3936817PYPM/M : MAJOR: PHARMACOLOGY; M.Sc. in Pharm.(Pharmacoloogy)
KEY WORDS : GEMFIBROZIL / FLUVASTATIN / HEPATOMEGALY / FACO PEROXISOME PROLIFERATION/CREATINE PHOSPHOKINASE / CATALASE / CYTOCHROME P-450 / TRANSAMINASE
TULAYA POTAROS : THE EFFECT OF FLUVASTATIN ON HEPATOTOXICITY OF GEMFIBROZIL IN WISTAR RATS. THESIS ADVISORS : SRICHAN PHORNCHIRASILP, Ph.D., ORAPHAN P. MATANGKASOMBUT, Ph.D., WICHET LEELAMANIT, Ph.D., URUSA INTRASUKSRI, Ph.D., 136 p.
ISBN 974-662-056-8

Gemfibrozil has been widely used to treat hypertriglyceridemia. However,there is evidence indicating that gemfibrozil induces hepatomegaly and hepatic peroxisomal enzymes in rodents. Fluvastatin is a new antihypercholesterolemic drug which has no effect on microsomal and peroxisomal enzymes. In this experiment, the effect of fluvastatin combined with gemfibrozil on plasma lipid parameters, liver mixed function oxidase and peroxisomal marker enzymes in male Wistar rats was studied and compared with gemfibrozil alone. Rats were orally administered gemfibrozil (200 mg/kg twice a day) alone, or in combination with fluvastatin (2.5, 5, and 10 mg/kg/day) for 4 weeks. Fluvastatin at 5 mg/kg/day increased both the cholesterol and triglyceride-lowering effect of gemfibrozil, whereas at 2.5 mg/kg/day increased only the cholesterol-lowering effect. With regard to hepatic effects, fluvastatin did not alter the percentage of liver weight per body weight ratio induced by gemfibrozil. However, it suppressed the effect of gemfibrozil on the total liver protein induction, particularly at the dose of 5 mg/kg/day. Only the 5 mg/kg/day dose of fluvastatin decreased the microsomal protein induction of gemfibrozil. Fluvastatin in this combination also exhibited an inhibitory effect on the elevation of cytochrome P-450 level-induced by gemfibrozil at the first week. This effect of fluvastatin was found to be dose-dependent. The effects on peroxisomal enzymes (catalase and fatty acyl CoA oxidase, FACO) were the same as those obtained on cytochrome P-450. The inductive activity of FACO was decreased after 2 weeks of drug treatment, whereas the induction of catalase activity was reduced after 1 (5mg/kg/day) and 4 (2.5 mg/kg/ day) weeks. Moreover, when gemfibrozil was administered concomittantly with 5 mg/kg/day of fluvastatin, marked increases in the activities of serum transaminase (SGOT,SGPT), and creatine phosphokinase (CPK) were found since the first week of drug treatment. Rats treated with gemfibrozil and fluvastatin 10 mg/kg/day died during the first week with a marked elevations of SGOT,SGPT and CPK activities. The result suggests that even though fluvastatin together with gemfibrozil increased gemfibrozil's serum lipid level reducing ability while, decreasing the microsomal and peroxisomal-inductive effect of gemfibrozil, the combination also increased drug toxicity. Thus, the clinical benefit seems to be low.