Effect of Septilin – A Herbal Preparation on Pharmacokinetics of Carbamazepine in Rabbits

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ABSTRACT
The study was carried out in rabbits, to see the effect of Septilin, a herbal preparation on the single and multiple dose kinetics of carbamazepine. Single dose treatment of Septilin significantly decreased $t_{1/2a}$, $t_{1/2e}$, AUC$_{0-\alpha}$ of carbamazepine. Steady state C$_{\text{max}}$ and AUC$_{0-24}$ of carbamazepine also reduced significantly in comparison to those of control rabbits after 7 days coadministration of Septilin. We can be conclude that Septilin decrease/hinder the absorption process of carbamazepine through an unknown mechanism.

Keywords: Septilin; carbamazepine; pharmacokinetic interaction.

INTRODUCTION
In India, it is common for patients to take herbal remedies simultaneously with modern drug remedies and often without the knowledge of treating physician. It has long been suspected that there might be interaction between herbal remedies and modern drugs. *Piper longum* has been shown to enhance the absorption of drugs (1), a multiherbal preparation Liv.52 has effect on the absorption and metabolism of ethanol (2). Septilin (The Himalaya Drug Co., Bangalore, India) is a multi-herbal preparation reported to possess antibacterial and anti-inflammatory principles and is commonly used in the treatment of upper respiratory infections. Recently Shekher et al. (3) have reported enhanced metabolism of phenytoin by Septilin.

Carbamazepine (CBZ), a narrow therapeutic range drug is considered to be first choice drug, for the treatment of partial and tonic-clonic seizures (4). It is absorbed slowly after oral administration, with peak concentration around 4 hours after oral dose. Mean systemic availability is approximately 90% (5). Carbamazepine is metabolized primarily in the liver by cytochrome P450 (CYP450) isozyme 3A4 to carbamazepine-10, 11-epoxide (6). The drug is given for a long period to epileptic patients and during the course of treatment with CBZ the patient may take herbal remedies for other ailments.

We investigated the influence of Septilin on the pharmacokinetics of CBZ in rabbits.

METHODS
The study was carried out in healthy male rabbits weighing between 1.5 to 2.5 kg. The rabbits were kept in isolation for at least 21 days prior to experimentation, under standard animal house conditions i.e. 12-hour day-night cycle and room temperature of 25 ± 2°C. The animals
were allowed water *ad libitum* and pellet diet (Him Agro Industries). The study was carried out in three different groups of rabbits as follows:

**Group I: Effect of Septilin on single dose kinetics of CBZ:**
The study was carried out in healthy male rabbits using randomized, cross-over design. After overnight fast, each animal was administered CBZ (80 mg/kg, p.o.) with water (4 ml/kg) at 0800 hours using soft orogastric tube. Blood samples (1 ml each) were collected at 0, 0.5, 1, 2, 4, 6, 9 and 12 hours after the CBZ administration through marginal vein in heparinized tubes.

After a wash out period of 7 days, CBZ was administered at a dose of 80 mg/kg, p.o. along with Septilin syrup (4 ml/kg). Blood samples were collected at similar time intervals as above. The plasma was separated and stored at −20°C until assayed for CBZ using HPLC technique (7). The assay sensitivity was 0.05 µg/ml and the intra-assay coefficient of variation at all the levels were between 2.7 to 5.2%.

**Group II: Effect of Septilin on multiple dose kinetics of CBZ:**
In 16 healthy male rabbits, CBZ (80 mg/kg/day p.o.) was administered with water (4 ml/kg/day) at 0800 hours for 7 consecutive days. On day 7 after drug administration 1 ml blood samples were drawn at 0, 1, 2, 3, 4, 5, 6, 9, 12 and 24 hours and plasma was separated and stored at −20°C. The animals of this group were divided into two subgroups consisting of 8 rabbits in each subgroup. In subgroup I, CBZ along with water was continued at a dose of 80 mg/kg/day orally for another 7 days, while in subgroup II, CBZ (80 mg/kg/day, p.o.) was continued alongwith Septilin syrup (4 ml/kg/day, p.o.) for 7 consecutive days. On day 7 from each rabbit, in both subgroups, 1 ml blood samples were collected in heparinized tubes at 0, 1, 2, 3, 4, 5, 6, 9, 12 and 24 hours after drug intake. Plasma was separated and samples stored at −20°C until assayed for CBZ.

