Saudi Pharmaceutical Journal (2015) 23, 177–181

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

The Effect of Pioglitazone on Pharmacokinetics of Carbamazepine in Healthy Rabbits

Issam Abushammala *

Department of Pharmaceutics and Industrial Pharmacy, College of Pharmacy, Al-Azhar University-Gaza, Gaza, P.O Box: 1277, Palestine

Received 13 March 2014; accepted 5 July 2014
Available online 9 July 2014

KEYWORDS

Pioglitazone;
Drug–Drug interaction;
Carbamazepine;
Pharmacokinetic;
CYP3A4

Abstract *Introduction:* Drug–drug interactions can lead to serious and potentially lethal adverse events. In recent years, several drugs have been withdrawn from the market due to interaction-related adverse events. The objective of this study was to evaluate the pharmacokinetic interaction between pioglitazone (PG) and carbamazepine (CBZ) in healthy male rabbits.

Methods: A randomized, two-crossover design study was conducted in six healthy male rabbits. The study consisted of two periods: period one, when each rabbit received a single dose of 70 mg CBZ-suspension. Period two, when each rabbit received a single dose of 70 mg CBZ-suspension co-administered with a single dose of 1.5 mg PG with a washout period of one week between the two periods. Serial blood samples were collected over a period of 48 h. Chemiluminescent enzyme immunoassay (CLEIA) was used to measure CBZ in serum. Pharmacokinetic (PK) parameters C_{max}, T_{max}, $t_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$, and k_e were determined for the two periods using non-compartmental analysis.

Results: In the two periods of treatment, C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$ and k_e for CBZ were administered alone and in combination with PG. C_{max}, the mean peak plasma concentration was 4.33 ± 2.4 μg/mL versus 4.76 ± 2.1 μg/ml, t_{max}, time taken to reach, was 2.91 ± 1.11 h versus 3.6 ± 1.83 h, total area under the curve AUC_{0-t} was 64.90 ± 43.6 μg·h/ml versus 102.90 ± 66.9 μg·h/ml, $AUC_{0-\infty}$ was 74.0 ± 52.6 μg·h/ml versus 124.3 ± 85 μg·h/mL, $t_{½}$ was 14.10 ± 2.5 h versus 16.43 ± 6.43 h and elimination rate constant k_e was 0.050 ± 0.009 h^{-1} versus 0.057 ± 0.049 h^{-1}, respectively. No statistical differences were found in pharmacokinetic of CBZ in both cases ($P > 0.05$).

Conclusion: The result of the study demonstrated that PG does not affect pharmacokinetic parameters of CBZ. Therefore, no cautions regarding dose or administration pattern of CBZ with PG should be taken.

1. Introduction

Interaction between drugs represents a major clinical concern for health care professionals and their patients. It occurs when one therapeutic agent either alters the concentrations or the biological effect of another agent (GhavimI et al., 2013). Many

* Tel.: +970599019757.
E-mail address: issam.abushammala@uv.es.
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2014.07.004

clinically important drug interactions are the result of induction or inhibition of cytochrome P450 (CYP) enzymes, the major drug-metabolizing enzymes mainly present in the liver (Wilkinson, 2005; Sahi et al., 2003). It has been estimated that 70% of human drug oxidation can be attributed to six main enzymes CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (Tanaka, 1999). Patients affected by both diabetes type 2 DM and epilepsy can be treated by pioglitazone and carbamazepine at the same time. Pioglitazone (PG) is a thiazolidinedione compound used in the treatment of type 2 DM. It is an insulin sensitizer that acts as an agonist of the peroxisome proliferator-activated receptor subtype gamma (PPAR-γ), (Yki-Jarvinen, 2004; Lehmann et al., 1995). It is well-absorbed, with a mean absolute bioavailability of 83% and reaching maximum concentrations in around 1.5 h (Hanefeld, 2001; Eckland and Danhof, 2000). Moreover, it is extensively metabolized by hydroxylation and oxidation to active and inactive metabolites in the liver predominantly via cytochrome P450 (CYP) isoenzymes, CYP2C8 and CYP3A4 (Hanefeld, 2001; Eckland and Danhof, 2000).

