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THE EFFECT OF VALERIAN ON THE PHARMACOKINETICS OF CARBAMAZEPINE IN HEALTHY RABBITS

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ABSTRACT: This article aimed to evaluate the effect of valerian on a single dose kinetic of carbamazepine in rabbits. Five healthy male rabbits in a randomized, two-crossover design were enrolled in this study. Rabbits were divided into two groups; the first received a single dose of 100 mg carbamazepine (CBZ) suspension. The second group received CBZ 100 mg suspension concurrently with valerian (VAL) 25 mg dry extract. After a washout period of one week, the doses were given in a reverse manner. Blood samples were collected over 24 hours. Serum was assayed for CBZ using chemiluminescent enzyme immunoassay (CLEIA). Pharmacokinetic (PK) parameters were determined for CBZ in both cases using non-compartmental analysis. Statistically insignificant differences $P \geq 0.05$ were found in PK parameters when CBZ was given alone or concurrently with VAL; the values were C_{max} $6.52 \pm 1.6 \mu\text{g/ml}$ versus $5.32 \pm 1.4 \mu\text{g/ml}$, t_{max} $2.6 \pm 0.9 \text{ h}$ versus $3.3 \pm 0.9 \text{ h}$, AUC_{0-24} $83.80 \pm 28.8 \mu\text{g}\cdot\text{h/ml}$ versus $60.4 \pm 12 \mu\text{g}\cdot\text{h/ml}$, $AUC_{0-\infty}$ $166.20 \pm 74 \mu\text{g}\cdot\text{h/ml}$ versus $104.75 \pm 12 \mu\text{g}\cdot\text{h/ml}$, k_e $0.033 \pm 0.006 \text{ h}^{-1}$ versus $0.038 \pm 0.012 \text{ h}^{-1}$ and $t_{1/2}$ $21.81 \pm 3.96 \text{ h}$ versus $20.71 \pm 10.09 \text{ h}$ respectively. The result of the study demonstrated that valerian does not affect PK of CBZ, there are no cautions, regarding to dose or administration pattern of CBZ with valerian should be taken.

INTRODUCTION: Carbamazepine (CBZ) is one of the commonly used conventional antiepileptic drugs. CBZ has a considerable low therapeutic index and a wide inter-individual variation at tolerable doses which make therapeutic drug monitoring necessary^{1, 2}. Also, CBZ is a potent enzyme inducer and is a subject to auto-induction. Those properties make CBZ prone to interactions with the co-administered drug, herbal products, and food.

Drug interactions are classified into pharmacodynamic and pharmacokinetic types³⁻⁵. The variability in drug pharmacokinetic is responsible for the lack of a consistent relationship between dose given of the drug and its concentration at the site of action⁶. Herb-drug interactions are mostly pharmacokinetic. Fluctuations in the bioavailability of drug and herb molecules in the body can result from changes in absorption, distribution, metabolism, and elimination. Induction or inhibition of hepatic and intestinal drug-metabolizing enzymes, *e.g.* CYP450 and drug transporters such as P-glycoprotein were suggested as possible mechanisms^{7, 8}.

The consumption of herbal products for a variety of health-related problems has steadily increased over the past few years^{9, 10}.

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Valerian (VAL) is a popular herbal product often used to treat insomnia and anxiety. It is the most common non-prescription sedative used in Europe^{11,12}. CBZ-herb interactions were an interesting and important issue for many researchers¹³. Possible pharmacokinetic VAL-CBZ interactions are still uninvestigated. The present study aims to examine the effect of VAL on PK of CBZ in healthy rabbits.

MATERIALS AND METHODS:

Animals: Five healthy male rabbits (weight: 3.26 ± 0.11 Kg, age: 7-9 months) were enrolled in the study. The rabbits were obtained from Asdda for animal production and welfare center, where follow up care and clinical examination was performed, and rabbits' health state was certified (khanunis, Palestine). Rabbits fasted for 12 hours with free access to water by *ad libitum* before the beginning of the study. The study was carried out at Al-Azhar University-Gaza, College of Pharmacy, Gaza, Palestine. The study was approved by the institutional ethics committee and was conducted under the supervision of a veterinary physician.

Study Design: A single dose, two-crossover design study was conducted in rabbits. The rabbits were divided into two groups. The first one received a volume equivalent to 100 mg CBZ from an oral suspension 2% (Tegretol, Novartis), whereas the second group received the same volume of CBZ suspension in combination with a volume of prepared in laboratory suspension equivalent to 25 mg valerian dry extract. It was prepared by pulverizing five tablets of commercial valerian film-coated tablets (Relaxing, Laboratoires Pharmaceutiques Trenker). Each tablet contains 500 mg of dry valerian extract. Weight of the powder equivalent to 0.5 g VAL dry extract was suspended in 20 ml distilled water. After one week the second group received CBZ suspension alone and the first received CBZ suspension in combination with VAL to complete the cross-over design. Carbamazepine oral suspension and valerian tablets were purchased from a local pharmacy (Gaza, Palestine). The dose was given orally by gavage to each rabbit. It was put in the corner of the mouth and the suspension was pushed down slowly, to avoid choking. General clinical safety was assessed by physical examination during the study, washout period and at the end of the study.

