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Research Article

Serum monitoring of carbamazepine in patients with epilepsy and clinical implications

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Abstract

Carbamazepine is a drug with a narrow therapeutic range that requires clinical monitoring, since its toxic effects are not easily predictable, and the therapeutic level can vary. Our study aimed to monitor the serum level and determine the concentration/dose relationship of carbamazepine in people with epilepsy, analyzing its clinical implication. It is observed that 90.48% of the study volunteers present serum level values (4.3–10.4 mg/L) within the therapeutic range (4–12 mg/L); 7.14% present supratherapeutic levels (12.7–14.4 mg/L), 2.38% subtherapeutic (0.93 mg/L). The findings indicate a negative correlation ($r = -0.616$; $r^2 = 0.379$; $p = 0.001$), between the dose (mg/day) and the dose ratio (mg/L/mg/day); and a positive correlation ($r = 0.544$; $r^2 = 0.296$; $p = 0.002$), between the dose (mg/day)-serum concentration (mg/L). ANOVA and Tukey's test mean difference is significant ($p<0.05$). It is concluded that there is a positive and significant linear correlation between daily doses and serum carbamazepine concentrations, which should be considered to individualize the dose and optimize clinical results.

Keywords

Carbamazepine, Level/dose, Serum monitoring, Personalized dose, Therapeutic range

Introduction

Precision medicine is especially applied to chronic diseases such as epilepsy, which is based on the association genotype-metabolic phenotype and drug, serum level/dose, ethnicity, miscegenation, and sex, to prescribe the antiepileptic drug (AED), with the precise dose from the start of pharmacological treatment, to minimize side effects and optimize pharmacological therapy (Alvarado et al. 2019, 2020; Aronson and Rehm 2015). In particular, drugs with a narrow therapeutic margin should be monitored, such as carbamazepine (5-H-dibenzazepine-5-carboxamide), a class 2 antiepileptic according to the Biopharmaceutical Classification System (BCS), iminostilbene type derived from tricyclic antidepressants (Chbili et al. 2017), whose N of the dibenzazepine ring gives

it a pKa of 2.3 and the free NH_2 group of the carboxamide generates pKa 13.9. This drug is absorbed in the intestinal mucosa, reaching a bioavailability of 70–85%, establishing the optimum range as a minimum effective plasma concentration (C_{mE}) of 4 mg/L and a maximum effective plasma concentration (C_{ME}) of 12 mg/L (Chbili et al. 2016; Johannessen Landmark et al. 2020); the maximum time (Tmax) is 4–8 hours, and between 21 and 28 days the serum concentration is reached in the steady-state (C_{ss}). After absorption, it circulates bound to plasma proteins (UP: 75–85%), and its volume of distribution (Vd) is 1.4 L/kg (Aldaz et al. 2011; Saavedra et al. 2008). At the hepatic level, it is metabolized in two phases: through phase I, carbamazepine is oxidized by means of the protein CYP3A4, CYP3A5, CYP2C9, CYP1A2, CYP1A1, and CYP2C8 in 10,11-epoxycarbamazepine (CBZ-EP-10,11) (Darwish et al. 2015; Gierbolini et al. 2016; Johannessen Landmark et al. 2020), this active metabolite is biotransformed by epoxide hydrolase into 10,11-dihydro-10,11-trans-dihydroxycarbamazepine (CBZ-diOH) (Chbili et al. 2017; Darwish et al. 2015), this latter inactive metabolite is metabolized by conjugation phase II with UDP-glucuronosyl transferase (UGT2B7), which catalyzes the transfer of the glucuronic group that comes from UDP-α-D- glucuronic acid (UDPGA) forming the metabolite O-β-glucuronide of carbamazepine (O- β-G-CBZ) that is eliminated in the urine (Darwish et al. 2015; Chbili et al. 2017).

