Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfda-online.com

Original Article

Beverage-induced enhanced bioavailability of carbamazepine and its consequent effect on antiepileptic activity and toxicity

Sanmoy Karmakar [a,b,*], Sreerupa Biswas [a], Rammohan Bera [a], Samiran Mondal [c], Amit Kundu [a], Md Asif Ali [a], Tuhinadri Sen [a,b]

[a] Division of Pharmacology, Department of Pharmaceutical Technology, Jadavpur University, Kolkata 700032, India
[b] School of Natural Product Studies, Jadavpur University, 188 Raja S.C. Mallick Road, Kolkata 700032, India
[c] Animal Health Centre, Purulia, West Bengal, India

ARTICLE INFO

Article history:
Received 14 April 2014
Received in revised form
14 July 2014
Accepted 16 July 2014
Available online 3 December 2014

Keywords:
bioavailability
black tea
carbamazepine
grapefruit juice
HPLC

ABSTRACT

The present study was undertaken to investigate the food–drug interaction of carbamazepine (CBZ). Common fruit juices [grapefruit juice (GFJ), lime juice (LJ)], known to inhibit the enzyme cytochrome P450 3A4 (CYP3A4), and some widely consumed beverages [milk (M), black tea (BT)] were involved in this study in the presence of CBZ, as might happen during clinical therapy. The effects of the beverages on the pharmacokinetics and drug-induced toxicity of CBZ was observed after concomitant administration for a period of 28 days. Accordingly, the influence of altered bioavailability of CBZ on its antiepileptic activity was investigated. A significant shift in the C_{max} as well as T_{max} of CBZ was observed in the presence of LJ and GFJ. This increase in bioavailability significantly enhanced hepatotoxicity and delayed the onset of tremor and piloerection against pentylene tetrazole (PTZ)-induced seizure in experimental animals. However, increased toxicity of CBZ was found to be absent with BT. Thus, from our observation, LJ or GFJ in the presence of CBZ significantly increased the bioavailability of CBZ, which might lead to increased toxicity and antiepileptic activity of the drug.

1. Introduction

Antipsychotics and antidepressants are clinically important drugs often used for chronic treatment thereby rendering adverse effects and aspects of drug–drug or food–drug interactions of these drugs to serious clinical vigilance [1]. Carbamazepine (CBZ), a drug with a comparatively narrow therapeutic index, is a concern among health care professionals because it may result in clinically significant drug interactions. Therefore, bioavailability studies in the presence of other drugs and food are becoming increasingly necessary to avoid toxic effects [2] or clinical failure. It has been observed that inhibition of cytochrome P450 (CYP) enzymes is the most common mechanism that produces serious and potentially life-threatening drug interactions [3]. CBZ undergoes

* *Corresponding author*. Division of Pharmacology, Department of Pharmaceutical Technology, Jadavpur University, 188 Raja S.C. Mallick Road, Kolkata 700032, India.
E-mail address: sanmoykarmakar@gmail.com (S. Karmakar).
http://dx.doi.org/10.1016/j.jfda.2014.07.012

biotransformation by CYP3A4 into carbamazepine-10,11-epoxide [4] and as a consequence of CYP inhibition or induction, plasma concentrations of CBZ may reach toxic or subtherapeutic levels.

Similar studies are available on incidents of increased bioavailability and enhanced pharmacodynamic effects following concomitant administration of citrus juice and calcium channel blockers such as felodipine and nifedipine [5].

In the present study, we investigated the *in vivo* pharmacokinetic interaction and pharmacodynamic effects of CBZ with commonly consumed beverages including lime juice (*Citrus aurantifolia*; LJ), grapefruit juice (*Citrus paradise*; GFJ), milk (M), and black tea (*Camellia sinensis*; BT) in experimental animals.

2. Methods

2.1. Chemicals and reagents

A CBZ suspension (Tegretol; Novartis Pharmaceuticals, Hyderabad, India), acetonitrile [high performance liquid chromatography (HPLC) grade; Sigma Aldrich, Maharashtra, India], potassium dihydrogen phosphate (Merck Pvt. Ltd, Mumbai, India), ortho-phosphoric acid (Merck Pvt. Ltd, Mumbai, India), methanol (HPLC grade, Sigma Aldrich, Maharashtra, India), and HPLC grade water (resistivity of 18.2 MU cm) generated from a Milli Q water purification system (Elix; Milli Q A10 Academic, Molsheim, France) were used throughout the analysis. Biochemical kits and pentylene tetrazole (PTZ) were obtained from Merck Pvt. Ltd. (Mumbai, India) Crude CBZ and valdecoxib were obtained as gifts from Cosmas Pharmacls (Ludhiana, Punjab, India).

