10.4274/tjps.249943
Research Article

The Effect of Panax Ginseng on Carbamazepine Pharmacokinetics in Rabbits

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ABSTRACT: Carbamazepine (CBZ) is a well-known prescribed drug to treat epilepsy and it is trigeminal neuralgia drug of choice. The present study is established for studying the effect of Panax ginseng extract (PGE) on disposition of CYP3A4 substrate Carbamazepine (CBZ) in rabbits.
Materials and Methods: An in vivo herb-drug interaction, a randomized, parallel designed study were conducted in 12 male rabbits; that were distributed into two groups. The first group consists of six rabbits (control group) the CBZ suspension (30mg/kg/day) was administrated orally for ten days as a single daily dose while, the second group consists of six rabbits (test group) CBZ was administered concomitantly with a dose of PGE (2.5 mg/kg/day) at the same time schedule as in the first group. Blood under analysis samples were withdrawn from the marginal ear vein of rabbits at the intervals 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 12.0 and 24.0 hours.
Results: Our results showed statistically insignificant differences ($P \geq 0.05$) in pharmacokinetic parameters (PK) as C_{max}, t_{max}, AUC_{0-24}, $AUC_{0-\infty}$, $t_{½}$ and K_e of CBZ when given alone or concurrently with PGE.
Conclusion: Our findings showed that, PGE may not likely to interfere the carbamazepine pharmacokinetics when co-administered with carbamazepine, so it can be used safely without precautions or dose monitoring.
Keywords: Carbamazepine, Panax ginseng, CYP3A4, Drug interaction, Pharmacokinetics.

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INTRODUCTION

Carbamazepine (CBZ) is a well-known prescribed drug to treat epilepsy, trigeminal neuralgia and bipolar depression[1,2]. The present study is established for studying the effect of Panax ginseng extract (PGE) on disposition of CYP3A4 substrate Carbamazepine (CBZ) in rabbits.
CBZ has several properties involving in clinical interactions with co-administered drugs, herbs and food[3,4]. CBZ exhibits a narrow therapeutic index[5]. CBZ is a

constructive inducing enzyme of several cytochrome P450 (CYP) isoenzymes and is a subject to auto-induction[3,6].
Carbamazepine-10,11-epoxide (CBZ-E) is the active metabolite of the CBZ whose concentration may be modified by concomitant drugs. Because of its widespread and long-term use, CBZ is mostly prescribed in co-drug feature, leading to drug interactions[4] .
Drug interactions are often classified as either pharmacokinetic or pharmacodynamic interactions[7]. The most tangible interactions that affect the PK of CBZ are that affecting its metabolic rate[5]. CBZ is mainly metabolized in liver by oxidation *via* CYP450 3A4 enzyme, while less than 5% of CBZ excreted unchanged in the urine[4,8,9,10]. CBZ-E is the major (up to 80%) and active metabolite of CBZ, which is further metabolized before excretion by hydration to a trans-dihydrodiol (carbamazepine-diol)[4,11]. CBZ is a substrate for CYP450 3A4 as well as an inducer of its enzymatic activity[8,11].
Subsequently, it was shown that CBZ can induce its own metabolism[4,9]. This phenomenon called autoinduction which is a time and dose dependent process[12].
Inhibition or induction of CYP450 enzymes has a significant impact on drug interactions that can cause unpredictable adverse effects or even therapeutic failures[13].
Herb-drug interaction is expected leading to various clinical effects. Moreover, the increased popularity of herbal medicines could explain the high incidence of herb-drug interactions[14]. This can occur when the co-administered herbal preparations modulate the drug metabolism either to be induced or inbibited of specific CYP enzymes[15,16].
Carbamazepine-herb interactions are important and were under the focus of interest, especially when these herbs affect the same enzymes that used to metabolize CBZ[17.]
PGE is one of the most popular and widely available herbal supplements[18,19]. PGE mainly used as adaptogenic, antineoplastic, immunomodulator, cardiovascular, CNS, endocrine, anti-inflammatory, antioxidant, anti-neurological and hypoglycemia agents[,20]. Several studies showed that PGE induces the activity of CYP3A4 in the liver as well as gastrointestinal tract[21,22]. Moreover, ginsenoside (an active compound in PGE) revealed an induction of CYP3A4 activity in vitro by interacting with CBZ, resulting in an increased CBZ metabolism[14]. The aim of this in-vivo research study is to find out a posible herb-drug interaction between PGE on Carbamazepine disposition.

