Epilepsy & Behavior 45 (2015) 261–264

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Cognitive adverse events of topiramate in patients with epilepsy and intellectual disability

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ARTICLE INFO

Article history:
Received 27 August 2014
Revised 26 December 2014
Accepted 31 December 2014
Available online 2 April 2015

Keywords:
Topiramate
Antiepileptic drugs
Cognition
Adverse events
Tolerability
Intellectual disability

ABSTRACT

Topiramate (TPM) is an effective antiepileptic drug (AED). A high proportion of patients, however, experiences cognitive adverse events (CAEs), especially in verbal fluency, memory spans, and working memory. To our knowledge, CAEs of TPM have not been studied systematically in patients with intellectual disability (ID). This may be due to the fact that many of those patients are not able to follow test instructions properly and that neuropsychological instruments are not validated for that group. Cognitive deterioration in patients with ID may thus easily be overlooked. Topiramate is in frequent use in persons with ID. We included 26 consecutive patients with epilepsy and ID in this observational study who had undergone neuropsychological examinations as part of clinical routine before and after the introduction of TPM into the therapeutic regimen (n = 4) or before and after the withdrawal of TPM (n = 22). Examinations under TPM showed reduced cognitive speed, reduced verbal memory, reduced verbal fluency, and reduced flexibility compared to examinations without TPM. Despite some limitations (especially small sample size, high interindividual variation of the results dependent on the degree of ID, effects of other – limited – changes in the therapeutic regimen), our study indicates that TPM in persons with epilepsy and ID may lead to CAEs comparable to those in persons with normal intelligence. Neuropsychological testing is mandatory in order not to miss CAEs that might severely impair quality of life.

1. Introduction

Topiramate (TPM) is an antiepileptic drug (AED) currently licensed in Germany as monotherapy for focal and generalized epilepsies in patients from six years on and as add-on treatment for focal and generalized epilepsies in patients from two years on as well as for Lennox–Gastaut syndrome (LGS). It is also licensed for the prophylactic treatment of migraine. Topiramate has a high antiepileptic efficacy but is frequently associated with psychiatric [1,2] or cognitive [3–5] adverse events (AEs), especially word-finding difficulties. Cognitive AEs have been shown to have a greater effect on treatment discontinuation of TPM than lack of efficacy [6]. Because of its broad antiepileptic efficacy in focal and generalized epilepsies and especially in LGS [7], the drug is in frequent use in patients with intellectual disability (ID). Cognitive decline in persons with ID may be overlooked or misinterpreted. Therefore, it is necessary to monitor cognitive AEs thoroughly. According to international consensus guidelines into the management of epilepsy in adults with an intellectual disability, baseline cognitive and behavioral assessments should be made and then remeasured after drug changes [8]. Validated measures should be preferred. Neuropsychological examinations, however, may be difficult to perform as the patients may not be able to follow test instructions and the tests are validated only for persons with normal intelligence.

The aim of our study was to assess how TPM affects cognitive functions in persons with epilepsy and ID and whether the effects are comparable with those in patients with normal intelligence.

2. Methods

Bethel Epilepsy Centre is a tertiary referral center for epilepsy with a specialized ward for patients with epilepsy and ID. Neuropsychological testing was done as part of clinical routine before adding TPM to an existing drug regimen and again after reaching the target dose under steady-state conditions and vice versa before tapering TPM and after withdrawal of the drug. For statistical purposes, this was unified to examinations with or without the presence of TPM, regardless of the chronological order. The degree of the ID had been assessed according to ICD-10 criteria by clinical judgment based on thorough observation and examination during inpatient treatment. Patients who could not be examined using formal neuropsychological instruments were tested in a semistandardized manner by occupational therapists. The results of these semistandardized tests will not be presented in this paper as a sufficient sample size is not reached yet.

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http://dx.doi.org/10.1016/j.yebeh.2014.12.043
1525-5050/

The neuropsychological tests used in this study covered the domains of memory, cognitive flexibility, and cognitive speed.

2.1. Memory

Verbal memory was assessed by a German version of the story recall from the Rivermead Behavioural Memory Test (RBMT) [9,10]. Immediately after the presentation of the story, the subject is asked to repeat the story. After an interval of 10–20 min filled with nonverbal tasks, the subject is asked to recall the story again. The performance score is built from the number of items of the story recalled (maximum: 21 items).

Verbal short-term memory and working memory were assessed by the digit span forward and backward task from the HAWIE-R (Hamburg Wechsler Intelligenztest für Erwachsene [11]).

2.2. Executive function

Semantic verbal fluency was assessed by a task requiring the subject to say as many words as possible from a special category (animals, food, names); 1 min is given for each category (Regensburger Wortflüssigkeitstest [12]). The number of produced items is taken as the performance score. The design fluency was examined by the Five-Point Test [13]. It consists of five-point matrices, and the subject is asked to produce as many different patterns as possible by connecting two, three, four, or five points of a matrix within 3 min. The number of correct patterns and the number of repetitions were used as performance measures.

