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The effect of serum levetiracetam concentrations on therapeutic response and IL1-beta concentration in patients with epilepsy

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ABSTRACT

Objective: Assessment of the relevance between serum drug concentration to its therapeutic response is a valid monitoring strategy for the clinical efficacy of antiepileptic drugs (AEDs). Levetiracetam (LEV) is a broad spectrum AED with a possible anti-inflammatory effect. We aimed to determine the relationship between LEV concentrations and its therapeutic response, and the effect of LEV on IL1-beta concentrations in patients with epilepsy.

Methods: Patients on monotherapy (n = 7) or polytherapy (n = 15) with LEV for their seizures management were included. Blood samples of each patient were collected: just before LEV intake, 1 h, 2 h, 4 h and 8 h following the last dose. Serum LEV concentrations were measured by liquid chromatography mass spectrometry and IL1-beta concentrations by chemiluminescent immunometric assay. Concentration to dose (C/D) ratio values was used for analyses. LEV concentrations were compared between responders (≤1 seizure/month) and non-responders (> 1 seizure/month) and patients with or without adverse reactions. IL1-beta concentrations before and at 2 h following LEV ingestion were compared in order to detect the effect of the increase in serum LEV concentration on IL1-beta.

Results: Although there was no change in LEV (C/D) ratio or LEV maximum concentration (Cmax)/D ratio of the responders and non-responders, the C/D ratio following 1 h of LEV intake (2.17 ± 0.59 kg.day/L) and Cmax/D ratio (2.25 ± 0.56 kg.day/L) in the patients with adverse effects was significantly higher than for the patients without adverse effects (1.09 ± 0.12 kg.day/L and 1.49 ± 0.14 kg.day/L respectively). A statistically significant decrease was found in the IL1-beta concentration to LEV (C/D) ratio with the increase in LEV concentration in patients on LEV monotherapy.

Conclusion: The possible relationship between LEV Cmax and its therapeutic response or IL1-beta concentrations may be an importance indication of LEV antiepileptic efficacy. Consequently, monitoring LEV Cmax values may enhance LEV adherence because patients would be less likely to develop adverse effects.

1. Introduction

Levetiracetam (LEV) is a broad spectrum antiepileptic drug (AED) which is used for focal epilepsy, myoclonic and tonic-clonic seizures. Patients on LEV therapy can show adverse effects such as dizziness, nasopharyngitis, affective symptoms, aggression, somnolence or anxiety (Bootsma et al., 2007; Hwang et al., 2014; Verrotti et al., 2015). LEV acts primarily by preventing neurotransmitter release through the synaptic cleft by binding to a synaptic vesicular protein, SV2A (Lynch et al., 2004). It has also been reported to inhibit cytokine levels such as IL1-beta, IL2 and IL6 in in-vitro experiments and this anti-inflammatory effect has been considered to be a part of its mechanism of action (Haghikia et al., 2008; Himmerich et al., 2013, 2014).

The relationship between serum drug concentration and therapeutic response has led to the use of therapeutic drug monitoring (TDM) to be an effective tool for guiding dose adjustments of patients with epilepsy on monotherapy or polytherapy with AEDs (Patsalos et al., 2008). For routine implementation of TDM, minimum serum concentration (Cmin

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or trough) is measured and correlated with the clinical outcome of patients. Therefore, blood samples collected at the end of the dosing interval are used following at least 4–5 elimination half-life values of the AEDs (Eadie, 1998). The association of AED serum concentration with the clinical outcome of the patient is based on the target reference range which guides optimal serum drug concentration for maximum clinical effect on seizure control and minimum toxicity (Patsalos et al., 2008). Furthermore TDM is helpful in identifying drug-drug interactions, drug non-compliance, identifying occurrence of adverse effects, the effect of genetic polymorphisms and for managing drug overdose. Genetic polymorphisms can affect the pharmacokinetics or pharmacodynamic characteristics of drugs and can alter their therapeutic efficacy. The relationship between polymorphic genes affecting metabolyzing enzymes such as CYP2C9, CYP2C19 or UGT1A4 and serum concentrations of AEDs, the effect of human leukocyte antigen (HLA) alleles and increased risk of idiosyncratic adverse drug reactions or the impact of pharmacogenetics (ABCB1) on AED resistance have been widely investigated (Balestrini and Sisodiya, 2018; Gulcebi et al., 2011; Petrenaite et al., 2018). In particular polymorphic metabolism enzymes can directly affect the serum concentration of drugs and can result in therapeutic failure or enhance drug related adverse and toxic effects.

Various LEV reference ranges have been reported including 3–34 mg/L, 12–46 mg/L or 20–40 mg/L and could be attributed to different patient populations being studied (Patsalos, 2003; Patsalos et al., 2008; Stepanova and Beran, 2014). LEV TDM is particularly helpful for the dose adjustments of elderly patients or patients with renal failure related with the increase in the elimination half-life values of LEV (Aldaz et al., 2018). Although LEV is generally not considered to be involved in clinically significant pharmacokinetic drug-drug interactions, consequent to the fact that it is not metabolized *via* CYP450 enzymes and is not plasma protein bound, there are some reports indicating a moderate effect of enzyme-inducing AEDs on serum LEV concentrations (Aldaz et al., 2018; May et al., 2003).

