Preliminarily Analysis of Carbamazepine (CBZ) C_0 in Patients Visited Isfahan Epileptic Clinics

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ABSTRACT

Background: Carbamazepine (CBZ) is mostly considered as the first line of effective treatment against simple or complex partial seizure and primary-secondary generalization. To prevent side-effects related to higher amount of CBZ minimum concentration (C_0) in body fluid or seizure attacks associated to lower amount of CBZ-C_0, the suggested minimum therapeutic concentrations range from 4 to 12 ng/ml (according to previous publications). The aim of this preliminarily study was to investigate the scope of discrepancy associated to the C_0 of CBZ in patients visited Isfahan Epileptic Clinic.

Methods: A cross-sectional study of 22 patients located in neurology ward of Isfahan Neurosciences Research Centre (INRC) was carried out between April 1, 2012 and December 31, 2012. Female (n = 9) and male subjects (n = 13) with a mean age of 27.4 years (range; 16-38 years) were studied. Pharmacological (CBZ-C_0) and demographical variables were recorded and processed in excel.

Results: The results of CBZ-C_0 showed wide inter-individual variability. The mean value of CBZ-C_0 was 7.2 ng/ml. In 10 out of 22 patients, CBZ-C_0 were lower than the suggested therapeutic window (4-12 ng/ml). CBZ-C_0 in nine patients was non-detectable and in one patient was 0.5 ng/ml (45% <4 ng/ml). In 55% of the patients, CBZ-C_0 ranged from 4.8 to 12 ng/ml.

Conclusions: A schedule therapeutic drug monitoring based on measurement of CBZ-C_0 for individual patient could be a practical marker to achieve therapeutic objectives. Further study related to correlating of CBZC_0 to clinical events in Iranian Epileptic population seems to be valuable.

Keywords: C_0, carbamazepine, epilepsy, Iranian

INTRODUCTION

Epilepsy is a mutual situation in which seizures, unintentional assaults of loss of consciousness and physical regulator, are experienced repeatedly. Carbamazepine is an anti-convulsant and mood-stabilizing drug used mainly in the management of epilepsy, bipolar disorder (trigeminal neuralgia), schizophrenia, phantom limb syndrome, complex regional pain syndrome, paroxysmal

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extreme pain disorder, neuromyotonia, intermittent explosive disorder, borderline personality disorder, and post-traumatic stress disorder. Carbamazepine belongs to a group that is called as drugs with narrow therapeutic window. Carbamazepine adverse effects may include lethargy, headaches, migraines, motor coordination impairment, and/or upset stomach.[1-4] Carbamazepine alleviates the deactivated state of sodium channels, producing fewer of these channels accessible to consequently exposed. This generally makes the affected cells less impulsive until the drug detach. Carbamazepine has also been shown to potentiate δ-aminobutiric acid Gamma-Amino Butric Acid (GABA) receptors.[5-9] Optimizations of treatment in epileptic patients requires achieving a delicate balance between having enough drugs available to prevent seizure attack but not so much that the patient is likely to develop toxic side-effects. Conventionally, this objective has been supported by blood-level monitoring of carbamazepine. Carbamazepine has a moderately narrow therapeutic index and the relationship between dose and blood concentrations is deprived as a consequence of inconsistency in pharmacokinetic parameters between epileptic patients.[10,11] Many of the toxic effects of carbamazepine are more frequent after oral administration with other antiepileptic drugs especially inducers or inhibitors of cytochrome P_{450}.[12-21]

As clinical management of carbamazepine needs an individualization scheduled program, the objective of this primary study was to examine the extent of variability related to minimum concentration (C_0) of CBZ in patients visited Isfahan Epileptic Clinic.

METHODS

A cross-sectional study of 22 patients visited Isfahan Epileptic Clinics conducted in Isfahan Neurosciences Research Centre (INRC) and carried out between April 1, 2012, and December 31, 2012. There was no induction in treatment procedure. The study was approved by the Institute Research Ethics Committee (IREC). The route of administration was oral. Trough level of carbamazepine was obtained from patients records. Pharmacological data such as minimum concentrations (trough levels; C_0) of CBZ and demographic data were recorded and processed in Excel.

RESULTS

The average age of the patients was 27.4 years old (range; 16-38 years). Nine patients were females (41%) and 13 were males (59%). However, the administration of carbamazepine was connected with marked unpredictability and large disparity in trough levels [Figure 1], the efficiency and the toxicity of carbamazepine appeared to be associated to plasma drug levels. The mean value of carbamazepine trough levels was 7.2 ng/ml. In one patient the value of carbamazepine trough levels was 0.5 ng/ml. In nine patients carbamazepine trough levels was not detectable. Trough levels of carbamazepine in approximately 45% of patients were lower than suggested therapeutic level (ranged: 4-12 ng/ml). The maximum value related to carbamazepine trough levels was 12 ng/ml. With a mean of 7.8 ng/ml (range; 4.8-12 ng/ml) in the approximately 55% of patients carbamazepine trough levels were in the suggested therapeutic range.

DISCUSSION

Existing literature designates that carbamazepine shows wide inter- and intra-individual dissimilarity in its pharmacokinetics. Monitoring carbamazepine is performed not only to make drug measurements in body fluids but also to regulate the dosage of drug according to the features of the individual being treated and their pharmacological response. Therapy with carbamazepine reduces seizure attack in epileptic patients. The wide range of values in pharmacological parameter (C_0), obtained during carbamazepine therapy is in accordance with previous publications.[12-21] Carbamazepine is mainly eliminated by the cytochrome P_{450} system

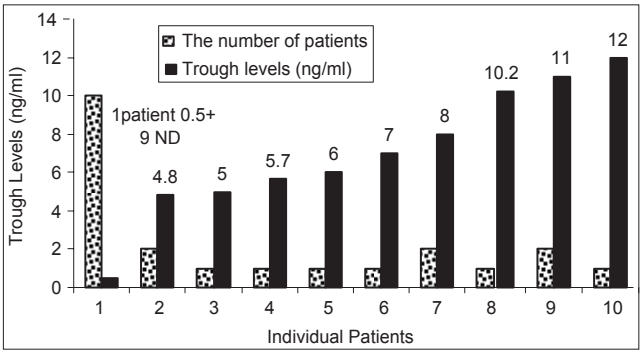

Figure 1: The distribution of carbamazepine trough levels (n = 22)

and has an active metabolite, carbamazepine-epoxide. Carbamazepine undergoes autoinduction in which clearance increases over time following exposure to the drug e.g., within 30 days after therapy begins, clearance increases by 300%. The half-life of carbamazepine ranges from 10 to 20 hours but diminish with autoinduction from 4 to 12 hours.[22-24] As the expected therapeutic range for carbamazepine range from 4 to 12 ng/ml, in the 45% of population studied here carbamazepine trough levels was less than 4 ng/ml, seems to be inadequate. Previous publications reported a significant correlation between drug levels and the incidence convulsion. Upon commencement of carbamazepine treatment, concentrations are predictable and follow individual pharmacokinetics parameters established for the specific patient.[23-28] In order to continue a vigilant monotherapy, monitoring CBZ-C_0 seems to be useful.

CONCLUSIONS

Interpretation of data presented in this paper confirmed heterogeneity between individual carbamazepine trough levels. Prescription of carbamazepine based on a rational basis could be helpful in prevention related to therapeutic failure. Finally, carbamazepine dosage adjustment based on trough levels measurement, seems beneficial in Iranian epileptic patients.

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