TIME DEPENDENT PHARMACOKINETIC INTERACTION BETWEEN PHENYL-PROPANOLAMINE AND CHLORPHENIRAMINE MALEATE IN HUMAN SUBJECTS

V.V. Sarveshwar Rao, D. Rambhau, B. Ramesh Rao* and P. Srinivasu

University College of Pharmaceutical Sciences, Kakatiya University, Warangal-506 009 (A.P), India

SUMMARY

The influence of time of administration on the serum levels of phenylpropanolamine when administered alone and in combination with chlorpheniramine maleate at two different times of a day was studied in healthy human volunteers in a randomized 4x4 Latin square crossover design with a washout period of ten days. Blood samples were collected at predetermined time intervals and serum samples were analysed for unchanged phenylpropanolamine using high performance liquid chromatography. The various pharmacokinetic parameters of phenylpropanolamine were calculated using model independent methods. There was a significant ($P<0.05$) decrease in the rate of absorption of phenylpropanolamine following its administration in combination with chlorpheniramine maleate at 2200 hours. However, such a change was not observed for treatment at 1000 hours. The observed change may be due to the time dependent gastrointestinal effect of these drugs.

KEY WORDS

phenylpropanolamine, chlorpheniramine maleate, pharmacokinetic interaction, circadian variations, healthy volunteers

* Author for correspondence

INTRODUCTION

Phenylpropanolamine hydrochloride, usually in combination with an antihistamine such as chlorpheniramine maleate, is widely used for the oral treatment of nasal and sinus congestion as a nonprescription 'over-the-counter' product. Owing to the high toxicity and cardiovascular adverse effects of phenylpropanolamine /1,2/, it is important to investigate the influence of concomitantly administered drugs on the pharmacokinetics of phenylpropanolamine. The present study was designed to investigate the possibility of pharmacokinetic interaction between phenylpropanolamine and chlorpheniramine maleate in healthy human subjects. At the same time the circadian influence on the pharmacokinetics of phenylpropanolamine in presence of chlorpheniramine maleate was studied.

MATERIALS AND METHODS

This study was conducted in eight healthy male volunteers (age range 25-32 years, weight 48-65 kg). The participants were enrolled in the study after a thorough medical examination and standard laboratory tests. They were not allowed to take any other drug 7 days before or during the study. They were all non-smokers. All the participants were briefed about the study and the study was approved by an Institutional Ethics Committee. The subjects were divided into four groups at random and the study was conducted in a 4x4 Latin square randomized cross-over design allowing a wash-out period of 10 days between each of the following treatments:
Treatment I: Phenylpropanolamine hydrochloride 100 mg at 1000 h.
Treatment II: Phenylpropanolamine HCl 100 mg + 10 mg chlorpheniramine maleate at 1000 h.
Treatment III: Phenylpropanolamine HCl 100 mg at 2200 h.
Treatment IV: Phenylpropanolamine HCl 100 mg + 10 mg chlorpheniramine maleate at 2200 h.

Blood sampling

Blood samples (3 ml) were collected from the median cubital vein at intervals of 0, 0.5, 1.0, 1.5, 2, 3, 4, 6, 9, 12 and 20 hours following

drug(s) administration. The samples were allowed to clot, serum was separated and stored frozen until analysis.

Assay

The serum samples were analyzed for phenylpropanolamine by a modified high performance liquid chromatography (HPLC) method of Dowse *et al.* /3/ on a HPLC unit (Shimadzu Corporation, Kyoto, Japan) equipped with a 15 cm x 4.6 mm octadecyl silane reversed phase column and UV spectrophotometric detector. The mobile phase was acetonitrile-water (10:90) with pH adjusted to 2.5 using 1 M hydrochloric acid. Flow rate was 1.5 ml/min, UV detector was set at 254 nm and the detector sensitivity was 0.005 aufs (absorbance value corresponding to the full scale recorder). Serum sample (1 ml) was transferred to a screw capped test tube containing 0.2 ml of ephedrine hydrochloride solution (400 ng/ml) in water as internal standard and mixed well. To this 200 µl of saturated solution of sodium carbonate was added and vortexed for 1 min. The mixture was extracted with 2.5 ml of chloroform by shaking for 15 min on a rotary shaker. The tubes were centrifuged for 10 min at high speed and about 2 ml of chloroform layer was separated and placed in another clean dry screw capped test tube. To this 100 µl of 5% glacial acetic acid was added and vortexed for 2 min. The tubes were centrifuged and the chloroform present in the tubes was reduced to 500 µl. 20 µl of the upper acetic acid phase was injected onto the column.

