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Brief Communication

Changes in hormone and lipid levels in male patients with focal seizures when switched from carbamazepine to lacosamide as adjunctive treatment to levetiracetam: A small phase IIIb, prospective, multicenter, open-label trial

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ABSTRACT

Treatment with enzyme-inducing antiepileptic drugs (AEDs) such as carbamazepine (CBZ) can lead to changes in reproductive, endocrine, and lipid parameters, resulting in clinical symptoms for some patients. Previous studies indicate that these changes can be reversed by switching to a nonenzyme-inducing AED. Lacosamide is a newer-generation AED, not known to induce or strongly inhibit cytochrome P450 (CYP450) enzymes. In this phase IIIb, prospective, multicenter, open-label, single-arm trial (NCT01375374), the serum concentrations of CYP-related reproductive hormones, thyroid hormones, and lipids were assessed in otherwise healthy male patients with focal seizures (N = 11), before and after a switch from CBZ (600–1200 mg/day at baseline) to lacosamide (target dose: 400 mg/day by the end of titration) as adjunctive treatment to the nonenzyme-inducing AED levetiracetam (LEV, stable dosage of >1000 mg/day throughout). Cross titration took place over 4 weeks, followed by an 8-week maintenance period. Serum measurements were conducted at baseline and at the end of maintenance. The median serum sex-hormone-binding globulin (SHBG) concentration was towards the higher end of the normal range at baseline and decreased following the switch (61.7 to 47.5 nmol/L, N = 10, p = 0.027 by Wilcoxon signed-rank test). Free androgen index (100 × testosterone/SHBG) and free thyroxine serum concentration increased (25.4 to 36.4 and 13.0 to 14.9 pmol/L, respectively, both N = 10 and p = 0.002). At baseline, the median progesterone serum concentration was below the normal range (0.7 nmol/L), whereas median cholesterol and low-density lipoprotein concentrations were above the normal range (5.5 and 3.6 mmol/L, respectively). By the end of maintenance, all measured parameters were within the normal range. The safety and tolerability profile of lacosamide was consistent with that observed in previous studies. Furthermore, antiseizure efficacy appeared to be maintained, suggesting that deinduction of CYP enzymes following a switch from CBZ to lacosamide as adjunctive therapy to LEV is feasible within 8 weeks and is associated with normalization of serum parameters.

Abbreviations: AE, adverse event; AED, antiepileptic drug; CBZ, carbamazepine; C-SSRS, Columbia Suicide Severity Rating Scale; CYP450, cytochrome P450; fT_4, free thyroxine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LEV, levetiracetam; SHBG, sex-hormone-binding globulin; T_3, triiodothyronine; T_4, thyroxine; TEAE, treatment-emergent adverse event; TSH, thyroid-stimulating hormone.

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1. Introduction

Long-term use of antiepileptic drugs (AEDs) that induce the cytochrome P450 (CYP450) enzymatic system has the potential to produce metabolic and reproductive abnormalities [1–3]. Carbamazepine (CBZ) is one such AED. Its use is associated with increases in serum lipids (including cholesterol), sex-hormone-binding globulin (SHBG), and thyroid-stimulating hormone (TSH) concentrations, with consequential reductions in free androgens and thyroid hormones. The long-term use of an enzyme-inducing AED can result in clinically relevant adverse effects for some patients, potentially contributing to sexual dysfunction, menstrual disorders, hyperandrogenism, weight gain, or loss of bone mass [4–10]. Nevertheless, evidence suggests that metabolic effects of enzyme induction can be reversed by switching to a nonenzyme-inducing AED, even after years of treatment [6,11].

Lacosamide is a newer-generation AED and does not strongly inhibit CYP450 enzymes or induce the drug-metabolizing enzymes CYP1A2, 2B6, 2C9, 2C19, or 3A4 [12,13]. Preclinical and clinical experiences show no indication of consistent and clinically relevant adverse effects of lacosamide on endocrine or metabolic functions in adult patients [14]. Lacosamide is approved at dosages up to 400 mg/day as monotherapy or adjunctive therapy in adults (≥17 years) with focal seizures in the United States and as adjunctive therapy in adults (≥16 years) with focal seizures in the European Union [12,13].

The aim of this trial was to assess whether a switch from CBZ to lacosamide, as adjunctive treatment to the nonenzyme-inducing AED levetiracetam (LEV), might influence the serum concentrations of reproductive hormones, thyroid hormones, and lipids, while maintaining anticonvulsant activity.

