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RESEARCH ARTICLE OPEN ACCESS

Dose-Dependent Histopathological and Biochemical Hepatotoxicity of Paracetamol in Rats

Dose-Dependent Paracetamol Hepatotoxicity in Rats

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Abstract

Objective: Paracetamol (acetaminophen), a widely used analgesic and antipyretic, poses hepatotoxic risks at overdose due to reactive metabolite (NAPQI) accumulation, glutathione depletion, and oxidative stress. This study investigated the dose-dependent histological effects of paracetamol on rat livers to evaluate subacute (14-day) hepatotoxic effects.

Methods: Thirty adult male Wistar rats were randomly assigned to control, low-dose (200 mg/kg/day), and high-dose (500 mg/kg/day) paracetamol groups. These doses were administered orally for 14 days. Liver tissues were processed for histopathological examination by hematoxylin-eosin staining, and lesions were semi-quantitatively scored (0 = none, 3 = severe) for necrosis, congestion, inflammation, vacuolization, and fatty changes.

Results: Liver biopsy showed dose-dependent liver injury. Compared to controls, the high-dose group showed marked hepatocellular necrosis (2.8 ± 0.6), sinusoidal congestion (2.5 ± 0.5), inflammatory infiltration (2.7 ± 0.6), vacuolization (2.0 ± 0.4), and fatty changes (1.5 ± 0.3) ($p < 0.01$). Low-dose rats exhibited less severe changes. The biochemical markers showed significant increases of alanine aminotransferase (ALT) (245.6 ± 32.7 U/L), aspartate aminotransferase (AST) (280.4 ± 40.5 U/L), alkaline phosphatase (ALP) (320.8 ± 35.9 U/L), and bilirubin (2.8 ± 0.6 mg/dL) in the high-dose group compared with the low-dose and control groups ($p < 0.01$).

Conclusion: Prolonged paracetamol administration induces hepatotoxicity, inflammation, and vacuolization in rat livers, with severity correlating to dose. Elevated liver enzymes confirm structural damage, underpinning the dangers of overdose and long-term use.

Keywords: Paracetamol, Acetaminophen, Hepatotoxicity, Rat, Injury, Oxidative stress, Mitochondrial dysfunction, Subacute toxicity

Plain English Summary

Paracetamol is a common painkiller and fever reducer, but taking too much can hurt the liver. In this study, we looked at how two weeks of paracetamol affects the tiny structures in rats' livers. Thirty rats were split into three groups: no paracetamol, a low dose (200 mg/kg/day), or a high dose (500 mg/kg/day). We found that longer-term use caused liver injury that got worse with higher doses.

Background

Paracetamol (acetaminophen) is one of the most used OTC medications owing to its analgesic and antipyretic effects. Due to its cheap price and ubiquitous availability, it has become a household medication in many nations (1). However, despite being commonplace and generally safe, paracetamol can cause toxicity under certain conditions. One of the common fears related to paracetamol use is its hepatotoxicity potential, especially in cases of overdose (2). In most areas, including the US and

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Europe, paracetamol overdose is one of the leading causes of drug-induced liver injury (DILI) and acute liver failure (3).

The liver mainly metabolises paracetamol. Paracetamol is metabolised at therapeutic doses through two major pathways: glucuronidation and sulfation (4). These metabolic pathways culminate in the generation of water-soluble paracetamol metabolites that can be readily excreted in urine. However, a small percentage of paracetamol is metabolised by the cytochrome P450 enzyme system, mainly CYP2E1, to produce a highly reactive intermediate N-acetyl-p-benzoquinone imine (NAPQI). In a healthy state, NAPQI is rapidly inactivated by the liver's major antioxidant, glutathione (GSH) (5). In paracetamol overdose, the pathways of glucuronidation and sulfation become saturated, which leads to more NAPQI production. Once hepatic GSH stores become depleted, significant levels of NAPQI are formed and interact with cellular macromolecules, such as proteins, lipids, and DNA. This interaction activates the pathophysiological cascade of events, oxidative stress, mitochondrial dysfunction, and activation of inflammatory pathways, resulting in hepatocellular necrosis (6).

