INTERACTION OF PARGYLINE WITH TOLBUTAMIDE IN RABBITS

S. SATYANARAYANA*, D. MURALI KRISHNA, Y.S.R. KRISHNAIAH AND D. VISWESWARA

Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam - 530 003

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Abstract: Acute treatment of rabbits with pargyline (50 mg/kg, ip, 30 min before tolbutamide) significantly increased the elimination half life and AUC of tolbutamide resulting in prolonged hypoglycaemia. Similar treatment also prolonged the half life of antipyrine which is used as model drug to indicate hepatic microsomal enzyme activity in vivo confirming that pargyline treatment delayed the elimination of tolbutamide in rabbits by inhibiting its hepatic metabolism.

Key words: tolbutamide pargyline antipyrine pharmacokinetics interaction

INTRODUCTION

The antidepressants of monoamine oxidase inhibitor (MAOI) type are reported to interact with food (1) and drugs (2-7) and are shown to inhibit liver microsomal enzymes in in vitro studies (8-10). Hence the influence of pargyline (MAOI) on pharmacokinetics and hypoglycaemic action of tolbutamide (which is metabolized by liver microsomal enzymes) was studied in rabbits to find the in vivo relevance of the possible interaction. The influence of pargyline on antipyrine pharmacokinetics was also studied to provide evidence for inhibition of hepatic drug metabolism.

METHODS

Albino rabbits of either sex weighing between 1.5 to 2.2 kg were divided into two groups. A group of five rabbits was fasted for 18 hours and blood samples were withdrawn for initial blood glucose estimation. Tolbutamide (as a suspension in 2% gum acacia) was administered (40 mg/kg) orally. Blood samples were withdrawn thereafter at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 18, and 24 hrs. After a washout period of two weeks, the same group of animals were treated with 50 mg/kg of pargyline hydrochloride (Sigma Chemicals, U.S.A) intraperitoneally. After 30 min, tolbutamide was administered (40 mg/kg) orally and blood samples were collected at the same time intervals as before and stored at -20°C until analysis. Blood tolbutamide concentration (11) and blood sugar (12) were estimated.

Another group of five rabbits were administered antipyrine (Wilson Laboratories, Bombay) intravenously (50 mg/kg) and blood samples were collected at 0.25, 0.5, 1, 2, 3, and 4 hrs. After a washout period of two weeks, the same animals were treated with pargyline hydrochloride (50 mg/kg, ip). After 30 min antipyrine was administered and blood samples were collected at similar time intervals as before and kept in a refrigerator until analysis (13).

*Corresponding Author
Data analysis: The pharmacokinetic parameters listed in Table I were calculated following one compartment open model using standard formulae (14, 15) assuming complete absorption of tolbutamide. The hypoglycaemic activity (percent blood glucose reduction) of tolbutamide at different time intervals was calculated with respect to the initial blood glucose.

Student's paired t-test was applied to find the significant difference in the mean values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tolbutamide Before treatment</th>
<th>Tolbutamide After treatment</th>
<th>Antipyrine Before treatment</th>
<th>Antipyrine After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co (μg/ml)</td>
<td>143.6±4.7</td>
<td>131.3±2.9*</td>
<td>59.4±2.5</td>
<td>61.1±2.8</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>0.65±0.07</td>
<td>0.62±0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kel (h⁻¹)</td>
<td>0.09±0.004</td>
<td>0.05±0.004***</td>
<td>0.49±0.045</td>
<td>0.28±0.01**</td>
</tr>
<tr>
<td>t¹/₂ (h)</td>
<td>7.56±0.37</td>
<td>13.21±0.89***</td>
<td>1.4±0.1</td>
<td>2.5±0.05***</td>
</tr>
<tr>
<td>AUC₀→∞*</td>
<td>1376±47</td>
<td>2329±159**</td>
<td>124±9</td>
<td>223±13***</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.60±0.26</td>
<td>4.47±0.35*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>102.8±2.1</td>
<td>103.5±2.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vd (mL)</td>
<td>458±19</td>
<td>490±27</td>
<td>1607±114</td>
<td>1534±58</td>
</tr>
<tr>
<td>CL (mL/h)</td>
<td>42±2</td>
<td>26±5***</td>
<td>780±32</td>
<td>432±15***</td>
</tr>
</tbody>
</table>

* AUC₀→∞ = μg. h/ml;  **P < 0.05;  ***P < 0.001

RESULTS AND DISCUSSION

The mean pharmacokinetic parameters of tolbutamide in rabbits before and after single dose treatment with pargyline are shown in Table I. Area under the curve from 0 to ∞ hours (AUC₀→∞), elimination half-life (t¹/₂) and the time to reach peak blood concentration of drug (Tmax) were increased significantly, whereas elimination rate constant (Kel) and clearance (CL) were decreased significantly after single dose pargyline treatment. Other parameters like absorption rate constant (Ka), maximum blood concentration of drug (Cmax) and volume of distribution (Vd) were altered marginally.

The mean pharmacokinetic parameters of antipyrine in rabbits before and after single dose treatment with pargyline are shown in Table I. Pargyline treatment significantly (P < 0.01) decreased Kel and CL while AUC₀→∞ and t¹/₂ were increased significantly (P < 0.01). Vd and Co (blood concentration at time zero) are not altered significantly.

Pargyline treatment did neither alter fasting glucose level nor the hypoglycaemic activity of tolbutamide up to 4 hrs. But after 4 hrs, the hypoglycaemic activity of tolbutamide was significantly higher (Fig. 1).

Pargyline had no influence on oral absorption and distribution of tolbutamide in rabbits. However, the drug delayed the elimination of tolbutamide. Since tolbutamide is metabolized almost completely (about 98%) as hydroxytolbutamide in liver microsomes and part of it is subsequently converted to carboxy­tolbutamide by cytosol enzymes, the delay in the elimination might be due to the inhibition of its hepatic metabolism. The prolonged t¹/₂ of iv administered antipyrine (a model drug for assessing the hepatic drug metabolizing enzyme activity in vivo) in rabbits in the presence of pargyline also confirmed the same.
Interaction of Pargyline with Tolbutamide

MAO inhibitors including pargyline are reported to inhibit cytochrome P<sub>450</sub> dependent hydroxylations of several substances including antipyrine in rat liver microsomes (8). Pargyline treatment (75 mg/kg, ip) for 3, 7 and 14 days in rats reduces hepatic microsomal ethylmorphine N-demethylase activity and cytochrome P<sub>450</sub> content in isolated liver microsomes whereas 15 mg/kg has no effect (9). MAO inhibitors also inhibit oxidation of several substrates by rat liver microsomes by binding to cytochrome P<sub>450</sub> (9). By a similar mechanism pargyline might have retarded the metabolism of tolbutamide and antipyrine in rabbits. The prolongation of its half life and elevated blood levels of tolbutamide in the elimination phase could result in its prolonged hypoglycaemic activity.

The enzyme inhibitory effect of pargyline seems to be nonspecific since it inhibited the hepatic microsomal enzymes in addition to MAO which is a nonmicrosomal enzyme. The interaction of other MAO inhibitors with tolbutamide needs to be studied further.

REFERENCES