Despite LEV having favorable pharmacokinetics and tolerability characteristics, there are patients with poor therapeutic response with uncontrolled seizures or adverse effects (Bootsma et al., 2007; Lee et al., 2013). According to the consensus proposal of ILAE commission on therapeutic strategies for drug resistant epilepsy, one case with LEV was shown as an example for the 'treatment failed' category (Kwan et al., 2010). Particularly behavioral or mood changes have been reported to be associated with intolerability of LEV and a subsequent dose reduction was suggested for the patients with behavioral problems (Chen et al., 2017). The majority of the results investigating the relationship between serum level of LEV and therapeutic response in the adult or pediatric patients with epilepsy showed non-significance (Lancelin et al., 2007; Sheinberg et al., 2015). However these studies included only the trough concentrations of LEV which were measured at the end of the dosing interval. In the present study we aimed to determine: 1) the relationship between LEV concentration and its therapeutic response for not only serum trough LEV concentration but also for the LEV concentrations measured at subsequent time points: 1 h, 2 h, 4 h and 8 h following the last dose in patients with epilepsy; 2) the effect of LEV on IL1-beta concentration in patients on monotherapy with LEV by comparing the two IL1-beta concentrations measured just before LEV ingestion and 2 h following the last dose.

2. Material and methods

Patients (18–50 years of age) on monotherapy (n = 7) or polytherapy (n = 15) with LEV for at least one month for the management of their seizures and attending the epilepsy outpatient clinic of the Department of Neurology at Healthsciences University, Medical Faculty, were included. The clinical features of the patients are presented in Table 1 and includes seizure types, electroencephalography (EEG) findings and magnetic resonance (MR) imaging findings. The demographic characteristics of the patients are shown in Table 2. LEV dose, use of other AEDs, seizure frequency and adverse effects were recorded from face to face interview of the patients and also from their hospital notes. Patients who did not want to participate in the study, patients with chronic hepatic or renal disease, with poor LEV compliance or with severe psychiatric disorders were excluded from the study. This study was carried out with the approval of the Marmara University Ethical Committee (MAR-YC-2007-0159). Written informed consent was obtained from all participating patients.

2.1. Measurement of serum LEV and IL1-beta concentrations

Venous blood samples were used for the measurement of serum LEV and IL1-beta concentrations. The blood samples were collected at: just before LEV intake (trough concentrations), 1 h, 2 h, 4 h and 8 h following the last dose representing steady state LEV concentrations. Sera were prepared by centrifugation of blood samples (4700 G-force for 10 min) at 10 min following the collection. Serum samples were transferred to Medical Pharmacology Department of Marmara University *via* cold chain and stored at −80 C until measurement of LEV and IL1-beta content. LEV concentrations were determined by liquid chromatography mass spectrometry (Shimadzu LC-20 AB Sciex 3200 Qtrap) using a commercial kit (Chromsystems-MassTox Antiepileptic Drugs) exactly as per manufacturer's instructions. The measurement/calibration range was 1.1–82.1 mg/L and the limit of quantification was 1.1 mg/L. IL1-beta concentrations were measured by chemiluminescent immunometric assay (SIEMENS-IMMULITE 1000) exactly as per manufacturer's instructions. The calibration curve with 0–1000 pg/ml.

2.2. Assessment of the relationship between serum LEV concentrations and therapeutic response

Seizure frequency of the patients per month and adverse effects of LEV were evaluated for the assessment of therapeutic response to LEV. Patients on LEV therapy were divided into groups. Patients who were seizure free or had 1 seizure per one month were classified as 'responders' whereas patients with more than 1 seizure per month were considered to be 'non-responders'. The recorded adverse effects of LEV were used for evaluation of the relationship between serum LEV concentrations and development of adverse effects. LEV concentration (mg/L) to dose (mg/kg/day) (C/D) ratio values and Cmax of LEV were compared between responders ($\leq$1 seizure/month, n = 11) and non-responders ($>$ 1 seizure/month, n = 11) and between patients with (n = 6) or without (n = 16) adverse effects. The C/D ratio was calculated by dividing each measured serum concentration of LEV (mg/L) by the total daily dose (mg/kg).

2.3. Assessment of the effect of LEV on IL1-beta concentrations

The effect of LEV on IL1-beta concentration was determined in the monotherapy patients (n = 7) in order to eliminate the possible influences of concurrent AEDs. Only blood samples collected just before LEV ingestion and at 2 h following last dose were used for this analysis. IL1-beta concentrations matched with Cmin and Cmax level of LEV were used in order to indicate the potential decreasing effect of LEV on IL1-beta concentration. The serum concentration of IL1-beta (pg/mL) to LEV (C/D) (kg/L.day) ratio values were used for the analysis of the effect of LEV on IL1-beta concentration.

2.4. Statistical analysis

The results were expressed as "mean ± SEM" and statistically evaluated by analysis of variance (ANOVA) (GraphPad Software Prism 4.0, San Diego, USA). Two-way ANOVA with repeated measures followed by the post-hoc Bonferroni test was used to analyze the statistical significance of C/D ratio values of LEV between responders and non-responders and between patients with or without adverse effects.