Histopathological changes in paracetamol hepatotoxicity have been widely studied in animal models, most commonly in rats. Paracetamol overdose has been shown to cause pathological patterns of liver injury, including centrilobular necrosis, sinusoidal congestion, and infiltration with inflammatory cells (7). Centrilobular necrosis develops as the CYP2E1 enzyme, the catalyst for NAPQI generation, is mainly present in the centrilobular zone of the hepatic lobule. As a result, this area is more vulnerable to injury during paracetamol overdose. Hepatocyte injury leads to sinusoidal congestion and inflammatory-cell infiltration, which are secondary and promote injury progression within the liver (8).

While most research has focused on acute overdose scenarios, prolonged administration over two weeks remains far less characterised (9, 10). In this study, we therefore evaluate the histological and biochemical effects of 14-day paracetamol administration in rats, addressing this gap in subacute dosing models.

Animal models, especially in rats, have played a vital role in examining paracetamol's histological and biochemical effects on the liver. Rats are often preferred because their metabolic pathways for paracetamol closely resemble those in humans. Moreover, the short lifespan of rats enables rapid evaluation of histological changes over weeks. We selected two dosage levels, 200 mg/kg and 500 mg/kg, based on prior rodent hepatotoxicity studies (11) and converted to approximate human equivalent exposures (1.6–4 g/day) via body-surface-area calculations (12). The histological effects of paracetamol on rat liver were studied to observe dose-dependent changes in liver architecture and cellular integrity. This study aimed to investigate the dose-dependent histological and biochemical effects of paracetamol administration on rat livers, specifically evaluating hepatotoxic potential at different dosage levels.

Materials and Methods

Experimental Design

Thirty adult male Wistar rats (180–220 g) were used in this study. The study protocol was approved by the Institutional Animal Care and was conducted following ARRIVE guidelines. A sample size of 10 rats per group was determined by power analysis to detect a 20% difference in histological scores (power = 80%, α = 0.05), based on previous rodent hepatotoxicity studies (13). Rats received all treatments once daily for 14 consecutive days. Rats were kept in standardised laboratory conditions with 12 hours of light and dark, temperature (22 ± 2 °C), and humidity (50 ± 10%). A standard rodent diet and water were provided ad libitum. Rats were acclimated for 1 week before the start of the experiment.

Grouping and Treatment

The rats were randomly divided into three groups of ten animals each:

Control Group: Received distilled water orally for 14 days.

Low-Dose Paracetamol Group: Administered 200 mg/kg of paracetamol orally for 14 days (11).

High-Dose Paracetamol Group: Administered 500 mg/kg of paracetamol orally for 14 days (11).

Paracetamol was dissolved in distilled water and administered using an oral gavage.

Blood sample collection:

Blood samples were collected directly from the hearts of animals and put in tubes without anticoagulant for serum separation, and the serum was used to estimate liver function.

Liver function estimation:

The ALT (Cat. Nos. ALT-12345, AST-23456, ALP-34567, Total Bilirubin-45678; Biolab, China), following the manufacturer's protocols. All assays have been validated for rat serum samples.

Sample Collection

At the end of the treatment period, rats were anaesthetised with ketamine (75 mg/kg) and xylazine (10 mg/kg) via intraperitoneal injection. Blood was withdrawn using cardiac puncture for biochemical analysis (not discussed in this

paper). The liver was subsequently excised, rinsed in cold saline, and separated into two halves. One half was fixed in 10% neutral-buffered formalin for histology, and the other half was held at −80°C for molecular analysis.

Histological Processing

The liver tissues were prepared using the standard histopathological methods. Tissues were dehydrated through ascending concentrations of ethanol, xylene cleared and embedded in paraffin wax. 5 µm-thick sections were cut using a microtome and stained with hematoxylin and eosin (H&E) for light microscopic examination.