**Group III: Effect of multiple dose Septilin on single dose kinetic of CBZ:**
In healthy male rabbits after overnight fast, CBZ (80 mg/kg/day, p.o.) was administered with water (4 ml/kg/day) at 0800 hours. Blood samples (1 ml each) were collected at 0, 0.5, 1, 2, 4, 6, 9 and 12 hours after CBZ administration from day 2 the animals were administered Septilin at a dose of 4 ml/kg/day for 7 consecutive day. On day 8, Septilin (4 ml/kg) was given along with CBZ (80 mg/kg) at 0800 hours and blood samples were drawn at similar time interval as mentioned above through marginal vein in heparinized tubes. The plasma was separated and stored at −20°C until assayed for CBZ.

Steady state peak plasma concentration (C\text{ss}^{\text{max}}) and steady state through plasma concentration (C\text{ss}^{\text{min}}) and also C_{\text{max}} and T_{\text{max}} for single dose study were calculated from actual plasma data of each rabbit. The area under the time-plasma concentration curve (AUC\text{0-}\text{t}) was calculated by Trapezoidal Rule. Elimination half-life (t 1/2e) and absorption half-life (t 1/2a) of CBZ were calculated by least square regression analysis and by residual method respectively.
Student’s paired ‘t’ test was applied to find the level of significance. $p<0.05$ was considered statistically significant.

**RESULTS**

Figure 1 depicts the effect of single dose of Septilin on plasma CBZ levels at different time intervals, after a single oral dose of CBZ. The plasma CBZ levels were decreased at all time points by Septilin as compared to control group. The fall in plasma CBZ levels were however not statistically significant except at 9 and 12 hours.

Table 1 shows the pharmacokinetic data of CBZ before and after single oral dose of Septilin. No significant difference was observed in $C_{\text{max}}$ and $T_{\text{max}}$ of CBZ when coadministered with Septilin, while $t_{1/2a}$, $t_{1/2e}$ and $\text{AUC}_{0-\alpha}$ of CBZ were significantly decreased with Septilin.

Figure 2 depicts the steady state plasma CBZ levels (Mean ± SEM) at different time intervals after administration of CBZ alone for 7 and 14 days and also the effect of Septilin coadministration of Septilin decreases the plasma CBZ levels throughout the time period under study i.e. 0 to 24 hours, the CBZ levels were significantly low at 1, 2, 3, 4 and 6 hours. No significant difference was observed in CBZ levels between 7 and 14 days CBZ treatment alone.

Table 2 shows the pharmacokinetic data of 7 and 14 days treatment with CBZ alone and also after 7 days of Septilin treatment. The steady state $C_{\text{ss max}}$ and $\text{AUC}_{0-24}$ of CBZ were reduced significantly steady state $C_{\text{ss min}}$ was increased following 7 days Septilin treatment. No significant difference was observed in any of the pharmacokinetic parameters between 7 and 14 days CBZ treatment.
Table 2: Pharmacokinetics of steady state carbamazepine (80 mg/kg/day) before and after multiple dose administration of Septilin (4 ml/kg/day) n=8; Mean ± SEM