The calibration curve was prepared by adding 25 to 500 ng of phenylpropanolamine to 1 ml of serum obtained from untreated volunteers. These samples were treated in the same manner as the test samples. The peak height ratios obtained at different concentrations of the drug were plotted against the drug concentrations. The slope of this plot determined by the method of least squares regression analysis was used to calculate phenylpropanolamine concentrations in the unknown samples. The reproducibility of the assay method was tested by analyzing the serum samples spiked with four different concentrations and estimating their drug content on the same day as well as on different days. The coefficient of variation of each concentration was lower than 5%. The lower limit of quantification of phenylpropanolamine using this method was 25 ng/ml.

Pharmacokinetic analysis

The peak serum concentration (Cmax) and time to reach peak levels (Tmax) were obtained from the experimental data. The other pharmacokinetic parameters: absorption rate constant (Ka), area under the serum concentration-time curve (AUC), area under the first moment curve (AUMC), elimination half-life ($t_{1/2}$), clearance (Cls/f), volume of distribution(Vd/f), and mean residence time (MRT), were obtained using the RAMKIN computer program based on model independent pharmacokinetic methods.

The difference in the pharmacokinetic parameters obtained were statistically validated using ANOVA and Student's two-tailed paired t-test. The difference was considered significant at a probability level of 95%.

RESULTS

The plots of time course of mean serum phenylpropanolamine (PPA) levels following its oral administration either alone or in combination with chlorpheniramine maleate (CPM) at 1000 h and 2200 h are shown in Figures 1 and 2. The pharmacokinetic data of PPA for the four treatments are given in Table 1. About 20% elevation in mean Cmax was observed following administration at 2200 h of PPA compared to administration at 1000 h. However, due to large inter-individual variation, this difference was not statistically significant ($P>0.05$). The Cmax of PPA was lowered by about 20% due to the concurrent administration of CPM at 2200 h.

Among the four treatments, a significant delay in the occurrence of Tmax was observed following the administration of PPA in combination with CPM at 2200 h compared to PPA alone administered at 2200 h ($p<0.05$) and the combination treatment at 1000 h ($p<0.05$). Accordingly a significant lowering in the absorption rate constant of PPA was observed following its combined administration with CPM at 2200 h compared to PPA alone at 2200 h ($p<0.01$) and the combined administration at 1000 h ($p<0.01$). These results indicate that CPM influenced the rate of absorption of PPA only in the night. Thus the interaction between CPM and PPA is time dependent.

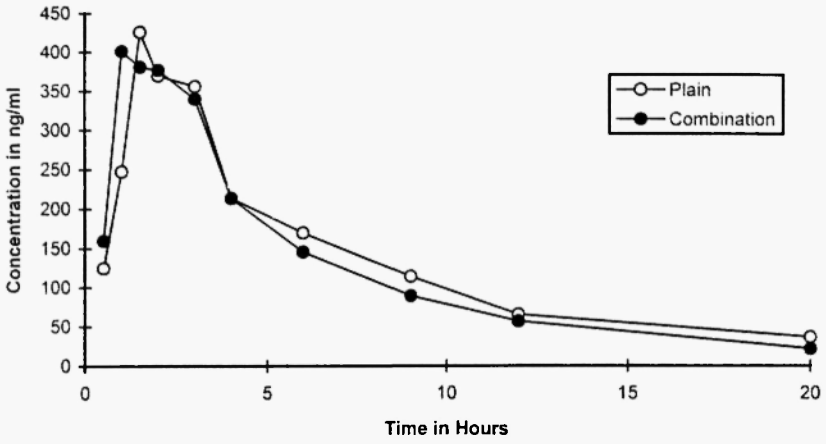

Fig. 1: Mean serum levels of phenylpropanolamine (ng/ml) following 100 mg oral administration either alone or with 10 mg chlorpheniramine maleate at 10.00 hours.

