Gemfibrozil was used frequently in clinical practice to lower plasma triglyceride levels, and was found to increase plasma HDL-C levels. However, a clinical trial conducted for 6 months, however, showed no benefit from the drug, and treatment was stopped.

Figure 1. Human hepatic biotransformation of repaglinide

Table 1. Plasma pharmacokinetic parameters for male Sprague-Dawley control and gemfibrozil-treated rats (n = 3/group) dosed once orally with 1 mg/kg repaglinide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control rats</th>
<th>Gemfibrozil-treated rats</th>
<th>Percentage change with gemfibrozil treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng mL⁻¹)</td>
<td>66.2 ± 8.9</td>
<td>284 ± 85</td>
<td>+339% (3.0 fold increase)</td>
</tr>
<tr>
<td>AUC₀-₅₀ (ng mL⁻¹ min⁻¹)</td>
<td>12.7 ± 2.7</td>
<td>447 ± 31</td>
<td>+251% (3.5 fold increase)</td>
</tr>
<tr>
<td>AUC₀-₅₀ (ng mL⁻¹ min⁻¹)</td>
<td>243 ± 33</td>
<td>954 ± 24</td>
<td>+251% (3.5 fold increase)</td>
</tr>
<tr>
<td>Vdₑ (L/kg)</td>
<td>282 ± 44</td>
<td>130 ± 23</td>
<td>-49%</td>
</tr>
<tr>
<td>Kₑ (h⁻¹)</td>
<td>1320 ± 2480</td>
<td>5160 ± 3400</td>
<td>-61%</td>
</tr>
<tr>
<td>t₁/₂ (h)</td>
<td>2.6 ± 0.8</td>
<td>2.6 ± 0.8</td>
<td>No significant change</td>
</tr>
</tbody>
</table>

In vitro experiments with the control and gemfibrozil-treated rat liver microsomes revealed negligible repaglinide clearance differences in microsomes from control and gemfibrozil-treated rats (Figure 5). Even when a pre-incubation period with gemfibrozil or gemfibrozil glucuronide as potential cytochrome P450 or UGT inhibitors was incorporated into the experiment, little alteration in repaglinide clearance was observed in either treatment group. The results did not support a change in drug metabolizing enzyme activity or in microsomal clearance of repaglinide as a direct result of gemfibrozil therapy.

Conclusions

- Gemfibrozil treatment altered the repaglinide pharmacokinetic profile in rats, significantly increasing repaglinide exposure.
- Gemfibrozil treatment resulted in a vectorial shift in repaglinide elimination pathways with increased urinary excretion of repaglinide and its metabolites.
- The drug-metabolizing enzyme activities observed do not account for the repaglinide exposure or elimination alterations caused by gemfibrozil treatment.
- The PK and altered excretion profile are consistent with hepatic transporter inhibition as the predominant cause of the gemfibrozil/repaglinide interaction in the rats.

References