THERAPEUTIC EFFECTS OF CIPROFLOXACIN ON THE PHARMACOKINETICS OF CARBAMAZEPINE IN HEALTHY ADULT MALE VOLUNTEERS

ANDLEEB SHAHZADI[1*], IJAZ JAVED[1], BILAL ASLAM[1], FAQIR MUHAMMAD[1], MUHAMMAD RAFIQUE ASI[2], MUHAMMAD YASIN ASHRAF[2] AND ZIA-UR-RAHMAN[1]

[1]Department of Physiology and Pharmacology, University of Agriculture, Faisalabad, Pakistan
[2]Nuclear Institute for Agriculture and Biology (NIAB), Jhang Road, Faisalabad, Pakistan

ABSTRACT

Carbamazepine is a (CYP1A2 and CYP3A4 enzyme inducer) medicine which is used by epileptic patients for a long time. During the course of therapy, patients are generally caught by other diseases like urinary tract infections, upper respiratory tract infection, skin and soft tissue infection etc. To cure them, physicians commonly prescribe fluoroquinolones like Ciprofloxacin (CYP1A2 inhibitor) along with Carbamazepine (CBZ). Interactions may result without recognition which may lead to unforeseen toxicity, untoward effects or even therapeutic failure. Therefore, studies were conducted to investigate the effect of Ciprofloxacin on the pharmacokinetics of carbamazepine in healthy adult male volunteers. The main objective of this study was to generate new knowledge regarding CBZ and ciprofloxacin interaction for physicians and research workers dealing with these medicines.

Eight healthy adult male volunteers were selected to assess the effect of ciprofloxacin on the pharmacokinetics of carbamazepine. After overnight fast the selected male volunteers were given CBZ orally. Blood samples were drawn at different time intervals after medication. Then the same volunteers were given CBZ along with ciprofloxacin. Blood samples were again drawn at the same time intervals as done previously. Plasma was separated from the blood samples. Concentration of CBZ in the plasma samples was determined by using HPLC technique.

Results of the present study indicated that ciprofloxacin significantly increased the plasma concentration of CBZ when given concurrently to the healthy adult male volunteers. Ciprofloxacin increased C_{max}, AUC and $t_{½}$ while it decreased the CL and Vd of CBZ when administered concurrently to the adult volunteers.

Change in pharmacokinetic parameters was due to slow metabolism or elimination of CBZ when given concurrently with ciprofloxacin to the adult volunteers. This is probably due to the inhibition of CYP3A4 isoenzyme by ciprofloxacin which is responsible for metabolism of CBZ. Ciprofloxacin increased the plasma concentration of CBZ so dose adjustment as well as drug monitoring of CBZ is required when both the drugs are given concurrently. The knowledge regarding interaction between ciprofloxacin and CBZ would be helpful for the pharmaceutical industries, physicians and a blessing for the patients.

Keywords: Carbamazepine, Ciprofloxacin, Cytochrome, Maximum plasma concentration of drug, Area under curve and half life, clearance and volume of distribution.

INTRODUCTION

The rational use of antiepileptic drugs needs the consideration of their pharmacokinetics which is influenced by the physiological and pathological factors (Tokola and Neuvonen, 1983). The knowledge regarding drug interaction is very important for pharmaceutical industries, regulatory agencies, clinical health care professionals and their patients (Badyal and Dadhich, 2001). The potential for development of drug-drug interaction increases with age, number of medicines in use and the number of physicians visited by the same patient (Silvana *et al*., 2007). Drug interactions can drastically enhance both the therapeutic effects of the drugs and also the risk of adverse effects (Dresser *et al.*, 2000). Epilepsy is a chronic neurological condition accompanied by recurrent, unprovoked seizures. The rate of prevalence of epilepsy was found to be 0.52% in Europe, 0.68% in the US while in developing countries this percentage is more than 1.5% (Adam *et al.,* 2008). Carbamazepine (CBZ) is the drug of choice for the treatment of epilepsy, neuropathic pain, schizophrenia and paroxysmal extreme pain disorder (Crawford *et al*., 1990). The utilization rate of CBZ is 8.8 to 23% with respect to any other antiepileptic drug (Schachter *et al*., 1998). Use of CBZ has increased in the last few years because of its application in psychiatric illness (Otani *et al.*, 1996; Reijs *et al.,* 2004). It is estimated that more than two million patients are treated with CBZ in United States alone (Seetharam and Pellock, 1991). Carbamazepine in chronic