Carbamazepine (CBZ) is one of the most commonly prescribed antiepileptic drugs and is also used in the treatment of trigeminal neuralgia and psychiatric disorders, particularly bipolar depression (Galal et al., 2004). It has a dissolution dependent oral bioavailability due to its low solubility in water (113 μg ml^{-1}, 25 °C) exhibiting a slow and irregular gastrointestinal absorption (Sethia and Squillante, 2004; Barakat and Radwan, 2006). CBZ is a potent inducer of CYP isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP3A4 (Anderson, 1998; Spina et al., 2005). However, it is metabolized by CYP3A4 to give carbamazepine-10,11-epoxide, the major active metabolite representing 80% of CBZ in man (Kerr et al., 1994; Patsalos et al., 2002). So, CBZ shows a relatively short half-life, in chronic treatment, due to autoinduction of the drug metabolism (Giunchedi et al., 1991). Furthermore, its half-life may be shortened by coadministration of other CYP3A4 inducer drugs (Galal et al., 2004).

PG showed in vitro inductive effects on CYP3A4 (Sahi et al., 2003). This could influence pharmacokinetic of CBZ. Alteration in pharmacokinetics of such antiepileptic may cause toxicity or loss of seizure control. Therefore, this study was conducted to assess the possibility of potential interaction of PG with CBZ.

2. Materials and Methods

2.1. Animals

Six healthy male rabbits with mean weight 3.4 ± 0.12 kg, aged 7–9 months were enrolled in the study. The rabbits were obtained from Asdda for animal production and welfare center, where follow up care and clinical examination were performed and rabbits' health state was certified (khanunis, Palestine). Rabbits were fasted for 12 h with free access to water by ad libitum before the beginning of the study.

The study was carried out at the Al-Azhar University-Gaza, College of Pharmacy, Gaza, Palestine. The study was approved by the institutional ethics committee and was conducted under supervision of a veterinary physician.

2.2. Study design

A single dose, two-crossover design study was conducted in rabbits. There was a washout period of one week between the two doses. The rabbits were divided into two groups. The first one received a 70 mg dose of CBZ oral suspension, whereas the second group received the same dose of CBZ co-administered with a single dose 1.5 mg of PG as a suspension prepared in laboratory. PG tablets were pulverized and a weight of the powder equivalent to 15 mg PG was suspended in 20 ml distilled water. Carbamazepine suspension (2%, Tegretol, Novartis) and pioglitazone tablet (30 mg, Actos, Takeda) were purchased from a local pharmacy (Gaza, Palestine). After one week the second group received CBZ alone and the first received CBZ concurrently with PG to complete the cross-over design. The dose was given by means of a syringe connected to an oral gavage. It was put in the corner of the mouth and the liquid was pushed down slowly, to avoid choking. General clinical safety was assessed by physical examination during the study, washout period and at the end of the study.

2.3. Blood sampling

Rabbits were placed in the rabbit restraining box device. The marginal ear vein was located and the hair was removed. Gentle stroking and tapping of the ear may make the vein more visible. Local anesthetic was applied to prevent the jerking of the rabbit as a result of venipuncture 15 min before starting the study by inserting a small needle (23 gauge) butterfly attached to a syringe in the marginal ear vein (Parasuraman et al., 2010). Serial venous blood samples were collected (1 ml) in vacutainer tubes according to the time schedule 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 24.0 and 48 h after receiving the dose. Blood samples were centrifuged at 3,000 rpm for 5 min and serum was transferred into clean plastic tubes. Serum samples (ca. 200 μl) were kept in refrigerator until being analyzed within 24 h.

2.4. Analysis of serum samples

The analysis was performed by the carbamazepine kit based on chemiluminescent enzyme immunoassay (CLEIA) and Immulite 1000 immunoassay system (Siemens Healthcare Diagnostics).

2.5. Pharmacokinetic analysis

The plasma pharmacokinetic parameters were estimated, which included the observed maximum plasma concentration C_{max}, the time to reach C_{max}, (T_{max}) and the area under the plasma concentration–time curve from 0 h to last measurable concentration ($AUC_{0\text{-}t}$) and 0 h to infinity ($AUC_{0\text{-}\infty}$). C_{max} and T_{max} were directly determined from the serum concentration versus time curves. The area under the curve from 0 h to t ($AUC_{0\text{-}t}$) was calculated by the linear trapezoidal rule. The area under the curve from 0 h to infinity ($AUC_{0\text{-}\infty}$) was estimated by summing the area from $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$, where $AUC_{0\text{-}\infty} = AUC_{0\text{-}t} + C_t / k_e$, with '$C_t$' defined as the last measured serum concentration at time t, and k_e is the