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Hepatic and Renal Histopathological Changes Following Therapeutic and High-Dose Loperamide Administration in Swiss-White Mice

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Abstract

This study investigates the effects of loperamide administration on the hepatic and renal histopathology. Twenty young white mice were randomly allocated into three groups: a control group given normal distilled water (n=6), a therapeutic-dose group receiving 2 mg/kg/day loperamide (n=7), and a high-dose group receiving 6 mg/kg loperamide/day (n=7) for 3 weeks. Following the treatment period, liver and kidney tissues were collected and processed for histopathological evaluation. Histological examination revealed that dose-dependent tissue change was found in both the liver and kidneys of the groups treated with loperamide. However, high-dose loperamide administration was associated with marked hepatic and renal lesions such as vascular abnormalities, hepatocellular degeneration, nuclear damage (karyolysis, pyknosis, karyorrhexis), and necrosis. Renal tissue exhibited prominent tubular necrosis together with other degenerative changes when compared to animals treated with the therapeutic dose which demonstrated mild histopathological alterations. In conclusion, these findings suggest that high-dose of loperamide administration induced marked hepatic and renal histopathological lesions in mice, indicating a dose-dependent increase between tissue injury/abnormalities and Loperamide abuse exceeding the recommended therapeutic dose leads to potential hepatoxic and nephrotoxic effects.

Keywords: Loperamide, Imodium, Histopathology, Hepatotoxicity, Nephrotoxicity

Introduction

Loperamide (Loperamide Hydrochloride); also known as Imodium; is an opioid, over-the-counter drug the systematic regulation of acute and chronic diarrhea by the complete restriction of gastrointestinal motility through targeting intestinal muscles and peripheral μ-opioid receptors, while also decreasing gastrointestinal secretions. The mechanism of action of Loperamide is through slowing the digestion process, and allowing more time for nutrient and fluid absorption, thus treating diarrhea symptoms rather than the underlying cause (1). Intracellular cyclic nucleotides are generated from various compounds produced by *E. coli* that enhance the opening of mucosal chloride channels and result in chloride, sodium, and water loss into the intestinal lumen. Studies found loperamide decreases chloride loss in isolated

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intestinal tissues and blocks castor oil–induced diarrhea in rats (ED50 0.15 mg/kg, 1 hour), demonstrating rapid and long-lasting antidiarrheal activity. It also decreases secretion induced by *E. coli* enterotoxin both in vivo and in vitro (2). However, there has been a rise in reported cases of intentional ingestion of loperamide overdose exceeding the recommended therapeutic levels by opioid addicts (3), often without fully understanding the potential adverse effects it may cause.

The liver mainly metabolizes loperamide, causing concerns regarding hepatic toxicity and impaired liver function with prolonged or overuse. Even though it was initially considered to have low abuse risk due to rapid metabolism and minor central nervous system penetration, abuse at high doses has been connected with severe adverse effects, including cardiac arrhythmias and arrest (3,4). Since the liver plays a role in drug metabolism and excretion in the kidney, both organs are suspected to toxic damage. While oxidative stress and similar biological mechanisms that involve inflammation, and programmed cell death may cause these effects, the present study investigates histopathological alterations in hepatic and renal tissues. Previous research have reported hepatic effects of loperamide, significant lesions including necrosis and structural degeneration, indicating overall disruptions in cellular integrity and organ function (3,5-8,16), as well as cardiovascular effects (9) while other studies indicated the potential toxicity of loperamide on organs other than the gastrointestinal tract in a dose-dependent cardiac toxicity and reports of DNA fragmentation in rats after loperamide exposure and multiple other effects (15,18,20). Reports of anti-tumor activity in loperamide was exhibited by inducing apoptosis in cancer cells (5), induces excessive bile acids accumulation in the liver of mice with profound histological liver damage which was influenced by dietary conditions (6), and recent in vivo and in vitro study associates loperamide abuse and inhibition in cardiac ion channels, poisoning (7-9), including reports of alterations in renal biochemical markers following loperamide administration in rodents but no definitive structural renal toxicity was reported (10).

