PHARMACOKINETICS OF PHENYTOIN: UNALTERED BY ENALAPRIL AND AMLODIPINE IN RHESUS MONKEYS

D. K. BADYAL, S. K. GARG*, V. K. BHARGAVA AND S. MAJUMDAR†

Departments of Pharmacology and Experimental Medicine†,
Post Graduate Institute of Medical Education and Research,
Chandigarh - 160 012

(Received on September 28, 1998)

Abstract: A cross over single and multiple dose study was carried out to find out pharmacokinetic interactions between diphenylhydantoin (DPH) (35 mg/kg, po) and antihypertensives enalapril (1.6 mg/kg; po) and amlodipine (0.4 mg/kg, po) in rhesus monkeys. Neither the plasma concentrations nor the pharmacokinetic parameters of DPH were altered by coadministration of enalapril or amlodipine, suggesting that enalapril and amlodipine can be safely administered to epileptic patients receiving phenytoin.

Key words: phenytoin enalapril amlodipine interaction rhesus monkey

INTRODUCTION

Hypertension and epilepsy are generally independent disorders but may sometimes co-exist in the same patient (1, 2). Both ailments require long term treatment.

Enalapril, an angiotensin converting enzyme (ACE) inhibitor is converted to its active moiety in the liver (3). Amlodipine is a dihydropyridine calcium channel blocker and metabolized in the liver by cytochrome P450 (CYP450) enzymes (4). Phenytoin, a drug of first choice for single drug therapy of partial, generalised tonic-clonic seizures or both (5), has been frequently implicated in clinically significant drug interactions because of its narrow therapeutic index, slow absorption and saturable kinetics (6, 7, 8, 9). The acceptable therapeutic plasma concentration ranges between 10-20 mg/L (7).

Interactions between antihypertensives and anticonvulsants may lead to increase in their adverse effects or loss of control over the disorder. Hence, the present study was designed to evaluate the effect of enalapril and amlodipine on the pharmacokinetics of phenytoin in rhesus monkeys (Macaca mulatta).

METHODS

Twenty four healthy adult male rhesus monkeys (Macaca mulatta) weighing between 4 to 7 kg were divided into four groups consisting of six monkeys in each group. The study design was cross over for each group.

*Corresponding Author
**Group I:** After overnight fast monkeys were given DPH (35mg/kg;po) through intragastric tube at 0800 h. Blood samples (2mL) were drawn from small saphenous vein in heparinised tubes at 0,0.5, 1,2,3,6,9,12,24 and 48 h after drug administration. After a wash out period of 10 days, DPH was administered along with enalapril (1.6 mg/kg; p.o.) at 0800 h. Blood samples were drawn at similar time intervals as described earlier.

**Group II:** Six overnight fasted monkeys were treated with DPH (35mg/kg;po) at 0800h and after 10 days of wash out period, they were treated with DPH along with amlodipine (0.4mg/kg;p.o.). Blood samples (2mL) were drawn at both the occasions i.e. before and after amlodipine treatment at similar time intervals as that of group I animals.

**Group III:** Six monkeys received DPH (35mg/kg/day;po) at 0800 h for consecutive 14 days. Blood samples (2mL) were drawn at 0,0.5,1,2,3,6,9,12 and 24 hours on day 1,7and 14 after drug administration.

**Group IV:** Six monkey received DPH (35mg/kg/day;po)-at 0800 h for consecutive seven days. Blood samples (2mL) were drawn at 0,0.5,1,2,3,6,9,12 and 24 hours on day 7 after drug administration. DPH was continued for another seven days along with enalapril (1.6mg/kg/day; p.o.). Blood samples were drawn as before on day 14. After a wash out period of 15 days, the monkeys were treated with DPH along with amlodipine (0.4mg/kg/day, p.o.) for consecutive seven days. Blood samples were drawn at similar time intervals on day 7 after drug administration.

**Analytical methods:** Plasma was separated from blood samples and stored at -20°C until assayed for DPH using HPLC technique (10). Recovery of DPH from plasma samples was >90% and sensitivity of the method was 0.01 µg/mL. The intraassay and interassay coefficient of variation for DPH at different concentrations were 9.51% and 8.71% respectively.

**Pharmacokinetic Parameters:** Single dose and steady Peak plasma concentration (Cmax) and time to reach peak plasma concentration (Tmax) were calculated from the actual plasma data. Absorption half-life (t1/2 a) and elimination half-life (t1/2 e) were calculated by the residual method and by least square regression analysis method respectively. Area under the plasma concentration-time curve AUC0-t was calculated by trapezoidal rule. Extension of the AUC data to infinity AUCt- was done by dividing the last observed concentration of the drug in plasma by the elimination rate constant (Kel). AUC0- was sum of the AUC0-t and AUCt-.