Chronic use of carbamazepine can induce its own metabolism, induce UGT2B7, epoxide hydrolase, CYP3A4 (Gierbolini et al. 2016), CYP1A2, CYP2C9 and CYP2C19 (Hernández and Marín 2017); Another factor to consider in therapeutic failure and side effects of carbamazepine is the metabolic phenotype of the patients depending on the allelic variants (*CYP2C9*2* and *CYP2C9*3*; *CYP3A5*3*) (Alvarado et al. 2019; Ganesapandian et al. 2019). The half-life time ($t_{1/2}$) of the drug varies according to age: 12–64 hours in newly born, 10–13 hours in children, and 8–20 hours in adults (Aldaz et al. 2011; Johannessen Landmark et al 2020). The following figure summarizes the metabolism and plasma level of carbamazepine according to the slow metabolic phenotype.

For these considerations, therapeutic drug monitoring (TDM) at the hospital level should be a routine clinical practice, to measure serum concentration, determine the level/dose ratio (N/D), identify possible drug interactions and side effects, which in many cases are the factors of therapeutic failure (Alvarado et al. 2020; Hutchinson et al. 2018; Nwobodo 2014). In this sense, determining the N/D allows knowing the hypothetical serum level reached with a theoretical dose of 1 mg/kg, and with this pharmacokinetic parameter the precise dose is adjusted (Cotuá et al. 2017; Alvarado et al. 2020). Therefore, monitoring carbamazepine (CBZ) levels is a valuable method for designing a safe and effective therapeutic regimen for epileptic patients (Sharma et al. 2012).

The PubMed-Medline database on studies of level/dose (N/D) and therapeutic monitoring of drugs has been reviewed, being limited these investigations in patients with epilepsy in Venezuela, for which it is worth carrying out them and mainly of drugs with a narrow margin therapeutic, generating scientific evidence so that these studies are a routine clinical practice in the Neurology Services of the National Hospitals and in the Clinics. The objective of the present study was to monitor the serum level and determine the concentration/dose relationship of carbamazepine in people with epilepsy, analyzing its clinical implication.

Materials and methods

Design, type of sampling and study population

Descriptive, cross-sectional, non-probabilistic sampling study with prospective recruitment from January 2019 to December 2021 (Cotuá et al. 2017; Alvarado et al. 2020).

Biological sample

A single blood sample was obtained from each patient attending the Neurology Service for their routine medical control. These samples were stored refrigerated at -21 °C until analysis (Sharma et al. 2012; Cotuá et al. 2017).

Inclusion and exclusion criteria

Patients who received CBZ monotherapy for 4 weeks (time in which the drug will be in its steady-state), do not consume medications that are not prescribed by the doctor of the Neurology Service, comply with the dose and frequency of administration of the medication, at the examination doctor, not manifest liver or kidney dysfunction and give their consent in writing (Cotuá et al. 2017; Alvarado et al. 2020). All patients with suspected overdose, noncompliance, and patients with renal or hepatic dysfunction were excluded (Sharma et al. 2012).

Carbamazepine quantification

Sample extractions were performed before the next scheduled dose and no less than 10 h after the last dose of CBZ (Sharma et al. 2012; Cotuá et al. 2017).

3 mL of venous blood was extracted in Vacutainer tubes, BD Bioscience, for the quantification of the drug in the serum, the samples were centrifuged within two hours of sampling at 8000 rpm for 10 minutes. Clear supernatant was taken from the serum fractions and stored at -21 °C until analysis. Then, 0.5 mL of each serum sample was measured, without any special treatment is necessary, determining total carbamazepine in the serum by the CEDIA method (Cloned Donor Enzyme Immunoassay) on the Indiko Thermo Fisher Scientific equipment (Waltham, Massachusetts, USES).

Ethical considerations

The study was developed in strict compliance with national and international ethical standards, in the Belmont Report, Declaration of Helsinki with the current revision. The Institutional Medical Board approved this study as a minimal risk investigation, for using blood samples from routine clinical practice, through certificate 002-JMI-2019. Each volunteer who signed the Informed Consent was assigned a code to guarantee confidentiality and anonymity.