Despite the extensive use of loperamide as an antidiarrheal drug, its potential effects on multiple organs require further investigation. Despite the well documented reports of past research revolving the pharmacological and toxicological effects of this compound on the gastrointestinal and cardiovascular systems, limitation regarding the potential histopathological effects of loperamide on the liver and kidney specifically remained insufficient. Considering the vital roles of both the liver and kidney in metabolic regulation and the balance of physiological homeostasis. The present study aims to investigate the dose-dependent histopathological effects of loperamide administration on hepatic and renal tissue toxicity levels associated with prolonged oral intake in Swiss albino mice.

Materials and Methods

Experimental Animals

Twenty healthy Swiss-white mice were obtained from animal house of Tikrit University. The animals were examined and treated for a duration of 21 days in all study groups, housed in mice cages (four animals per cage) and were given a pellet rodent diet in addition to water. They were kept under controlled environmental conditions during spring, well-ventilated housing and a 12-h light/darkness cycle. Care was taken to avoid any unnecessary stress such as noise, cage

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crowding, and smell. Additionally, the animals were kept for 7 days before starting the experiment for acclimatization.

Experimental Design

Mice were divided randomly into three groups: Group A (control) were given 1ml of distilled water, whereas two treatment groups were introduced with orally administered loperamide: group B (therapeutic dose) at a dose of 1 mg/kg body weight of loperamide twice daily, giving a total daily dose of 2 mg/kg/day (11), and group C (high-dose) at a dose of 3 mg/kg body weight twice daily (6 mg/kg/day). Mice were given the drug daily throughout these 21 days as summarized in Table .1

Table. 1: The Experimental Design

Group	Treatment	Dose/Day	No. of Animals	Duration Time
A (Control)	Distilled water	-	Six	21 Days
B (Therapeutic)	Loperamide	2 mg/kg	Seven	
C (High-dose)		6 mg/kg	Seven	

Histopathological Processing

At the end of the treatment period, the mice were euthanized following exposure to chloroform vapor using a small piece of cotton placed inside an enclosed glass box, and dissection was performed immediately following the confirmation of death. Tissue samples from the kidney and liver were carefully collected using aseptic dissection techniques and processed (11,12). Organs were obtained and then fixed in 10% neutral buffered formalin solution for 22 hours at room temperature. These organs were then dehydrated by forming a graded ethanol-serial concentrations baths (50-100%) and rinsed with distilled water. Tissue samples were then cleared in two changes of xylene for 20 minutes to achieve the required tissue transparency. This was followed by paraffin infiltration and tissue embedding through two changes of molten paraffin wax (melting point 56-58^{o}C) for 30 minutes, to ensure the complete removal of any traces of xylene. The tissues were embedded using stainless steel container blocks while ensuring proper tissue alignment. Paraffin-embedded tissue was sectioned using a Rotary Microtome (LKB-UK). and cut at 5-6 micrometer (µm) thickness then sections were collected using labelled slides. To ensure the adhesion of these sections onto the slide, Mayer's glycerol-albumin mixture was used prior to section placement.

This was followed by de-waxing and hydration by passing the slides through two changes of xylene and then rehydrating through ethanol-serial concentration baths (100-50%), followed by rinsing with distilled water. The slides were then stained with Hematoxylin and Eosin dye (H&E) according to a standard staining procedure followed. Finally, the slides were dehydrated, cleared, and mounted using Distrene Plasticizer Xylene (DPX). The prepared slides

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were later examined under the microscope for histopathological alterations, and images were obtained using NOVEL/SN Microscope (212973, Italy) equipped with a digital imaging screen.

