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EFFECT OF EGRET RIVER TEA (AN ANTIHYPERTENSIVE HERBAL SUPPLEMENT TEA) ON THE PHARMACOKINETIC PROFILE OF ORAL TELMISARTAN IN RABBITS

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ABSTRACT

The study is aimed at investigating the effect of Egret River tea (an antihypertensive herbal supplement tea), on the pharmacokinetic profile of oral single dose telmisartan in rabbits. In the first phase, a dose of oral telmisartan (40mg/kg) was administered to rabbits after overnight fast. Blood samples (3.0 ml) were drawn from an indwelling catheter into EDTA bottles at 0.0, 0.5, 1, 2, 4, 6, 8, 10 and 24 hours. The blood samples were centrifuged at 3000rpm for 10 minutes and plasma harvested. In the second phase, the rabbits were allowed free access to their normal feeds for two weeks. The Egret River tea (150 ml) prepared by merceration of one tea bag in hot water was administered orally for three days. The rabbits were fasted overnight after the last dose of the tea and Telmisartan (40mg/kg) was administered to the rabbits orally. Blood samples were collected and treated as earlier. Telmisartan was analysed using UV-spectrophotometeric method after liquid-liquid extraction from plasma using diethyl-ether and dichloromethane (60:40 % v/v), at 238 nm. Method validation parameters found method to be efficient enough for the comparative pharmacokinetic work with linearity between 8-90µg/ml with a correlation coefficient (r^2) of 0.994 and %Recovery of 96.95% with, RSD of 0.0098. Egret River tea significant ($p<0.05$) decrease C_{max}, AUC_{0-24}, AUCo - ∞ and $t_{1/2\beta,}$ while there was significant ($p<0.05$) increase in Vd. However Egret River tea did not statistically ($p>0.05$) affect the T_{max}, Cl/F and the $t_{1/2\alpha}$.

KEYWORDS: Telmisartan, Egret River tea, Green tea, Pharmacokinetics, Drug-drug interaction, Herb-drug interaction.

INTRODUCTION

Drug interaction is a common phenomenon in medicine that is said to occur when the effect of one drug is changed by another drug, food, drink or environmental chemical agents. It is also a common practice for patients of life-long diseases placed on 'orthodox medicines' (e.g. Telmisartan) to take other supportive therapies such as dietary supplements (e.g. herbal teas like Erget River tea) or specialised diet. It is therefore possible for the 'medicines' to interact at pharmacokinetic or pharmacodynamic levels. Pharmacokinetic interactions result in changes in absorption and disposition of drugs including possible influence on drug metabolizing enzyme activities (Fugh-Berman and Ernst 2001, Fugh-Berman 2003).

Typical examples of herb-drug interactions and observed effects include: bleeding when warfarin is combined with ginkgo (Ginkgo biloba), garlic (Allium sativum), dong qual (Angelica sinensis), or danshen (Salvia miltiorrhiza); mild serotonin syndrome in patients who mix St John's wort (Hypericum perforatum) with serotonin-reuptake inhibitors; decreased bioavailability of digoxin, theophylline, cyclosporin, and phenprocoumon when these drugs are combined with St John's wort; induction of mania in depressed patients who mix antidepressants and Panax ginseng; decreased blood concentrations of prednisolone when taken with the Chinese herbal product xaio chai hu tang (sho-saiko-to); and decreased concentrations of phenytoin when combined with the Ayurvedic syrup shankhapushpi. Anthranoid-containing plants (including senna [Cassia senna] and cascara [Rhamnus purshiana]) and soluble fibres (including guar gum and psyllium) can decrease the absorption of drugs Roby et al., (2000), Fugh-Berman and Ernst (2001). Pharmacokinetic results show that chronic grapefruit juice (GFJ) ingestion has a great influence on paracetamol metabolism, slowing it down Samojlik et al., (2002). Telmisartan has been reported tointeract with hydrochlorothiazide, acetaminophen or Ibuprofen, Enalepril **(**Stangier, et al., 2000, Tatarchenko, et al, 2011).