Blood Sampling: Rabbits were placed in rabbit restraining box device. The marginal ear vein was located, and the hair was removed. Gentle stroking and tapping of the ear may make the vein more visible. Local anesthetic was applied to prevent the jerking of the rabbit as a result of venipuncture 15 minutes before starting the study. Inserting a small needle (23 gauge) butterfly attached to a syringe in the marginal ear vein¹⁴. Serial venous blood samples were collected (ca 0.7 ml) in vacutainer tubes according to the time schedule 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0 and 24.0 h after receiving the dose. Blood samples were centrifuged at 3,000 rpm for 5 minutes, and serum was transferred into clean plastic tubes. Serum samples (ca. 200 μ l) were kept in the refrigerator until being analyzed within 24 h.

Analysis of Serum Samples: The analysis was performed by Carbamazepine kit based on chemiluminescent enzyme immunoassay (CLEIA) and Immulite 1000 immunoassay system (Siemens Healthcare Diagnostics).

Pharmacokinetic Analysis: The plasma pharmacokinetic parameters were estimated, which included the observed maximum plasma concentration C_{max} , the time to reach C_{max} , (T_{max}) and the area under the plasma concentration-time curve from 0 hours to last measurable concentration (AUC_{0-t}) and 0 hours to infinity ($AUC_{0-\infty}$). The C_{max} and T_{max} were directly determined from the serum concentration versus time curves. The Area under the curve from 0 hours to t (AUC_{0-t}) was calculated by the linear trapezoidal rule. The area under the curve from 0 hours to infinity ($AUC_{0-\infty}$) was estimated by summing the area from AUC_{0-t} and $AUC_{0-\infty}$, where $AUC_{0-\infty} = AUC_{0-t} + C_t / k_e$, with ' C_t ' defined as the last measured serum concentration at time t , and k_e is the elimination rate constant. The elimination rate constant k_e was estimated 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 half-life $t_{1/2}$ was calculated as $0.693/k_e$. Pharmacokinetic analysis was performed using model-independent method (Non-Compartmental Approach) WinNonlin Professional Software (Version 6.3, Pharsight Corporation, Cary, NC).

Statistical Analysis: Analysis of Variance (ANOVA) was used to compare the calculated pharmacokinetic parameters of CBZ alone or with VAL, using general linear model procedures, in which sources of variation were subject and period. The statistical analysis was performed using SPSS, version 16. A statistically significant difference was considered when $P \leq 0.05$.

RESULTS AND DISCUSSION: Carbamazepine (CBZ) is a first-line antiepileptic drug which may be prone to drug interactions. Serious herb-carbamazepine interactions with clinical evidence were reported. The majority were pharmacokinetic-based¹³.

In this study, the effect of VAL on PK of CBZ was investigated using rabbits. The mean plasma concentrations of CBZ when administered alone or in combination with VAL are shown in **Fig. 1**.

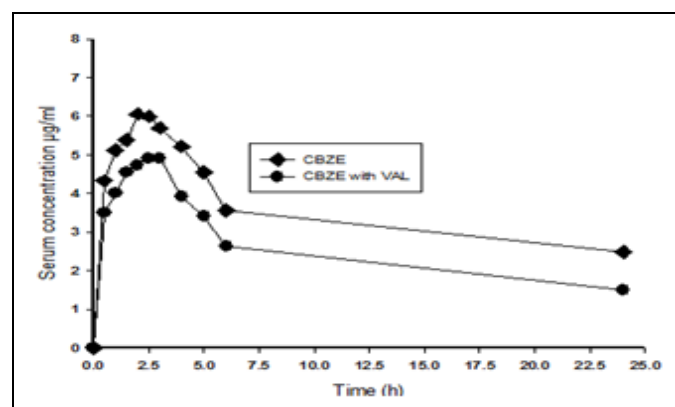


FIG. 1: THE MEAN RABBIT SERUM CONCENTRATION-TIME PROFILE OF CBZ WHEN ADMINISTERED ALONE AND IN COMBINATION WITH VAL (n = 5)

The concentration-time profile in both cases indicated that they were comparable. The mean C_{max} was $6.52 \pm 1.6 \mu\text{g/ml}$ versus 5.32 ± 1.4

$\mu\text{g/ml}$, and t_{max} was 2.6 ± 0.9 h versus 3.3 ± 0.9 h, of CBZ after alone and concomitant administration of CBZ with VAL, respectively **Table 1**. VAL has not changed the absorption phase of CBZ. Some herbal products increased absorption of poor water-soluble CBZ - through enhancement of dissolution or altering gastric emptying rate^{15, 16}. Psyllium, septicin, and soya bean decreased bioavailability and plasma level of CBZ by affecting its gastric absorption¹⁷⁻¹⁹.

