

EFFECT OF TRIKATU, AN AYURVEDIC PRESCRIPTION, ON THE PHARMACOKINETIC PROFILE OF CARBAMAZEPINE IN RABBITS

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Abstract : The effect of single and multiple doses of a herbal preparation Trikatu was studied on the bioavailability and pharmacokinetics of carbamazepine in rabbits. Rabbits (n=10) were administered a single dose of carbamazepine (80mg/kg; p.o.) and after a washout period of 7 days in combination with a single dose of Trikatu (500mg/kg; p.o.). In the other study, six rabbits were administered a single dose of carbamazepine (80mg/kg; p.o.) before and after multiple doses of Trikatu (500mg/kg X 7d; p.o.). The blood samples were collected at 0, 1, 2, 4, 6, 9, 12 and 24 hours after drug administration and assayed for carbamazepine. In the animals treated with single dose of Trikatu, there was a significant decrease in T_{max} of carbamazepine ($P < 0.05$). Multiple doses of Trikatu also shortened the T_{max} of carbamazepine although not to statistically significant level. Our results suggest that the steeper rise and fall in the plasma levels of carbamazepine brought about by Trikatu, do not constitute significant advantage.

Key words : trikatu carbamazepine interaction

INTRODUCTION

Trikatu® a commonly used herbal preparation in Ayurvedic medicine, consists of three crude drugs namely dried fruits of black pepper (*piper nigrum* Linn.), dried fruits of long pepper (*piper longum* Linn.) and dried rhizomes of ginger (*Zingiber officinalis* Rosc.) in the ratio of [1:1:1; w/w] (1). The active principle of piper species is an alkaloid piperine or 1-peperoyl piperidine. Several studies have reported enhancement of blood levels of drugs like vasicine, sparteine, phenytoin, propranolol, theophylline, sulphadiazine, tetracycline

and rifampicin when coadministered with Trikatu or piperine (1-3). The enhanced plasma levels of drugs has been attributed to an increase in the rate of absorption of drugs and to a non specific inhibition of drug metabolising enzymes by piperine (2,3). It has been shown to inhibit arylhydro carbon hydroxylation, ethylmorphine-N-demethylation, 7-ethoxycoumarin-o-deethylation and 3-hydroxybenzo(a) pyrene glucuronidation (4-5). Carbamazepine is a first line drug for the management of partial and tonic-clonic seizures. Because of limited aqueous solubility, carbamazepine is absorbed slowly and erratically after oral

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administration (6). The present study was planned to see the effect of single and multiple doses of Trikatu on the pharmacokinetics of carbamazepine.

METHODS

The study was carried out in male Newzealand white rabbits (1.5–2.5 kg). The animals were maintained on a standard laboratory diet and were housed at ambient temperature. All drug administrations were done at 8 a.m. Trikatu (500mg) containing 10mg of pure active principle piperine (available commercially) and carbamazepine (Sigma Chemicals, USA) in pure powder form were used in the study.

Single dose study:

After overnight fasting, ten rabbits received carbamazepine (80mg/kg; p.o.) through an intragastric tube. Blood samples were collected in heparinized tubes from the marginal ear vein at 0, 1, 2, 4, 6, 9, 12 and 24 hours after drug administration. The rabbits, after a washout period of 7 days were administered carbamazepine (80 mg/kg; p.o.) alongwith Trikatu (500 mg/kg; p.o.). Blood samples were drawn at similar time intervals as with carbamazepine alone.

Multiple dose study:

After an overnight fast, six rabbits were administered carbamazepine (80 mg/kg; p.o.) on day 1. Blood samples were collected at 0, 1, 2, 4, 6, 9, 12 and 24 hours after drug administration. From day 2 to day 7, rabbits were treated with Trikatu (500 mg/kg; p.o.) once daily. On day 8, after an overnight fast, carbamazepine (80 mg/kg; p.o.) along

with Trikatu (500 mg/kg; p.o.) was given. Blood samples were collected at similar time intervals as on day 1.

