Effect of Oral Administration of Valerian Extract at Different Doses on Pharmacokinetic Parameters of Carbamazepine in Rabbits

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Abstract

Carbamazepine (CBZ) is a narrow therapeutic index drug used in the treatment of trigeminal neuralgia and psychiatric disorders. Valerian (VAL) is a popular herbal product which should be prescribed to treat insomnia and anxiety. The study was designed to investigate the presence of significant pharmacokinetic (PK) interaction between Valerian (VAL) at different concentrations on Carbamazepine (CBZ) pharmacokinetic parameters in healthy male rabbits. In an *in vivo*, parallel-randomized controlled trial, the rabbits in three groups "first (control), second and third" were given oral doses of CBZ (50 mg/kg), for "second and third" groups (as test groups) rabbits were given (20 and 40 mg/kg/day) of the VAL respectively, as suspension in normal saline for eight consecutive days. On the eighth day, CBZ was co-administered an hour after adding the last dose of VAL suspension. Venous blood samples (1.0-1.5 mL) were obtained from rabbits' ears' marginal vein at predetermined different periods. The plasma of this blood separation was done using centrifugation and stored at -80°C, prior to analysis by using CBZ chemiluminescent enzyme immunoassay detection kit. Different PK parameters such as C_{max}, t_{max}, $t_{\frac{1}{2}}$, k_e, AUC_{0-24} and $AUC_{0-\infty}$ were determined for the three groups, applying Statistical testing (ANOVA). The results showed statistical insignificant differences for all PK parameters among the three groups with ($p > 0.05$). The findings showed that VAL at both concentrations is not likely to interfere with PK parameters related to CBZ, Further confirmation in humans shoud be done before these findings are applied to patient care.

Keywords: Carbamazepine, CYP3A4, Valerian, Herb-drug interaction Pharmacokinetic parameters.

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تأثير التعاطي الفموي لمستخلص حشيشة الهر بجرعات مختلفة على عوامل حركية الكاربامازيبين في الارانب

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الخلاصة

صممت الدراسة للتحقق من وجود تداخل فى عوامل حركية الدواء (PK) بين مستخلص حشيشة الهر (VAL) بتركيزات مختلفة على عوامل حركية الدواء للكارباماربين (CBZ) في ذكور الأرانب السليمة مستخدمين ارانب سليمة صحيا ، متوازية معشاة ذات شواهد ، أعطيت الأرانب في المجموعات الثلاث (الأولى والثانية والثالثة) جرعات فموية من (50) CBZ ملغم/ كلغم) ؛ بالنسبة للمجموعتين "الثانية والثالثة" (كمجموعات اختبار) أعطيت الأرانب على التوالي (٢٠ و ٤٠ ملغم / كلغم / يوم) من مستخلص حشيشة الهر (VAL) في محلول ملحي عادي لمدة ثمانية أيام على قاعدة متتالية. في اليوم الثامن ، تمت إعطاء CBZ بشكل مشترك بعد ساعة من إضافة آخر جرعة من مستخلص حشيشة الهر (VAL). تم الحصول على عينات الدم الوريدي (١,٠-١,٥ مل) من الوريد الهامشي لآذان الأرانب في فترات مختلفة ومن ثم تم إجراء فصل الدم بالبلازما باستخدام الطرد المركزي وتم تخزينه في درجة حرارة -٨٠ درجة مئوية قبل التحليل باستخدام مجموعة الكشف المناعي للإنزيم الكيميائي الخاصة للكارباماربين. تم تحديد معلمات PK مختلفة مثل C_{max}, t_{max}, $t_{\frac{1}{2}}$, k_e, AUC_{0-24} and $AUC_{0-\infty}$ للمجموعات الثلاث ومن ثم تم تطبيق الاختبار الإحصائي (ANOVA). أظهرت النتائج فروق ذات دلالة إحصائية غير معنوية (p>0.05) لجميع عوامل حركية الدواء بين المجموعات الثلاث. تظهر النتائج أن مستخلص حشيشة الهر في كلا التركيزين من غير المحتمل أن يتداخل مع معلمات PK المتعلقة بـ CBZ ، يجب إجراء مزيد من التجارب قبل تطبيق هذه النتائج في رعاية المرضى.

