Histological Study Effects of Paracetamol on Livers and Kidneys of Adult Mice

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ABSTRACT

Background: paracetamol is an atypical opioid with monoamine re-uptake inhibition properties. Aim of work: This study was examined the histological changes in liver and kidney after administration of paracetamol-induced mice

Materials and methods: The study was conducted on 10 adult male mice. Mice were divided evenly into two groups: control group, received 1 ml normal saline 0.9% Treated group received (0.5) ml of paracetamol/ body weight intra-peritoneally for 30 days. Results: The histological analysis of the liver showed that the thickening wall with minimal fibrosis in the periportal area infiltration of inflammatory cells in necrotic change of the hepatocytes massive vacuolation of the hepatocyte, kupffer cell were present intensity in the sinusoid. The histopathological examination of kidney revealed lymphocyte infiltration , congestion, glomerulus and tubular damage. The tubular was containing hypertrophied epithelial cell which block the lumen . Conclusion: The histopathological alterations of liver, and kidney tissues threw lights on the possible risks of increased hepatic, renal and neurological damages evoked by repeated administration of paracetamol for long periods.

Introduction

Paracetamol (Acetaminophen or , N-acetyl-p-aminophenol; APAP) is one of the most widely used of all drugs, used to treat pain and fever. It is usually used for mild to moderate pain. It has an excellent safety profile when administered in proper therapeutic doses, Acetaminophen metabolism occurs primarily in the liver (1). In the present study was carried out to investigate the histological changes in the liver, kidney, and brain of mice exposed to high doses of paracetamol .
Materials and Methods

The experimental study was carried out on 10 mice (about 1.5-2.1 kg), during the period from May to June 2016, in the animal house of the college of veterinary medicine / Tikrit University. The animals were maintained under controlled environmental conditions. They were provided a free access to standard pellet diet and tap water. The animals were divided into 2 groups each group consists of 5 animals:

**Group 1 (G1):** healthy control mice.
**Group 2 (G2):** mice received (0.5) ml of paracetamol/ body weight (intraperitoneal).

Treatment was done once daily for continuous 30 days.

Histological study

The animals were killed at the day after the last dose under intensive dose of chloroform. Abdominal cavity was opened, livers and kidney excised and covered with physiological normal saline and cleaned from attached fat and connective tissue. Blocks of tissues were immediately fixed in 10% neutral buffered formalin, dehydrated with graded series of ethyl alcohol and embedded in paraffin. Sections of 5 microns were cut and stained with eosin and hemotoxylin according to (2). Photomicrographs of the stained slides were taken using digital camera attached to light microscope.

Result:

In the control group, showed the structure of liver the central vein and hepatocytes were arranged in radical form and normal size and shape also sinusoid appeared normal in the size as well as Kupffer cells.

The present study of liver treated group showed different changes such as necrosis, degeneration, and the disorganization the hepatocytes column toward the central vein and disappearance of the hexagonal pattern of the individual liver cell, thickening wall of central vein, congestion, infiltration lymphocytes.(figure: 1, 2, 3).

**Figure (1):** Liver of mice administrated with paracetamol (0.5 ml) for 30 days showed:-(,Black arrow) atrophy of liver cell was seen.(red arrow) the lymphocytic local aggregation.
Figure(2): Liver of mice administrated with paracetamol (0.5 ml) for 30 days showed:-(black arrow) showed thickening wall with minimal fibrosis in the periportal area.(Red arrow)infiltration of inflammatory cells in necrotic change of the hepatocytes massive vacoulation of the hepatocyte, kupffer cell were present intensity in the sinusoid. (H&E 40 X).

In the control group, showed the structure of kidney, the glomerulus appeared normal size and shape and tubules brush border and basement membrane. The histological study of the kidney showed that aggregation of the inflammatory cell in the cortex and medulla with interstitial blood hemorrhage and certain number of glomeruli and damage glomeruli, the proximal &distal convoluted tubules were degeneration. as in figures (4,5,6,7).

Figure(3): liver of mice administration with paracetamol (0.5ml) for 30 days showed:-(black arrow) local aggregation of lymphocytes, (red arrow) hepatocytes were enlarged and degenerated, necrotic change of the hepatocytes(H&E 40 X).
Figure(4): Kidney of mice administration with paracetamol(0.5ml) for 30 days ,Showed :- (Black arrow), glomerular damage and tubular damage, lymphocyte infiltration (H&E 40 X).

Figure(5): Kidney of mice administration with paracetamol(0.5ml) for 30 days ,Showed :- (black arrow) the cortex was containing aggregation of lymphocytes (local and interstitial ), (red arrow) the epithelial cells that linins the P.CI and H.C.T were hypertrophy And lose number of epithelia cells. (H&E 40 X).
Figure(6): Kidney of mice administration with paracetamol(0.5ml) for 30 days ,Showed :- the epithelial cells that linins the P.CI and H.C.T were hypertrophy and lumens of these tubular were rarely seen glomeruli damage, tubular damage ,infiltration lymphocyte , (H&E 40 X)

Figure(7): Kidney of mice administration with paracetamol (0.5)for 30 days ,showed glomerulus damage and tubular damage ,lymphocytes infiltration , (H&E 40 X)

Discussion:

Paracetamol is primarily metabolized in the liver to excretable glucuronide and sulphate conjugates. A small percentage is metabolized through cytochrome P450 to N-acetyl-p-benzoquinone imine (NAPQI). Which Interacts with glutathione (GSH), forming 3-glutathion-S-yl-acetaminophen and by reduction to acetaminophen the reaction Maybe catalyzed by glutathione transferase , thus overdoses of paracetamol It may lead to the depletion of the GSH , when will cause drain NAPQI to connect with Cellular proteins, leading to formation of highly reactive
radicals because of oxidative threat, mitochondrial dysfunction is known to disturb the integrity of cell membranes, resulting in the leakage of cytoplasmic enzymes, DNA fragmentation. Massive liver necrosis, damage and death (3-5). This result is consistent with the findings of the previous study (6,7).

The kidneys are involved in the secretion of several toxins and therefore they are liable to liberate high quantities of free radicals which contribute to high oxidative stress that is involved in Causing kidney damage (8). Liver histology revealed thickening wall with minimal fibrosis in the periportal area infiltration of inflammatory cells in necrotic change of the hepatocytes massive vacoulation of the hepatocyte, kupffer cell were present intensity in the sinusoid. The possible mechanisms postulated include: a- The Binding of NAPBQ, an oxidative product of Paracetamol, to sulphhydryl groups of protein, which are responsible in mediating cellular damages and renal toxicity (9). b- In the kidney by deacetylation reaction, P-aminophenol formed from paracetamol and its excretion in the urine make it candidate for its role in the pathogenesis in renal damage. The fact that P-aminophenol formed from paracetamol by deacetylation and its excretion in the urine make it candidate for its role in the pathogenesis in renal damage (10). C- Inhibition of prostaglandin synthesis e.g. PGE2 and PGI2 (11). These results are in agreement with Madhukiran P, (12), In contrast, Ahmed et al. (13). who detected that the administration of paracetamol (500 mg/kg/day) did not produce papillary necrosis nor interstitial nephritis.

Conclusion:
Our findings pointed out the risk of hepatic and renal damage due to long term use of paracetamol. Although this drugs are reported to be effective in pain management, their toxic effects must be kept in mind during chronic usage. Liver and renal function monitoring is recommended.

References