Plasma was separated and stored at -20°C until assayed for carbamazepine by the HPLC method (7). The sensitivity of the assay method was $0.1\ \mu\text{g/ml}$. The intra assay coefficient of variation at $0.5\ \mu\text{g/ml}$ and $16\ \mu\text{g/ml}$ were 6.83% and 4.96% respectively. The interassay coefficient of variation at the same concentration were 8.41% and 6.72% respectively. Peak plasma concentration [C_{max}] and time to reach the peak plasma concentration [T_{max}] were calculated from the actual plasma data. Rate constant for elimination i.e. k_{el} was calculated by regression analysis of the monoexponential declining line of the log plasma drug concentration versus time graph, while elimination half life ($t_{1/2\text{el}}$) was obtained from the formula $t_{1/2\text{el}} = 0.693/k_{\text{el}}$ (8). Area under the plasma drug concentration versus time curve (AUC_{0-t}) was calculated by the trapezoidal rule. Extension of the AUC data to infinity ($\text{AUC}_{t-\infty}$) was done by dividing the last observed concentration of drug in plasma by the elimination rate constant (k_{el}). $\text{AUC}_{0-\infty}$ was the sum of AUC_{0-t} and $\text{AUC}_{t-\infty}$. The data was statistically analysed by employing the students paired "t" test.

RESULTS

Fig. 1 compares the plasma concentration (mean \pm s.e.m.) of carbamazepine at different time intervals, when given alone or with single dose of Trikatu. In the absorption phase, Trikatu significantly enhanced ($P < 0.05$) the plasma concentration of carbamazepine at 1, 2 and 4 hours after drug administration. However no significant

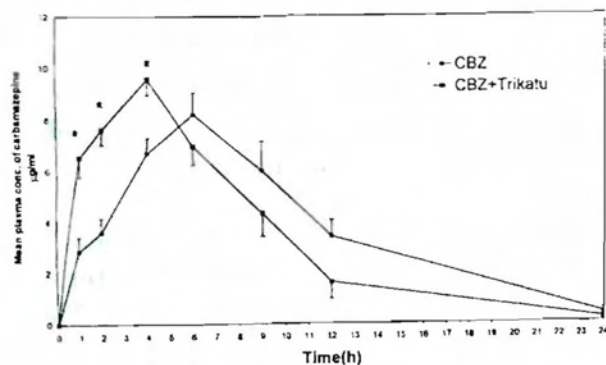


Fig. 1: Mean plasma concentration of carbamazepine (CBZ, 80 mg/kg, p.o) and carbamazepine + Trikatu (500 mg/kg, p.o.) in rabbits (n=10; * = P<0.05).

TABLE I : Carbamazepine kinetics before and after single oral dose of Trikatu.

| Pharmacokinetic parameters | Carbamazepine | Carbamazepine + Trikatu |
|-------------------------------|---------------|-------------------------|
| C_{max} (ug/ml) | 9.38 ± 0.78 | 10.46 ± 0.38 |
| T_{max} (h) | 6.00 ± 0.58 | 3.00 ± 0.42* |
| Kel (h ⁻¹) | 0.22 ± 0.04 | 0.22 ± 0.03 |
| t1/2 el (h) | 3.95 ± 0.54 | 3.75 ± 0.52 |
| AUC ₀₋₂₄ (µg/ml.h) | 92.21 ± 10.45 | 84.84 ± 10.42 |

Values represent mean ± SEM (n=10; *P<0.05)

difference was observed in the elimination phase. Table 1 compares pharmacokinetic parameters (mean ± s.e.m.) of carbamazepine before and after single oral dose of Trikatu. T_{max} in the Trikatu + carbamazepine group was significantly lower (P<0.05), while other pharmacokinetic parameters were unaltered. Figure 2 compares the plasma concentrations (mean ± s.e.m.) of carbamazepine at different time intervals before and after multiple doses of Trikatu. In the absorption phase, the mean plasma concentrations of carbamazepine after Trikatu treatment were significantly higher at 1 and 4 hours. Table II compares various