Statistical analysis

The data obtained were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's test as post-hoc analysis. A value of $p<0.05$ was considered statistically significant. Pearson's correlation coefficient was also calculated to establish the relationship between carbamazepine level and dose. The Statistical Software GraphPad Prism 9 was used. Version 9.1.2.

Results

Of a total of 100 patients informed about the study, 42 met the selection criteria. Table 1 shows the demographic data of the voluntary patients with epilepsy, all of whom were of legal age (>19 years), of both sexes (59.52% male and 40.48% female), obtaining a mean serum concentration (Cp) of 7.67 mg/L with a mean dose of 730.95 mg/day.

Table 2 shows that 90.48% of the volunteer patients in the study have serum level values within the therapeutic range (accepted values for adults 4–12 mg/L), while 7.14% could present some secondary effects when exceeding the maximum effective concentration (C_{ME}). The accepted therapeutic range for adults was 4–12 mg/L.

Table 1. Patient demographics, and carbamazepine concentrations (n=42).

Statistic	Dose (mg/day)	Cp (mg/L)	Age (years)	Sex	
				Male n (%)	Female n (%)
Mean	730.95	7.67	36.26	25(59.52%)	17(40.48%)
SD	356.47	2.52	11.59		
Range	300–1600	0.93–14.4	19–62		

SD: standard deviation; Cp: serum concentration; n: number of volunteer patients

Table 2. Therapeutic, subtherapeutic and supratherapeutic level of carbamazepine.

Statistic	Therapeutic level (4-12 mg/L)	Subtherapeutic (<4 mg/L)	Supratherapeutic (>12 mg/L)	Dose ratio range (mg.L/mg.day)
n(%)	38 (90.48%)	1 (2.38%)	3 (7.14%)	
Mean	7.39	0.93	13.37	0.78
SD	1.75		0.91	0.29
Range	4.3–10.4		12.7–14.4	0.30–1.64

Fig. 2 shows the relationship between the daily dose of carbamazepine (mg/day) and the dose ratio (mg/L/mg/day) of each patient participating in the study; a negative correlation (r = -0.616) and a coefficient of determination

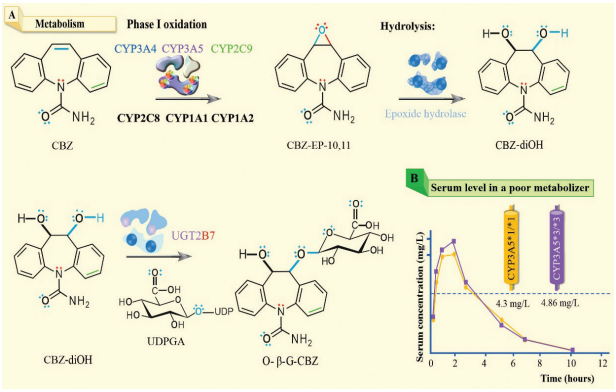

Figure 1. Metabolism (**A**) and plasma level of carbamazepine in people with slow metabolic phenotype (**B**).

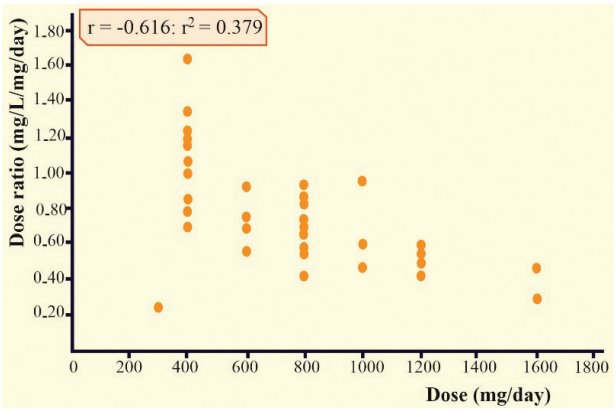

Figure 2. Relationship between the daily dose of carbamazepine and dose ratio in adults (ANOVA p = 0.001; Tukey test $p<0.05$).

