

Prospective Study of First-choice Topiramate Therapy in Newly Diagnosed Infantile Spasms

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Abstract

Objective:

This was a prospective open study to establish the efficacy, tolerability, and problems associated with the use of topiramate as first-choice drug in children with infantile spasms.

Methods:

Open-label follow-up study, ranging from 24 to 36 months, of the cases of 54 patients with infantile spasms treated initially with topiramate as first-choice drug.

Results:

Thirty-one patients (57.4%) were seizure free for more than 24 months; 9 patients were treated with topiramate alone and 22 patients with topiramate plus nitrazepam and/or valproate. In 44 cases (81.4%), the reduction of seizure frequency from baseline was greater than 30%, whereas in 10 cases (18.6%), there was poor or no response. The average dosage applied was 5.2 mg/kg per day (maximum dosage, 26 mg/kg per day; minimum dosage, 1.56 mg/kg per day). Adverse events occurred in 14 patients (26%). They included poor appetite leading to anorexia, absence of sweating, and sleeplessness.

Conclusions:

Topiramate proves to be an effective and safe first-choice drug not only as adjunctive but also as monotherapy of infantile spasms in children younger than 2 years.

Key Words: topiramate, infantile spasms, first choice, epilepsy

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Infantile spasm is an early onset epileptic syndrome presenting with epileptic spasms, a characteristic interictal electroencephalogram (EEG) pattern of hypsarrhythmia, and mental deterioration. It may present as a symptom of neurological disorders, such as tuberous sclerosis, but the cause often

remains unknown. The treatment of infantile spasms is still an unresolved problem because the disease is often resistant to multiple antiepileptic drugs^{1–3} and has a poor outcome. Hormonal therapy with corticotropin (ACTH) or corticosteroids may have significant, potentially fatal, adverse effects.^{2,4} Previous controlled studies support vigabatrin as first-line therapy,⁵ but visual-field constriction with the drug may limit its use⁶; in a recent study of Glauser et al⁷ on 5 patients under 2 years, vigabatrin monotherapy failed to control infantile spasms.

Topiramate is a new antiepileptic drug with proven efficacy against spasms in a broad range of seizure types, including infantile spasms.^{7–14} It seems to have multiple mechanisms of action, including a state-dependent blockade of voltage-activated sodium channels and high voltage-activated calcium channels, antagonism of glutamate-mediated neurotransmission, and potentiation of γ -aminobutyric acid-mediated neurotransmission.^{8,15} Thus, topiramate exerts beneficial effects on several seizure types, including those that are resistant to the old-generation antiepileptic drugs such as carbamazepine, nitrazepam, and valproate.^{15–17} Recent studies suggest that topiramate may be useful as add-on therapy for treating infantile spasms.^{8,9,18–20} However, topiramate monotherapy of infantile spasms has been applied only rarely^{8,9,12} and only in 1 study¹⁴ as initial monotherapy, according to published data. Therefore, we aimed to establish efficacy, tolerability, and safety of the use of topiramate as a first-choice drug

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in patients with infantile spasms who have a history of untreated infantile spasms.

METHODS

Patients

Fifty-four patients in whom infantile spasms was newly diagnosed between March 2000 and June 2001 were regularly examined for more than 4 years by pediatric neurologists at Beijing Children's Hospital, Capital University of Beijing, China. A spasm was defined as a sudden symmetrical contraction of the muscles of the neck, trunk, and extremities. In 50 cases, mainly flexors were involved; in 4 cases, mainly extensors. The EEG was recorded in all patients before entry into the study. The study included 43 boys and 11 girls ranging in age between 2 and 24 months (mean age, 9.2 months). Eleven cases were considered cryptogenic, whereas 43 cases were symptomatic.

The principal inclusion criterion was a newly diagnosed and previously untreated infantile spasms in which the EEG demonstrated either classic or modified hypsarrhythmia. The principal exclusion criterion was a previous treatment with ACTH, prednisolone, hydrocortisone, or any antiepileptic drug.

