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Original article

Implications of metabolic parameters of carbamazepine in the therapeutic monitoring of Tunisian patients with epilepsy

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ABSTRACT

Carbamazepine (CBZ) is widely used in the control of simple and complex focal seizures and generalized tonic–clonic seizures in patients with epilepsy. The toxic effects of CBZ are not easily predicted, and this is due to the difficulty of delivering the optimal dose and/or plasma concentration of CBZ necessary to achieve beneficial effects, and especially to prevent the onset of toxicity associated with its use. Our study aimed to determine the relationship between the administered daily dose of CBZ and its pharmacokinetic parameters, including concentrations of CBZ and carbamazepine-10,11-epoxide (CBZ-E) plasma levels, and the metabolic ratio of CBZ-E to CBZ, in Tunisian patients with epilepsy. To accomplish this, a high-performance liquid chromatography method with ultraviolet detection was used for quantification in the simultaneous analysis of CBZ and one of its active metabolites, CBZ-E, in human plasma. A statistically significant positive correlation was found between the daily doses administered (mg/kg/day) and plasma concentrations of CBZ and CBZ-E, and the CBZ-E/CBZ ratio increased significantly as a function of the specific dose (in mg/kg/day). The increase in plasma concentrations of CBZ-E was non-linear in relation to plasma concentrations of CBZ, and there was no correlation between the CBZ-E/CBZ metabolic ratio and CBZ plasma concentrations. Our findings suggest that monitoring of CBZ as well as CBZ-E blood levels should be considered, as it may play a useful role in the therapeutic management of patients with epilepsy.

1. Introduction

Carbamazepine 5-H-dibenz[b,f]azepine-5-carboxamide (CBZ), an iminostilbene derivative of tricyclic antidepressants, is an important anticonvulsive drug for the treatment of epilepsy. It is widely used in the control of simple and complex focal seizures as well as generalized tonic–clonic seizures [1–6]. CBZ is usually administered to patients with epilepsy in daily oral doses ranging from 200 to 1200 mg, which gives rise to drug

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plasma levels of 4–12 μg/mL [7,8]. In humans, CBZ is metabolized into the active metabolite carbamazepine-10,11-epoxide (CBZ-E) in the liver by the CYP3A4 subtype of the cytochrome P450 system [7–9]. CBZ-E is mainly converted into the inactive metabolite carbamazepine-10,11-diol (CBZ-D), which is excreted through urine in free and conjugated forms [3]. In clinical practice, drug blood levels should be considered especially in cases of a lack of efficacy (to assess compliance) and the occurrence of side effects that could be attributed to the antiepileptic drug. CBZ monitoring for plasma concentrations is recommended during pregnancy, in the elderly and in patients using drugs that interact with CBZ [10]. Also, the toxic effects of CBZ are not easily predicted, and this is due to the difficulty of delivering the optimal dose and/or plasma concentration of CBZ necessary to achieve beneficial effects, and especially to prevent the onset of toxicity associated with its use.

Indeed, the optimal dose and plasma concentration of CBZ would provide optimal therapeutic dose efficiency, which is highly variable from one epileptic patient to another. Some studies attribute the individual variations in response to CBZ therapy to biological factors such as age and gender, which can influence the pharmacokinetics of the medication [11]. Other studies suggest that genetic and/or environmental factors could modify CBZ metabolism in patients despite receiving the same daily dose. Given the wide variability in cell ability to metabolize CBZ, which has the consequence of making it impossible to determine a standard dose for all patients, metabolic CBZ studies are necessary to reduce the occurrence of toxic effects with this drug.

Thus, the aim of the present study was to determine the relationships between the administered daily dose of CBZ and its pharmacokinetic parameters, including concentrations of CBZ and CBZ-E plasma levels, and the metabolic ratio of CBZ-E/CBZ. The objective in combining these three pharmacokinetic parameters is to better control the metabolic parameters of CBZ that may have implications in terms of optimization of CBZ therapeutic efficacy in patients with epilepsy.

2. Patients and methods

2.1. Patients

A group of 94 epileptic patients treated with CBZ monotherapy for at least four weeks (34 patients with symptomatic epilepsy and 60 patients with cryptogenic epilepsy) were recruited at the neurology department of Central Hospital University (CHU) Sahloul in Sousse (Tunisia). These patients comprised 40 men and 54 women, ranging in age from 14 to 80 years with a mean age of 38.26 ± 17 years. Most of these patients (50 patients, 53.19%) had focal seizures with or without secondary generalized seizures. The remaining patients presented with generalized tonic–clonic seizure (44 patients, 46.80%).

The study protocol was approved by the local ethics committee, and informed consent was obtained from each study participant.

2.2. Methods

Recruited patients were taking CBZ for at least 4 weeks. All confirmed their adherence to the medication, and no patient was taking an extended-release form. In all, 63% of patients were taking it twice a day, and 37% of them three times a day.

At 0800 hours in the morning, the participants arrived at the neurology department of CHU Sahloul. Before the morning CBZ dose (12 hours since the previous dose), venous blood samples were taken from one arm of each participating patient. Samples (with EDTA) were sent immediately to the Laboratory of Metabolic Biophysics. After centrifugation at 3000 g for 20 minutes at 4 °C, the plasma was separated and stored at −20 °C until analysis. Plasma samples were analyzed using a high-performance liquid chromatography (HPLC) method as described previously [12].

2.3. Statistical analysis

Pearson's correlation was used to study the possible relationship between pharmacokinetic parameters, such as plasma concentrations of CBZ and CBZ-E, and the metabolic ratio of CBZ-E/CBZ, and values of the daily dose given as the unit weight (specific dose in mg/kg/day). Using the Kolmogorov–Smirnov test, the studied sample variables followed a normal distribution when a parametric test (Pearson's r correlation) was used. These differences were considered statistically significant at $P \leq 0.05$. The fitted curves (Figs. 1–4) were obtained using Origin 6.0 software.

3. Results

3.1. Association between daily dosages and plasma CBZ concentrations

A statistically significant positive correlation was found between the administered daily dose (mg/kg/day) and plasma concentrations of CBZ ($Y = 2.52 + 0.51 * X \pm 0.0095 * X \wedge 2$; $r = 0.17$, $P = 0.01$). This result showed that the increase in CBZ plasma concentration was almost linear with doses < 12 mg/kg/day.

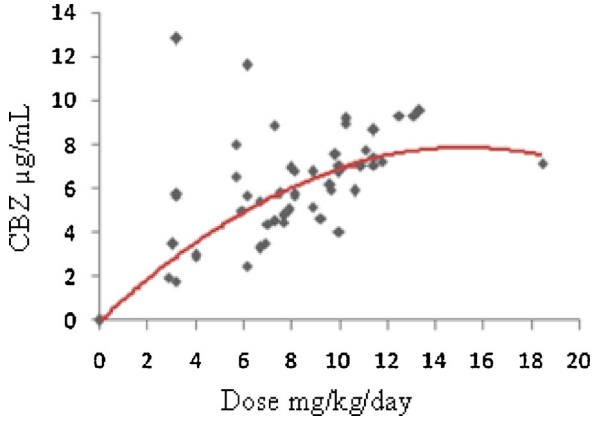

Fig. 1 – Relationship between mean steady-state concentrations of carbamazepine (CBZ) and dosage (mg/kg/day).

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