**Corresponding author*: e-mail: shahzadi_andleeb@yahoo.com

use is found to be a CYP1A2 and CYP3A4 enzyme inducer (Parker *et al.,* 1998). As the epileptic patients have to take antiepileptic drugs for long time so, they may develop many other diseases like urinary tract infections, upper respiratory tract infection, skin and soft tissue infection, dental pain; they can also suffer from typhoid and many other infectious diseases. To get rid of infectious diseases, fluoroquinolones are used as first line of therapy nowadays.

Fluoroquinolones are broad-spectrum antibiotics, active against wide range of aerobic gram-positive and gram-negative organisms. Ciprofloxacin is one of the widely used quinolones these days. It has been seen that ciprofloxacin (Szalek *et al.*, 2007) and carbamazepine both are metabolized by CYP1A2 (Jerling *et al.*, 1994) and ciprofloxacin reversibly inhibits CYP3A4 isoenzyme (VonMoltke *et al.*, 1996) which is the major enzyme responsible for the metabolism of CBZ.

Both the drugs are prescribed commonly by the physicians and interaction may result without recognition which may lead to unforeseen toxicity, untoward effects or even therapeutic failure. Therefore, studies were conducted to investigate the effect of Ciprofloxacin (CYP1A2 inhibitor) on the pharmacokinetics of CBZ (CYP3A4 and CYP1A2 inducer) in healthy adult male volunteers as it is necessary to generate new knowledge/information regarding CBZ and ciprofloxacin interaction and pharmacokinetics for physicians and research workers dealing with CBZ.

MATERIALS AND METHODS

Experimental volunteers

Effect of ciprofloxacin on the pharmacokinetics of CBZ was investigated in eight healthy adult male volunteers. The following experimental protocol was observed. Complete information regarding experiment was provided to the volunteers both in verbal and writing form. Each individual furnished written consent before start of the experiment.

All the subjects, 20-25 years old (average = 23 years), were selected on the basis of their previous medical history. Weight of the individuals ranged from 65-75 kg (average = 70 kg). None of the subjects was smoker. The volunteers falling under the following criteria were excluded from the study. Obesity, allergy or intolerance to CBZ or ciprofloxacin and donation of blood prior to study initiation.

Methodology

For the collection of blood, one of the brachial veins was cannulated under strict aseptic conditions with plastic cannula/branulla. A commercial preparation of carbamazepine, tablets, 200 mg and of ciprofloxacin tables 500mg were used in the present study. After over night fast, the selected volunteers were given 200 mg CBZ orally. After a washout period of 10 days (6 x $t_{1/2}$ CBZ), CBZ was administrated with ciprofloxacin (500 mg) orally to the same volunteers. Blood samples were collected in heparinized plastic centrifuge tubes. Prior to the drug administration, a control blood sample was collected from every volunteer. Following the administration of CBZ alone and along with ciprofloxacin, the blood samples were drawn at one h and then with hourly interval up to 6 h. Thereafter, the blood samples were drawn at 8, 10, 18 and 36 h. Afterwards, the sampling was continued with 12 h interval up to 72 h after medication. Plasma was separated from the blood samples and preserved at –20^{o}C until analysis.

Analytical procedures

Carbamazepine in plasma samples was determined by using High Performance Liquid Chromatographic (HPLC) method with some modification as described by Demirkaya and Kadioglu (2005).

Calculations

Disposition Kinetics

Pharmacokinetics calculations were done with computer programme MW/ PHARM version 3.02 by F. Rombout, in cooperation with University Centre for Pharmacy, Department of Pharmacology and Therapeutics, University of Gronigen and Medi/Ware (Netherlands) (copyright 1987-1991). Kinetic parameters were calculated according to two compartment open model.

Statistical analysis

Mean value and standard error of means ± (SE) for each concentration and parameter was calculated. The significance was determined by using 't' test ($p<0.05$).