Results

Hepatic Histopathological Findings

Basic components of the liver are primarily composed of hepatocytes, which are epithelial cells forming two thirds of the liver mass. The hepatic lobules, portal space, and the central vein. Hepatic sinusoids can be seen with the presence of kupffer cells found on the luminal surface of the epithelial cells, within the sinusoids as shown in Figure (1). However, a clear normal radial alignment is observed in both hepatocytes and sinusoids, with slight expansion observed in group treated with 1 mg/kg Loperamide with parts of the tissue and cells lining the central vein containing endothelial cells as shown in Figure (2B). Partial congestion and haemolysis were found in the central vein and/or in all parts of hepatocytes with minimumal inflammatory cells infiltration seen in Figure (2C).

In the high-dose treatment group, the hepatocytes exhibited a disruption in their radial arrangement of hepatocytes towards the central vein (CV), karyorrhexis, with the presence of severe congestion within hepatocytes and the central vein, and a clear narrowing and/or absence of hepatic sinusoids is found. The nuclei show necrosis at various stages seen in Figure (3A). Nuclei Pyknosis was characterized by chromatin condensation and reduced unclear size, making the chromatin difficult to distinguish. The cells showed signs of nuclear condensation (pyknosis), and kupffer cells were found within the sinusoidal endothelium cells and appeared to exhibit cellular enlargement. The endothelium cells found in the central vein appear damaged and segregated in various places, while karyolysis is also seen in Figure (3 A).

A partial haemolysis accompanied with congestion was present in the central vein with the presence of macrophages in the tissue. However, the hepatic cell structure exhibited a well-preserved radial arrangement/alignment present in the central being, but narrower sinusoidal space, Figures (3 B and C).

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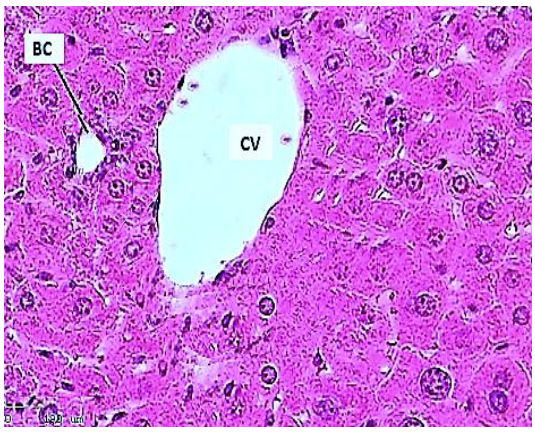


Figure. 1: Histopathological examination of liver cross section of the controlled group: Cross section of the Liver given distilled water showing normal morphology of cell structure. The central vein in the liver is seen (CV) with the presence of Bile Canaleculi (BC). All images were taken at 40× magnification (H&E 40X).

