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Induction of P450 3A1/2 and 2C6 by gemfibrozil in Sprague-Dawley rats

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Abstract:
Fibrates are a group of peroxisome proliferator-activated receptor α agonists used in the treatment of dyslipidemia; however, they have been reported to cause species-related hepatocarcinogenesis and clinical myotoxicity. Gemfibrozil is one of the most commonly used fibrates, and it shows the highest risk for myotoxicity among the fibrates. The inhibitory drug-drug interaction mechanism associated with gemfibrozil has been explored recently, and the induction of human P450 3A4 and 2C8 has been reported. In this study, *in vivo* induction of rat P450 by gemfibrozil was studied in Sprague-Dawley rats. After the rats were dosed with gemfibrozil by oral gavage, microsomes were prepared. The metabolic activities of P450 3A1/2, 2C6, and 2D2 were assayed using probe substrates, and the systemic concentration of gemfibrozil during its administration was determined. P450 3A1/2 and 2C6 activities were induced 32–77% in the rats by gemfibrozil when the exposure concentration was in the clinical range. These data indicate that the inducibility of homologous P450 isoforms by gemfibrozil is similar in Sprague-Dawley rats and in humans. Inductive drug-drug interactions and inhibitory actions are involved in the co-administration of gemfibrozil with other drugs, which suggests the relevance for a fibrate-toxicology investigation.

Key words:
induction, rat, P450, gemfibrozil