**Statistical analysis:** To find out level of significance student's paired t test was applied and P value <0.05 was considered as statistically significant.

**RESULTS**

**Group I:** Table I illustrates the pharmacokinetic parameters of DPH before and after single dose of enalapril. No significant difference was observed in any of the parameters. The DPH levels could be detected upto 96h.

There was no significant difference in the plasma concentrations of DPH at any
TABLE I: Pharmacokinetics of DPH before and after single oral dose of enalapril in rhesus monkeys (n=6).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DPH alone</th>
<th>DPH + Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>8.33±1.36</td>
<td>8.50±0.92</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</td>
<td>14.58±2.16</td>
<td>16.03±1.30</td>
</tr>
<tr>
<td>t½ a (h)</td>
<td>2.20±0.42</td>
<td>2.46±0.40</td>
</tr>
<tr>
<td>t½ e (h)</td>
<td>20.84±2.62</td>
<td>21.26±6.86</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→&lt;infty&lt;/sub&gt; (µg·h/mL)</td>
<td>468.24±84.25</td>
<td>618.35±151.77</td>
</tr>
</tbody>
</table>

Values represent Mean ± SEM

TABLE II: Pharmacokinetics of DPH before and after single oral dose of amlodipine in rhesus monkeys (n=6).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DPH alone</th>
<th>DPH + Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>9.50±0.92</td>
<td>11.00±2.76</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</td>
<td>17.82±2.19</td>
<td>19.60±2.40</td>
</tr>
<tr>
<td>t½ a (h)</td>
<td>2.94±0.41</td>
<td>3.19±0.79</td>
</tr>
<tr>
<td>t½ e (h)</td>
<td>13.63±1.64</td>
<td>11.87±1.62</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→&lt;infty&lt;/sub&gt; (µg·h/mL)</td>
<td>600.12±94.13</td>
<td>550.58±76.87</td>
</tr>
</tbody>
</table>

Values represent Mean ± SEM

time point before and after single dose of amlodipine. Table II compares the various pharmacokinetic parameters of DPH before and after single oral dose of amlodipine revealing no significant difference in any of the parameters. The DPH levels could be detected upto 72h.

The DPH levels were significantly decreased in elimination phase after 7 days and 14 days treatment as compared to single dose treatment with DPH. But no significant difference was observed in DPH levels between 7 days and 14 days treatment with DPH alone.

After multiple doses of oral enalapril or amlodipine the DPH plasma levels were lower in monkeys treated with DPH along with enalapril as compared to DPH alone, but the decrease in plasma levels was not statistically significant. No significant difference was observed in steady state DPH plasma levels before and after multiple oral doses of amlodipine at any time point. Table III shows no significant difference in various pharmacokinetic parameters of DPH before and after multiple oral doses of enalapril or amlodipine.

TABLE III: Pharmacokinetics of DPH before and after multiple oral dose of enalapril or amlodipine in rhesus monkeys.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DPH alone</th>
<th>DPH + Enalapril</th>
<th>DPH + Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>4.67±1.14</td>
<td>3.17±0.60</td>
<td>3.50±0.87</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</td>
<td>14.65±3.13</td>
<td>11.18±1.14</td>
<td>11.07±1.74</td>
</tr>
<tr>
<td>t½ a (h)</td>
<td>1.20±0.36</td>
<td>1.02±0.22</td>
<td>1.20±0.29</td>
</tr>
<tr>
<td>t½ e (h)</td>
<td>11.19±4.50</td>
<td>11.04±2.35</td>
<td>11.83±3.62</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→&lt;infty&lt;/sub&gt; (µg·h/mL)</td>
<td>222.95±70.98</td>
<td>158.48±29.41</td>
<td>155.79±44.23</td>
</tr>
</tbody>
</table>

Values represent Mean ± SEM

DISCUSSION

Phenytoin is one of the most widely prescribed anticonvulsants. Drug interactions of DPH are important because of alterations in its efficacy and risk of toxicity.

In the present study enalapril and amlodipine did not influence the overall pharmacokinetics of DPH absorption or elimination. The lack of pharmacokinetic
interaction between these drugs may be due to their different metabolic pathways. While enalapril is mainly deesterified by carboxyesterases in the liver (3), amlodipine and phenytoin mainly undergo oxidation by CYP450 isozymes 3A4 and 2C9/2C19 respectively (4, 9).

These results suggest that enalapril and amlodipine can be safely administered to epileptic patients receiving DPH. However the species variation may affect hepatic expression of different CYP450 isozymes (11), so the present findings need further confirmation in epileptic patients.

REFERENCES