الكلمات المفتاحية: الكارباماريبين، مستخلص حشيشة الهر، التفاعلات الدوائية، معاملات الحركية الدوائية.

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Introduction

Herbal-drug interactions can be characterized as either pharmacodynamic or pharmacokinetic (PK) by nature. Pharmacodynamic interactions may occur when constituents of herbal products have either synergistic or antagonist activity concerning a conventional drug meanwile, PK interactions result from alteration of absorption, distribution, metabolism, or elimination of a conventional drug by herbal product or other food supplements [1,2].

Carbamazepine is a common drug used for treating partial and tonic-colonic seizers [3]. Cytochrome P450 (CYP450) monooxygenase is a superfamily of hemoproteins, which is responsible for the phase I metabolism of various xenobiotics and some endogenous substances as steroids. Nearly 70–80% of all prescribed drugs are metabolized by the CYP system. CYP3A4 is involved in CBZ metabolic sequences. Carbamazepine has a narrow range of therapy and might show drug interaction with several drugs either by induction or inhibition of CYP3A4. Despite its clinical popularity, CBZ possesses several PK properties which make it a possible candidate to interact with substances upon co-administration, including synthetic drugs, pharmaceutical herbs and food. CBZ is classified not only as an effective inducing agent of CYP450 system, but also as autoinduction agent [4-8].

Valerian (VAL) is the common name given to the crude drug consisting of underground organs of species of (Valerianaceae). The major components of VAL include the monoterpenebornyl acetate and the sesquiterpene valerenic acid which, in addition to other types of sesquiterpene, are characteristic features of the species. The constituents of the volatile oil are variable due to population differences in genetics and environmental factors. VAL -as a traditional herb- was used to treat insomnia and anxiety. It is also considered as the largest attended non-prescribed sedative in European countries [9,10].

Herb/CBZ interaction was catchy and crucial topic for many researchers all over the world [11,12]. Therefore, interaction potency should be taken into consideration upon using herbs as medication to avoid reduction in drug efficiency and/or increase the side effects of concomitantly administered drugs [13]. Possible herb-drug interaction of VAL-CBZ is still underestimated. This research was conducted to study the effect of co-administration of VAL at different doses on PK parameters of CBZ in rabbits.

Subjects and Methods

Animals

Eighteen New Zealand strains of adult male rabbits weighted (3.1-3.4 kg) and aged (7-9) months were divided into three groups (six subjects in each) and were used as animal model for the current drug – herb PK interaction study. All rabbits were kept under standard laboratory conditions in a 12-hour light/dark cycle at 25°C ± 2°C provided with pellet diet with free acces to water (ad libitum) and were fasted overnight before the experiments.

Study design and blood sampling

The study design was parallel-randomized controlled trial. Eighteen male rabbits were assigned into three groups. In the first group (control group), rabbits were given orally a volume equivalent to CBZ (50 mg/kg) from a 2% oral suspension (Tegretol, Novartis). Post dosing venous blood samples (1.0-1.5 mL) obtained from ear vein of the rabbits using special cannula (21G) at different time periods (0.50, 1.0, 1.50, 2.00, 2.50, 3.50, 4.0, 6.00, 12.00, 18.0 and 24.00 hr) [14]. In the second and third groups (test groups), the rabbits were given a volume of CBZ 2% oral suspension also in a dose of (50 mg/kg) at the same conditions as in the first group concurrently with volumes equivalent to (20 and 40 mg/kg/day, repectively) VAL suspension. This suspension was commercially prepared by pulverizing the film coated tablets of VAL Relaxin, Lab. Pharma Trenker) in normal saline. VAL suspension was given for eight continuous days. On the eighth day, CBZ was administered one hour after administration of the last dose of VAL suspension, and blood was collected from rabbits from the second and the third groups at the same periods mentioned above. Plasma was collected by centrifugation of samples and was stored at (-80°C) until analysis. The analysis was performed by CBZ detection kits (CLEIA) and Immulite 1000 Immunoassay System.