Telmsartan,{4'-[(1,7'-dimethyl-2'-propyl-1H,3'H-2,5'-bibenzimidazol-3'-yl)-methyl]biphenyl-2-carboxylate} is a non-peptide angiotensin II receptor (Type AT1) antagonist used in the management of hypertension (Goebel et al., 2006). Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of

angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. (Burner 2009). Egret River tea is a brand of Chinese herbal supplement tea with label claim of antihypertensive activities and that it contains; selfheal spike, Ramilusuncariae cumuncis, fructorsleonuri, and Chinese Oolong tea (Chinese Tea and Herbal drink 2012, http//www.Teasetc.com: Oolong tea and weight loss 2012).

Herbal teas or food supplements are non-prescription medications, therefore any patient can obtaine and use at will, moreso when it claims to treat a disease condition. This study is aimed at investigating the effect of Egret River tea (a Chinese antihypertensive tea), on the pharmacokinetics of oral single dose telmisartan (antihypertensive agent) in rabbits. To the best of our knowledge there are no reports in the literature on the interaction of these drugs.

METHOD AND MATERIAL

Chemicals and reagents were of Analytical grade and obtained from the Department of Pharmaceutical Chemistry, University of Jos. Drug - Micardis (Telmisartan 40mg Boehringer Ingelheim Company, Germany), was purchased from a registered Pharmacy in Jos, Nigeria. Items of equipment such as Clifton Centrifuge machine (Nickel Weston-s-mare electro LTD) and UV- spectrophotometer (JENWAY 6405 UV-VIS spectrophotometer) were of the Department.

Analytical method and Validation processes

The UV-spectrophotometric methods of Palled et al., 2006, and Illango and Shiji 2011, was adapted and modified. A stock solution of telmisartan in methanol was prepared to give a concentration of 100 µg/ml. Varying concentration of standard solutions (10-80 µg/ml) of Telmisartan in methanol solution were prepared.

A 0.5 ml portion of pooled plasma of seven rabbits was spiked with serial dilutions of telmisatan to produce a concentrations of 10, 20, 30, 50 and 80 µg/ml. Telmisartan was extracted from plasma by adding 2.0 ml of an admixture solution of diethyl-ether and dichloromethane (60:40 % v/v) to the different concentrations and vortex mixed for a 10 seconds. The mixture was allowed to settle down and the clear supernatant removed and evaporated to dryness at ambient temperature (25^{o}C). The dried supernatant was reconstituted in 0.01M NaOH. Absorbance was taken at 238 nm against reagent blank. The procedures were done in triplicate for each concentration and the mean recorded.
The calibration curve was then plotted as shown in Figure 1.

Validation (Linearity, Range and Limit of quantification (LOQ))

The calibration curve concentrations were altered for between 15% over the lowest and highest concentrations and the graphs plotted. The validation parameters of Linearity, range and LOQ were determined from the graph.

Recovery, Precision and Accuracy

Three concentrations of 10, 20, 40 µg/ml telmisartan were prepared in plasma and analyzed as above. The corresponding concentrations were obtained from the calibration curve. The percentage recovery and percentage relative standard were calculated. The process was repeated three times daily for five days to determine the precision and accuracy.

Application- Animal treatment

Seven (7) healthy male rabbits weighing (2.35- 2.56 kg) were obtained from the University of Jos animal house. The rabbits were confirmed healthy by a veterinary doctor at the National Veterinary Research Institute, Vom.

Phase1. Untreated Rabbits

A dose of 40mg/kg of telmisartan was administered to each of the seven rabbits orally, after overnight fasting. Blood samples (3.0 ml) were taken with a sterile needle and syringe in triplicate from each rabbit at the following time interval at 0, 0.5, 1, 2, 4, 6, 8, 10 and 24 hours. Blood samples were taken into EDTA pretreated sample bottles. The blood samples were centrifuged at 3000 rev/min (rpm) for 10 minutes and plasma harvested. A 1.0 ml portion of the plasma was used for for the analysis as in calibration method.

