Conversion from carbamazepine or oxcarbazepine to topiramate in adolescents and adults with epilepsy


Objective – To explore effectiveness, tolerability and changes in quality of life in patients with epilepsy converting to topiramate (TPM) from carbamazepine (CBZ) or oxcarbazepine (OXC) due to insufficient effectiveness and/or tolerability. Methods – A multicenter, open-label, non-interventional trial was used to examine patients (≥12 years) with epilepsy, changing to TPM monotherapy from baseline mono- or combination therapy with CBZ or OXC. TPM was added to the existing antiepileptic drug (AED) treatment and started at a dose of 25 mg once daily. The dose was titrated up with 25 mg/day increments, once every 1–2 weeks, until a final dose between 50 and 200 mg/day was reached. On the basis of clinical judgment, the treating physician decided whether or not the existing AED treatment with CBZ or OXC could then be withdrawn. Type and number of seizures, preferred TPM dose, quality of life (QOLIE-10 questionnaire), subjective perception of improvement and adverse events (AE) were documented. Results – 140 patients (53.5% women, mean age 47 years) decided to switch to TPM due to insufficient effectiveness (75% of patients) and/or poor tolerability (80%) of the CBZ/OXC treatment. Average duration of follow-up was 24 weeks with an overall discontinuation rate of 19.3%, mainly due to AEs (12.1%). At study endpoint, the intended shift to TPM monotherapy was achieved in 73% of patients at a median TPM dose of 100 mg/day. A seizure reduction of ≥50% was achieved in 91% of patients in the last scheduled period (weeks 12–26); 62% of patients entering that period remained seizure free. Quality of life at endpoint improved significantly when compared with baseline for all domains of QOLIE-10 (P < 0.001). Most frequent AEs (reported by ≥5% of patients) were paresthesia (9.3%), weight loss (7.9%), convulsions (5.7%) and memory disorders (5.0%). Conclusion – In patients with epilepsy, previously not satisfactorily treated with CBZ or OXC, conversion to TPM may result in an improvement in seizure control as well as in quality of life.

Introduction

Carbamazepine (CBZ) and oxcarbazepine (OXC) are antiepileptic drugs (AEDs) frequently used as first-line monotherapy for localization-related epilepsies (1, 2). Until recently, it was thought that less than 50% of patients become seizure free for at least 1 year on their first prescribed AED, and that upon treatment failure chances to become seizure free with a second or third AED given in monotherapy were decreasingly lower (13% and 1% respectively) (3, 4). This notion was lately challenged by Luciano...
and Shorvon who showed that in individuals with refractory epilepsy changes in AED therapy are associated with a comparatively high seizure freedom rate (5). This suggests that a subset of patients with apparently untreatable epilepsy might still become seizure free and that the overall situation of individuals with epilepsy might be less dismal than was previously thought (5). However, evidence qualifying suitable AED combinations and guidelines to determine which AED should be chosen as either first or second add-on therapy, or as second or third monotherapy, are lacking. Some evidence for a potential synergistic effect of specific AED combinations derives from both clinical studies and basic preclinical research (6–9), but for most AEDs the best combination or best sequence is unknown. In fact, efficacy data after conversion of add-on therapy to subsequent monotherapy have so far been provided for just a few AEDs and some authors question whether there is a difference in efficacy between add-on and monotherapy at all (10–12).

For the majority of epilepsy patients, the selection of a second or third AED is solely based on the treating physician’s personal experience and preference.

Topiramate (Topamax®; Janssen-Cilag GmbH, Neuss, Germany) is approved for the use in add-on therapy or monotherapy of epilepsy in children and adults, based on its proven efficacy in newly diagnosed patients as well as in patients with drug-refractory epilepsy (13–16). Due to its low potential for pharmacokinetic interactions, its good tolerability at moderate doses, and its broad spectrum anticonvulsant efficacy (13, 15, 17), topiramate (TPM) also appears to be a promising option as initial monotherapy.

To explore the effectiveness of TPM after failure of a first or second AED, we decided to study patients in whom a transition from CBZ or OXC to TPM was necessary due to insufficient effectiveness or tolerability of the baseline AED. A brief disease-specific quality-of-life questionnaire (QOLIE-10) was used to explore the impact of treatment on seizure occurrence and general well-being (18, 19).

