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LETTER TO THE EDITOR

EFFECT OF LIV-52 AN AYURVEDIC PREPARATION ON THE PHARMACOKINETIC PROFILE OF CARBAMAZEPINE IN MONKEYS

Sir,

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Liv-52 is a commonly prescribed ayurvedic formulation for the treatment of hepatic disorders. Liv-52 contains active principles of the following herbs *Capparis Spinosa, Phyllanthus amarus, Tamarix gallica, Achillea millefolium, Terminalia arjuna, Cassia occidentalis, Cichorium intybus* and *Solanum nigrum*. Active ingredients of Liv-52 have shown to protect liver from damage produced by alcohol and other toxic substances (1, 2). Carbamazepine (CBZ) and iminostilbene is now considered the primary drug for the treatment of partial and tonic-clonic seizures (3). There is no contraindication of carbamazepine administration in the patients having liver diseases since adverse effects of carbamazepine on liver are rare (4). Epileptic patients on carbamazepine therapy may also have liver disorders for which Liv-52 may be prescribed. Co-administration of herbal drugs has been reported to influence the blood levels of number of drugs (5, 6). Since no study has been reported regarding the effect of Liv-52 administration on the pharmacokinetics of carbamazepine. Present study has been planned to see the effect of single and multiple doses of Liv-52 administration on the pharmacokinetics of carbamazepine in rhesus monkeys.

The study was carried out in six rhesus monkeys (weighing between 5 to 7 kg) of either sex. Animals were kept under standard laboratory conditions and were fed on standard diet and water *ad libitum*. Liv-52 syrup (Himalaya Drug Co. India) and carbamazepine (Tab. Tegretol, Novartis) were used in this study. Monkeys after an overnight fast received carbamazepine (46 mg/kg, p.o.) with 30 ml water through an intragastric tube at 7.00 am and blood samples (2ml) were collected from the small saphenous vein in heparinized tubes at 0, 0.5, 1, 2, 3, 6, 9, 12, 24 and 48 hours after drug administration. After a wash out period of 7 days monkeys received CBZ (46 mg/kg, p.o.) and syrup Liv-52 (0.5 ml/kg, p.o.) with 30 ml water at 7.00 am after overnight fast. Blood samples were collected at similar time intervals as with CBZ alone. After another washout period of 7 days same monkeys received CBZ (46 mg/kg, p.o.) with 30 ml water daily for 14 days. On day 14 blood samples were drawn at 0, 0.5, 1, 2, 3, 6, 9, 12, 24 and 48 hours after the carbamazepine administration. After collecting the last blood sample animals further received CBZ (46 mg/kg, p.o.) and Liv-52 (0.5 mg/kg, p.o.) with 30 ml water daily for next 2 weeks. After the last dose, blood samples were again drawn at same time intervals. Plasma

was separated and stored at –20°C until assayed for carbamazepine (CBZ) by HPLC technique (7). The sensitivity of the method for CBZ was 0.1 µg/ml. The recovery of carbamazepine was 92.30%. Intraassay and interassay coefficient of variations were 7.70% and 5.0% respectively. Following pharmacokinetic parameters were calculated. Peak plasma concentration (Cmax), time to reach peak plasma concentration (Tmax), elimination half-life (t½e), absorption half-life (t½a), area under plasma concentration versus time curve ($AUC_{0-\alpha}$).

Pharmacokinetic parameters were expressed as mean ± SEM and student's paired 't' test was applied for statistical calculations and $P<0.05$ was considered statistically significant. Table I gives the comparison of various pharmacokinetic parameters (mean ± SEM) of CBZ before and after single and multiple dose of Liv-52 administration. No significant difference was observed in any of the pharmacokinetic parameters of CBZ after single dose of Liv-52 administration. After multiple doses of Liv-52 administration the Cmax (9.05 ± 0.65 vs 6.895 ± 0.47 µg/ml), t1/2e (4.12 – 0.25 vs 2.82 0.29h) and $AUC_{0-\alpha}$ (71.34 ± 4.89 vs 47.71 ± 3.78 µg/ml h^{-1}) of CBZ were significantly increased.

Present study shows that single dose administration of Liv-52 did not alter the kinetics of CBZ while multiple doses altered the pharmacokinetics of CBZ by increasing the Cmax, t½ e and AUC. The increased levels of CBZ may either be due to increased and better absorption or due to reduced metabolism and excretion of the CBZ. Liv-52 is a known hepatoprotective herbal formulation and it's hepatoprotective

TABLE I: Carbamazepine Kinetics before and after singh dose and Multiple doses of Liv-52 in Rhesus monkeys.

Parameters	*CBZ Kinetics*			
	Single dose		*Multiple dose*	
	Before	*After*	*Before*	*After*
Cmax (µg/ml)	10.96±0.89	11.52±0.79	6.89±0.47	9.05±0.65*
Tmax (h)	2.83±0.17	2.83±0.17	2.83±0.17	3.0±0
t½e (h)	4.08±0.24	3.54±0.27	2.82±0.29	4.12±0.25*
t½a (h)	0.79±0.08	0.81±0.11	0.82±0.08	0.8±0.1
$AUC_{0-\alpha}$ (µg/ml.h^{-1})	84.67±4.75	83.75±4.37	47.71±3.78	71.34±4.89*

Values are represented as mean ± SEM; (n=6).
*P<0.05

abilities are attributed to Vitamin A and C, α and β-carotenes and flavonoids present in this formulation (2). Flavonoids are present in number of plant products and are responsible for number of drug-drug interactions (8,9). Flavonoids present in Liv-52 might be responsible for decreased metabolism of CBZ in the present study by inhibiting the microsomal enzymes and thereby altering the kinetics of CBZ in rhesus monkeys. Therefore, it is warranted that therapeutic drug monitoring of CBZ should be done whenever Liv-52 is co-administered along with CBZ and dose of CBZ should be adjusted accordingly.

R. K. DIXIT, N. KUMAR, S. K. GARG* AND V. K. BHARGAVA

Department of Pharmacology,
Post Graduate Institute of Medical Education and Research,
Chandigarh – 160 012

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*Corresponding Author