Study Design

The study was designed as a prospective open-label study with open end. All patients were treated according to the following protocol (Fig. 1): on the first phase (duration, 0–20 days), topiramate therapy was started with a dosage of 6.25 mg/d. Subsequently, the dosage was raised by 6.25-mg increments every 5 days (subsequent dosage, 37.5 mg/d). On the second phase (duration, 21–60 days), the therapy of the patient who did not respond to topiramate within the first phase of treatment was added with nitrazepam (dosage, 0.1–0.2 mg/kg per day). After reaching a seizure-free status, nitrazepam was withdrawn. On the third phase, if none of the mentioned treatments could control the spasms, valproate was administered as an

addition. The patients were not treated with ACTH because their parents did not agree.

Recording of EEG

Electroencephalogram was recorded with 18 electrodes (in 10–20 system) during wakefulness and sleeping induced by chloral hydrate. The EEG was evaluated before and after treatment (>5 times).

Efficacy Evaluation

The efficacy of each drug was estimated by recording the frequency of spasms and the interictal EEG findings. During long-term follow-up, efficacy data were collected at week 4 and months 2 and 3, although the patients could remain in the study for as long as 4 years. Throughout the trial, the patients' parents or legal caregivers kept diaries to record the type, frequency, and adverse events of seizures. At each visit, the investigator reviewed the patient's seizure diary, recorded any adverse experience, and monitored the vital signs and patients received EEG or video EEG. Patient visits were scheduled for day 15, months 1 and 2, and every 3 to 6 months until the final visit. The efficacy measure was the comparison of the seizure rate during the 2-week baseline period with the median seizure rate and topiramate periods with respect to the number of seizures and by calculating the response scores and response ratios. Response to therapy was divided into the following categories: (1) reduction of spasm frequency as compared with baseline (29–0%, 69–30%, and 99–70%), and (2) seizure-free status. A response range of 0% to 29% was not considered to be clinically significant because patients may have dozens of clusters and several hundred spasms per day, but individual variability in seizure frequency is often large.

Tolerability and Safety

The presence or absence of adverse events was noted in each patient. The severity of adverse events was coded using

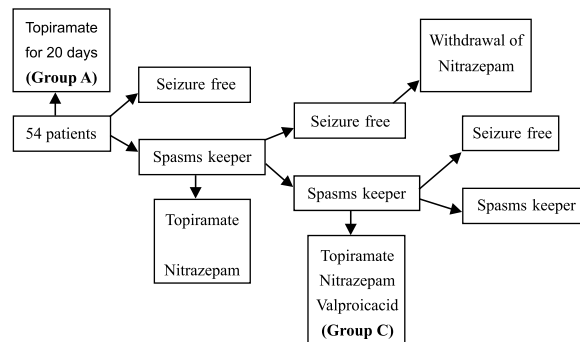


FIGURE 1. Study design.

a severity score ranging from 0 (nonexistent) to 3 (severe enough to warrant discontinuation and/or change of therapy). A score of 1 indicated mild severity of the adverse event; 2, moderate.

Ethics

The trial was conducted in accordance with the international rules of good clinical practice. Informed consent was obtained from each patient’s parents before trial-related procedures were initiated.

RESULTS

Patients Involvement

A total of 54 patients with infantile spasms received topiramate initially as first choice and throughout the whole study period of up to 4 years. The patients could be evaluated for drug safety for 3 years. Complete data sets for efficacy analyses were available from 47 patients (87.1%). Seven (12.9%) of 54 patients were withdrawn before completing the study. The reasons for the withdrawal of these patients were

seizure freedom for 2 years or more (4 patients), noncompliance (2 patients), and dissatisfaction in the treatment (1 patient).

Efficacy of Topiramate Treatment

The mean total duration of topiramate therapy was longer than 3 years. The average maximal dosage after the titration phase was 5.2 mg/kg per day (maximum dosage, 26 mg/kg per day) for all patients with topiramate treatment. Thirty-one patients remained seizure-free for more than 2 years. Their lowest dosage during the course of topiramate treatment was 1.56 mg/kg per day. The highest dosage administered to seizure-free patients was 10.7 mg/kg per day. Two nonresponders received dosages of at least 25 mg/d.

Within 10 days after initiating topiramate monotherapy, 9 patients (16.6%) were free of infantile spasms, according to the caregivers’ reports as demonstrated in Table 1. Twelve patients (22.2%) were seizure free for at least 1 month in the topiramate + nitrazepam group if nitrazepam was withdrawn after

TABLE 1. Reduction of Spasms in Patients With Infantile Spasms Treated With Topiramate for 24 to 36 Months

Treatment	Seizure Free	99–70% Reduction of Spasms	69–30% Reduction of Spasms	29–0% Reduction of Spasms	Died
Group A	9	—	—	—	—
Group B	6	4	5	—	1
Group C	16	1	3	—	2
Total	31 (57.4)	5 (9.2)	8 (14.8)	7 (12.9)	3 (5.5)

Values are given as n (%).

