Exploring the Drug-Drug Interaction Between Gemfibrozil and Repaglinide in Rats: Metabolism and Transport

Joanna E. Barbara, Seema Muranjan, Forrest Stanley, Chandra Kollu, Sylvia Kandel, Clayton J. Otwell, and David B. Buckley

XenoTech, LLC, 16825 W 116th St, Lenexa, KS, USA

Introduction

Gemfibrozil treatment greatly altered repaglinide clearance in rats (Figure 2). Table 1. Gemfibrozil-treated rats exhibited a 4.4-fold higher repaglinide Cmax and a 3.5-fold greater AUC0-∞ than control rats, but the l12 (1.2 and 1.7 h) and l2 (2.5 h) values were similar between treatment groups. The observed plasma clearance and volume of distribution were both approximately 60% lower in gemfibrozil-treated rats than control rats.

Figure 1. Human hepatic biotransformation of repaglinide

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 treatment.

Results

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 2. Enzyme activities in pooled liver microsomes from male Sprague-Dawley control and gemfibrozil-treated rats (n = 3/group) dosed once orally with 1 mg/kg repaglinide

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 activity differences observed do not account for the repaglinide exposure or elimination alterations caused by gemfibrozil treatment. The PK data and altered excretion profile are consistent with hepatic transporter inhibition as the predominant cause of the gemfibrozil/repaglinide interaction in the rats.

References