2. Material and methods

2.1. Trial design

This was a phase IIIb, prospective, multicenter, open-label, single-arm trial conducted in 5 centers in Austria, Germany, and Spain (SP0978; EudraCT: 2010-022534-84; NCT01375374). The trial started in July 2011 and was terminated early, owing to poor recruitment, in December 2013. Protocol and informed consents were reviewed by regional, national, independent, or institutional ethics committees and met the requirements of the Declaration of Helsinki and all local laws. The trial was conducted in accordance with the applicable International Conference on Harmonisation Good Clinical Practice guidelines.

After a 1-week screening period, the baseline assessments were conducted. This marked the start of a 12-week treatment period. During the screening and treatment period, the dose of LEV remained stable, and no AEDs other than lacosamide were added. Rescue AED treatment was permitted. Lacosamide was initiated at 100 mg/day (50 mg twice a day, oral tablets) at the start of a 4-week cross-titration period. Lacosamide dosage was increased by 100 mg/day per week, while the daily dose of CBZ was reduced by 25% per week. Patients entered the 8-week maintenance period on 400 mg/day of lacosamide, had discontinued CBZ, and remained on a stable dosage of LEV. At the discretion of the investigator, the lacosamide dose could be changed to between 300 and 600 mg/day during the first 4 weeks of maintenance. Final assessments were conducted at a termination visit. All patients completing the trial could opt to receive commercial lacosamide. Patients could discontinue where clinically appropriate but were not included in the final analysis.

2.2. Patients

This trial enrolled male patients, 18 to 45 years of age, with a diagnosis of focal seizures [15,16]. Additional criteria included treatment with CBZ for at least 12 months (with a current stable dosage of ≥600 mg/day to ≤1200 mg/day) and concomitant LEV therapy (≥1000 mg/day), maintained for at least 30 days prior to trial entry. Eligible patients were expected to benefit from a switch from CBZ to lacosamide in the opinion of the investigator, which could have been based on seizure control, treatment tolerability, endocrine or metabolic functioning, and/or drug interactions. Patients were excluded from the trial if they had taken an AED other than CBZ or LEV, any lipid-lowering drug, any medication known to affect endocrine functions, to any other CYP-enzyme inducers within 30 days prior to screening or if they had a condition that may have influenced their serum SHBG concentration and lipid, reproductive, or thyroid hormone concentrations.

2.3. Trial outcomes

The primary outcome was the change from baseline to end of maintenance in SHBG concentration. Secondary outcomes were changes in free androgen index (100 × testosterone/SHBG), free thyroxine (fT_4), and total cholesterol concentration. Several other serum parameters were measured as part of routine panels and included as supportive outcomes. These included changes in serum reproductive hormone concentrations (testosterone and progesterone), thyroid hormone concentrations (TSH, thyroxine [T_4], and triiodothyronine [T_3]), and lipid concentrations (high-density lipoprotein [HDL] cholesterol, triglycerides, non-HDL cholesterol fraction, and low-density lipoprotein [LDL] cholesterol) from baseline to the end of maintenance.

Additional assessments included the reporting of adverse events (AEs), an electrocardiogram, physical and neurological examinations, a Columbia Suicide Severity Rating Scale (C-SSRS) assessment, measurement of vital signs, body weight, clinical hematology values, clinical chemistry values, and urinalysis.

2.4. Statistical analyses

A sample size of 22 patients was required to provide approximately 85% power to detect a change of −6 nmol/L (standard deviation: 9 nmol/L) in SHBG serum concentration at the 5% type I error level. Therefore, enrollment of 28 patients was planned to allow for potential exclusions due to premature discontinuations or important protocol deviations. Because of the early termination of the study, fewer than the planned number of patients were enrolled. Outcomes were summarized as median (range) for all enrolled patients with available data for the baseline and termination visit. The planned assessment of the primary and secondary variables using a Wilcoxon signed-rank test is presented for exploratory purposes only.

3. Results

3.1. Patient disposition, demographics, and epilepsy characteristics

Of the 11 patients who received treatment, all but one completed the trial and opted to continue to commercially supplied lacosamide (Fig. 1). The patient who discontinued did so owing to an AE of partial seizures that occurred early in the cross titration.

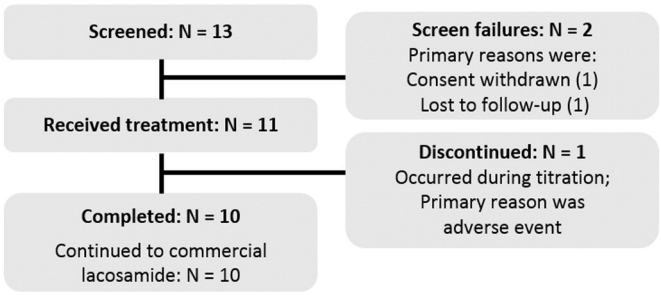

Fig. 1. Patient disposition.