MATERIALS AND METHODS

Animals and study design

Twelve healthy male rabbits weighted 3200-3500 gr used in this study were bought from Assdda animal center (Gaza, Palestine), both clinical tests and follow up care were run. Rabbits were fasted for 12 hours with free access to water before administration of drugs. The study was carried out at AUG; Faculty of Pharmacy, Gaza, Palestine.
An in vivo herb-drug interaction study between CBZ and PGE was conducted in healthy male rabbits. The experiments were carried out on one period, two groups of male rabbits were used. The first group of six rabbits was given a single oral dose of CBZ (30mg/kg/day) from an oral suspension of CBZ (Tegretol®) meanwhile, the second group of six rabbits as well was given the same volume of CBZ suspension combined with a single oral dose of PGE (2.5mg/kg/day) prepared in laboratory by a special oral gavage for 10 days. CBZ oral suspension and Panax ginseng capsules were bought from private pharmacies. The dose was given orally as an oral gavage to each rabbit; by being placed in a corner of rabbit mouth and the suspension was pushed down in slow rate to prevent choking. Physical tests were followed to assess clinical safety during this research.

Blood sample collection

Rabbits ear hair was removed while marginal ear vein was located. Local anesthetic (lidocaine 4%) was used to prevent the jerking of the rabbit. Installation IV-cannula to the ear marginal vein for each rabbit was applied. 1ml of blood sample was collected in vacutainer tubes according to the time schedule: 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 12.0 and 24.0 hours after receiving the last dose. Blood samples were centrifuged at 3,000 rpm for 5 minutes and serum was seperated, collected into clean tubes and kept at 2-8°C for analysis within 24 hours.

Analysis of CBZ serum samples

Carbamazepine blood concentrations were assayed by a chemiluminescent immunoassay CLIA using an ARCHITECT analyzer 1000 Abbott Laboratories, Abbott Park, IL, USA.

Pharmacokinetic analysis

Pharmacokinetic parameters for both groups including; (C_{max}), (t_{max}), (AUC_{0-t}), ($AUC_{0-\infty}$), ($t_{1/2}$) and (K_e) were determined. The C_{max} and t_{max} were directly determined from the plasma concentration versus time curves. The AUC_{0-24} was calculated by the linear trapezoidal rule. The $AUC_{0-\infty}$ was determined by the following equitation: $AUC_{0-\infty} = AUC_{0-24} + Ct / k_e$, where, Ct is defined as the last measured serum concentration at time t, and K_e is the elimination rate constant. The K_e was determined by the least squares regression of plasma concentration-time data points lying in the terminal region by using semilogarithmic dependence that corresponds to first-order kinetics. The $t_{1/2}$ was calculated as $0.693/K_e$. Pharmacokinetic analysis was determined by means of model independent method (Non-Compartmental Approach) WinNonlin Professional Software (Version 6.3, Pharsight Corporation, Cary, NC) and (GraphPad Prism versión 4.00;San Diego, CA, USA).

Statistical analysis

Statistical methods including descriptive analysis and Mann-Whitney test were applied to compare the PK parameters of CBZ alone or with PGE. (SPSS) program (version 16.0) was applied to analyze data. A statistically significant difference was considered when $P \leq 0.05$.

RESULTS

Plasma concentrations versus time profiles and pharmacokinetic parameters of CBZ were compared when administered alone (control group) and with PGE (test group) are shown in Fig.1. The statistical significance following their comparison are given in Table 1.

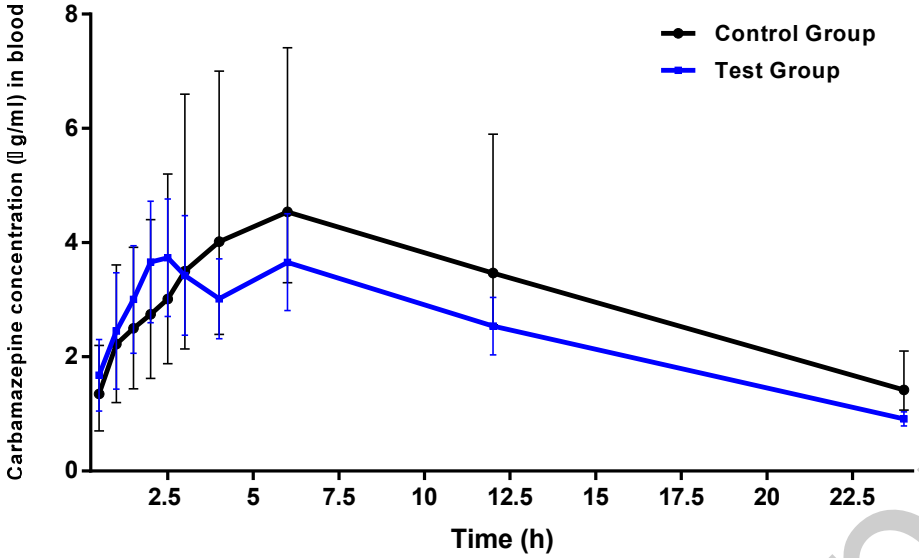

Figure 1: Plot of the mean serum concentration-time profile of CBZ alone (control group) and when co-administered with PGE (2.5mg/kg/day) (test group).