**Methods**

A multicenter, open label, single arm, non-interventional trial was conducted in 45 neurology practices and ambulatory care centers across Germany. Patients (age ≥12 years) with any type of epilepsy or epilepsy syndrome, being treated with CBZ or OXC, were eligible if the treatment results were unsatisfactory and a conversion to TPM was considered. During the initial visit, baseline demographics and disease characteristics were recorded as well as previous and current AED use. Seizure frequency during the past 3 months was recorded retrospectively, including all seizure types. A follow-up of 26 weeks was planned with visits at baseline, 6, 12 and 26 weeks during which type and frequency of the seizures, currently used drugs and doses, as well as adverse events (AEs) were documented.

**Quality of life**

Quality of life was assessed at the start and end of the study using QOLIE-10 (19), a disease-specific screening tool derived from QOLIE-89 (19). Change in therapy was rated on a four-point rating scale by physicians and patients with regard to effectiveness and tolerability of TPM (much improved, a little improved, unchanged or worse), the overall change (much better, a little better, unchanged or worse) and the change in the clinical situation as viewed by the patient.

Tolerability parameters included documentation of treatment-emergent AEs throughout the trial. Body weight was assessed at the start and final visits.

**Data management and statistical analysis**

Documented data were checked for consistency and completeness and then entered into the database using double data entry. AEs were coded according to WHO Adverse Reaction Terminology. Monthly seizure rates were calculated as the number of seizures between two consecutive visits, divided by the number of days in the observation period, and multiplied by 30.5.
Descriptive statistical methods, like frequency counts and summary statistics with mean, standard deviation (SD), median and range, were used. Moreover, pre–post comparisons were performed using Wilcoxon’s test for dependent samples. P-values are two sided and have to be interpreted as exceeding probabilities. If not stated otherwise, results are presented as arithmetic mean ± SD. Confidence intervals (95% CI) for percentages were calculated according to Clopper and Pearson (22). No adjustment for multiple testing was performed.

The evaluation was performed according to the intention-to-treat (ITT) principle. All enrolled patients who had received at least one dose of TPM, and who had at least one follow-up efficacy assessment were available for the ITT efficacy analysis. Efficacy data were presented as changes (reductions) in epileptic seizure frequency or as response rates, where response was defined as an at least 50% (75% or 100%) reduction in seizure frequency.

QOLIE-10 was analyzed according to published literature (19) using three subscales ('epilepsy effects', 'mental health' and 'role function') as well as a total score. QOLIE-10 scores were transformed to values between 0 (worst) and 100 (best). The analysis was performed with the program package SAS version 9.1 (SAS Institute Inc., Raleigh, NC, USA). One missing question was allowed as a maximum, and the missing value was replaced by the mean score of the answers provided by the other patients.

Ethics

The study was performed in accordance with the German drug law, European Union regulations as well as European pharmacovigilance guidelines. An independent ethics committee was notified about the trial.

Results

Demographics and baseline characteristics

A total of 142 patients were selected in 45 investigational sites and enrolled in the study between 29 October 2003 and 19 January 2006. One hundred and forty of these patients were eligible for the ITT analysis.

Demographic data are summarized in Table 1. Fifty-four percent of patients were women, 72% had CBZ as baseline anticonvulsant drug. During the 3-month retrospective baseline, 84% of patients experienced one or more epileptic seizures.

Table 1: Demographic data and disease characteristics (N = 140)

| Gender | Female n (%) | 75 (53.6) |
|        | Male n (%)   | 65 (46.4) |
| Age (years) | Mean ± SD | 47 ± 18 |
| Median (range) | 47.5 [12–90] |
| Age categories (years) | <18 | 7.9% |
|                  | 18 to <60 | 65.0% |
|                  | ≥60 | 27.1% |
| Duration of epilepsy (years) | Mean ± SD | 14.3 ± 13.7 |
| Median (range) | 9.5 [0–59] |
| Age categories (years) | <1 | 9% |
|                  | 1 to <5 | 18% |
|                  | ≥5 | 73% |
| Epilepsy classification | Primary generalized | 26% |
|                  | Partial onset | 71% |
|                  | Others/unknown | 3% |
| Seizure types at baseline (% of patients)* | Partial seizures | 16.4% |
| | Simple partial | 25.7% |
| | Complex partial | 25.7% |
| | Secondarily generalized tonic–clonic seizures | 30.7% |
| Generalized seizures | Primary generalized tonic–clonic seizures | 21.4% |
| | ‘Absences’ | 5.7% |
| | Other seizures | 4.3% |
| No seizures | 15.7% |

*Multiple answers possible.