Histopathological Evaluation

The stained sections were examined under a light microscope by a pathologist blinded to the treatment groups. The following parameters were assessed:

Hepatocellular necrosis
Sinusoidal congestion
Inflammatory cell infiltration
Vacuolization
Fatty changes

The severity of histological changes was scored on a scale of 0–3: 0 = no change; 1 = mild (<10% area involvement); 2 = moderate (10–30% involvement); 3 = severe (>30% involvement).

Statistical Analysis

Data were analysed using SPSS software (version 25). Before analysis, all data were tested for normality using the Shapiro–Wilk test and for homogeneity of variances using Levene's test. Histological scores that satisfied these assumptions are presented as mean ± standard deviation (SD) and were compared by one-way ANOVA with Tukey's post hoc test. For any parameter that violated normality or homogeneity, we used the Kruskal–Wallis test followed by Dunn's multiple-comparisons correction. Statistical significance was set at $p < 0.05$.

Results

Table 1 shows a synopsis of the histological findings among the three groups.

Table 1: Histological findings

Parameter	Control Group	Low-Dose Group	High-Dose Group
Hepatocellular necrosis	0.0 ± 0.0	1.2 ± 0.4*	2.8 ± 0.6**
Sinusoidal congestion	0.0 ± 0.0	1.0 ± 0.3*	2.5 ± 0.5**
Inflammatory cell infiltration	0.0 ± 0.0	1.1 ± 0.3*	2.7 ± 0.6**
Vacuolisation	0.0 ± 0.0	0.8 ± 0.2*	2.0 ± 0.4**
Fatty changes	0.0 ± 0.0	0.5 ± 0.1	1.5 ± 0.3**

**Values are expressed as mean ± SD. *p < 0.05 compared to control; **p < 0.01 compared to control and low-dose group*

Histopathological analysis revealed dose-dependent liver damage, including hepatocellular necrosis, sinusoidal congestion, inflammatory cell infiltration, vacuolisation, and degeneration with mild hyperplasia in the treated groups (Figures 1 and 2). The high-dose group exhibited more severe damage compared to the low-dose group.

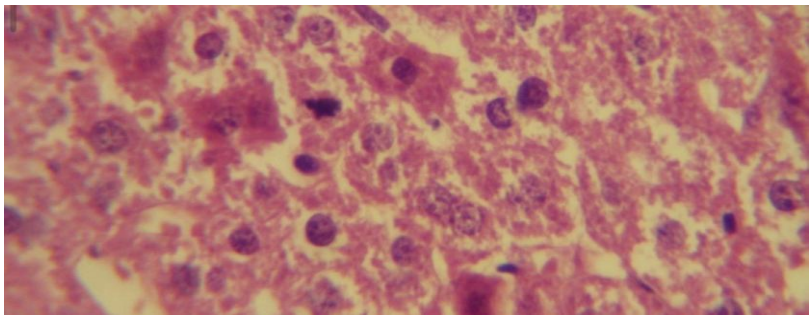

Figure 1: Representative H&E-stained micrograph showing centrilobular hepatocellular necrosis in the high-dose paracetamol group (500 mg/kg/day) on Day 14. (X200)

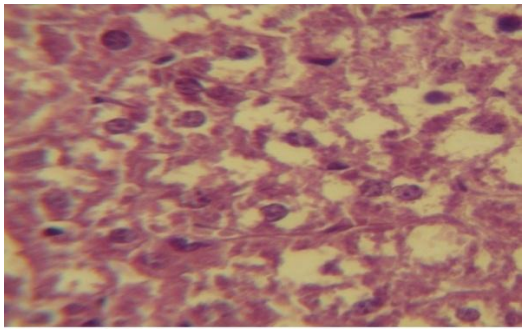

Figure 2: Representative H&E-stained image of hepatocyte microvacuolisation characterised by cytoplasmic ballooning in the high-dose paracetamol group (500 mg/kg/day) on Day 14

In addition to the histological findings, the effects of paracetamol on liver enzymes were assessed to evaluate the functional impact of hepatotoxicity. Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin were measured. The results are summarised in Table 2.