Table 1: Pharmacokinetic parameters of CBZ alone and with PGE in healthy male rabbits. (6 rabbits for each group).

PK Parameter	Group	N	Mean ± SD	Median ± IQR	P-value
C_{max}	CBZ alone	6	4.66 ± 1.44	4.31 ± 1.69	**0.818**
	CBZ+ PGE	6	4.16 ± 0.95	4.14 ± 1.83	
t_{max}	CBZ alone	6	5.33 ± 1.03	6.00 ± 2.00	**0.394**
	CBZ+ PGE	6	4.08 ± 2.11	4.25 ± 4.00	
$t_{1/2}$	CBZ alone	6	30.35 ± 18.81	26.51 ± 25.79	**0.240**
	CBZ+ PGE	6	17.51 ± 4.45	16.99 ± 8.59	
Ke	CBZ alone	6	0.03 ± 0.02	0.03 ± 0.02	**0.240**
	CBZ+ PGE	6	0.04 ± 0.01	0.04 ± 0.01	

AUC_{0-24}	CBZ alone	6	71.22 ± 25.04	63.63 ± 26.85	**0.394**
	CBZ+ PGE	6	57.41 ± 10.58	61.06 ± 19.56	
$AUC_{0-\infty}$	CBZ alone	6	120.56 ± 64.65	92.76 ± 113.89	**0.132**
	CBZ+ PGE	6	80.29 ± 12.25	82.48 ± 19.13	

DISCUSSION

CYP3A4 is one of the major CYP enzymes catalyzing 50% of drug metabolism[23,24] and participates in the metabolism of CBZ, so any drug affects CYP3A4 has the potential to cause a drug interaction with CBZ[4]. Several popular herbs have been reported to as strong candidates for interactions with medicinal drugs. Herb-CYP interactions may have significant clinical and toxicological consequences[15].

Carbamazepine plasma profiles illustrated in Fig.1, apparently showed decreased AUC_{0-24} and $AUC_{0-\infty}$ after concommitant administration of CBZ with PGE, but the change was statistically insignificant and P values were ≥ 0.05. Further, the other pharmacokinetic parameters were also not altered significantly for both groups after PGE administration. The mean C_{max} of control group showed slight decreasing when compared with the test group and with P-value = 0.53 and inspite of decreaed values of half-life $t_{1/2}$ from 26.51 ± 25.79 h to 16.99 ± 8.58 for control and test groups respectively, the P-value was 0.24 demonstrated, that the differences was statistically insignificant.

PGE is a herbal medicine used worldwide for a variety of purposes[25]. With complicated pharmacokinetics and pharmacodynamics; PGE may cause a sort of a significant risk for patients once being taken synchronizingly with other medications through PGE-drug interactions[26].

Possible drug interactions have been reported between PGE and warfarin, phenelzine and alcohol[19,25]. Studies showed that CBZ may reduce blood concentrations of warfarin and induces mania if used synchronizingly with phenelzine[27].

These results were similar to the findings of Abushammala in 2014, who found that CBZ can be used safely with valerian preparations because his results showed that valerian did not alter PK parameters of CBZ in rabbits[17]. Moreover; clinical trials have recently shown that American ginseng did not significantly cause any effect on indinavir and zidovudine pharmacokinetics. No significant differences in the area under curve of the plasma concentration versus time relationship after the co-administration of American ginseng, compared to zidovudine and indinavir alone[28,29]. Despite the stimulating effect of PGE on CYP3A4 activity, CBZ pharmacokinetic parameters have not shown significant effect on healthy rabbits after the combined administration.

CONCLUSION:

According to the conducted experimental conditions CBZ and PGE can be used safely without precautions or dose monitoring. More studies should be designed in humans to confirm our obtained results. In addition, we recommend performing more studies with higher doses of PGE, larger time of duration, and more sample number.

ACKNOWLEDGMENT

Many thanks to all staff in the Faculty of Pharmacy at AUG for their kind support and help. Also thanks to Mr. Mohamed Abu Affash, the director of MRS-Gaza for the facilitating analysis in their laboratory.

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