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ORIGINAL ARTICLE

Effect of *Panax ginseng* on Carbamazepine Pharmacokinetics in Rabbits

Panax ginseng'in Tavşanlarda Karbamazepin Farmakokinetiğine Etkisi

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ABSTRACT

Objectives: Carbamazepine (CBZ) is a well-known drug prescribed to treat epilepsy and the preferred drug for trigeminal neuralgia. This study was conducted to investigate the effect of *Panax ginseng* extract (PGE) on the disposition of CBZ, a CYP3A4 substrate, in rabbits.

Materials and Methods: An *in vivo* randomized parallel design was used to examine herb-drug interactions in 12 male rabbits distributed into 2 groups. In the 1st group (control group), 6 rabbits (control group) were administered orally with CBZ suspension (30 mg/kg/day) as a single daily dose for 10 days. In the 2nd group (test group), 6 rabbits was treated concomitantly with CBZ and a dose of PGE (2.5 mg/kg/day) at the same time as in the 1st group. Blood samples were withdrawn from the marginal ear vein of the rabbits at intervals of 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 12.0, and 24.0 h.

Results: CBZ had no significantly different pharmacokinetic (PK) parameters, namely, C_{max}, t_{max}, AUC_{0-24}, $AUC_{0-\infty}$, $t_{½}$, and K_e, when it was given alone or concurrently with PGE ($p \geq 0.05$).

Conclusion: PGE may unlikely interfere with the PK of CBZ when it is co-administered with CBZ. Therefore, PGE can be used safely without precautions or dose monitoring.

Key words: Carbamazepine, *Panax ginseng*, CYP3A4, drug interaction, pharmacokinetics

ÖZ

Amaç: Karbamazepin (CBZ), epilepsiyi tedavi etmek için reçete edilen, bilinen ve trigeminal nevraljide tercih edilen ilaçtır. Bu çalışma, *Panax ginseng* ekstresinin (PGE) tavşanlarda bir CYP3A4 substratı olan CBZ'nin dağılımı üzerindeki etkisini araştırmak için yapılmıştır.

Gereç ve Yöntemler: Bitki-ilaç etkileşimini incelemek için 12 erkek tavşan *in vivo* rastgele paralel bir tasarım kullanılarak 2 gruba ayrıldı. Birinci gruptaki 6 tavşana (kontrol grubu) 10 gün süreyle günde tek doz CBZ süspansiyonu (30 mg/kg/gün) oral yoldan uygulandı. İkinci gruptaki 6 tavşana (test grubu), 1. grupla eş zamanlı olarak CBZ ve bir doz PGE (2,5 mg/kg/gün) birlikte uygulandı. Uygulamayı takiben tavşanların kulak marjinal venlerinden 0,0, 0,5, 1,0, 1,5, 2,0, 2,5, 3,0, 4,0, 6,0, 12,0 ve 24,0. saatlerde kan örnekleri alındı.

Bulgular: Tek başına veya PGE ile birlikte verildiğinde CBZ'nin, C_{maks}, t_{maks}, AUC_{0-24}, $AUC_{0-\infty}$, $t_{½}$ ve K_e gibi farmakokinetik (PK) parametreleri arasında farklılık saptanmadı ($p \geq 0,05$).

Sonuç: PGE, CBZ ile birlikte uygulandığında, CBZ'nin PK parametreleri etkilenmeyecektir. Bu nedenle PGE, önleme gerek olmadan veya doz takibi yapılmadan güvenle kullanılabilir.

Anahtar kelimeler: Karbamazepin, *Panax ginseng*, CYP3A4, ilaç etkileşimi, farmakokinetik

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INTRODUCTION

Carbamazepine (CBZ) is a well-known drug prescribed to treat epilepsy, trigeminal neuralgia, and bipolar depression.[1,2] The present study is performed to investigate the effect of *Panax ginseng* extract (PGE) on the disposition of CBZ, the substrate of CYP3A4, in rabbits.