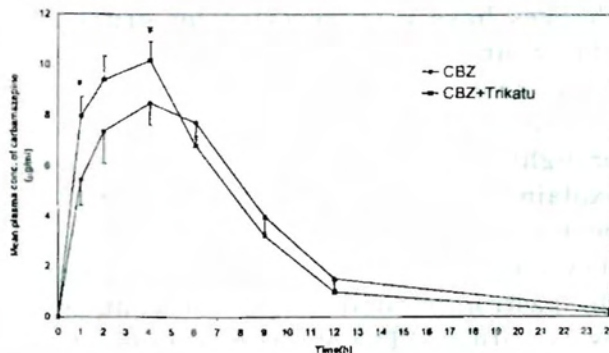


Fig. 2: Mean plasma concentration of carbamazepine (CBZ, 80 mg/kg, p.o) before and after multiple doses of Trikatu (500 mg/kg, p.o.) in rabbits (n=6; * = P<0.05).

pharmacokinetic parameters (mean ± s.e.m.) of carbamazepine before and after multiple doses of Trikatu. No significant difference was observed in any of the pharmacokinetic parameters calculated.

TABLE II : Carbamazepine kinetics before and after multiple oral doses of Trikatu.

| Pharmacokinetic parameters | Carbamazepine | Carbamazepine + Trikatu |
|-------------------------------|---------------|-------------------------|
| C_{max} (ug/ml) | 9.67 ± 0.69 | 10.61 ± 0.73 |
| T_{max} (h) | 4.00 ± 0.73 | 3.67 ± 0.61 |
| Kel (h ⁻¹) | 0.22 ± 0.03 | 0.27 ± 0.03 |
| t1/2 el (h) | 3.54 ± 0.58 | 2.83 ± 0.37 |
| AUC ₀₋₂₄ (ug/ml.h) | 78.78 ± 7.61 | 73.77 ± 6.25 |

Values represent mean ± SEM (n=6)

DISCUSSION

In the present study, coadministration of single dose of Trikatu significantly enhanced the rate of absorption of carbamazepine. This is evident by, significantly high plasma levels in the absorption phase and a shorter T_{max} in the Trikatu group. Similar pharmacokinetic

changes have been reported for drugs like phenytoin, propranolol and theophylline, when given along with piperine. However the increase in the rate of absorption brought about by piperine has not been explained so far (2, 3). We believe it could be because of increased splanchnic blood flow and rate of transport of drugs across the gastrointestinal mucous brought about by Trikatu (9). The other important actions of Trikatu on the gastrointestinal tract include its ability to increase the gastric pH and delay the gastric emptying (9). However carbamazepine is a highly lipophilic, neutral compound and does not ionize in an aqueous environment (10). Thus the latter two effects of Trikatu on the gastrointestinal tract probably did not contribute to the enhanced absorption of carbamazepine. The metabolism of carbamazepine follows first order kinetics, which explains the steep fall in plasma carbamazepine levels during the elimination phase in the Trikatu treated group.

The shortening of the T_{max} by multiple doses of Trikatu was not statistically significant. This could be attributed to a smaller sample size ($n=6$) as compared to the single dose study ($n=10$).

The results further show that single dose of Trikatu did not significantly alter the $AUC_{0-\infty}$ and $t_{1/2}$ of carbamazepine. These findings do not correspond with the reported bioavailability enhancing action of Trikatu. One possible inference is that the cytochrome P-450 isoenzymes involved in carbamazepine metabolism may have a low or no affinity for piperine. It is also possible that the isoenzymes responsible for the metabolism of carbamazepine in rabbits may have different substrate specificities (11).

To conclude, the steeper rise and fall in the plasma levels of carbamazepine along with no change in the $AUC_{0-\infty}$ and $t_{1/2}$ brought about by Trikatu co-administration, has no significant advantage.

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