(r^2 = 0.379) were found, which indicates a 37.9% relationship at the linear level of both variables, that is, there is a decrease in the dose relationship with the increased dose of carbamazepine. The analysis of variance (ANOVA) shows a p value of 0.001, and multiple variables were compared in pairs using Tukey's test, observing that the difference in means is significant ($p<0.05$).

The relationship of the dose (mg/day)-serum concentration (mg/L) and the therapeutic range is shown in Fig. 3; a positive (r = 0.544) and moderate (r^2 = 0.296) correlation was found. At ANOVA (p value = 0.002) and Tukey's test, the difference in means is significant ($p<0.05$).

Discussion

In the present study, the serum concentration level was determined with a single sampling point, observing that the range of the serum concentration level is 4.3–10.4 mg/L, in 90.48% (38/42) of the patients. These values are above the minimum effective serum concentration (C_{mE} 4 mg/L) and below the maximum effective serum concentration (C_{ME} 12 mg/L) (Aldaz et al. 2011; Chbili et al. 2016). To ensure that the drug is in the steady-state, the blood sample was taken after 4 weeks of starting treatment with carbamazepine, however, in 2.38% (1/42) of the patients a

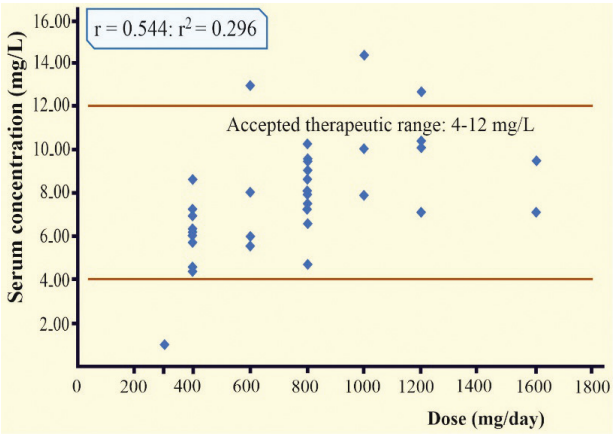

Figure 3. Dose-concentration relationship of carbamazepine showing the therapeutic range (ANOVA = 0.002; Tukey test $p<0.05$).

level higher than the C_{mE}, despite having controlled that the drug is taken two hours before meals since it is known that the drug-nutrient interaction, enzyme autoinduction, and variable half-life may be the cause of the low serum level (Aldaz et al. 2011). In this group of patients, it was suggested to adjust the dose based on the dose level index (N/D), to carry out Pharmacotherapeutic Follow-up for compliance with pharmacological therapy, and to detect possible adverse effects with the new dose. In 7.14% (3/42) of the patients, serum levels were observed to be in a range of 12.7–14.4 mg/L, which indicates that it is in the supratherapeutic range, in this sense it was decided to suspend the prescribed dose, then the change in treatment was evaluated. Sharma et al. (2012) report that serum levels of 12–20 mg/L are considered supratherapeutic, and higher than 20 mg/L neurotoxic levels.

Regarding the correlation, a negative or inverse correlation was observed in the level/dose ratio (mg.L/mg.day) between the dose (mg/day); and a positive and statistically significant linear correlation between the daily doses administered (mg/day) and serum concentrations (mg/L). Our findings are based on and contrasted with several previously published studies. Lackner (2002) and Jiao et al. (2003) indicated that age is one of the factors that alter serum concentration. Suzuki et al. (1991) indicated that a negative correlation occurs when increasing the dose decreases concentrations lower than expected, while a decrease in dose produces a lower concentration decrease than expected. Subsequently, Sánchez et al. (1986) and Sharma et al. (2012) describe that a negative correlation may be due to slow and delayed absorption of carbamazepine, and a fast elimination rate constant, generating a volume of distribution that diffuses slowly to the brain. Burianová and Bořecká (2015) observed serum levels of CBZ-EP-10,11 (0.34 and 6.94 mg/L) with a mean value of 1.74 mg/L; finding a close correlation between the chemiluminescence microparticle immunoassay method (CMIA) and the high-performance liquid chromatography method (HPLC); while Chbili et al. (2016) reported a positive correlation between the daily doses administered and the plasma concentrations of CBZ and its metabolite CBZ-EP-10,11; the CBZ-EP-10,11/CBZ ratio increased significantly as a function of the specific dose (mg/kg/day). Araki et al. (2020) indicate that the dose-concentration ratio of CBZ is 2.14 ± 0.23 ($p<0.001$), which is higher than that observed in the present study. Recently, Kacirova et al. (2021) observed significant correlations between serum and breast milk levels of carbamazepine and CBZ-EP-10,11; levels were 1.4–10.4 mg/L in serum and 0.5–6.7 mg/L in milk.