CBZ has several properties involved in clinical interactions with co-administered drugs, herbs, and food.[3,4] It has a narrow therapeutic index.[5] It is a constructive inducing enzyme of several cytochrome P450 (CYP450) isoenzymes and subject to autoinduction.[3,6]

CBZ-10,11-epoxide (CBZ-E) is the active metabolite of CBZ whose concentration may be modified by concomitant drugs. It is mostly prescribed in codrug features because of its widespread and long-term use, thereby inducing drug interactions.[4]

Drug interactions are often classified as either pharmacokinetic (PK) or pharmacodynamic interactions.[7] The most tangible interactions that affect the PK of CBZ include those influencing its metabolic rate.[5] CBZ is mainly metabolized in the liver through oxidation catalyzed by the CYP450 3A4 enzyme, and less than 5% of CBZ becomes excreted and remains unchanged in urine.[4,8-10] CBZ-E is the major (up to 80%) active metabolite of CBZ, which is further metabolized before excretion through hydration to a trans-dihydrodiol (CBZ-diol).[4,11] CBZ is a substrate of CYP450 3A4 and inducer of its enzymatic activity.[8,11] It can induce its own metabolism[4,9] through autoinduction, which is a time- and dose-dependent process.[12] The inhibition or induction of CYP450 enzymes significantly influences drug interactions that can cause unpredictable adverse effects or even therapeutic failures.[13] Herb-drug interactions are expected, thereby eliciting various clinical effects. Moreover, the increased popularity of herbal medicines can explain the high incidence of herb-drug interactions.[14] These interactions can occur when the co-administered herbal preparations modulate drug metabolism either to be induced or inhibited by specific CYP enzymes.[15,16] CBZ-herb interactions are important and have been widely explored, especially when herbs affect the same enzymes involved in CBZ metabolism.[17]

PGE is one of the most popular and widely available herbal supplements.[18,19] It is mainly used as an adaptogenic, antineoplastic, immunomodulating, cardiovascular, CNS, endocrine, antiinflammatory, antioxidant, antineurological, and hypoglycemic agent.[20] Several studies have shown that PGE induces the activity of CYP3A4 in the liver and gastrointestinal tract.[21,22] Moreover, ginsenoside (an active compound in PGE) induces the CYP3A4 activity *in vitro* by interacting with CBZ, resulting in an increased CBZ metabolism.[14] The present *in vivo* research aims to determine the possible herb–drug interactions between PGE and CBZ disposition.

MATERIALS AND METHODS

Animals and study design

Twelve healthy male rabbits weighing 3200-3500 g were bought from Assdda Animal Center (Gaza, Palestine). Clinical tests and follow-up care were performed. The rabbits were subjected to fasting for 12 h and given free access to water before they were treated. The study was carried out at the AUG Faculty of Pharmacy, Gaza, Palestine.

An *in vivo* herb-drug interaction study between CBZ and PGE was conducted in healthy male rabbits. Experiments were carried out in 1 period, and 2 groups of male rabbits were used. The first group of 6 rabbits was given a single oral dose of CBZ (30 mg/kg/day) from an oral suspension of CBZ (Tegretol®), and the 2nd group of 6 rabbits was administered with the same volume of CBZ suspension combined with a single oral dose of PGE (2.5 mg/kg/day) prepared in laboratories via a special oral gavage for 10 days. CBZ oral suspension and PG capsules were purchased from private pharmacies. The dose was given to each rabbit via oral gavage by placing the drug in a corner of the rabbit's mouth, and the suspension was pushed down at a slow rate to prevent choking. Physical tests were subsequently carried out to assess clinical safety.

Blood sample collection

The hair on the rabbits' ear was removed as the marginal ear vein was located. Local anesthetic (4% lidocaine) was used to prevent the jerking of the rabbits. An IV cannula was installed in the marginal ear vein of each rabbit. Then, 1 mL of blood sample was collected in vacutainer tubes at the following time points: 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 12.0, and 24.0 h after the last dose was received. Blood samples were centrifuged at 3,000 rpm for 5 min, and serum was separated, collected into clean tubes, and kept at 2°C-8°C for analysis within 24 h.

Analysis of CBZ serum samples

CBZ blood concentrations were assayed via a chemiluminescent immunoassay by using an ARCHITECT analyzer (1000 Abbott Laboratories, Abbott Park, IL, USA).