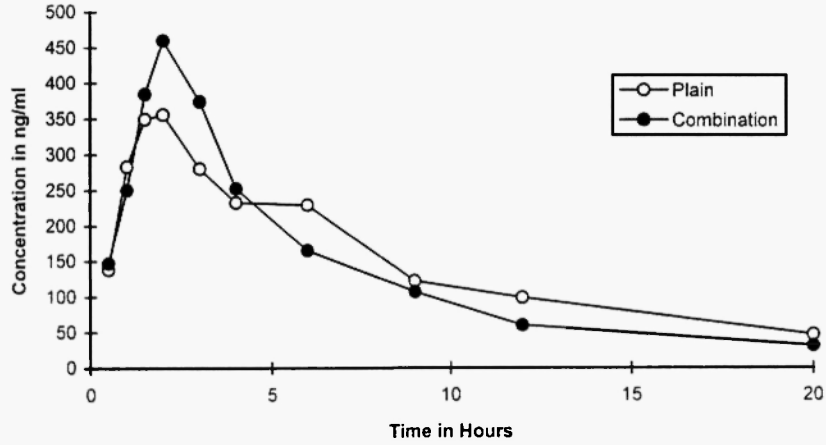

Fig. 2: Mean serum levels of phenylpropanolamine (ng/ml) following 100 mg oral administration either alone or with 10 mg chlorpheniramine maleate at 22.00 hours.

TABLE 1

Mean (SD) pharmacokinetic parameters from serum levels of phenylpropanolamine following 100 mg oral administration either alone or in combination with 10 mg chlorpheniramine maleate at 10.00 and 22.00 h

	1000 hours		2200 hours	
	Plain	**Combination**	**Plain**	**Combination**
Cmax (ng/ml)	474.3 (176.5)	496.8 (180.8)	570.2 (115.3)	471.7 (189.40)
Tmax (h)	1.88 (0.52)	1.44 (0.73)	2.0 (0.46)	2.94* (1.47)
Ka (h^{-1})	2.59 (0.57)	3.75 (1.26)	2.31 (0.41)	1.88* (0.75)
$t_{1/2}$ (h)	4.42 (0.53)	4.29 (1.23)	4.2 (1.1)	3.90 (0.80)
AUC_{0-t} (ng/ml/h)	2190 (697)	2126 (543)	2209 (480)	2236 (1032)
$AUC_{0-\infty}$ (ng/ml/h)	2633 (996)	2492 (761)	2676 (505)	2735 (1032)
$AUMC_{0-\infty}$ ($ng/ml/h^2$)	18128 (10291)	15967 (8009)	17749 (5232)	18978 (10528)
MRT (h)	6.64 (1.07)	6.11 (1.19)	6.60 (1.41)	6.61 (1.49)
Cls/f (l/h)	43.37 (18.48)	44.39 (16.31)	37.42 (9.18)	45.30 (21.02)
Vss/f (l/kg)	4.59 (1.88)	4.24 (0.94)	4.16 (1.46)	4.23 (1.73)
Vd/f (l/kg)	4.84 (2.41)	4.65 (1.97)	4.07 (1.26)	4.01 (1.62)

Cmax = peak serum concentration; Tmax = time to reach peak serum level; Ka = absorption rate constant; $t_{1/2}$=elimination half life; AUC_{0-t} = area under the serum concentration-time curve from time zero to t; $AUC_{0-\infty}$ = area under the serum concentration-time curve from time zero to infinity; $AUMC_{0-\infty}$ = area under the first moment curve from time zero to infinity; MRT = mean residence time; Cls/f = oral clearance; Vss/f = steady state volume of distribution; Vd/f = apparent volume of distribution.

*Values significantly different at $P<0.05$ based on paired t-test.