By comparing the rest PK parameters, statistically insignificant differences were found in **Table 1**. The elimination of CBZ was not affected by VAL; K_e and $t_{1/2}$ were not changed when VAL was co-administered significantly. CYP3A4 is the most important enzyme involved in the metabolism of CBZ as it leads to the formation of the active metabolite CBZ 10,11-epoxide, which appears to contribute to the toxicity and efficacy of CBZ^{20, 21}. CYP3A6 is responsible for CBZ metabolism in the rabbit²². The rabbit CYP3A6 and human CYP3A4 isoform have similar p-450 predominance, and substrate specificity, and both are induced by rifampicin²³.

CYP3A4 is the most important isoform of CYP450 in critical tissues, such as hepatic and gastrointestinal tract. This enzyme is involved in the biotransformation of over 70% of the drugs in use today; hence, the possible risk of adverse events due to alterations in this pathway is high⁷.

Some herbal products induced CYP3A4 and diminished CBZ plasma level, e.g. Ginko biloba²⁴ and soybean¹⁹. Others like grapefruit juice and Polygonum cuspidatum inhibited CYP3A4 led to an elevated plasma level of CBZ^{25, 26}.

TABLE 1: SUMMARY OF MEAN PHARMACOKINETIC PARAMETERS OF CBZ 100 MG WITH AND WITHOUT VAL 25 MG (n=5)

Pharmacokinetic parameter ^a	CBZ alone Mean \pm SD ^b	CBZ and VAL Mean \pm SD ^b	p-Value ^c
C_{max} ($\mu\text{g/ml}$)	6.52 ± 1.66	5.320 ± 1.386	0.355
T_{max} (h)	2.60 ± 0.96	3.300 ± 0.975	0.404
AUC_{0-24} ($\mu\text{g.h/ml}$)	83.80 ± 28.80	60.43 ± 12.08	0.833
$AUC_{0-\infty}$ ($\mu\text{g.h/ml}$)	166.20 ± 74.50	104.75 ± 12.08	0.420
$t_{1/2}$ (h)	21.81 ± 3.96	20.71 ± 10.09	0.202
K_e (h^{-1})	0.0326 ± 0.0058	0.0381 ± 0.0124	0.161

^a: Abbreviations are C_{max} : Maximum serum concentration, T_{max} : Time to C_{max} , AUC_{0-24} : Area under the curve from 0 h to 24 h, $AUC_{0-\infty}$: Area under the curve from 0 h to infinity, $t_{1/2}$: Terminal half-life and K_e : Terminal elimination constant, ^b: SD: Standard deviation, ^c: Statistical significance $p \leq 0.05$.

Extracts from the valerian root have been shown to inhibit CYP3A4 activity *in vitro*²⁷⁻²⁹. The effects of valerian on co-administered medications *in vivo* appear to be less significant than those observed *in vitro*. Studies designed to probe *in-vivo* drug interactions between valerian and substrates for CYP3A4 or CYP2D6 have come back negative. Minimal effects on CYP3A4 activity and no effect on CYP2D6 activity were reported following 14 days of valerian administration (1 gram/day)³⁰. Similar results were found in volunteers for a variety of probe substrate relating to CYP450 3A4, 1A2, 2E1, and 2D6 following administration of valerian for a month. The results showed that valerian is unlikely to cause pharmacokinetic interaction mediated by major CYP450 enzymes³¹.

The absorption and elimination phases of CBZ were not affected by co-administration of VAL; therefore, the bioavailability; area under the curve AUC, of CBZ was not changed significantly by VAL. Changes in the bioavailability of CBZ were reported with unknown mechanisms¹³. The utility of animals to study drug-herb interactions is well documented^{7, 32}. Pharmacokinetic of a drug showed not be modified by repeated blood withdrawal from the same rabbit³³. All five rabbits had completed the study, and there were no death or replacement during the study. Clinical physical examination during and post-study indicated no abnormalities. The present study showed good tolerability at the given doses for CBZ and VAL.

CONCLUSION: Despite the widespread of herbal medicines documented herb-drug interactions are few. The result of the study indicated that valerian had not altered PK parameters of CBZ in rabbits. CBZ can be used safely with VAL preparations.

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CONFLICT OF INTEREST: Nil

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