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RESULTS

The plasma concentration of orally administered CBZ alone reached its maximum 9.874 ± 0.253 µg mL^{-1} (mean ± SE) at 8 h and then declined with passage of time to 2.025 ± 0.243 at 72 h. The mean ± SE values for plasma concentration obtained from eight adult subjects have been plotted against time in Fig. 1. Similarly, C_{max} plasma concentration of CBZ with ciprofloxacin was 16.606 ± 0.212 at 6 h which declined with the passage of time to 3.316 ± 0.162 at 72 h. The mean ± SE values for plasma concentration of CBZ along with ciprofloxacin in the eight adult subjects have been plotted in fig. 1. against time after concurrent oral administration of both the drugs. The comparative mean ± SE values (µg mL^{-1}) of CBZ (200 mg) following its oral administration alone and with ciprofloxacin (500 mg) to the eight volunteers have been presented in fig. 1. This reflected approximately 41% increase in the peak plasma concentration of CBZ. Moreover, this percentage of CBZ increase was also

Table 1: Comparative mean ± SE values for the disposition kinetics of carbamazepine (200 mg) alone and with ciprofloxacin (500 mg) in healthy adult male volunteers.

Parameters	Units	Carbamazepine	Carbamazepine with ciprofloxacin
C_{max}	µg mL^{-1}	9.153 ± 0.235*	14.243±0.371
t_{max}	h	7.658 ± 0.651^{NS}	7.875±0.556
K_{abs}	h^{-1}	0.243 ± 0.037 ^{NS}	0.184±0.018
$T_{1/2abs}$	h	3.310 ± 0.455 ^{NS}	4.03±0.391
A	µg mL^{-1}	9.167 ± 1.545*	21.033±1.602
α	h^{-1}	0.186 ±0.028 ^{NS}	0.183±0.018
$T_{1/2}\alpha$	h	4.900 ± 1.316 ^{NS}	4.037±0.393
B	µg mL^{-1}	8.104 ± 0.518*	9.923±0.642
β	h^{-1}	0.018 ± 0.017^{NS}	0.014±0.001
$T_{1/2}\beta$	h	38.318 ± 4.691*	50.01±3.359
V_d	L kg^{-1}	0.348 ± 0.042*	0.262±0.022
K_{el}	h^{-1}	0.036 ± 0.003 ^{NS}	0.039±0.002
k_{12}	h^{-1}	0.073 ± 0.016 ^{NS}	0.086±0.009
k_{21}	h^{-1}	0.088 ± 0.010 *	0.0686±0.010
AUC	µg. h mL^{-1}	357.2 ± 12.707*	548.6 ± 16.698
MRT	h	57.156 ± 6.563^{NS}	64.782 ± 4.714
Vc	L kg^{-1}	0.179 ± 0.010*	0.099 ± 0.008
Cl_B	L $h^{-1}kg^{-1}$	0.00635 ± 0.005065*	0.00371 ± 0.000286

* = Significantly different (P< 0.05) different from the respective value.
NS = Non significantly (P> 0.05) different from the respective value.

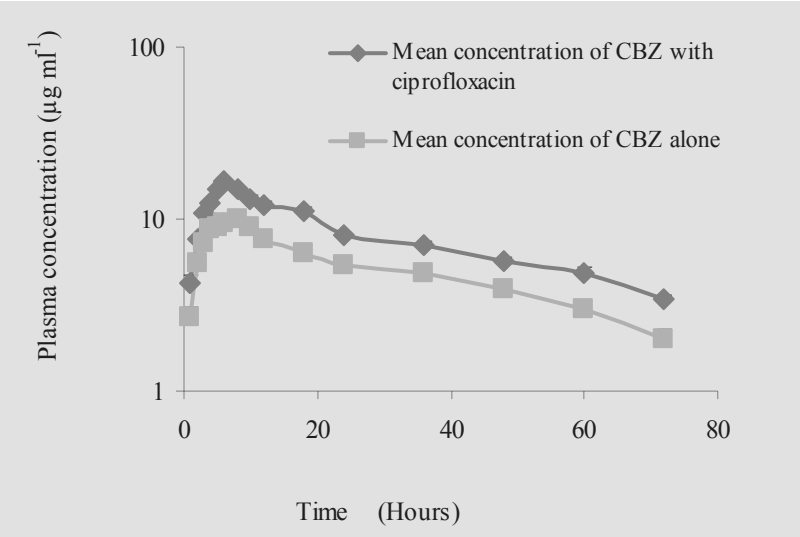

Fig. 1: Comparative mean plasma concentrations of carbamazepine (200 mg) on a semilogrithmic scale versus time following its oral administration alone and with ciprofloxacin (500 mg) to eight healthy adult male volunteers.