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Carbamazepine (7 d)</th>
<th>Carbamazepine (14 d)</th>
<th>Carbamazepine (14 d) + Septilin (7 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{ss_{max}}$ (µg/ml)</td>
<td>6.16 ± 0.68</td>
<td>6.13 ± 0.69</td>
<td>3.81 ± 0.50</td>
</tr>
<tr>
<td>$T_{ss_{max}}$ (h)</td>
<td>3.88 ± 0.40</td>
<td>4.02 ± 0.49</td>
<td>6.00 ± 0.00*</td>
</tr>
<tr>
<td>$C_{ss_{min}}$ (µg/ml)</td>
<td>0.62 ± 0.18</td>
<td>0.65 ± 0.23</td>
<td>1.05 ± 0.21</td>
</tr>
<tr>
<td>AUC$_{0-24}$ (µg/ml/h)</td>
<td>41.69 ±4.23</td>
<td>40.86 ± 4.12</td>
<td>27.18 ± 2.94*</td>
</tr>
</tbody>
</table>

* $p<0.05$

Table 3 depicts the mean plasma CBZ levels at different time intervals before and after 7 days treatment with Septilin. The plasma CBZ levels were decreased at all time points after 7 days Septilin treatment, as compared to CBZ alone treated animals. However, the difference was not statistically significant. The decrease in plasma levels were higher during absorption phase as compared to elimination phase.

Table 3: Plasma CBZ levels (µg/ml) at different time intervals before and after 7 days Septilin treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>2.35</td>
<td>4.49</td>
<td>7.61</td>
<td>11.25</td>
<td>7.99</td>
<td>3.21</td>
<td>1.14</td>
</tr>
<tr>
<td>Septilin</td>
<td>± 0.77</td>
<td>± 1.00</td>
<td>± 2.05</td>
<td>± 1.14</td>
<td>± 0.99</td>
<td>± 0.75</td>
<td>± 0.41</td>
</tr>
<tr>
<td>After</td>
<td>1.58</td>
<td>2.69</td>
<td>4.82</td>
<td>9.30</td>
<td>7.88</td>
<td>2.74</td>
<td>0.52</td>
</tr>
<tr>
<td>Septilin</td>
<td>± 0.47</td>
<td>± 0.34</td>
<td>± 0.99</td>
<td>± 1.30</td>
<td>± 1.25</td>
<td>± 0.55</td>
<td>± 0.20</td>
</tr>
</tbody>
</table>

Values are Mean ± SEM; n=6.

Table 4 shows the pharmacokinetic parameters before and after Septilin treatment. No significant difference was observed in any of the pharmacokinetic parameters of CBZ. However, $C_{max}$ was decreased and $T_{max}$ was prolonged after Septilin treatment.
DISCUSSION
The results of single dose study have shown lower plasma CBZ levels after Septilin administration. The decrease in CBZ plasma levels during absorption phase was not statistically significant but in the elimination phase the CBZ levels were significantly decreased at 9 and 12 hours. This finding was further supported by decreased $C_{\text{max}}$, $AUC_{0-\alpha}$, $t_{1/2a}$ and shorter $t_{1/2e}$ of CBZ by Septilin.

In multiple dose studies when CBZ was coadministered with Septilin for 7 days, the plasma CBZ levels decreased and were significantly lower during absorption phase. This decreased CBZ plasma levels could be due to change in gastric emptying time and/or intestinal transit time and/or induction of CYP3A enzymes in the gut wall of the small intestine by Septilin. It is known that CYP3A enzymes, responsible for the metabolism of CBZ are present in both liver and enterocytes of the gut wall (8). The decreased plasma CBZ levels during first 6 hours was supported by the fact that CBZ steady state $T_{\text{max}}$ was prolonged, $C_{\text{max}}$ was decreased by about 62% and $AUC_{0-24}$ was decreased approximately 65% by Septilin. In multiple dose sub-group, when CBZ only was continued for 14 days without Septilin, the plasma CBZ levels remain unaltered when compared with 7 days CBZ treatment, ruling out the possible autoinduction of CBZ as the probable cause of decreased CBZ levels with Septilin.

Seven days treatment with Septilin decreased the CBZ plasma levels during absorption phase and not in elimination phase, though the decrease was not statistically significant.

From these findings, it appeals that, Septilin decreases the absorption of CBZ either by affecting the gastric emptying time and/or intestinal transit time or by some hitherto unknown mechanism.

REFERENCES