Phase2. Treated Rabbits

The rabbits were allowed free access to their normal feeds for two weeks. The Egret River tea was prepared by percollation of one tea bag in hot water (150 ml). Each Rabbit was administered orally with the tea, once a day for three days. The rabbits were fasted overnight and telmisartan (40mg/kg) was administered to the rabbits orally. Blood samples were collected and treated as above.

Determination of pharmacokinetic parameters

Respective concentrations (µg/ml) were determined using the regression equation from the calibration curve. Pharmacokinetic parameters were determined from the plasma concentrations-time curve assuming one compartment open model, first order kinetics.

Data Handling and analysis

The peak plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were obtained from the graph. Terminal elimination half-life ($t_{1/2\beta}$) was calculated as $0.693/k_\beta$, where k_β is the absolute value of the slope of the terminal log-linear portion of the plasma concentration-time curve. The area under curve (AUC) was calculated from zero to 24 hours (AUC_{0-24}) by use of the linear trapezoidal rule and AUC_0-∞ was calculated by AUC_{0-t} +

Ct/k_{β}, where t is the last measurable sampling time and Ct is the last measured plasma concentration.

Statistical analysis

The pharmacokinetic parameters were presented as Mean ± SD. Treatment effects were evaluated by unpaired student's t-test (using graphpad statistical package) with $P<0.05$ as level of significance.

RESULT AND DISCUSSION

Validation and analysis

The result of validation and analysis are presented in Table 1 and Figure 1. The calibration curve was found to be linear over a concentration range of 5-90µg/ml with a correlation coefficient (r^2) of 0.994. Percentage recovery was found to be 96.95% and RSD of 0.0098. The adapted spectrophotometeric method is therefore efficient enough for the comparative pharmacokinetics and drug interaction study.

The pharmacokinetic profile is presented on Table 2 and Figure 2. The pharmacokinetic parameters obtained compared well with previous reports (Boehringer Ingelhein 2003, Strangier et al., 2000, Abu et al., 2012). Also as previously observed, the pharmacokinetic values vary from one animal model to another and also dose dependent. Absorption phase was slow. The absorption half life $t_{1/2\alpha}$ is 2.23 h with a T_{max} of 6 h. Egret tea administration did not influence the absorption or absorption rate. There is no statistically significant difference ($P>0.05$) between values of the treated and untreated rabbits for both the $t_{1/2\alpha}$ and T_{max}. These observation might be due to the time laps between the time of administration of the tea and that of the drug, thereby allowing time for the tea to have been totally cleared.

The C_{max} values were 10.35 ug/ml in the untreated rabits and 7.12 µg/ml, in the treated rabbits. The C_{max} for the treated rabbits is statistically significant ($P<0.05$) lower as compared with the untreated (see Table 2), The AUC values ranged from 133.96 to 212.50 µg.h/ml. The AUC_{0-24} and $AUC_{0-\infty}$ were statistically ($P<0.05$) reduced after the administration of the Egret river tea. The Egret river tea vividly decreases bioavailability of Telmisartan in rabbits.

The elimination phase was bi-phasic, with initial rapid elimination followed by a slow phase. This may be attributed to possible displacement from the plasma binding site. Telmisartan is 99% plasma protein bound. Also this is evident in the increased Vd in the treated rabbits. The Vd of the treated rabbits were found to be significantly ($P<0.05$) higher than those of the untreated rabbits (Table 2). Telmisartan metabolites are similar in all animal species and consisted mainly of glucuronidation to 1-O-acylglucuronide mediated thruogh the glucuronoacyltransferases. The termination elimination half life ($t_{1/2\beta}$) of 12.35 hours is similar to previous reports of rats, rabbit, dog and man 11, 13, 8 and 14 h respectively (Boehringer Ingelhein 2003, Strangier et al., 2000). The $t_{1/2\beta}$ was significantly decreased ($P<0.05$) from 12.33 h to 9.76 h in the treated rabbits. This implies a longer residency time for the drug. However, the Total oral Clearance (Cl/F), was not significantly altered ($P>0.05$) by the administration of the Egret River tea. This therefore implies that the metabolic enzymes were not significanly inhibited or enhanced.