The median observation period was 26 weeks (mean ± SD 24 ± 7 weeks, range 3–33 weeks). A total of 19.3% of the 140 patients discontinued treatment prematurely due to AEs (12.1%), loss to follow-up (5.0%), lack of efficacy (2.9%) or medication non-adherence (1.4%) respectively.

Disease characteristics

Most commonly reported seizure types during the 3-month retrospective baseline were secondarily generalized tonic–clonic seizures (31%) and complex partial seizures (26%) followed by primary generalized tonic–clonic seizures (21%), simple partial seizures (16%) and ‘absences’ (5.7%) (Table 1). Overall, the mean monthly seizure rate during the 3-month baseline was 6.0 ± 20.8 (median 1); this included 22 patients (16%) who had no seizures during baseline. However, 58% of patients did have one or more seizures per month at study entry (Table 1).

Antiepileptic therapy and reasons for switch

At the start of the study, 72% of patients were being treated with CBZ and 28% received OXC.
Fifteen percent of patients received one to two other AEDs in addition to CBZ or OXC. 42.9% of patients had been previously treated with one AED, 26.4% with two AEDs, 17.1% with three AEDs and 13.6% of patients with four or more AEDs. On average, patients reported 1.2-1.4 ongoing concomitant diseases for which they received 1.0-1.8 concomitant medications other than AEDs.

The median doses of CBZ and OXC at the beginning of the study were 800 mg (mean ± SD 825 ± 397 mg) and 1200 mg (mean ± SD 1254 ± 555 mg) respectively. Lack of efficacy (75.0% of patients) and/or poor tolerability (80.0%) were stated as the reason for the decision to try to switch from CBZ/OXC to TPM (55.7% of patients stated both reasons). Table 3 summarizes the side effects that were reported for CBZ and OXC prior to study entry.

### Add-on topiramate and shift to monotherapy

Topiramate was given to all patients. At study endpoint, 73% of patients were on TPM monotherapy for an average of 18.5 ± 7.3 weeks and 27% of patients still received one or more additional AEDs. Distribution of TPM doses at endpoint is displayed for mono vs add-on therapy in Fig. 1. The mean (±SD) daily dose of TPM was 156 ± 85 mg (median 150 mg) in monotherapy and 114 ± 84 mg (median 100 mg) in add-on therapy. The TPM dose used in monotherapy was statistically significantly higher than in add-on therapy (P < 0.005). Of the 38 patients who received additional AEDs, 32 were treated with one additional AED (mostly OXC or CBZ), five were treated with two other AEDs, and one patient with three AEDs in addition to TPM.

### Seizure frequency

The number of monthly seizures in between visits, and the change in the monthly seizure rate from baseline are displayed in Figs 2 and 3. Comparing the number of seizures between various visits and baseline, a significant reduction from 6.0 ± 20.9 to 1.23 ± 5.86 seizures/month was found, i.e. a relative reduction in seizure rate of 61 ± 180% (P < 0.001). Seizure reduction reached statistical significance already after 6 weeks (visit 2; P < 0.001). At subsequent visits, seizure frequency fell even more. In the final period, i.e. between week 12 and week 26, the mean monthly seizure rate diminished to 0.80 ± 2.69 (n = 118 patients). The mean monthly seizure rate for the entire TPM treatment period was 1.36 ± 5.08 (Fig. 2).
Of the 98 patients who experienced seizures during the baseline period, 91% had a reduction in seizures of at least 50% (95% CI: 83.3–95.7%). Overall, 60 of the 140 patients (43%) were seizure free during the entire trial. This included 43 patients who had seizures at baseline, and 17 of 22 patients who had been without seizures during the 3-month baseline (Fig. 4). Further results are listed in Table 5.

