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Assessing long-term effects of eslicarbazepine acetate on lipid metabolism profile, sodium values and liver function tests

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ABSTRACT

Introduction: Older dibenzazepines with a carboxamide substitution have been demonstrated to cause deleterious effects on lipid metabolism profile, as well as frequent hyponatremia. The aim of our study is to assess the effects of eslicarbazepine acetate, a novel AED, on lipid metabolism profile, sodium values and liver function tests, as well as to compare them with previous effects of carbamazepine and oxcarbazepine.
Methods: This report describes a retrospective cohort study of 108 patients who were treated with eslicarbazepine. Of these patients, 52% had switched to eslicarbazepine from prior treatment with carbamazepine or oxcarbazepine. Laboratory values concerning lipid metabolism profile, liver function tests and sodium were assessed before and after beginning/switching treatment. Patients who began treatment or whose treatment for dyslipidemia was modified during the study period were excluded from the analysis. Co-medications that could impact lipid metabolism profile, sodium or hepatic function were kept stable during the study period.
Results: The mean total cholesterol of the entire group decreased significantly from prior pathological to normal values after beginning/switching treatment. The percentage of patients with pathological values decreased. Patients switching from prior carboxamides also showed significant reductions in mean LDL and triglycerides. Patients beginning treatment without prior carboxamides did not develop dyslipidemia after titration. A tendency for an increased percentage of patients with hyponatremia was detected in both groups.
Conclusions: Compared with older carboxamides, eslicarbazepine acetate exhibits a safer profile related to lipid metabolism. No relevant changes were detected in liver function tests. Consequently, a vascular risk factor could be avoided in patients with chronic epilepsy, while hyponatremia still needs to be ruled out. Prospective studies are still needed.

1. Introduction

Eslicarbazepine acetate (ESL) is a new antiepileptic drug (AED) indicated for the treatment of focal onset seizures with or without tonic–clonic bilateral evolution (Gil-Nagel et al., 2013). After intake, ESL is extensively (<95%) hydrolyzed to eslicarbazepine (Almeida and Soares-da-Silva, 2007). The primary metabolic differences between ESL and carbamazepine (CBZ) are that with ESL, no epoxide is generated, no autoinduction of metabolism occurs, and the ratio of conversion to oxcarbazepine (OXC) is notably low. But on the other hand a mild induction of CYP3A4 and inhibition of CYP2C19 have been demonstrated. In the same way, the ratio of conversion to R-licarbazepine, as well as to OXC, is also notably low when comparing ESL with OXC (Hainzl et al., 2001). The pharmacodynamic and pharmacokinetic profiles of ESL differ significantly from those of CBZ and OXC (Almeida et al., 2008; Almeida and Soares-da-Silva, 2004; Bialer and Soares-da-Silva, 2012; Doeser et al., 2014; Elger et al., 2013; Falcão et al., 2007, 2012; Fontes-Ribeiro et al., 2008; Maia et al., 2008; Perucca et al., 2011), with lower affinity for the voltage-gated sodium channel resulting in higher selectivity for rapid firing epileptic neurons. The most frequent adverse events related to ESL are usually dose-dependent (Zaccara et al., 2013), and no clinically relevant effects on cognitive

Abbreviations: ESL, eslicarbazepine acetate; CBZ, carbamazepine; OXC, oxcarbazepine; ColT, total cholesterol; LDL, low-density lipoproteins; TGC, triglycerides; HDL, high-density lipoproteins; GOT, glutamic-oxalacetic transaminase; GPT, glutamic-piruvic transaminase; GGT, gammaglutamil transpeptidase.

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functions have been detected (Milovan et al., 2010). In terms of lipid metabolism, an interaction between ESL and rosuvastatin or simvastatin has been described, which results in lower levels of statins (Falcão et al., 2013). This finding suggests that dose-adjustment of simvastatin could be needed after titration of treatment with ESL, if changes on lipid metabolism profile are noted when combining these drugs. However, no direct effects of ESL on lipid metabolism profile were concluded in those studies. Prior studies have demonstrated adverse effects of older dibenzazepines and other metabolic inducers on lipid metabolism profile (Chuang et al., 2012; Nikolaos et al., 2004), while authors have suggested a milder but still deleterious effect of OXC (Franzoni et al., 2006; Garoufi et al., 2014; Papacostas, 2000; Yiş and Doğan, 2012), and little is known regarding the effects of ESL. In patients with epilepsy presence of dyslipidemia related to chronic use of AEDs represents a chronic vascular risk factor (Cockerell et al., 1994), with the consequent increased mortality due in part to the increased vascular risk (Chuang et al., 2012). Thus, avoidance of a vascular risk factor could lead to increased life expectancy, quality of life and reduced requirements of medical care in patients with epilepsy. In the case of patients with previous treatment with older dibenzazepines, preliminary data has suggested that an abrupt switch from treatment with OXC to ESL could be performed (Steinhoff et al., 2011), regardless of the need for sodium values controls. Nonetheless, the small sample size and short follow-up of works published thus far warrant prospective studies. However, there are no data comparing progressive/abrupt switching from OXC or CBZ to ESL, and the clinical and laboratory changes related to this switch have not been properly detailed. Hence, the effects of switching from CBZ/OXC to ESL on lipid metabolism profile, liver function tests, vitamin D or hormonal values still need to be assessed (Brown and El-Mallakh, 2010).

