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Research paper

Pharmacokinetic variability, efficacy and tolerability of eslicarbazepine acetate–A national approach to the evaluation of therapeutic drug monitoring data and clinical outcome

Torleiv Svendsen[a,*], Eylert Brodtkorb[b,c], Arne Reimers[d,e], Espen Molden[f], Erik Sætre[a], Svein I. Johannessen[a,g], Cecilie Johannessen Landmark[a,g,h]

[a] The National Center for Epilepsy, Sandvika, Oslo University Hospital, Oslo, Norway
[b] Department of Neurology and Clinical Neurophysiology, St. Olav's University Hospital, Trondheim, Norway
[c] Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway
[d] Dept. of Clinical Pharmacology, St. Olav's University Hospital, Trondheim, Norway
[e] Dept. of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[f] Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway
[g] Dept. of Pharmacology, Oslo University Hospital, Oslo, Norway
[h] Programme for Pharmacy, Dept. of Life Sciences and Health, Faculty of Health Sciences, Oslo and Akershus University College of Applied Sciences, Oslo, Norway

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ABSTRACT

Background: Eslicarbazepine acetate (ESL) is a new antiepileptic drug (AED), still insufficiently studied regarding pharmacokinetic variability, efficacy and tolerability. The purpose of this study was to evaluate therapeutic drug monitoring (TDM) data in Norway and relate pharmacokinetic variability to clinical efficacy and tolerability in a long-term clinical setting in patients with refractory epilepsy.
Methods: This retrospective observational study included TDM-data from the main laboratories and population data from the Norwegian Prescription Database in Norway, in addition to clinical data from medical records of adult patients using ESL for up to three years, whenever possible.
Results: TDM-data from 168 patients were utilized for assessment of pharmacokinetic variability, consisting of 71% of the total number of patients in Norway using ESL, 2011-14. Median daily dose of ESL was 800 mg (range 400–1600 mg), and median serum concentration of ESL was 53 μmol/L (range 13–132 μmol/L). Inter-patient variability of ESL was extensive, with 25-fold variability in concentration/dose ratios. Additional clinical data were available from 104 adult patients out of the 168, all with drug resistant focal epilepsy. After 1, 2 and 3 years follow-up, the retention rate of ESL was 83%, 72% and 64%, respectively. ESL was generally well tolerated as add-on treatment, but sedation, cognitive impairment and hyponatremia were reported. Hyponatremia (sodium <137 mmol/L) was present in 36% of the patients, and lead to discontinuation in three.
Conclusion: Pharmacokinetic variability of ESL was extensive and the demonstration of usefulness of TDM requires further studies. In patients with drug resistant focal Epilepsy, the high retention rate indicated good efficacy and tolerability. Hyponatremia was observed in one third of the patients. The present results point to a need for individualization of treatment and TDM may be useful.

1. Introduction

Antiepileptic drugs (AEDs) are often used for life-long treatment of Epilepsy, and careful considerations of efficacy and tolerability are important for an optimal treatment outcome. A number of new AEDs have been launched during the last years. Eslicarbazepine acetate (ESL) is a new compound that has been developed based on the knowledge of pharmacodynamics and –kinetics of carbamazepine (CBZ) and oxcarbazepine (OXC) (Soares-da-Silva et al. 2015; Bialer and Soares-da-Silva, 2012; Verotti et al., 2014; SPC). After administration, ESL is almost instantly converted to S-licarbazepine, the active S-enantiomer of the racemic monohydroxy metabolite (R- and S-licarbazepine) of OXC (Bialer and

* Corresponding author.
E-mail addresses: torle-sv@online.no, Torleiv.Svendsen@ous-hf.no (T. Svendsen).

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Soares-da-Silva, 2012; Bialer et al., 2013). This is the main compound present in serum following oral administration of ESL, and its antiseizure properties are supposed to be due to slow inactivation of sodium currents (Bialer and Soares-da-Silva, 2012; Elger et al., 2013).

Pharmacokinetic variability is incompletely studied in clinical trials of newly introduced AEDs and needs further investigation in different patient populations (Johannessen Landmark and Johannessen, 2012). Therapeutic drug monitoring (TDM) may be implemented to adjust for factors that contribute to inter- and intraindividual variability, such as physiological alterations or polytherapy (Patsalos et al., 2008; Johannessen Landmark et al., 2012a). The same reference range for racemic mono-hydroxcarbazepine as used in OXC treatment (12–140 μmol/L) has been proposed (Patsalos et al., 2008; Patsalos and Berry, 2013). Additional implementation of "individual therapeutic concentrations" for AEDs implies that TDM may be a useful tool to individualize treatment (Perucca, 2000; Patsalos et al., 2008; Johannessen Landmark and Johannessen, 2012). Data from clinical studies demonstrates responder rates (>50% seizure reduction) of 50–57%, and good tolerability (Rocamora et al., 2015). However, short-term clinical phase III studies do not evaluate efficacy and tolerability in a naturalistic clinical setting, considering flexible dosing and complex polytherapy.