persistent up to 72 h of post-medication, with 2.025 ± 0.243 µg mL^{-1} and 3.316 ± 0.162 µg mL^{-1} CBZ after its single and concurrent administration, respectively. A significant (P < 0.05) increase in plasma concentrations of CBZ when administered with ciprofloxacin as compared to its administration alone may be attributed to the interaction of CBZ with ciprofloxacin as both the drugs are metabolized by the same CYP450 enzymes.

The comparative Mean ± SE values of pharmacokinetic parameters of CBZ alone and after its administration with ciprofloxacin have been presented in Table 1. After single oral administration of CBZ the C_{max} was 9.153 ± 0.235 µg mL^{-1} but when administrated with ciprofloxacin, it increased significantly upto 14.243 ± 0.371 µg mL^{-1}.

The statistical analysis revealed non-significant difference in the values of t_{max} of CBZ alone, 7.658 ± 0.651 h and 7.875 ± 0.556 h with ciprofloxacin.

The $t_{½\ abs}$ of CBZ with ciprofloxacin was 4.03 ± 0.391 h. The value was non- significantly ($P > 0.05$) different than the value 3.310±0.455 h obtained with carbamazepine alone. The value of $t_{1/2\ \alpha}$ after the co-administration of CBZ and ciprofloxacin, 4.037 ± 0.393 h, did not affect ($P>0.05$) the value of $t_{1/2\ \alpha}$ 4.900 ±1.316 h when CBZ was given orally alone. Half-life of elimination ($t_{1/2\ \beta}$) of CBZ (200 mg) with ciprofloxacin (500 mg) was 50.01 ± 3.359 h, which was statistically significant ($P<0.05$) from that of CBZ alone i.e. 38.318 ± 4.691 h.

Volume of distribution (V_d) was 0.348 ± 0.042 L kg^{-1} in case of 200 mg dose of carbamazepine administrated to the eight adult subjects. This value was significantly ($P<0.05$) reduced to 0.262 ± 0.022 L kg^{-1} when carbamazepine and ciprofloxacin were given at a time to the same individuals.

The total body clearance (Cl_B) of carbamazepine, 0.00635 ± 0.005065L h^{-1} kg^{-1}, in the eight subjects was significantly reduced to 0.00371 ± 0.000286 L h^{-1} kg^{-1} when carbamazepine (200 mg) was administered with ciprofloxacin. Area under the curve (AUC) of carbamazepine (200 mg) after its oral administration was noted as 357.2 ± 12.707 µg h L^{-1}. The AUC of carbamazepine with ciprofloxacin (500 mg) was 548.6 ± 16.698 µg h L^{-1}. A significant ($P<0.05$) increase was observed in the AUC of carbamazepine administration with ciprofloxacin as compared to carbamazepine alone.

DISCUSSION

In the present study, peak plasma concentration of carbamazepine ranged from 9.073 ± 0.242 to 9.874 ± 0.253 µg mL^{-1} reached during 5-10 h interval (fig. 1). However, in other human studies, peak concentration of carbamazepine was achieved at relatively shorter time intervals of 4-8 h (Helms *et al*., 2006) and 1-7 h (Rawlins *et al*., 1975), post medication. During the course of antiepileptic therapy, the drug must maintain a certain therapeutic level in the plasma or serum. The therapeutic concentration of carbamazepine has been reported as, 5-12 µg mL^{-1} (Alexander, 2007). The variation in the peak plasma concentration has also been observed due to species variations (Javed *et al*., 2003). The change in peak plasma concentrations can also be influenced due to environmental variations (Dresser *et al.*, 2000), difference in human race (Chan *et al.*, 2001), difference in age and weight and utilization of different food items during the course of study (Su-qin *et al.*, 2006). Badyal and Garg (2000) found that clarithromycin increased plasma concentration of carbamazepine when both the drugs were administered simultaneously. Increase in plasma concentration of carbamazepine by erythromycin results in neurotoxicity (Wong *et al.,* 1983). Nair and Morris, (1999) found that carbamazepine administration with fluconazole in epileptic patients increased the seizures which were due to toxic levels of carbamazepine in plasma. Gemfibrozil also increased the plasma levels of carbamazepine when administered together (Denio *et al.*, 1988).