In the case of the group of patients with subtherapeutic and supratherapeutic levels, they require routine clinical monitoring, and based on the N/D index, adjust the dose, to propose the correct dose and at the correct time (Cotuá et al. 2017; Sánchez et al. 2005; Alvarado et al. 2020), carry out Pharmacotherapeutic Follow-up, to detect side effects, adverse reactions, and noncompliance with therapy. To perform clinical monitoring, the blood sample must be drawn before the morning dose of the drug, whose plasma concentration obtained is called the trough, basal, minimum, or pre-dose concentration (Cotuá et al. 2017). Taking into account the factors that affect the N/D and the ratio, such as the prescribed doses, pharmaceutical form, frequency of daily administration, concomitant consumption of enzyme-inducing and inhibitory drugs, enzyme autoinduction of the drug (Aldaz et al. 2011; Sharma et al. 2012; Cotuá et al. 2017), incorrect prescription compliance, gender, age, ethnicity, miscegenation, pregnancy, organ dysfunction (Johannessen Landmark et al. 2016; Alvarado et al. 2020), and by polymorphism of the genes that express metabolizing proteins CYP3A4 (*CYP3A4*1B*; **20*), CYP2C9 (*CYP2C9*2*2; *2*3*), and others (Darwish et al. 2015; Gierbolini et al. 2016; Alvarado et al. 2019, 2021). Due to the particular characteristics of the 27 AEDs (Johannessen Landmark et al. 2016; Patsalos et al. 2018) and of epilepsy, TDM has a significant clinical implication in epilepsy, since it allows measuring the serum concentration of the drug, interpreting whether the drug is within the therapeutic range for disease control; If the drug does not reach the minimum effective concentration (C_{mE}), the risk of therapeutic failure increases, and if it exceeds the maximum effective concentration (C_{ME}), it predisposes to side effects and even neurotoxicity of the drug. Knowing the therapeutic level makes it possible to adjust and individualize the dose, to optimize the clinical outcome in patients with uncontrollable epilepsies, and in vulnerable populations such as pregnant women, children, and the elderly (Jacob and Nair. 2016; Patsalos et al. 2018; Canisius et al. 2020).

Our results must be considered in the context of several limitations. First, the sample size was not calculated from patients with a diagnosis of epilepsy (n = 42), so it is not representative of the population that attends the Neurology Service, its selection was for convenience and prospective. Second, the use of the CEDIA method that is available in our hospitals; both limitations are being considered for incorporation in future studies by our research group, to obtain a more robust statistical relationship, using the high-resolution chromatographic method to obtain serum levels with greater precision. Notwithstanding the foregoing, this

study shows a significant correlation between dose/serum level. At the same time, it is recommended to incorporate pharmacogenetic studies that allow detecting poor metabolizer patients, to avoid overdose and toxicity of carbamazepine and other antiepileptic drugs (Alvarado et al. 2020, 2021; Johannessen Landmark et al. 2020).

Conclusion

It is concluded that there is a positive and significant linear correlation between the daily doses and the concentrations of carbamazepine in serum, which should be considered to individualize the dose and optimize the clinical result. TDM should be a routine clinical practice in our hospitals for the management of patients with epilepsy, minimizing side effects, and avoiding therapeutic failure.

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