At the end of the trial, 79.3% of patients considered themselves as little or much better than at the start of the study. This corresponds well to the number of 80.0% of patients who were considered little or much better by their treating physician. Effectiveness of the TPM treatment was rated good or very good by 82.1% of physicians (results not shown).

Quality of life
The mean total QOLIE-10 score significantly improved, i.e. from 56 ± 20 at baseline to 74 ± 19 at the end of the trial (change +17.7 ± 21.9, P < 0.001) in 102 patients with assessments both at the start and end of the trial (Fig. 5). There were no relevant differences in QOLIE scores between genders nor regarding seizure frequency at baseline (<1 vs ≥1 seizures/month).

Tolerability
During the study, AEs were reported by 48 of the 140 patients (34%). The majority of reported AEs were assessed as causally (possibly, probably or very likely) related to the use of TPM (Table 4). Body weight decreased by 1.9 ± 3.7 kg over the course of the trial (P < 0.001). A total of 16 serious adverse events (SAEs) were reported by

Table 4  Adverse events reported on topiramate during the study

<table>
<thead>
<tr>
<th>Adverse event (preferred term)</th>
<th>% patients with at least one AE report</th>
<th>% patients with at least one related AE</th>
<th>% of patients discontinuing due to AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia</td>
<td>9.3</td>
<td>9.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>7.9</td>
<td>7.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Convulsions</td>
<td>5.7</td>
<td>2.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Memory disorder</td>
<td>5.0</td>
<td>5.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Depression</td>
<td>4.3</td>
<td>4.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.3</td>
<td>2.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Speech disorder</td>
<td>3.6</td>
<td>3.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Aggressive reaction</td>
<td>2.9</td>
<td>2.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.9</td>
<td>2.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2.9</td>
<td>2.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2.1</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Headache</td>
<td>2.1</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.1</td>
<td>1.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.1</td>
<td>1.4</td>
<td>0.7</td>
</tr>
<tr>
<td>% with any AE</td>
<td>34.3</td>
<td>26.4</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Listed are adverse events occurring in >2% of patients treated with topiramate. Some patients could have more than one adverse event.

Overall, 60 of the 140 patients (43%) were seizure free during the entire trial. This included 43 patients who had seizures at baseline, and 17 of 22 patients who had been without seizures during the 3-month baseline (Fig. 4). Further results are listed in Table 5.

At the end of the trial, 79.3% of patients considered themselves as little or much better than at the start of the study. This corresponds well to the number of 80.0% of patients who were considered little or much better by their treating physician. Effectiveness of the TPM treatment was rated ‘good’ or ‘very good’ by 82.1% of physicians (results not shown).
nine patients. All but one SAE (medically significant elevation of hepatic enzymes) were rated as such due to patient hospitalizations. SAEs reported were convulsions (8× in six patients), increase in hepatic enzymes, brain neoplasm, staphylococcal infection, acute renal failure, hepatic encephalopathy, asthenia, impairment of psychomotor skills and personality disorder (each reported by one patient). While 11 SAEs were not considered causally related to TPM treatment, five SAEs in two patients were reported to be at least possibly related to the treatment with TPM. One of these patients suffered convulsions requiring hospitalization. The other was hospitalized due to personality change. The other was hospitalized due to personality disorder (each reported by one patient). This corresponds well to the 79% of patients who rated themselves as ‘much better’ or ‘slightly better’.

Discussion

The present trial explored efficacy outcomes in patients with epilepsy who were treated with TPM after therapy failure with CBZ or OXC. More than half of the patients decided to switch to TPM because of both lack of tolerability and lack of efficacy; 24% switched solely due to insufficient tolerability. Doses used of CBZ and OXC were within the recommended dose range for effective seizure control (4). Looking at the existing baseline seizure frequency on AED therapy, it seems fair to conclude that the majority of these patients fit the definition of therapy resistance (23). Despite this, the monthly seizure rate dropped significantly with a further decrease at the subsequent visits for all seizure types already during the first 6 weeks of TPM treatment. Twenty-one percent of patients had a diagnosis of primary generalized tonic–clonic seizures, and responder rates appeared to be slightly higher for these patients with primary generalized epilepsies compared with other seizure types, which is in accordance with earlier reports [e.g. (24)]. This is also consistent with the known broad anticonvulsant spectrum of TPM (25). Moreover, these results suggest that the positive results with TPM were not solely due to enrollment of patients with primary generalized seizures, but also due to effectiveness of TPM in partial epilepsies.

