% was found in 1 out of 20 patients, seizure reduction of <50% was found in 6 of 20 patients. Seizure frequency remained unchanged in 6 of 20 and increased in 2 out of 20 patients without TPM. Coppola *et al* evaluated the efficacy of TPM adjunctive therapy in children. TPM was added to one or two other baseline drugs. After 9 months of treatment, 11 patients (20%) were seizure free, 5 patients (9.1%) had a <50% decline; seizure frequency remained unchanged in 8 patients (14.5%) and increased in 6 patients (10.9%).[12]

As for adverse reactions, TPM as adjunctive therapy was well tolerated. The effects on liver, renal and hematological functions were mild. The most frequent adverse effect was loss in appetite. CNS adverse effects in this trial were aggressive reaction found in 1 out of 20 patients and decreased of awareness of surroundings found in 1/20. Elterman *et al*[6] reported the incidence of aggressive reaction in 7 out of 45 patients, and Coppola *et al*[12] also reported the presence of adverse effects of decreased awareness of surroundings.

We concluded that the result of this trial strongly suggested that topiramate is effective and well tolerated in reducing seizures of intractable epilepsy.

References

1. Shorvon SD. The epidemiology and treatment of chronic and refractory epilepsy. Epilepsia 1996;37:S1-3.
2. Patsalos PN, FrÖsher W, Pisani F, Van Rijn CM. The importance of drug interactions in epilepsy therapy. Epilepsia 2002;43:365-85.
3. Ritter F, Glauser TA, Elterman RD, Wyllie E, Topiramate YP Study Group. Effectiveness, tolerability and safety of topiramate in children with partial onset seizures. Epilepsia 2000;41: S82-5.
4. Sharief M, Viteri C, Menchem EB, Weber M, Reife R, Pledger G, Karim R. Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy. Epilepsy Res 1996;25:217-24.
5. Glauser TA. Topiramate. Epilepsia 1999;40 (Suppl 5): S71-80.
6. Elterman RD, Glauser TA, Reife R, Wu SC, Pledger G, the Topiramate YP Study Group. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. Neurology 1999;52:1338-44.
7. Reife RA, Pledger GW. Topiramate as adjunctive therapy in refractory partial epilepsy: pooled analysis of data from double- blind, placebo controlled trials. Epilepsia 1997;38:S31-3.
8. Commission on classification and terminology of International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489-501.
9. Commission on classification and terminology of International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1989;30:389-99.
10. Budiarto G. Patofisiologi epilepsi (kaitannya dengan pengobatan). Epilepsi 1998;3:6-22.
11. Chadwick D. Epilepsy. J Neurol Neurosurg Psychiatry 1994;57:264-77.
12. Coppola G, Caliendo G, Terraciano MM, Buono S, Pellegrino L, Pascoto A. Topiramate in refractory partial-onset seizures in children, adolescent and young adults: a multicentric open trial. Epilepsy Research 2001;43:255-60.