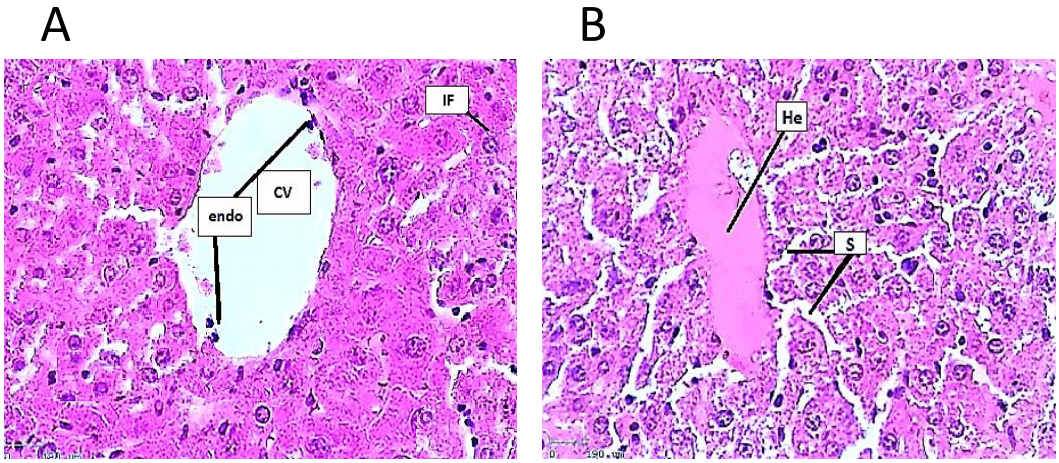


Figure. 2: Histopathological examination of liver sections following administration of 2 mg/kg loperamide therapeutic-dose. A) Cross-section of the liver showing lymphocytic infiltration (IF), endothelial cells (endo), and the central vein (C.V). B) Cross-section of the liver shows the sinusoids (S) and presence of haemolysis (He) (H&E 40X).

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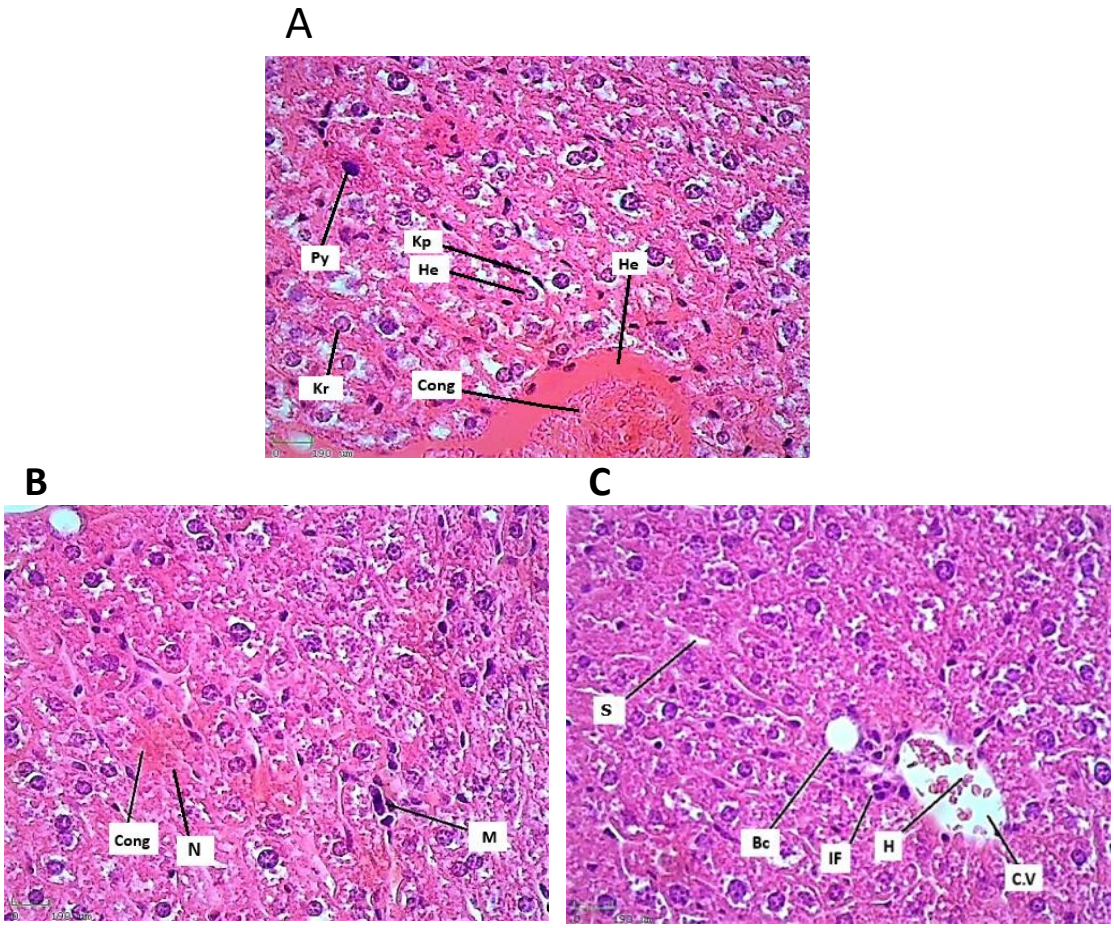