Cognitive flexibility was assessed by means of the Trail Making Test "Switching" condition from the D-KEFS (Delis Kaplan Executive Function System) [14]. It requires the subject to trace the numbers 1 to 16 and the letters A to P which are displayed in an irregular arrangement on a sheet of paper. In doing this, the subject has to alternate between numbers and letters in ascending order. The time needed to complete the task is used as the performance score.

2.3. Cognitive speed

Cognitive speed and speed of spatial visual exploration were assessed by means of the Trail Making Test from the D-KEFS. This test consists of four tasks and requires the subject to cancel the number "3" in a scanning task and to trace the numbers 1 to 16 and the letters A to P, which are displayed in an irregular arrangement on a sheet of paper, as quickly as possible in ascending order. The fourth task is a simple psychomotor task. The time needed to complete the tasks is used as the performance score. Psychomotor speed with additional cognitive challenge was assessed by means of the digit symbol test from the HAWIE-R. This task contains nine digit–symbol pairs, and the subject must write the appropriate symbols to a line of digits. The subject must write as many symbols as possible within 2 min. The performance scores for these tests were the number of correct symbols.

The neuropsychological tests were administered in the same order. However, only subsets of the tests were administered in individual patients. The testing took on average 50 min.

We assessed demographical data, data concerning epilepsy type and duration, concomitant drugs, seizure frequency, and psychosocial variables, as well as MRI findings. The degree of ID was estimated by clinical judgment according to ICD-10 criteria.

Statistical analysis was performed primarily with descriptive and explorative methods using SPSS 21.0. If results, on and off TPM, for at least six patients were available for a given neuropsychological test, a Wilcoxon test was done. Benjamini–Hochberg correction of false-detection rate was used to correct for multiple testing [15]. The mean AED load was computed for both points of time (neuropsychological examination under TPM vs. examination without TPM) expressed as the sum of defined daily doses (DDDs) according to the WHO DDD list [16]. Topiramate itself was not included in the sum of DDDs. The rationale for this was the following: as this was not a prospective study but an evaluation of routine procedures, there were additional changes in the medication besides the withdrawal or introduction of TPM. The mean drug load (*not* including TPM) was assessed in order to get an overview of the burden of AEDs that might have an impact on cognitive performance by itself. The mean drug load with and without TPM was then compared by t-test.

Table 1
Patients' characteristics.

Sex	15 females and 11 males
Age at first examination	37.2 ± 13.5 years (19–67)
Age at epilepsy onset	10.0 ± 14.9 years (0–53)
Duration of epilepsy	26.0 ± 13.7 years (3–50)
Epilepsy syndrome	23 focal, 1 generalized, and 2 focal + generalized
Degree of intellectual disability (ID)	17 learning disability/mild ID and 9 moderate–severe ID
DDDs with TPM (not including TPM)	2.80 ± 1.48
DDDs without TPM	3.05 ± 1.22

3. Results

Twenty-six patients with epilepsy and ID underwent neuropsychological examinations before and after the introduction or before and after the withdrawal of TPM as part of clinical routine. Topiramate was introduced in 4 and withdrawn in 22 patients. The mean dose of TPM at the time of neuropsychological examination under TPM was 306 ± 158 mg/day (range: 100–800; serum trough concentration: 6.2 ± 4.2 μg/ml (range: 1.3–20.4)). Table 1 shows the demographic and epilepsy data. These data show that the majority of our patients had a long-standing epilepsy, in most cases focal, and that about two-thirds of the patients had milder forms of intellectual impairment.

Table 2 shows the results of examinations on and off TPM for $n \geq 6$. All tests except digit span backward, naming test, and RWT (letter B) showed significant differences on and off TPM, indicating an impairment of cognitive functioning by TPM in patients with ID. This means, in detail, that the patients, when tested without TPM, showed significantly better cognitive speed, verbal short-term memory and working memory, and semantic verbal fluency. The results for RWT Animals, digit span forward, and RWT Food remained significant after correcting for multiple testing. The mean drug load (±SD) under TPM was 2.80 ± 1.48 (not including TPM) and 3.05 ± 1.48 at the time of neuropsychological examination without TPM. The values for the mean drug load at both points of time did not differ significantly.

4. Discussion

It is well known that TPM may affect cognitive functioning [17]. Patients on TPM have been shown to perform significantly worse

Table 2
Results of examinations under and without TPM for $n \geq 6$.

Test	n	Mean ± SD		p-Values[a] (two-sided)
		Under TPM	Without TPM	
TMT psychomotor	6	132 ± 83.1	70.0 ± 54.5	0.031
Digit span forward	14	3.57 ± 0.65	4.43 ± 0.85	0.004*
Digit span backward	11	2.18 ± 1.54	2.73 ± 1.49	(0.266)
RWT Animals	19	7.37 ± 4.34	11.5 ± 4.95	0.001*
RWT Food	13	6.92 ± 3.66	10.7 ± 5.71	0.014*
RWT letter B	6	2.67 ± 1.86	5.17 ± 2.64	(0.313)
Naming test	8	78.8 ± 12.4	81.8 ± 5.92	(0.656)

TMT: s; digit span: counts; RWT: counts per minute.
[a] Two-sided, exact Wilcoxon test.
* Significant after adjustment for multiple testing according to Benjamini–Hochberg [15].