P4. THE EFFECT OF FLUVASTATIN ON HEPATOTOXICITY OF GEMFIBROZIL IN WISTAR RATS

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ABSTRACT

Gemfibrozil has been widely used to treat hypertriglyceridemia. But there are evidences indicated that gemfibrozil induced hepatomegaly and hepatic peroxisomal enzymes in rodents. Fluvastatin is a new antihypercholesterolemic drug which has no effect on microsomal and peroxidomal 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 had been 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. The plasma cholesterol-lowering effect of gemfibrozil was obtained after 4 weeks of continuous drug treatment (the cholesterol level is 84.47% of control group). When gemfibrozil was fed in combination with fluvastatin, at doses of 2.5 and 5 mg/kg/day, rats serum cholesterol level could be seen since the fourth and the first week (the cholesterol level are 91.38% and 93.34% of gemfibrozil-treated group). All drug-treated groups exhibited significant hypotriglyceidemic effect at the first week. But only fluvastatin, at dose of 5 mg/kg/day, could potentiate the triglyceridemic-lowering effect of gemfibrozil (the triglyceride level decrease from 86.23% to 81.36%) after 2 weeks of drug treatment. Fluvastatin did not alter the percentage of liver weight per body weight ratio induced by gemfibrazil. But fluvastatin 2.5 mg/kg/day singnificantly decreased the induction effect of gemfibrozil on total liver protein content after 2 weeks of drug treatment (the total protein content is 96.21% of gemfibrozil-treated group). In addition, this dose of fluvastatin also markedly reduced the induction effect of gemfibrozil on microsomal protein content at the fourth week (the microsomal protein content is 96.60% of gemfibrozil-treated group). On the contrary, 5 mg/kg/day dose of fluvastatin could reduce the total liver protein and microsomal protein content induced by gemfibrozil since the first week of drug administration. Fluvastatin in this combination also exhibited the inhibitory effect on the elevation of cytochrome p-450 level-induced by gemfibrozil at the first week (the cytochrome p-450 level are 77.40% and 63.38% of grmfibrozil-treated group). 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 that obtained in cytochrome p-450, but occurred after 2 week (dose 2.5 mg/kg/day) and 1 week (dose 5 mg/kg/day) of drug administration (the catalase activites are 94.61% and 89.77% and the FACO activities are 85.74% abd 91.18% of gemfibrozil-treated group). Moreover, when gemfibrozil was administered concomittantly with 5 mg/kg/day of fluvastatin, a marked increase in the actibity of serum transaminase (SGOT, SGPT), and creaine phospholinase (CPK) were found since the first week of drug treatmnet (the

activites of SGOT, SGPT and CPK are 110.31%, 111.31% and 113.50% of gemfibrozil-treated group). Rats treated with gemfibrozil and fluvastatin 10 mg/kg/day were died during the first week with a marked elevation of these enzymes activity. Our data suggested that eventhough fluvastatin could potentiate gemfibrozil in reducing serum lipid levels, decreasing the microsomal and peroxisomal-induction effect of gemgibrozil, but it increased drug toxicity. Thus, the clinical benefit seemed to be low.