Table 2: Some liver function tests in control and treated groups

Parameter	Control Group	Low-Dose Group	High-Dose Group
ALT (U/L)	35.2 ± 4.1	78.5 ± 10.3*	245.6 ± 32.7**
AST (U/L)	40.8 ± 5.6	85.2 ± 12.4*	280.4 ± 40.5**
ALP (U/L)	120.3 ± 15.2	185.6 ± 20.7*	320.8 ± 35.9**
Total Bilirubin (mg/dL)	0.5 ± 0.1	1.2 ± 0.3*	2.8 ± 0.6**

**Values are expressed as mean ± SD. *p < 0.05 compared to control; **p < 0.01 compared to control and low-dose group*

Discussion

The observed histopathological alterations align with established mechanisms of paracetamol-induced hepatotoxicity. Under high-dose conditions, phase II hepatic metabolism generates excessive quantities of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), depleting glutathione (GSH) reserves and inducing systemic oxidative stress. This oxidative imbalance precipitates mitochondrial dysfunction, disrupts calcium homeostasis, and activates apoptotic pathways, culminating in hepatocellular necrosis (12). The centrilobular predominance of necrosis observed in high-dose cohorts corresponds to the zonal expression of cytochrome P450 2E1 (CYP2E1), the primary enzyme responsible for NAPQI generation, which is densely localised in centrilobular hepatocytes. After initial cellular injury, secondary pathological features including sinusoidal congestion and inflammatory infiltration emerge as critical drivers of progressive parenchymal damage, consistent with established models of hepatotoxic progression (13). Our findings demonstrate clear dose-dependence: low-dose animals showed only mild centrilobular injury, whereas high-dose animals exhibited extensive necrosis, vacuolization, and steatosis.

The histological changes were dose-dependent in this study and served to emphasise the importance of appropriate dosages within recommendations. While mild changes were the norm in the low-dose group, the high-dose group exhibited substantial damage, indicating that high dosage can cause irreversible hepatic injury from paracetamol administration (11). Histopathological findings in the present study have important clinical implications, especially when considering long-term paracetamol administration.

While immediate dosages might still be within treatment limits, cumulative dosing may exceed toxic thresholds, triggering liver injury, which usually goes unnoticed until permanent harm occurs (14). These findings are consistent with mechanistic studies that show paracetamol overdose impairs endogenous antioxidant defences, causing an exacerbation of hepatic inflammation, which then synergistically drives both apoptosis and cellular necrosis (15). The observed hepatocellular degeneration and necrosis within the centrilobular region of treated rats are consistent with previous studies reporting necrotic focal hepatocytes and necrobiotic alteration in the centrilobular zone, which are known features of paracetamol-induced toxicity (15).

Furthermore, the prominent vacuolar degeneration noted in this study, characterised by cytoplasmic ballooning and obscured sinusoids, reflects a consistent histopathological signature of drug-induced hepatotoxicity, as documented in earlier literature (16). Nuclear

anomalies, including pyknotic and irregularly condensed nuclei, further mirror degenerative cellular states described in analogous models (17).

The inflammatory infiltrates within lobules and perivascular regions, alongside sinusoidal and portal venous congestion, reinforce the interplay between vascular dysfunction and immune responses in disease progression (18, 19). Notably, the high-dose group exhibited marked vacuolization, indicative of intracellular lipid accumulation (steatosis), likely attributable to mitochondrial impairment and suppressed β-oxidation (20). While such fatty changes may regress upon discontinuation of the hepatotoxic agent, persistent injury risks progression to steatohepatitis and fibrosis, emphasising the need for vigilant monitoring in long-term therapeutic use (21). Collectively, these findings substantiate the dose-dependent hepatotoxic trajectory of paracetamol, bridging histopathological evidence to underlying molecular mechanisms and clinical ramifications.