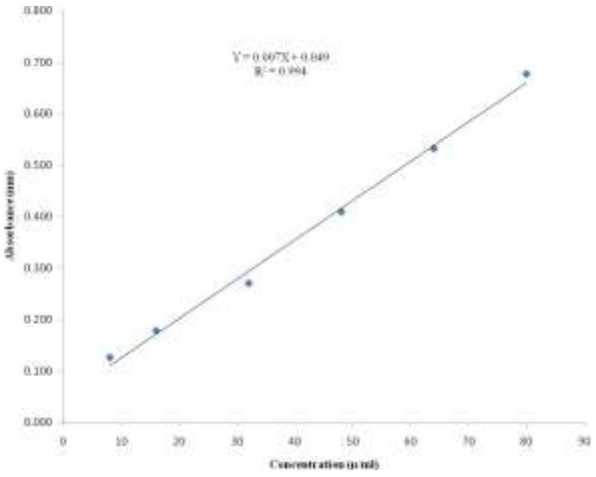

Figure1. Calibration curve of Absorbance versus Concentration of telmisartan in plasma.

Table1. Method validation table showing accuracy and %Recovery

Spiked Concentration (µg/ml)	Concentration Obtained (µg/ml)	% Recovery ± RSD
10	9.68	96.80%
20	19.26	96.30%
30	28.79	95.97%
40	39.35	98.38%
50	48.66	97.32%
Total		96.96 ± 0.0098

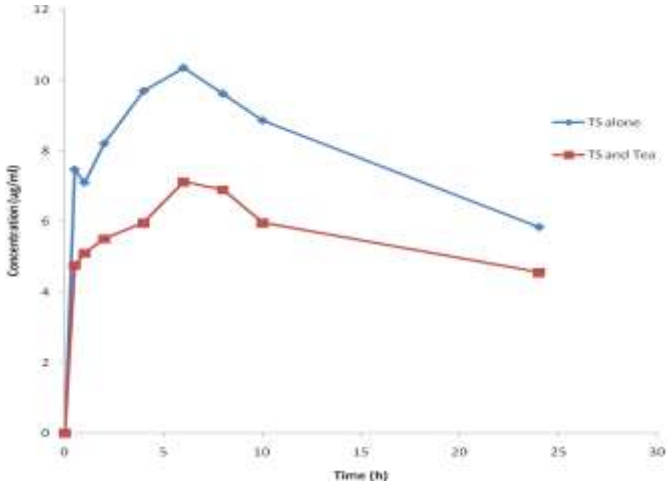

Figure 2: Plasma concentration-time curve of oral Telmisartan in rabbits before and after taking 'Egret river' tea.

Table2. Table showing the Pharmacokinetics parameters of oral Telmisatan (40mg) in rabits (n=8), administered alone (TS) and after oral administration of Egret river tea (TST) Mean±SD

Parameter	C_{max} ug/ml	T_{max} h	AUC_{0-24} ug.h/ml	$AUC_{0-\infty}$ ug.h/ml	Cl_T ml/min	Vd L	$t_{1/2\alpha}$ h	$t_{1/2\beta}$ h
TS	10.35	6.00	192.41	212.50	0.208	0.596	2.23	12.35
	±2.10	±0.55	±20.11	±25.00	±0.08	±0.20	±0.25	±2.52
TST	7.12*	6.00	133.96*	147.20*	0.299	0.872*	2.04	9.76*
	±1.65	±0.80	±10.52	±15.00	±0.10	±0.29	±0.55	±1.51

Key: * P < 0.05 Stastically significant

CONCLUSION

From the results obtained there were statistically significant (P<0.05) changes in the absorption and bioavailability parameters of C_{max} and AUC, but no significant changes (P> 0.05) in the $t_{½\alpha}$ and T_{max} in the treated rabbits. The elimination parameters, $t_{½\beta,}$ and Vd showed significant changes (P<0.05) while Cl_T/Fdid not show significant changes (P>0.05) after the treatment. The bioavailability of telmisartan is reduced by Egret River tea. It is therefore not advisable to combine the two in the treatment of hypertension.

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