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Clinical experience with eslicarbazepine acetate in adults with sub-analysis of elderly

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ABSTRACT

Purpose: Eslicarbazepine acetate (ESL) is indicated for treatment of focal epilepsy. Our aim was to evaluate the effect and tolerability of ESL in elderly and younger adults. The primary objective was to measure changes in seizure frequency before and after at least six months of treatment. Secondary objective was to analyse the safety profile. Sub-analysis was performed in patients previously treated with oxcarbamazepine.

Method: A single-centre, retrospective study of patients with focal epilepsy treated with ESL. Data were collected by reviewing the clinical and laboratory files. Seventy-two patients received ESL, of which 14 were ≥60 years old, and were analysed for adverse effects. Fifty-nine patients received treatment for ≥6 months and were included in the evaluation of seizure frequency; in this group 12 were ≥60 years old.

Results: Seizure frequency (n = 59) was reduced for both young adults (< 60 years) and elderly adults (≥60); both groups achieved better seizure control from an average of 2 to 0.5 (p-value: 0.002) and 3.5 to 0.65 (p-value:<0.05) seizures per month, respectively. Adverse effects leading to treatment discontinuation (n = 72) were more frequent in elderly (42.9%) than in young adults (17.2%) (p-value 0.04). There was no significant difference in mild adverse effects between young (15.5%) and elderly adults (14.3%). Most common adverse effects were somnolence, gastrointestinal disturbances and dizziness.

Conclusions: The study indicates that ESL has an advantageous profile in relation to seizure control. The discontinuation rate might be higher in elderly than in younger adults. Further prospective studies are needed to confirm these conclusions.

1. Introduction

1.1. Background and significance

Epilepsy is among the most significant chronic neurological diseases globally and has both major economic and non-economic implications. Focal-onset epilepsy has a prevalence in developed countries between 3 and 10 per 1000 [1,2] affecting people of all ages, with highest prevalence among the elderly [3].

The goals of epilepsy treatment are to achieve seizure freedom without significant adverse events, increase quality of life, and reduce morbidity and mortality. Seizure control has been achieved in around 70% of patients with appropriate anti-epileptic drug (AED) therapy in either mono- or polytherapy. The remaining 30% have inadequate seizure control with AEDs [4], and around 25% experience significant adverse effects [5].

Age is a major factor influencing the effect and tolerability of AEDs. The frequency of epilepsy due to progressive neurological disorders and focal epilepsies of unknown etiology increases with age and is associated with a poorer prognosis of epilepsy [6]. Furthermore drug-interactions in elderly taking concomitant medication may influence both the efficacy and tolerability of AEDs. Moreover, age-related changes in liver- and kidney function may also influence the pharmacokinetics and thereby the effect and adverse effects of AEDs.

Eslicarbazepine acetate (ESL) is one of the third generation AEDs that have been developed in the last ten years with a favorable safety profile [7,8]. As data on using ESL in elderly patients is still limited, our intention in the present study was to evaluate ESL with a sub-analysis of elderly adults.

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1.2. Eslicarbazepine acetate

Eslicarbazepine acetate is a novel once-daily voltage-gated sodium channel (VGSC) blockerindicated for treatment of focal epilepsy. Even though ESL belongs to the same dibenzoazepine family as carbamazepine (CBZ) and oxcarbazepine (OXC), it has different pharmacokinetic characteristics.

The ability to alter fast inactivation of VGSC characterised by CBZ and OXC is not shared by ESL, but similarly to Lacosamide it enhances the slow inactivation of VGSC [9]. Eslicarbazepine acetate is rapidly metabolized via a hydrolytic first-pass metabolism into almost exclusively its active component S-licarbazepine, which is better tolerated and able to cross the blood brain barrier more effectively than R-licarbazepine [10]. Oxcarbazepine is metabolized slower, both to its active S-licarbazepine and inactive *R*-licarbazepine (around 20–25%) which may cause adverse effects.

Eslicarbazepine acetate has enhanced inhibitory selectivity for rapid firing 'epileptic' neurons over those with normal activity [11]. In comparison with CBZ, ESL lacks the inhibitory effects upon K_v 7.2 outward currents, which reduces ESLs ability to facilitate repetitive firing. And ESL has a 10-to 60-fold higher potency for blockade of low- and high affinity hCa_v 3.2 inward currents, which enhances potential for antiepileptogenic effect [12]. An add-on effect of ESL to CBZ has been identified in patients whose CBZ treatment has failed [7]. Unlike CBZ, ESL is not inclined to autoinduction or enzyme induction. The elimination of ELS is renal (66%) and therefore dose adjustment is recommended for patients with renal impairment [13].