On the other hand, certain study results are somewhat at odds with previously published data (4). Extrapolating from treatment results of studies in newly diagnosed epilepsy, it became common knowledge that, if a patient did not respond to initial therapy, chances to obtain a satisfactory response by modifying the AED therapy were only minimal (4).
However, some recently published retrospective data indicated that attempting further treatment modifications, such as combination therapy, may result in 28% of patients becoming seizure-free for at least 1 year (5). This suggests that treatment modifications, such as adding on another AED, can result in a significant reduction in seizure and even in an increase in seizure free rates. Our results support the latter retrospective data though differences in patient selection (seizure duration, number of previously used drugs) and treatment duration exist (6 vs 19 months in Luciano’s study) (5).

The current study is in so far unique in its kind as few data are presently available on the conversion from one monotherapy to another (e.g. with TPM). Some studies are, however, available (26, 27) and they do mimic to some extent the situation that results when clinicians convert their patients from an existing to a new AED administered in monotherapy. However, these trials also raise ethical concerns (e.g. randomizing patients to a subtherapeutic treatment regimen) and show limitations regarding clinical relevance, e.g. forced exit criteria due to efficacy or seizure severity. Therefore, conducting a study in a naturalistic setting with allowance of baseline drug withdrawal, based on patients’ seizure response, is a safer approach. Results have to be interpreted with caution, however, due to the open-label design and the absence of a control group.

Close to 30% of patients could not be changed to TPM monotherapy, a decision based on the physician’s clinical expertise. Whether this decision was based on insufficient effectiveness of TPM monotherapy, or was due to other considerations such as the patient’s desire to maintain current seizure control with the existing (combination) treatment regimen, was not documented.

The average daily dose at which TPM was used was slightly below 150 mg with a median of 100 mg. Earlier studies have indicated that a good therapeutic effect may be achieved with even lower doses of TPM in individual patients, and that 100 mg per day is usually sufficient in monotherapy for newly diagnosed patients (13, 20). Some refractory patients might benefit from higher doses. Raising the AED dose in apparently refractory patients could result in an approximately additional 20% of patients becoming seizure free (28). This might explain why, on average, somewhat higher doses were used for TPM monotherapy in this study when compared with the initial monotherapy studies.

The high retention rate in this trial, i.e. 80.7% of patients completing 26 weeks of TPM treatment, is an overall indicator of both good effectiveness and tolerability. This was associated with a significant improvement in disease-related quality of life as measured by QOLIE-10 and its individual subscales.

This finding is also in line with the AE profile and the good overall tolerability assessment. At the start of the study, 18.8% of patients on CBZ had listed weight gain as a reason to switch (5.1% of patients treated with OXC). Weight loss was reported as an AE on TPM (by 7.9% of patients), but did not appear to represent a relevant tolerability issue because only 1.4% of patients discontinued TPM treatment because of the reported weight loss. In addition, the overall incidence of weight loss was most likely higher than was reported as an AE. The weight-lowering effect of TPM has been shown in several trials with epilepsy patients as well as in non-epilepsy indications (29–31). TPM-induced weight reduction appears to be related to baseline body mass index, treatment duration, as well as dose of TPM used, and plateaus over time. This has been shown for both adults and children (32, 33). Mechanisms are potentially diverse including reduction in food intake and body fat gain with an associated decrease in cholesterol and triglyceride levels (34).

In the present trial, we had few reports of cognitive impairment (5.0% of patients reported memory disorders), but we have to add that we did not specifically test for any subclinical cognitive impairment with a sensitive test battery.

In summary, the present observational trial lends support to the view that TPM is a good option in the treatment of difficult to treat epilepsy patients, even if it is used as second- or third-line monotherapy. The study demonstrated improvement in efficacy outcomes with good tolerability as was illustrated by the high retention and the limited number of treatment discontinuations due to AEs. Results of this trial should be interpreted in the context of its comparatively short treatment duration and its naturalistic non-comparative open-label study design.

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