In phase III clinical trials, ESL showed no effects on clinically relevant laboratory parameters concerning hematology, blood chemistry, urine and coagulation. Low sodium levels shifting from normal values were detected in 3.1–8.8% in the different groups, and no changes were detected in cholesterol fractions or triglycerides. Post-authorization studies have suggested that ESL has no effects on lipid metabolism (Massot et al., 2014), as well as a good efficacy related to seizures (Mauri-Llerda, 2012; Serrano-Castro et al., 2013; Villanueva et al., 2014). Taken together, these data offer a promising profile of ESL with respect to lipid metabolism compared to older drugs, such as CBZ or OXC. Nonetheless, all of these studies were not designed to evaluate the long-term effects of ESL on lipid metabolism profile.

The objective of our study is to assess the long-term effects of ESL on lipid metabolism profiles, sodium values and liver functions tests, as well as to compare them with previous effects of CBZ or OXC, in a group of patients treated in our comprehensive epilepsy center since the introduction of ESL to the market.

2. Methods

2.1. Patients and study design

We performed an observational, retrospective cohort study of patients who attended our outpatient epilepsy clinic from February 2011 to July 2014. The patients were evaluated by epileptologists, who assessed the patients' clinical variables and decided to begin treatment with ESL as an add-on de novo treatment, or by switching from another AED to ESL. Titration or discontinuation of treatment with ESL was independent from study inclusion. The patients' laboratory values were systematically assessed before and during treatment with ESL, with blood test performed at least once during the last year before treatment with ESL (inclusion criteria), between 3 and 6 months after treatment initiation, and then yearly. ESL dosage was selected based on clinical criteria of efficacy and tolerability. The duration of treatment was variable, and determined by the clinical assessment of the individual patients. Data related to lipid metabolism profile, sodium values and liver function tests were retrospectively recollected from clinical diaries. The inclusion criteria for the analysis were as follows: patients over 18 years old, focal onset seizures, treatment with ESL during at least three months and existing laboratory parameters concerning lipid metabolism, liver function tests or sodium values during the last year previous and during treatment with the drug. The exclusion criteria were as follows: patients under 18 years old, pregnancy, systemic disease with life expectancy less than one year, treatment with ESL for less than three months and titration or dose changes of treatment with drugs that could affect the patient's lipid metabolism profile during treatment with the drug.

The lab values assessed prior and during treatment were as follows: total cholesterol, triglycerides (TGC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), glutamic-oxalacetic transaminase (GOT), glutamic-piruvic transaminase (GPT), gammaglutamil transpeptidase (GGT) and plasma sodium values. Multiple determinations of each single value were available in the majority of patients, and variability was analyzed. When multiple lab value determinations were available, the last lab value before and during treatment was taken in account for the analysis. All values were determined in the same laboratory to avoid methodological bias that could interfere with the results. Blood extractions were always performed during the morning and before breakfast. Treatment with other AEDs was not an exclusion criteria because ESL was approved exclusively as an add-on treatment during the study period. Titration or tapering of other AEDs or switching from one AED to another was assessed and monitored, especially with regards to metabolic inducers. For the analysis of lab values, patients were subdivided into two groups, titration of treatment with ESL without prior treatment with older dibenzazepines and switching to treatment with ESL from CBZ/OXC. Concomitant treatment with statins, colestiramine, colestipol, gemfibrozil, ezetimibe, nicotinic acid and fibrates was strictly assessed. If these drugs were titrated or the doses were modified during the study period, the patients were excluded from the analysis. Other factors that could affect a patient's lipid metabolism profile, such as presence or absence of diabetes mellitus and changes in the treatment, presence or absence of familiar hypercholesterolemia or hypertriglyceridemia, beta-blocking agents or thiazides, were assessed and documented. Demographic data, epilepsy concerning data, seizure outcome and other than AEDs epilepsy treatments were also assessed but were not used as primary endpoints.

2.2. Statistics

Statistical analysis was performed with SPSS 19.0. For continuous variables, the Saphiro–Wilk test was used to distinguish between normal and abnormal distributions. Normally and non-normally distributed variables were analyzed by using the Student *t* and the Mann–Whitney *U*-tests for the comparison of means and medians, respectively. Paired sample *T* and Wilcoxon's tests were used to compare laboratory values before and during treatment with ESL in the same group of patients. The X^2 test was used for the comparison of proportions. With regards to lab values, the patients were subdivided in two groups for the analysis, switching to ESL from CBZ/OXC or beginning treatment with ESL de novo and without prior treatment with older dibenzazepines. Univariate and multivariate analysis were performed to detect statistically significant correlations. Two-sided p values <0.05 were considered significant.