TABLE 2. Cumulative Incidence of the Most Frequent Adverse Effects Emerging During Topiramate Treatment of up to 3 Years

Adverse Event	No. Patients	Adverse Effects Score	Proportion (%)
Weight loss/no weight increase	12	1.8	22
Anorexia	14	1.9	26
Irritability	10	2.4	18.5
Adiaphoresis/hypohidrosis	6	1.6	11
Insomnia	7	2.6	12
Low fever (temperature, 37–38°C)	3	2.2	5

6-month therapy of combined topiramate and nitrazepam treatment. Thirty-one (57.4%) of 54 patients were free of infantile spasms for more than 2 years if all 3 treatment groups (ie, topiramate alone for group A, topiramate + nitrazepam for group B, and topiramate + nitrazepam + other drug for group C) are considered. Seventeen seizure-free patients received topiramate monotherapy for more than 2 years, including those who needed adjunctive nitrazepam intermediately. Five patients showed at least 70% seizure rate reduction, whereas 8 patients showed at least 30% seizure rate reduction and 7 patients showed poor response or did not show a response. Three patients died during the study period.

Tolerability and Safety of Topiramate Treatment

All 54 patients exposed to topiramate could be evaluated for tolerability and safety of drug treatment for at least 3 years. Adverse events occurred in 14 patients (26%) as shown in Table 2. The respective patients often had 2 or more adverse effects simultaneously. The most common adverse events were mild to moderate central nervous system–related effects, including anorexia (leading to weight loss), insomnia, and irritability. There is hint on a dose dependency of frequency and/or severity of topiramate-related adverse effects. Three of the patients died. In 2 cases, the cause of death was attributed to serious infections and refractory status epilepticus, whereas the third death was caused by hypersensitivity secondary to antibiotic treatment and, thus,

was not related to topiramate treatment. However, adiaphoresis (hypohidrosis) was another topiramate-related adverse effect, which may impair the patients' well-being, but it did not threaten their life. In summary, topiramate was well tolerated in most of patients with infantile spasms at age younger than 2 years.

DISCUSSION

This study investigated the clinical efficacy, safety, and tolerability of topiramate treatment in cases of infantile spasms associated with hypsarrhythmia in EEG. The results of the study with a long-term follow-up showed that topiramate is effective and safe for treatment of infantile spasms as a first-line therapy in newly diagnosed infantile spasms. Our study showed that within 10 days of initiating topiramate monotherapy, 9 patients (16.6%) were free of infantile spasms, according to caregiver report, and 12 patients (22.2%) were seizure free within 1 month in group B. Most responders achieved spasm-free status (31 cases; 57%) within group C. Observations from this study may have important implications for therapy as a first-line therapy in newly diagnosed infantile spasms. To our knowledge, there is only 1 recently published study¹⁴ in which topiramate was administered as initial monotherapy. In that study, Hosain et al used a maximum dosage of 27 mg/kg per day, which is similar to our maximum dosage of 26 mg/kg per day, and followed up 15 patients during the first 2 months of treatment for efficacy and tolerability. They

found 3 patients to be spasm free, 5 with more than 50% reduction, 3 with more than 25% reduction, and 4 nonresponders. The drug was well tolerated in all but 1 patient.

The mean topiramate dosage of 5.2 mg/kg per day applied in our study is relatively low compared with an older study by Glauser et al,⁹ with a mean dosage of 29 mg/kg per day; however, it is similar to a more recent study by Albsoul-Younes et al,¹⁹ who recommended a dosage of 6 to 12 mg/kg per day. Although only 9 patients (16.6%) were spasm free in our study as a result of topiramate monotherapy compared with 3 patients (38%) in the study by Glauser et al,⁹ the overall results of all treatments, including the combination of topiramate with nitrazepam and valproic acid, are rather satisfying, with 31 patients (57.4%) reaching spasm-free status and 13 patients (24%) reaching a spasm reduction of more than 30%. Our results also show that some patients respond quickly to the drug; 21 patients (38.8%) started to respond to the drug within the first month of treatment, and the proportion of responders continued to increase throughout the study.