PK parameters determination

The plasma level -time profile of CBZ was constructed for the control and herb treated groups. The PK parameters of CBZ in the control and test groups were calculated using Model -Independent Approach (Non-Compartmental Model (NCM)). WinNonlin Professional Software (Version 6.3, Pharsight Corporation, Cary, NC) and (GraphPad Prism versión 4.00, San Diego, CA, USA) were used in the calculation and statistical analysis of the following PK parameters: Maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), elimination rate constant (K_e), elimination half-life ($t_{1/2}$), area under plasma concentration -time curve up to 24 hours (AUC_{0-24}) and to the infinit time ($AUC_{0-\infty}$) for the control and herb treated groups.

Statistical analysis

Data were presented as Mean (plasma conc. Of CBZ) ± SD. Differences in PK parameters of CBZ upon administering without VAL (first group) and with VAL suspension at different concentrations (second and third groups) were assessed by analysis of variance (ANOVA) using SPSS program (version 22.0) taking 95 % confidence interval and significant statistical differences as *p value* <0.05.

Results

This study was carried out to determine the influence of VAL at two different concentrations (20 and 40 mg/kg/day) on PK parameters of CBZ when given concurrently. The PK parameters of CBZ in the control group (first group) were compared to those of the test groups treated with VAL 20 and 40 mg/kg/day (second and third groups respectively). Plasma level -time profiles of CBZ in the three groups are shown in Figure 1.

The calculated PK parameters: C_{max}, t_{max}, $t_{1/2}$, K_e, AUC_{0-24} and $AUC_{0-\infty}$ of the three groups were mentioned in table 1. In this study, C_{max} of CBZ (first group) was 6.64±1.12 µg/mL and t_{max} was 1.95±0.22 h. The rabbits treated with VAL 20 mg/kg/day (second group) produced C_{max} and t_{max} of 6.82±1.25 µg/mL and 2.11±0.27 h, respectively. A slight, but statistically nonsignificant, increase of C_{max} and t_{max} of CBZ were found when VAL was co-administered with CBZ (second group). The systemic exposures according to $AUC_{0-\infty}$ showed nonsignificant differences between the two groups (94.32±11.7 µg.hr/mL vs. 73.71±28.1 µg.hr/mL; *p*=0.063). Other PK parameters including $t_{1/2}$, K_e and

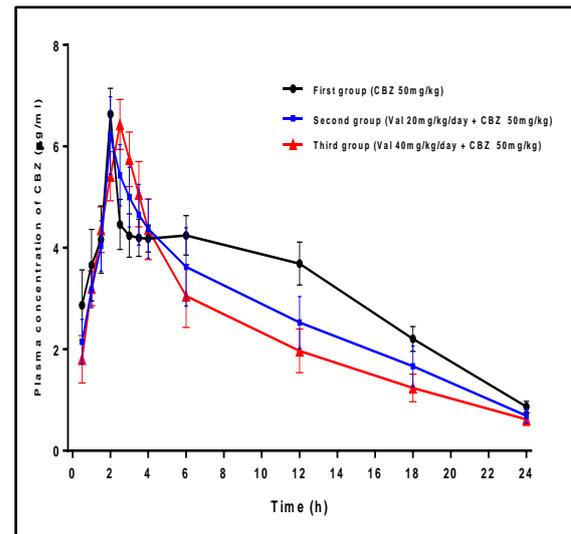AUC_{0-24} showed no significant differences between both groups (Table 1).

Figure 1. Concentration -time profile of CBZ without VAL (First group) and with VAL (Second and third groups) in rabbits.

Table 1. Pharmacokinetic Parmeters of CBZ without VAL (First group) and with VAL (Second and Third groups) in Rabbits.

PK Parameters	Groups	Mean ± SD	*P*-value
C_{max} (µg/mL)	First group	6.64±1.12	0.770¥
	Second group	6.82±1.25	
	Third group	6.41±1.13	0.296§
t_{max} (hr)	First group	1.95±0.22	0.054¥
	Second group	2.11±0.27	
	Third group	2.10±0.20	0.726§
$t_{1/2}$ (hr)	First group	13.70±4.40	0.055¥
	Second group	10.30±2.87	
	Third group	8.91±2.47	0.131§
K_e (hr^{-1})	First group	0.054±0.012	0.181¥
	Second group	0.053±0.025	
	Third group	0.081±0.018	0.052§
AUC_{0-24} (µg*hr/mL)	First group	76.49±13.85	0.360¥
	Second group	62.54±21.27	
	Third group	55.53±20.50	0.090§
$AUC_{0-\infty}$ (µg*hr/mL)	First group	94.32±11.7	0.063¥
	Second group	73.71±28.1	
	Third group	64.30±27.1	0.173§

n= 6 rabbits for each group.
(¥) : p value of the differences between the first group and the second group.
(§) : p value of the differences between the first group and the third group.

