Ineffectiveness of topiramate and levetiracetam in infantile spasms non-responsive to steroids

Open labeled randomized prospective study

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ABSTRACT

الأهداف: مقارنة بين فعالية العقارين توبيرامات وليفيتراسيتام كخط ثاني لعلاج التشنجات الطفلية بعد فشل الكورتيزونات الفموية.

الطريقة: أجريت دراسة على 40 رضيعاً في غضون عامين ممن يعانون من تشنجات طفلية غير مستجيبة للكورتيزون الفموي وتقسيمهم عشوائياً إما على عقار توبيرامات (المجموعة الأولى 1 ملغ/كلغ في اليوم لمدة 3 أيام ثم ترفع الجرعة لتصل إلى 6 ملغ/كلغ في اليوم أو عقار ليفيتراسيتام (المجموعة الثانية 10 ملغ/كلغ في اليوم لمدة 5 أيام ثم ترفع الجرعة لتصل إلى 60 ملغ/كلغ في اليوم). أجريت هذه الدراسة في قسم أعصاب الأطفال، المركز الوطني للعلوم العصبية، مدينة الملك فهد الطبية، الرياض، المملكة العربية السعودية خلال الفترة من يناير 2008م حتى ديسمبر 2010م.

النتائج: من بين 20 مريض أدرجوا في المرحلة النهائية لتحليل البيانات 11 (55%) مريض تم علاجهم بعقارٍ توبيرامات و9 (45%) بعقار ليفيتراسيتام. لوحظ أن واحداً فقط من كل مجموعة أظهر استجابة للعلاج ولم يستجب 10 من المجموعة الأولى و8 من المجموعة الثانية.

خاتمة: أظهرت الدراسة الحالية أن كلا من عقار توبيرامات وعقار ليفيتراسيتام غير فعاليين في علاج التشنجات الطفلية. المزيد من البحث الدؤوب من أجل علاج فعال للتشنجات الطفلية استجاب مريضان فقط للعلاج؛ الأمر الذي يقترح فعالية العقارين ويستحق إجراء المزيد من الاختبارات.

Objective: To compare the effectiveness of 2 novel antiepileptic drugs, topiramate and levetiracetam, as a second line treatment for infantile spasm when oral steroids fail.

Methods: Forty infants under 2 years with clinically- and EEG-proven infantile spasms that did not respond to prednisone (2mg/kg/day in 2 divided doses) were recruited and randomized into 2 groups. They were randomly assigned to either topiramate (group 1; 1mg/kg/day for 3 days then increased by 1mg/kg/day every third day up to 6mg/kg/day) or levetiracetam (group 2; 10mg/kg/day for 5 days and then increased by 10mg/kg/day every 5 days up to 60mg/kg/day). The study was conducted in the Pediatric Neurology Department at the National Neuroscience Institute of King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia between January 2008 and December 2010.

Results: Of the 20 patients included in the final data analysis, 11 (55%) were administered topiramate and 9 (45%) levetiracetam. Eighteen patients did not respond to the first drug, and subsequently to the other drug when crossed-over. Two patients with infantile spasm responded to either one drug without crossover. Their EEGs improved with time.

Conclusion: The present study demonstrated the ineffectiveness of topiramate and levetiracetam suggesting current treatment modalities are grossly inadequate underscoring the urgent need for more research efforts to overcome current deficiencies. Two patients with cryptogenic infantile spasm responded to treatment suggesting the potential for treatment of such patients with these 2 drugs, and merits further multicenter investigation.

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Infantile spasm (IS) or West syndrome is a well recognized age-related malady that begins between 4 and 6 months, with most cases occurring prior to 12 months in over 90% of affected infants. This is important as cases with IS presenting late are usually overlooked.[1] The American Academy of Neurology and the Child Neurology Society established practice guidelines for the treatment of IS in children.[2] The practice guidelines suggest that steroids are "probably effective" while vigabatrin (VGB) is "possibly effective" in treating IS. Studies proved the superiority of VGB in cases of tuberous sclerosis. However, parents express reluctance to the administration of VGB because it could predispose the patient to retinal toxicity or demyelination,[3,4] especially when the child is free of either tuberous sclerosis or blindness. At the present moment, there is no consensus on the drug of choice if adrenocorticotropic hormone (ACTH) failed to elicit the desired response, when VGB is not suitable or recommended. There is an obvious need to identify other efficacious treatment modalities for IS. Topiramate (TPM) is a monosaccharide derivative with sulfamate functionality. It was developed as an antiepileptic as McN-4853 and showed potency equal to that of phenytoin. Topiramate has been utilized in the United Kingdom since 1995 and was approved by the Federal Drug Administration (FDA) in 1997. Its exact pharmacology has not been established, but its various attributes may explain its role in the treatment of epilepsy. Its anhydrase-inhibiting effect may contribute to its antiepileptic properties.[5] Levetiracetam (LEV) is a pyrrolidone derivative unrelated to any of the antiepileptic drugs currently in use. It was approved by the FDA, the European Union, and various other countries. Its chemical name is (S)-alpha-ethyl-2-oxo-pyrrolidine acetamide.[6] Its mechanism of action is not known. Its mode of action may explain its pharmacology. In vivo studies show that inhibitory CNS effects of LEV are due to ion channel modulation.[7]

In the present study, we investigated the effectiveness of TPM and LEV in eligible IS patients in situations where oral steroids had failed.