2. Objective

Our aim was to evaluate the effect and safety profile of ESL in elderly and younger adults. The primary objective was to measure the change in seizure frequency before and after at least six months of treatment with ESL. Secondary objectives were to analyse the safety profile of ESL by evaluating the tolerability and serum sodium levels, as well as to evaluate seizure frequency and serum sodium levels in patients previously treated with OXC

3. Methods

3.1. Study design and subjects

This retrospective study covers patients with focal epilepsy treated with ESL at our clinic, a tertiary medical treatment centre for epilepsy. The clinical and paraclinical data were collected by reviewing the medical records of the patients. Data on previously used AEDs, the effective dose of ESL and its side effects were collected as well. Finally, concomitant medications were evaluated with emphasis on drugs that can cause hyponatremia.

Eslicarbazepine acetate was introduced either in mono-, or as an adjunctive therapy in patients with either uncontrolled epilepsy or unacceptable adverse effects to their previous AEDs, and the drug was up-titrated from 400 mg to the effective dose (max. 3000 mg). Patients were monitored at the clinic regularly, and their treatment was optimized as needed, in order to achieve sufficient seizure control.

Seventy-two patients were identified in our patient-registry treated with ESL between 2010 and 2015 (Fig. 1). The patients were divided into two groups according to age: Younger Adults (YA) aged 20–59 years, n = 58, and Elderly Adults (EA) 60 years or older, n = 14. For the effect analyses both groups were further divided according to whether they received ESL for at least six months or more, i.e. patients "included"; Young Adults Included (YAI), n = 47, and Elderly Adults Included (EAI), n = 12. The patients who received ESL less than six months were not included in evaluation of efficacy, i.e. patient "excluded", Young Adults Excluded (YAE), n = 11 and Elderly Adults Excluded (EAE), n = 2.

3.2. Ethical considerations

The data were anonymized for the statistical analysis, and the study was approved by the Danish Data Protection Agency.

3.3. Data analysis

The effect analysis was carried out by comparing seizure frequencies in the YAI and EAI prior to and after at least six months of treatment with ESL. Seizure frequencies were registered in a patient self-administered seizure calendar.

The safety profile of ESL was evaluated based on the tolerability, i.e. self-reported adverse effects, and on the serum sodium levels. Adverse effects to ESL were registered for all patients receiving ESL independent of treatment duration. Serum sodium levels were examined by comparing levels prior to and after at least six months of treatment with ESL, but only for YAI and EAI. Information on sodium levels were missing for 13 out of 47 YAI and for one out of 12 EAI.

3.4. Statistical analysis

Data was evaluated assuming a significance level of α=0.05, and analysed by Wilcoxon signed ranks test or Mann-Whitney *U* test, since data was skewed or not following normal distribution. Binary

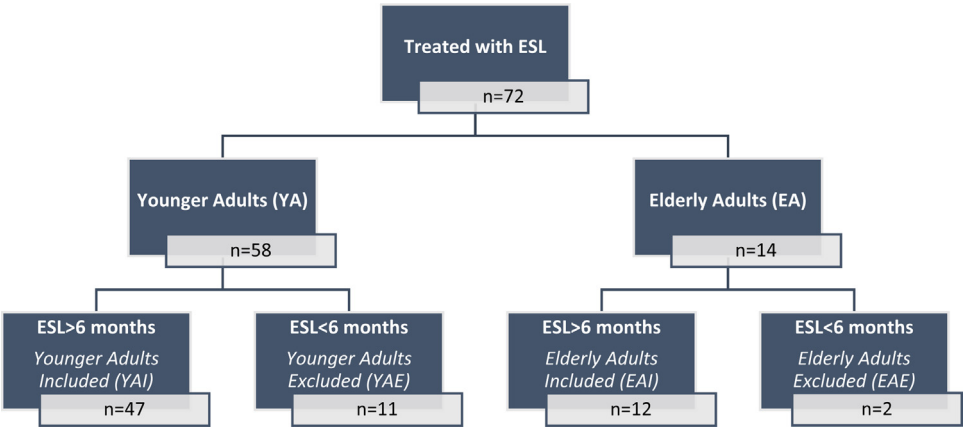

Fig. 1. Patients treated with ESL.