The estimated model-independent PK parameters of CBZ alone (first group) and co-administered with VAL 40 mg/kg/day (third group) were also listed in table 1. In this case, the differences in C_{max} and t_{max} of CBZ between first and third groups were insignificant since, ($p > 0.05$). Furthermore, other PK parameters including $t_{1/2}$ and k_e of CBZ in the first and third groups were also, statistically insignificant. Besides, no significant differences were recorded between the first and third groups regarding the systemic exposures defined by AUC_{0-24} and $AUC_{0-\infty}$ (Table 1).

Discussion

Since the antiepileptic CBZ drug is given on a short-term basis, the opportunity of a significant clinical interaction between CBZ and co-administered substances is common. The clinical sequence of interactions may be lack of efficiency, toxicity, unexpected effects, and vague side effects [15,16]. Regarding the lack of studies investigating VAL-CBZ interactions, the present study was conducted. All rabbits enrolled in this study had finished the study period without any deviation.

The isoform CYP3A4 of CYP450 is being a significant enzyme that is responsible for biotransformation of 70% of the drugs in use today. As antiepileptic regimens are normally given on a long-term basis, the opportunity of a clinically significant interaction between CBZ and co-administered substances is considerably high. Herbal medicines, dietary supplements, and food may interact with CBZ pharmacokinetically and/or pharmacodynamically which leads to potential clinical consequences. One of the contributing factors towards increasing the incidence of herb-drug interaction is the increased popularity of herbal medicines [17].

Some herbal products such as Cassia auriculata Linn., piperine (an active compound in Piper longum Linn.), Platycodonis Radix, and Polygonum cuspidatum were demonstrated to increase the plasma level/oral bioavailability of CBZ through decreasing the metabolism of CBZ or improving gastric solubility of CBZ meanwhile, others like ginkgo biloba, Hu-gan-ning pian, Jia-wei-xiao-yao-san, and Xiao-yao-san decreased the plasma level/oral bioavailbaility of CBZ through increasing the metabolism of CBZ via CYP 3A4 induction [18-24].

The results of the PK interaction study between CBZ and VAL commercial dry extract at two different doses (20 and 40 mg/kg/day) in rabbits showed no statistical differences in PK parameters ($p>0.05$). Similar results were found by Jiang and his collaborators when studied the effect of berberine on PK of CYP3A4 and P-gp substrates [25], who found that a statistically insignificant differences after a 2-week pretreatment with bebeerine. The PK interaction study between Saiko-ka-ryukotsu-borei-to and CBZ in rats published by

Ohnishi and his collaborators showed a lack of PK interactions [26]. Similar findings were ontained by Burstein et al. who demonstrated that treatment with St John's Wort for 14 days did not further induce the clearance of CBZ [27]. In other study Abushammala et al. demonstrated that CBZ had no significantly different pharmacokinetic (PK) parameters, namely, C_{max}, t_{max}, AUC_{0-24}, $AUC_{0-\infty}$, $t_{1/2}$, and K_e, when it was given alone or concurrently with Panax Ginseng [28].

Conclusion

Herb-drug interaction is of great importance for patient safety, especially with the increased popularity of herbal medicines. PK interaction of CBZ was recorded when it was co-administered with some herbs. In this study, VAL spspension that was prepared from Valerian Root Extract showed minimal effect on PK profile of CBZ. Further research should also be performed by using higher VAL doses, a longer treatment duration and a larger sample size before the confirmation of the present results in humans.

Ethical Statement

The study was approved and performed under ethical principles laid down by the Faculty of Pharmacy, Al-Azhar University-Gaza, Palestine.

Conflict of Interest

No conflicts of interest relevant to this article.

Acknowledgments

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