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Modification of carbon tetrachloride-induced hepatotoxicity by clofibric acid in rats

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Effects of clofibric acid (*p*-chlorophenoxyisobutyric acid) on carbon tetrachloride (CCl₄)-induced hepatocellular necrosis and fatty liver were investigated. Male rats were fed a diet containing 0.5% (w/w) clofibric acid for 7 days before administration of CCl₄ (1 ml/ kg, p.o.) and the treatment with clofibric acid continued throughout the time course of the study. In rats given only CCl₄, the serum activity of alanine aminotransferase (ALT) increased rapidly and reached a maximum level at 24 h after the administration of CCl₄. The rats pretreated with clofibric acid exhibited a significantly lower serum level of ALT compared with the rats treated with CCl₄ alone until 24 h following CCl₄ dosing. However, the maximum level that was observed at 48 h after the administration of CCl₄ to the rats pretreated with clofibric acid was similar to the highest level observed in the CCl₄ alone group at 24 h after CCl₄ dosing. The hepatic glycogen level steeply decreased at 3 h after the administration of CCl₄ and reached to the lowest level at 12 h preceding the definite appearance of necrosis, with gradual recovery noted by 96 h. An evident decrease in glycogen level was also in the group given clofibric acid throughout the time course. In rats treated with both CCl₄ and clofibric acid (clofibric acid + CCl₄), hepatic glycogen was exhausted from 3 h and the depletion lasted until 96 h after

dosing of CCl₄. The serum level of glucose was not increased, but rather decreased markedly after the administration of CCl₄ in both the rats receiving CCl₄ alone and in the rats treated with clofibric acid + CCl₄. The hepatic content of triglyceride increased rapidly and reached a level about 5-fold greater than the control at 12 h after the administration, then the elevated level lasted until 96 h of the time course. The increase in the hepatic content of triglyceride induced by CCl₄ was significantly suppressed by pretreatment with clofibric acid and returned to the basal level by 96 h after dosing of CCl₄. The results of histopathological examination of liver sections stained by hematoxylin and eosin, and oil red O, were very consistent with the biochemical changes mentioned above. These results indicate that dietary pretreatment with clofibric acid suppressed the necrosis of hepatocytes in the initial stage, but not in the late stage; rather, the recovery of liver from necrosis was delayed. Also this drug significantly suppressed fatty liver caused by CCl₄.