It has been reported that concentration of carbamazepine above 12 µg mL^{-1} produced toxic effects. However, 9 µg mL^{-1} plasma level has also been reported as neurotoxic one (Bialer *et al.,* 1998). Therefore, physicians suggest that therapeutic dose of carbamazepine may range from 4 µg mL^{-1} to 8 µg mL^{-1} (Hoppener *et al.,* 1980). The toxic levels of other antiepileptic drugs have been observed as 100 µg mL^{-1} for valproic acid, 30 µg mL^{-1} for phenobarbital and 20 µg mL^{-1} for phenytoin (Alexander, 2007). These studies alarm the significance of drug interaction as a result of combined therapy.

Genetic variability (polymorphism) in these enzymes may influence a patient's response (Weinshilboum 2003). The change in pharmacokinetic parameters can be subjected to the change in genetic makeup of the individuals. It has been observed that Asians and black Americans are poor metabolizers of CYP450 enzymes (Lynch and Price, 2007), as reported by Abraham and Adithan, (2001) that in white 7% and in black 2-7% of persons are poor metabolizers of drugs which depends upon CYP2D6 responsible for the metabolism of beta blockers, antidepressants and opioids.

Literature on the influence of ciprofloxacin on the pharmacokinetics of carbamazepine is scanty. Thus the increase in C_{max} of carbamazepine after its administration with ciprofloxacin may be explained on the basis of rapid absorption or decreased activity of metabolizing enzyme CYP450. Significant difference was observed in $t_{1/2\ \beta}$ of carbamazepine ($P<0.05$). Pharmacokinetics regarding interaction of clarithromycin with carbamazepine in rhesus monkeys showed an increase in half life value when carbamazepine was administered with clarithromycin (Badyal and Garg, 2000). Similarly, the effect of omeprazole administration on the pharmacokinetics of a sustained-release preparation of carbamazepine in healthy male volunteers, was manifested through the increase in half life of elimination (Dixit *et al*., 2003). Sodium valproate also increased the half life of elimination of carbamazepine by 12% (Macphee *et al*., 1988). In the present study, ciprofloxacin significantly reduced the Cl_B of carbamazepine. In contrast to the above findings, the Cl_B of carbamazepine was increased by probenecid upto 26% after the administration of single oral dose of carbamazepine (200 mg) with 500 mg of probenecid twice a day to ten healthy male subjects for ten days (Kim *et al.,* 2005).

AUC of carbamazepine significantly increased after concurrent administration of ciprofloxacin to the adult volunteers. Literature indicates that quinine markedly

increased the AUC of carbamazepine after concomitant administration with carbamazepine (Amabeoku *et al.*, 1993). It has been seen that omeprazole also increased the AUC of carbamazepine when administered concurrently in male volunteers (Dixit *et al.*, 2001). Badyal and Garg, (2000) also found that there was increase in AUC of carbamazepine when administered with clarithromycin. Similarly, AUC was increased when carbamazepine was given with Mentat, a psychotropic drug (Tripathi *et al*., 2000).

CONCLUSION

The change in pharmacokinetic parameters is due to slow or inhibited metabolic elimination of CBZ when given concurrently with ciprofloxacin to healthy adult male individuals. This is probably due to inhibition of CYP3A4 or CYP1A2 isoenzyme by ciprofloxacin which are responsible for the metabolism of CBZ. Our results are in agreement with previous finding in which ciprofloxacin has inhibited the metabolism of F506 which is mainly metabolized by CYP3A4 isoenzyme. The epileptogenic potential of ciprofloxacin significantly increased the plasma concentration of CBZ, which may enhance the risk of central nervous system toxicity when administered concurrently. So, dose adjustment as well as drug monitoring of CBZ may be required when both the drugs are given concurrently. The knowledge regarding the drug interaction between ciprofloxacin and CBZ in healthy adult male individuals will be helpful for the manufactures of CBZ and ciprofloxacin and a blessing for the patients using this combination. Genetic variability affects the pharmacokinetic parameters of a drug so this study further stresses the pharmacokinetics investigations in the populations in which the drug is to be employed clinically.

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