Pharmacokinetic analysis

The following PK parameters of both groups were determined: C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, and K_e. C_{max} and t_{max} were directly identified from the plasma concentration versus time curves. AUC_{0-24} was calculated in accordance with the linear trapezoidal rule by using the following equation: $AUC_{0-\infty}=AUC_{0-24} + Ct/K_e$, where Ct is the last measured serum concentration at time t, and K_e is the elimination rate constant. K_e was determined via the least squares regression of plasma concentration-time data points in the terminal region by considering the semilogarithmic dependence that corresponds to first-order kinetics. $t_{1/2}$ was calculated as $0.693/K_e$. PK analysis was conducted via an independent model method (non-compartmental approach) in WinNonlin version 6.3 (Pharsight Corporation, Cary, NC) and GraphPad Prism version 4.00 (San Diego, CA, USA).

Statistical analysis

Statistical methods, including descriptive analysis and Mann-Whitney U test, were applied to compare the PK parameters of CBZ alone or with PGE. SPSS version 16.0 was applied to analyze data. Data were considered significantly different when $p \leq 0.05$.

RESULTS

The plasma concentration versus time profiles and PK parameters of CBZ (Figure 1) were compared after it was administered alone (control group) and combined with PGE (test group). The significant results of their comparison are given in Table 1.

DISCUSSION

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

The plasma profiles of CBZ are illustrated in Figure 1. AUC_{0-24} and $AUC_{0-\infty}$ apparently decreased after the concomitant administration of CBZ with PGE, but this change was not statistically significant ($p \geq 0.05$). The other PK parameters of both groups were also not altered significantly after PGE administration. The mean C_{max} of the control group slightly decreased compared with that of the test group ($p=0.53$). Despite the decreased half-life ($t_{1/2}$) from 26.51±25.79 h to 16.99±8.58 h in the control and test groups, respectively, their differences were not statistically significant ($p=0.24$).

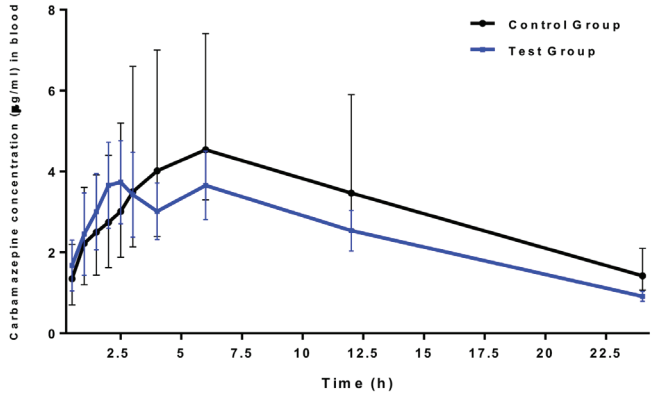

Figure 1. Plot of the mean serum concentration-time profile of CBZ alone (control group) and co-treatment with PGE (2.5 mg/kg/day; test group)
CBZ: Carbamazepine, PGE: *Panax ginseng* extract

PGE is an herbal medicine used worldwide for a variety of purposes.[25] With complicated PK and pharmacodynamics, PGE may pose a significant risk for patients once it is taken synchronously with other medications through PGE-drug interactions.[26]

Possible drug interactions have been reported between PGE and warfarin, phenelzine, and alcohol.[19,25] CBZ may reduce the blood concentrations of warfarin and induces mania if it is used synchronously with phenelzine.[27]

Similarly, Abushammala[17] found that valerian does not alter the PK parameters of CBZ in rabbits and concluded that CBZ can be used safely with valerian preparations. Moreover, clinical trials have shown that American ginseng does not significantly affect the PK of indinavir and zidovudine. No significant differences in the AUC of the plasma concentration versus time relationship are observed after the co-administration of American ginseng compared with that after either zidovudine or indinavir is administered alone.[28,29] Despite the stimulating effect of PGE on the CYP3A4 activity, the PK parameters of CBZ do not significantly affect healthy rabbits after the combined administration.

CONCLUSION

Under the experimental conditions, CBZ and PGE can be used safely without precautions or dose monitoring. However, more studies on humans should be designed to confirm our obtained results. Further research should also be performed by setting

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	
K_e	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	

CBZ: Carbamazepine, PGE: *Panax ginseng* extract, PK: Pharmacokinetic, SD: Standard deviation, IQR: Interquartile range

higher PGE doses, a longer treatment duration, and a larger sample size.

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