Another important aspect of our study is the young age (<2 years) of patients at the start of treatment, which has only been shown in 28 patients by Watemberg et al¹⁶ to date. Thus, a favorable topiramate effect on the seizure rate may not be age related.¹⁰ Concerning the dosages applied, mean target dosages higher than 20 mg/kg per day were used in most studies in otherwise intractable infantile spasms (for review, see the work of Ormrod and McClellan¹⁰). Although a pharmacokinetic study by Glauser et al⁸ suggests that infants may require significantly larger topiramate doses based on body weight than do children, adolescents, and adults, our results show that this may not be necessarily the case. Most published studies used topiramate, at least initially, as adjunctive add-on therapy to classic or new-generation antiepileptic drugs such as vigabatrin.^{8-12,19,20} In contrast, we show that a reverse strategy (ie,

starting with topiramate monotherapy and escalating with nitrazepam and valproic acid) provides at least similar therapeutic benefit. Moreover, children younger than 4 years may have a particularly good tolerability of topiramate,¹⁸ especially if slow and progressive dose titration is applied.^{10,18,19}

Generally, topiramate proves to be well tolerated and safe; the adverse effects tend to occur early during treatment and to be not life threatening.^{14,21} In our study, 14 patients (26%) revealed adverse events. The most common adverse events during topiramate treatment were mild to moderate central nervous system-related effects, including anorexia, insomnia, and irritability. Eleven percent of patients were directly questioned regarding the symptoms of decreased sweating and heat intolerance, and 5% of patients have reported drug-induced fever (temperature, 37–38°C). Most adverse events occurred during dose escalation and tended to disappear when the patients became acclimated to topiramate. No acute or long-term idiosyncratic organ toxicity was observed with topiramate, which is consistent with the safety profile in earlier studies.^{11,16,19,21,22} In addition, metabolic acidosis may occur,^{21,23,24} and approximately 1.5% of patients treated with topiramate develop kidney stones in adult²⁵ and patients with metabolic acidosis, but they have not been registered in our study according to the observation of legal caregivers and the long-time follow up. The results were similar to those of the study by Ritter et al.²⁶

In newly diagnosed patients with infantile spasms in our study, the parents were often not patient enough to wait for topiramate escalation to reach the target dose. Therefore, they recorded the spasms day by day. If no spasm-free status was obtained after 20 days of topiramate therapy, nitrazepam (dosage, 0.1–0.2 mg/kg per day) was added, but withdrawn after the children maintained a seizure-free status. Nitrazepam was applied because of its favorable effect on continuous intractable seizures. Dreifuss et al,²⁷ in a comparative trial of nitrazepam

and corticotropin in patients with previously untreated infantile spasms, reported similar response in both groups (>75% reduction in 50% of the children). However, it is suggested that nitrazepam is safer and better tolerated than corticotropin. Therefore, we concluded that nitrazepam may be an effective adjunctive antiepileptic drug for patients with infantile spasms, which did not respond sufficiently to topiramate. Rintahaka et al²⁸ reported a higher mortality rate in children with epilepsy taking nitrazepam in comparison with children with epilepsy who did not take nitrazepam. The adverse effects were usually dose related and decreased with dose reduction. Our study showed that nitrazepam was an effective adjunctive drug for patients with infantile spasms. The patients' tolerance was good (ie, they did not develop serious adverse effects) if the nitrazepam dosage was not higher than 0.2 mg/kg per day and the starting dosage was 0.05 mg/kg per day. Valproic acid, used as third-choice add-on drug in patients who did not respond well to topiramate + nitrazepam treatment, was also well tolerated and further increased the proportion of patients with well-controlled infantile spasms. It remains to be proven whether these patients reveal the characteristic blood genomic profile, which correlates with seizure freedom according to a recent report of Tang et al.²⁹

Although the limitations of our study include its open-label design and the lack of a control group, the results provide evidence that topiramate is effective as a first-line therapy in newly diagnosed infantile spasms. Topiramate may not only be applied in older children¹⁸ but also in infants younger than 2 years.¹⁶ Adverse side effects^{20,21} may be managed by slow dose titration of patients with refractory partial-onset seizures.¹⁰ In summary, topiramate was well tolerated in most of patients with infantile spasms at age younger than 2 years.

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