DISCUSSION

Are pharmacokinetic interactions time dependent? This point has been addressed in several studies in our laboratories. According to Rao and Rambhau, the pharmacokinetics of naproxen was altered when given with diazepam at 1000 h /4/, but not at 2200 h /5/. Diazepam lowered the mean peak serum naproxen concentrations (83.4 to 64.5 μg/ml), prolonged the time to peak concentrations (1.32 to 2 h) and decreased the absorption rate (4.07 to 2.42 h^{-1}) following the combined treatment at 1000 h, and no such changes were noted after the same treatment at 2200 h. In contrast to this, Mahender *et al.* /6/ reported that under the influence of diazepam, the Cmax of diclofenac was raised by 112% for treatment at 2200 h and 68% for treatment at 1000 h. Furthermore, 60% increase in AUC, 36% decrease in clearance and 24% decrease in Vss/f of diclofenac were noted due to the concomitant treatment with diazepam at 2200 h only. Concomitant administration of diazepam with quinidine at both 1000 and 2200 h did not alter the pharmacokinetics of quinidine /7/. According to Bapuji *et al.* /8/, concomitant administration of diazepam with ibuprofen resulted in an increase in elimination half-life (2.39±0.42 to 3.59±0.35 h) and decrease in clearance (62.7±8.9 to 41.7±2.6 ml/h/kg) of ibuprofen administered at 2200 h. Thus, it is evident that pharmacokinetic interactions can be time dependent.

Gastrointestinal motility, gastric emptying and gastrointestinal secretion are known physiological factors which influence the absorption of drugs. Gastrointestinal motility is due to migrating myoelectric complexes (MMC). The cycle of MMC is split into four phases. Phase I is characterized by the absence of contractions, phase II by irregular contractions, phase III by a burst of regular contractions and phase IV by return of quiescence /9/. The contractions in the antrum of the stomach help to propel materials (especially solids into the duodenum) and contractions in the intestine help to expose the intestinal contents to a large absorption surface. Abolition of contractions in the antrum and corpus of the stomach lead to delayed emptying.

Delay in gastric emptying is increasingly recognized as an adverse effect of drugs, particularly for those possessing anticholinergic activity. Such changes may impair and delay the absorption of concurrently administered drugs /10/.

Phenylpropanolamine is a sympathomimetic and chlorpheniramine maleate is an H_1 antagonist with anticholinergic properties /11/. Both of them are reported to relax the smooth muscles of the gastrointestinal tract leading to a reduction in contractions. Thus the retardation in the absorption of phenylpropanolamine observed in the present study for the combination treatment at 2200 h may be due to the decrease in gastrointestinal motility and delayed gastric emptying.

Phase III contractions of MMC are associated with increased secretion in the gastrointestinal tract. Abolition of these contractions reduces gastrointestinal secretion. Reduced gastric secretion may lower gastric acid output, thereby raising the pH of the intestinal contents. Under these conditions the absorption of phenylpropanolamine, a basic drug with a pKa of 9, should normally be increased. But our results showed delayed absorption of phenylpropanolamine. This could be because of the fact that H_1 antagonists are reported to have no effect /11/ on gastric acid secretion.

It is interesting to observe that the gastrointestinal smooth muscle relaxing effect of PPA and CPM seems to have occurred upon their nocturnal administration, resulting in a delayed rate of absorption of PPA following its administration in combination with CPM at 2200 h. This may be because of circadian changes in gastrointestinal tract receptor binding of these drugs. Statistically significant 24-hour rhythms have been validated in all the receptors studied by Wirz-Justice and colleagues /12/ in whole rat forebrain homogenates, namely in α_1, α_2, and β-adrenergic, muscarinic, cholinergic, dopaminergic, 5HT-1, 5HT-2, adenosine, opiate, benzodiazepine, GABA and imipramine receptors.

In addition to the circadian variation in receptor binding of PPA and CPM, a significant reduction in the duration of phase-II contractions of MMC during sleep /13,14/ might have contributed to the delayed absorption of PPA during the night.

Furthermore, we have earlier reported a significant elevation in the Cmax of PPA following its 50 mg oral administration at 2200 h compared to administration at 1000 h /15/. The circadian changes in Cmax observed in this study following 100 mg plain PPA treatment are in agreement with these observations. In both studies there was an approximately 20% elevation in Cmax. However, the Cmax changes observed in the present study did not attain statistical significance. This could be because of large interindividual variation (Cmax: 316.4

to 759.30 ng/ml for administration at 1000 h; 446.47 to 716.63 ng/ml at 2200 h) and the limited number of observations.

We administered both PPA and CPM in the form of immediate release capsules in the present study. Such a combination is marketed both in the form of immediate release capsules and as sustained action capsules, as over-the-counter (OTC) products. The time dependent interaction observed in this study should be borne in mind when designing sustained action dosage products of this combination should the same time dependent interaction be established following the administration of sustained action preparations.

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