Methods. We conducted this study in the Pediatric Neurology Department, National Neuroscience Institute of King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia between January 2008 and December 2010. The patients were in their first 2 years of life with clinically- and EEG-proven IS. The study recruited 40 patients that had failed to respond to treatment with steroids (namely, prednisone). Prednisone was used instead of ACTH due to non-availability. The inclusion criteria were infants less than 2 years of age, and IS proven clinically and by EEG manifestations. Children with epileptic syndromes other than IS (for example, Ohtahara, early myoclonic epilepsy of infancy or Lennox-Gastaut syndromes) were excluded. Infants exhibiting adverse events were documented. For ethical considerations and in accordance with the Helsinki Declaration and Belmont Report Ethical codes, we stopped recruitment at 20 patients due to the ineffectiveness of LEV and TPM. Thus, only 20 children were included in our final data analysis. The Institutional Review Board at King Fahad Medical City (KFMC), Riyadh, Kingdom of Saudi Arabia approved the study. The study was performed with parents' informed consent.

Study design. The study was performed in an open labeled randomized prospective manner. The randomization sequence was generated by the STATA computer program version 10 (STATACorp LP, College Station, TX, USA). Infantile spasm patients non-responsive to prednisone (Austria GmbH, Linz, Austria) for 2 weeks were recruited, and those that underwent the following investigations were eligible for inclusion in the study. During their initial visit, all patients in this trial underwent the following baseline investigations; namely: complete blood count, electrolytes, liver function test, EEG, MRI, CT of the brain, metabolic work up, and vital signs. Urine dipsticks were used to measure sugar twice daily or whenever required. Electrolytes were measured whenever required. The patients were carefully monitored for signs of infection. Vital signs were recorded thrice daily and whenever required.

Eligible patients were assigned to 2 groups for treatment with either TPM (group 1) or LEV (group 2) in a randomized manner. For reasons of good medical practice, a washout period for prednisone was not considered, as the infants needed medication to counter the seizures. At four weeks of therapy, patients that did not respond to either drug were subsequently crossed-over to the other drug without a washout period. If the patients responded to the crossed-over drug, the treatment was continued for 2 weeks more and examined during follow-up subsequently. At six weeks, treatment was continued for a further 2 weeks if either drug elicited a positive response. Patients that did not show a response to treatment were considered as failed treatment. Successful treatment was defined as a decrease in clinical seizures by more than 50% as well

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as disappearance of abnormal EEG findings. Failure of treatment was defined as inability to achieve successful treatment.

The TPM was initially administered at a dosage of 1mg/kg/day for 3 days then increased by 1mg/kg/day every third day up to 6mg/kg/day. Patients achieving the primary end-point at any stage above the dosage of 5mg/kg/day would be maintained on that dose until the end of the 4 weeks of therapy. After 4 weeks of therapy, the patient was evaluated for achievement of the primary end-point. If the primary end-point was not achieved LEV was administered and dosage escalated as per protocol.

Likewise, LEV was administered at a dose of 10mg/kg/day for 5 days and then increased by 10mg/kg/day every 5 days up to 60mg/kg/day. Patients achieving the primary end-point at any stage above the dose of 40mg/kg/day would be maintained on that dose until the end of the 4 weeks of therapy. After 4 weeks, the patient was evaluated for achievement of the primary end-point. If the primary end-point was not achieved TPM was administered and dosage escalated as per protocol.

The infants' parents were informed regularly and when needed regarding their infants' progress. The parents notified the team of any adverse events as well as frequency and duration of seizures.

Descriptive statistics for the study was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 18.

Results. Twenty patients received treatment. Seventy percent of the infants were males. Of the 20 infants, 2 (10%) were diagnosed with cryptogenic infantile spasm. Eleven patients received TPM and the remaining 9 received LEV with a random allocation. However, 2 (10%) of the patients with the cryptogenic type of IS responded successfully to either one of the drugs (**Table 1**) Medication was crossed-over for 18 non-responsive patients. These 18 patients did not respond to either drug when administered individually with one drug and following crossover, with the other drug.

Discussion. The present study intended to include at least 40 patients with IS in the investigation, with 20 patients on each drug (TPM or LEV). However, it became clear to the investigators that both drugs failed to control the spasm or to normalize the EEGs in the first 18 of 20 patients. Consequently, the investigators were compelled to terminate the study prior to completion due to ethical considerations when the ineffectiveness of the drugs (TPM and LEV) became apparent during the course of the study.