The purpose of this study was to evaluate therapeutic drug monitoring (TDM)-data in Norway and relate pharmacokinetic variability to clinical efficacy and tolerability in a long-term clinical setting in patients with refractory epilepsy.

2. Material and methods

2.1. Therapeutic drug monitoring data and drug analyses

Four main laboratories in Norway where TDM analyses of AEDs are preformed were included in the study to collect nation-wide TDM data regarding ESL: Section for Clinical Pharmacology, The National Center for Epilepsy and Ullevål Hospital, Oslo University Hospital, Dept. of Pharmacology, St. Olav's University Hospital, and Center for Psychopharmaology, Diakonhjemmet Hospital. The analyses were performed using validated routine methods (HPLC-UV or UPLC–MS/MS). All laboratories used a non-stereoselective method that analysed both isomers of the racemic monohydroxy-derivative of OXC (i.e., R- and S-licarbazine). Retrospective data were retrieved for the period 2012–2014. For every patient, the most recent measurement of serum concentrations of AEDs at assumed steady-state conditions was used. All blood samples were drawn drug-fasting in the morning (prior to intake of the morning dose). Patients with insufficient data regarding serum concentrations, dosage or time of intake of last dose or dosage titration where steady-state was not achieved were excluded. Totally, 168 patients were included from these databases.

2.2. Population data

The total number of patients using ESL in Norway, divided by gender, was retrieved from the Norwegian Prescription Database (NorPD), from 2010 to 2015 (the Norwegian Prescription Database) as a comparison to the total number of patients included with TDM-data for ESL. NorPD consists of data from all prescriptions from all pharmacies in Norway and is well evaluated (e.g. Baftiu et al., 2016).

2.3. Patients

Retrospective clinical evaluations of adult patients with refractory focal epilepsy treated with ESL were recruited from the National Center for Epilepsy, St. Olav's University Hospital, and Oslo University Hospital in Norway. In 104 of the 168 patients with TDM data we had access to complete medical records. ESL medication was started in the period of January 2010–December 2013, and follow-up ended in October 2015.

Data regarding gender, age, seizure type, seizure onset, pharmacological treatment, efficacy and tolerability were collected from the medical records. Retention rate was evaluated after 1, 2 or 3 years of follow-up. Efficacy was evaluated from the medical records by a modified Likert scale: 1) no effect, 2) some effect (modest reduction of seizure frequency and/or duration), 3) good effect (defined as >50% reduction of seizure frequency) and 4) complete seizure freedom over a period of at least one year. Tolerability was evaluated by the treating clinician and observed or reported adverse effects were recorded. When ESL was discontinued, the reason was documented as either lack of effect or adverse effects or both.

2.3.1. Ethical approval

All patient data were anonymized, and data regarding gender, age, utilization of AEDs, dose and serum concentration measurements were collected. The study was approved by the Regional Committee for Medical and Health Research Ethics.

2.4. Calculations

2.4.1. Serum concentration- dose relationships

Serum concentration measurements, doses, and concentration/dose (C/D) ratios are presented as mean values, standard deviation and median, range, were used to express variability.

For calculations related to age, the patients were divided into the following categories: youth (<18 years), adults (18–65 years) and elderly (>65 years).

2.4.2. Statistical analyses

For statistical analyses, IBM SPSS Statistics version 22 (SPSS Inc, Chicago, IL, USA) was used. Students' two-sided *t*-test with unequal variance was used to calculate significant pair-wise differences between groups. Univariate analysis was used to study the relation between dose and serum concentration, and age and C/D-ratios, respectively. Non-parametric analysis, One-Way Anova post hoc test by Dunnett (2-sided) was used to compare multiple groups regarding clinical efficacy (categorized as some effect, uncertain, or no effect), and adverse effects. Variability within each group was expressed as standard deviation (SD). Statistical significance was considered as $p < 0.05$.

3. Results

3.1. TDM-data, number of users of ESL in Norway and pharmacokinetic variability

3.1.1. Number of patients based on TDM-data related to the total use of ESL in Norway

Four main laboratories in the country were included to collect TDM-data in a nation-wide scale and to elucidate the use of TDM for one of the newest AEDs, ESL. There were 168 patients included in the study of pharmacokinetic variability of ESL. Their mean age was 41.3 years (range 4–82 years), gender distribution 95 women/73 men (56% women), and they used 0–3 other AEDs as stated in the TDM request forms.

During the period of data collection from the TDM-databases (2010-13), the number of patients using ESL in Norway increased from 205 to 293, with a mean number of users of 236 patients per year in this period. The included number of patients in the TDM study corresponds to 71% of the population using ESL. The use of ESL