2.2. Animal husbandry and maintenance

Healthy adult male Wistar rats weighing 170–180 g and male Swiss albino mice of 25–30 g, procured from TAAB Biostudy Services, 67/1B, Ibrahimpur Road, Kolkata 700032, India, were used for the study. The animals were grouped and housed in wire cages with not more than six animals per cage in a controlled environment (12 h light–dark cycle, temperature of 25 ± 2°C and 50 ± 20% relative humidity). During the period of study, the animals had free access to standard dry pellet diet (Nutrilab Rodent; Provimi) and water *ad libitum*. The study was conducted in accordance with the Institutional Ethical Committee (constituted under the Guidelines Committee for the Purpose of Control and Supervision of Experiments on Animals, Reg. No. 367).

2.3. Preparation of beverages

LJ (*Citrus aurantifolia*), GFJ (*Citrus paradise*), and M were obtained from local commercial sources. Juice was obtained by squeezing the edible portion of the fruits and then filtered. BT (*Camellia sinensis*) extract was prepared by soaking 2 g of black tea leaves (Lipton; Hindustan Unilever Ltd.) in 10 mL of boiling water followed by filtration [6]. Beverages were administered at a dose of 10 mL/kg.

2.4. High performance liquid chromatography conditions

The HPLC system consisted of an LC-20A Dvp pump (Shimadzu, Kyoto, Japan), a Shimadzu UV absorbance detector, a Hamilton syringe, and a Shimadzu SDP-20Avp system controller. The system was equipped with a Luna 5μ C18 column (250 mm × 4.6 mm, 5 μm; Phenomenex, Torrance, CA, USA), preceded by a precolumn. The isocratic mobile phase comprised a mixture of 100 mM potassium dihydrogen orthophosphate (KH_2PO_4, pH 3.2) and acetonitrile in a ratio of 60:40 v/v was delivered at a flow rate of 0.8 mL/min at 25°C. The UV detector was set at 245 nm and the volume of injection was 20 μL. The column was equilibrated for at least 20 minutes with the mobile phase flowing through the system prior to the injection of the drug standards. The run time was set at 15 minutes with the system operating at air-conditioned temperature (20°C).

2.5. Grouping and dosing of animals for pharmacokinetic study

The maximum tolerated dose of CBZ in humans was extrapolated to a rat dose [7]. Rats were randomly grouped into nine ($n = 9$). CBZ at a dose of 105.70 mg/kg was administered orally (equivalent to 17.14 mg/kg in humans). Group I received CBZ and water (W) whereas Groups II, IV, VI, and VIII received CBZ 30 minutes after a dose of LJ, GFJ, M, and BT, respectively. Groups III, V, VII, and IX received LJ, GFJ, M, and BT, respectively.

2.6. Serum biochemistry

Serum samples collected on Day 0, Day 2, Day 15, and Day 29 were analyzed for serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphate (ALP), total protein (TP), albumin (ALB), albumin/globulin ratio (A/G), blood urea nitrogen (BUN), and creatinine (CR) using a Microlab-300 auto-analyzer.

2.7. Histopathological study

On Day 29, the animals were sacrificed by cervical decapitation under anesthesia. The liver and kidney tissues were fixed in neutral phosphate-buffered 10% formalin solution and kept in a fridge until the tissues were prepared for histological examination. The tissues were processed, embedded in paraffin, and sectioned at 3–5 μm. The sections were examined after staining with hematoxylin and eosin (H&E).

2.8. Pharmacokinetic experiment

On Day 1 and Day 28, each animal of Groups I, II, IV, VI, and VIII was anesthetized and blood was collected from the retro-orbital plexus or tail vein into tubes containing EDTA at time points of 0 hours, 0.25 hours, 0.50 hours, 1 hour, 3 hours, 6 hours, and 8 hours. The samples were immediately centrifuged at 1150*g* at 15°C for 5 minutes and the plasma was separated. The plasma sample collected was stored at −20°C until analysis.