In the present study involving 20 children aged less than 2 years suffering from IS, only 2 patients with the cryptogenic type of the disease became seizure-free after 10 days of treatment, one with TPM and the other with LEV without crossover indicated by return to normal EEG patterns. It is of interest that 2 patients with cryptogenic IS responded to treatment suggesting a potential trend for treatment of such patients with these 2 drugs; however, this requires a larger sample size and a multicenter investigation to conclusively determine the effectiveness of TPM and LEV.

The use of TPM in IS has been reported by Glauser et al,[8] who noted that only 4 of 13 (30.8%) patients with symptomatic spasms responded when doses up to 25 mg/kg/day were used. The most frequently reported adverse effects were: drowsiness, irritability, hyperthermia, and anorexia.[9] In an earlier open label study on the long-term response to TPM in 8 children with IS, 7 (87.5%) patients experienced >50% spasms

Table 1 - Ineffectiveness of topiramate and levetiracetam in infantile spasms non-responsive to steroids.

Gender	Age of onset	Symptomatic or idiopathic infantile spasm	Drug	Clinical response
F	4 m	Symptomatic	TPM	Failed
F	3 m	Symptomatic	LEV	Failed
M	2 D	Symptomatic	TPM	Failed
M	15 m	Symptomatic	LEV	Failed
F	1st day	Symptomatic	TPM	Failed
F	4 m	Symptomatic	LEV	Failed
M	1 m	Symptomatic	TPM	Failed
M	16 m	Symptomatic	LEV	Failed
M	1 m	Symptomatic	TPM	Failed
M	1 D	Symptomatic	LEV	Failed
M	7 m	Symptomatic	LEV	Failed
M	1 m	Symptomatic	TPM	Failed
M	10 m	Symptomatic	TPM	Failed
M	8 m	Symptomatic	LEV	Failed
M	4 m	Cryptogenic	TPM	Succeeded
M	5 m	Cryptogenic	LEV	Succeeded
F	1 m	Symptomatic	TPM	Failed
M	5 m	Symptomatic	TPM	Failed
M	3 m	Symptomatic	TPM	Failed
F	3 m	Symptomatic	LEV	Failed

m - months, D - days, TPM - topiramate, LEV - levetiracetam

reduction, and 4 of 8 (50%) became seizure-free on a mean dose of 29mg/kg/day.[8] It is not possible to generalize the findings of these studies due to the very small sample sizes.

Studies on TPM performed in recent years have shown it to be nontoxic to, and well tolerated by infants. In the present study, TPM and LEV appeared to be well tolerated in the study population, but a previous study implicates TPM in development of asymptomatic kidney stones.[10] In an open label study undertaken by Hosain et al[11] on 10 newly diagnosed cases of IS, treatment with TPM with doses up to 20mg/kg/day revealed none had symptomatic acidosis. Of these 10 patients, one patient was seizure-free, 4 had a 50% reduction, and 3 had at least 25% reduction.[11] Likewise, a number of other studies have shown the limited efficacy of more than 50% reduction in spasms in a few patients following administration of TPM.[8,11,12] However, Hrachovy et al[13] noted that ≥50% reduction in seizure rate is not regarded as a reliable end-point in West syndrome. The normalization of EEG is thought to be the key measurement of efficacy.

A multicenter, retrospective, and uncontrolled study[9] to evaluate the effectiveness and safety of LEV in 81 children younger than 4 years with refractory epilepsy observed that LEV maintained its effectiveness in patients with focal epilepsy and West syndrome. The study noted LEV was well tolerated. The study recorded adverse events in 18 (34%) patients of which the main side effects were drowsiness and nervousness. These adverse events were either within tolerable limits or were resolved in time with dosage reduction or discontinuation of the drug. Lawlor and Devlin[14] reported a case of successful cessation of seizures and resolution of seizure activity as demonstrated by normalized EEG following treatment with LEV in an 11-month-old infant with a 5-months history of seizures and a 3-months history of IS resistant to treatment with Clobazam.

The most crucial outcome of the present study is the demonstration of the ineffectiveness of both TPM and LEV in ameliorating IS. This finding was ascertained by demonstration of abnormal EEG in the treated patients. It is cautioned that a decrease in symptoms alone is insufficient evidence for effectiveness of treatment. The most accurate means of determining effectiveness of the treatment is attainment of normal EEG.[13] The literature does not offer other efficacious treatment modalities for IS, and the present study has clearly demonstrated the ineffectiveness of TPM and LEV in alleviating IS. This situation underscores the urgent need for more research efforts to overcome current deficiencies pertaining to the treatment of symptomatic IS.

In conclusion, the present study has demonstrated that both TPM and LEV are not effective in controlling seizures or in normalizing the EEG in symptomatic IS. Two patients with cryptogenic IS responded to treatment suggesting the potential for treatment of such patients with these 2 drugs; however, this requires a larger sample size and a multicenter investigation to conclusively determine the effectiveness of TPM and LEV.

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