The pronounced elevation of serum ALT (alanine aminotransferase) and AST (aspartate aminotransferase) levels observed, particularly in the high-dose cohort, signifies extensive hepatocellular damage, with ALT being more specific to hepatocytes and AST reflecting broader tissue distribution, including cardiac and skeletal muscle. Their concurrent rise strongly implicates the liver as the principal injury site, corroborating prior findings (22, 23). Similarly, toxic doses of paracetamol have been shown to significantly increase both enzymes in rat models (19, 24). Furthermore, the observed elevation in serum ALP (alkaline phosphatase) underscores concurrent cholestatic injury and biliary dysfunction, implicating paracetamol's dual impact on hepatocellular integrity and bile flow regulation. This biochemical evidence aligns with histopathological features, such as sinusoidal congestion and inflammatory infiltration, that may obstruct biliary architecture and exacerbate cholestasis. The dose-dependent escalation of ALP further substantiates the correlation between higher paracetamol exposure and exacerbated hepatobiliary injury (25). The elevations seen even in the low-dose group suggest that moderate, repeated dosing may produce subclinical liver injury.

The prominent vacuolar degeneration, characterised by cytoplasmic ballooning and sinusoidal compression, reflects mitochondrial permeability transition pore opening, impaired β-oxidation, and endoplasmic reticulum (ER) stress, which together trigger the unfolded protein response and further ROS generation (26). Fatty changes (steatosis) likely arise from suppressed mitochondrial β-oxidation and SREBP-1c activation under oxidant stress, linking histology to these deeper subcellular dysfunctions.

Translating these results to humans requires caution: rodent CYP2E1 expression patterns and activity differ quantitatively from humans, potentially altering NAPQI formation rates. However, the subacute 14-day dosing mirrors scenarios of chronic high intake or repeated supratherapeutic dosing in patients with pre-existing liver disease (e.g., nonalcoholic fatty liver disease), who may have diminished antioxidant reserves. Our data suggest that even moderate, repeated dosing, if prolonged, can precipitate subclinical injury that may progress unnoticed, underscoring vigilance in at-risk patients.

Study Strengths and Limitations

This study demonstrates the histological effects of paracetamol on rats` livers in a dose-related manner. The results highlight the critical balance between paracetamol's therapeutic efficacy and its potential for irreversible hepatic damage, advocating for prudent clinical utilisation and further research into protective pharmacological interventions. However, this study used only male Wistar rats, precluding assessment of sex-specific metabolism and susceptibility; female rodents exhibit different glucuronidation rates and CYP2E1 activity (27). Additionally, the 14-day period does not capture true chronic exposure, and interspecies variation limits direct extrapolation of dose thresholds.

Conclusion

This study demonstrates that prolonged administration of paracetamol induces dose-dependent hepatotoxicity in Wistar rats, characterised histologically by hepatocellular necrosis, sinusoidal congestion, inflammatory cell infiltration, and vacuolization, with pronounced severity in the high-dose group. Biochemical corroboration revealed significant elevations in serum ALT, AST, ALP, and bilirubin, consistent with impaired hepatic function and structural damage. The observed toxicity aligns with the proposed mechanisms of NAPQI-mediated oxidative stress, glutathione depletion, mitochondrial dysfunction, and subsequent inflammatory cascades. These findings underscore the hepatotoxic risk of paracetamol overdose and prolonged use, emphasising the necessity of strict adherence to therapeutic dosages, vigilant clinical monitoring, and early intervention strategies, such as N-acetylcysteine administration, to mitigate liver injury.

List of abbreviations

DILI: Drug-induced liver injury
ALF: Acute liver failure

NAPQI: N-acetyl-p-benzoquinone imine
GSH: Glutathione
H&E: Hematoxylin and eosin
ALT: Aminotransferase
AST: Aspartate aminotransferase
ALP: Alkaline phosphatase

Declarations

Ethical approval and consent to participate

This study was approved by the Committee on Publication Ethics at the College of Medicine, University of Babylon, Iraq. The study protocol, subject information, and the consent form were reviewed and approved by a local ethics committee according to document number 6, on 1/11/2024, to get this approval.

Consent for publication

All the authors gave consent for the publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials

The data and materials associated with this research will be made available by the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

The authors contributed equally to conceptualising the research, data collection, analysis, write-up, editing and review.

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