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Experimental Massive Necrosis Induced by Acetaminophen Administration in Rats: Alterations of Biochemical and Histopathological Findings

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BACKGROUND AND AIMS

Acetaminophen (APAP) is a widely used analgesic and antipyretic drug. APAP overdosage has been associated with hepatic necrosis in humans. Toxicity is thought to be related with the production of a highly reactive metabolite, N-acetyl-p-benzoquinoneimine.

The aim of the present study was to investigate and correlate serum biochemical parameters and histolopathological findings after the administration of a single sublethal dose of APAP in rats.

MATERIALS AND METHODS

Sixty male Wistar rats (200-250 gm each) received 3.5 gm APAP per Kg of body weight, using gastric tube. Animals were sacrificed at 0,8,16,24,32,40,48,56,64,72,84 and 96 h post-APAP administration. Blood samples and liver tissue specimens were collected from each animal, in order to examine the activities of alanine (ALT) and aspartate aminotransferase (AST) and the histopathological injury respectively.

RESULTS

Acute APAP administration caused 30% lethality during the experimental time. The massive necrosis produced by APAP is reflected by the elevated levels of serum AST and ALT activities with peaks at 24 and 32 h post-administration. At 56 h serum enzyme activities returned to baseline values. Nevertheless a second peak of AST and ALT activities at 64 h was observed, followed by a decreasing trend up to 96 h. Extensive centrilobular necrosis (zone III) was observed at 24 h post-toxin administration appearing spreading of inflammatory cells in zone II. At the time period of 32 up to 56 h post-treatment, the appearance of both cells exerting the hepatic stem cell phenotype in periportal areas (zone I) and mitotic activity in hepatocytes throughout the lobule supported evidence for increased hepatocellular proliferation. The peak of hepatocyte mitotic activity was observed at 56 and 64 h post-APAP administration. At 64 h collapse of perivenular reticulin framework and increased inflammatory infiltrations and necrosis were evident in zone II, appearing simultaneously with the second peak of serum aminotransferase activities. At further time points examined a progressively decreased hepatocellular necrosis was observed and recovery of the liver from APAP toxic effects was evident.

CONCLUSIONS

Our study correlates serum biochemical parameters and liver histology after acute APAP administration at a sublethal dose in rats, supporting evidence for a biphasic pattern of liver toxicity in this animal model.This second peak of APAP hepatotoxicity could be attributed to special circulation conditions and secretion of mediators in zone II.