Figure. 3: Histopathological examination of liver sections following administration of 6 mg/kg Loperamide (High-dose). (A) Cross-section of the liver showing pyknotic cells (Py) and karyolysis (Kr), haemolysis (He), congestion (Cong.), central vein (CV), hepatocytes (He), and presence of Kupffer cells (Kp). (B) the liver shows signs of congestion (Cong.) Necrosis (N) and macrophages (M). (C) Cross-section of the liver showing lymphocytic infiltration (IF), sinusoids (S), bile canaliculi (Bc), haemorrhage (H) in the central vein (CV), and lymphocytic infiltration (IF) (H&E 40X).

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Renal Histopathological Findings

A normal renal tissue was distinguished by the presence of a normal renal cortex, medulla and renal pelvis. Nephrons made up of glomerulus capsule (Bowman's capsule), a normal preserved proximal convoluted tubule, loop of henle and the distal convoluted tubule in addition to the collecting duct were all demonstrated with well aligned structure and shape, as shown in Figure (4).

The kidney sections in groups treated at 1 mg/kg show normal tubules lining the kidney in both arrangement and appearance relative to control. However, parts of the cells show the presence of enlargement which can be found in the cavity as shown in Figure (5A). A normal shaped glomerulus and the presence of desquamation in parts of the cells lining the urinary tubules, with indication of infiltration of inflammatory cells seen with minimum haemorrhage demonstrated in Figure (5B).

Histopathological examination of the renal tissue treated with 3 mg/kg shows pronounced alterations in renal urinary tubular morphology of the epithelial cells, such as enlargement of cells lining the tubules, causing marked narrow of the tubular lumina, with complete luminal occlusion observed in parts of these tubules. Degenerative tubular epithelium and necrosis were apparent, with nuclear and cytoplasm changes, characterized by cellular swelling, nuclear enlargement, loss of distinct chromatin matter, congestion between urinary tubules accompanied by atrophy of some glomeruli, as shown in Figure (6A and B). Furthermore, focal separation and desquamation of tubular epithelial cells were present accompanied by clear sign of necrosis and pyknosis as shown in Figure (6C).

Focal segmentation/structural alteration was observed in parts of the glomeruli, while other parts of the renal tubule appear to contain desquamation and segregation from the basement membrane leading to their aggregation in the tubule center. Additionally, these renal tubular cells underwent various stages of degradation, accompanied by nuclear alterations such as karyolysis and karyorrhexis, as seen in Figure (6C). Figure (6B) shows complete necrosis of the renal tubular epithelium, while Figure (6C) shows glomerular atrophy with congestion. Furthermore, severe haemorrhage was observed located between the renal tubules with evidence of erythrocyte lysis and associated congestion, Figure (6D).

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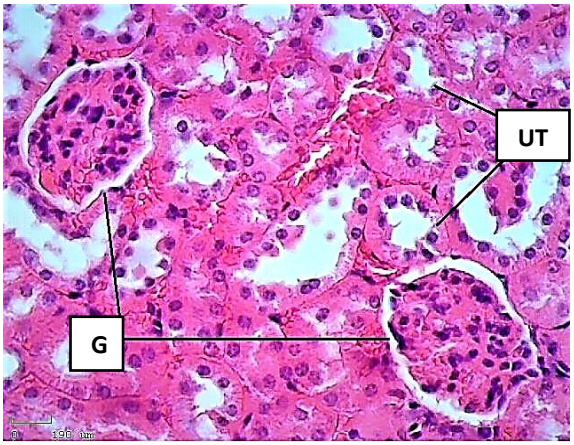


Figure. 4: Histopathological examination of normal kidney sections. Cross-section of the kidney showing normal urinary tubules (UT) (H&E 40X).

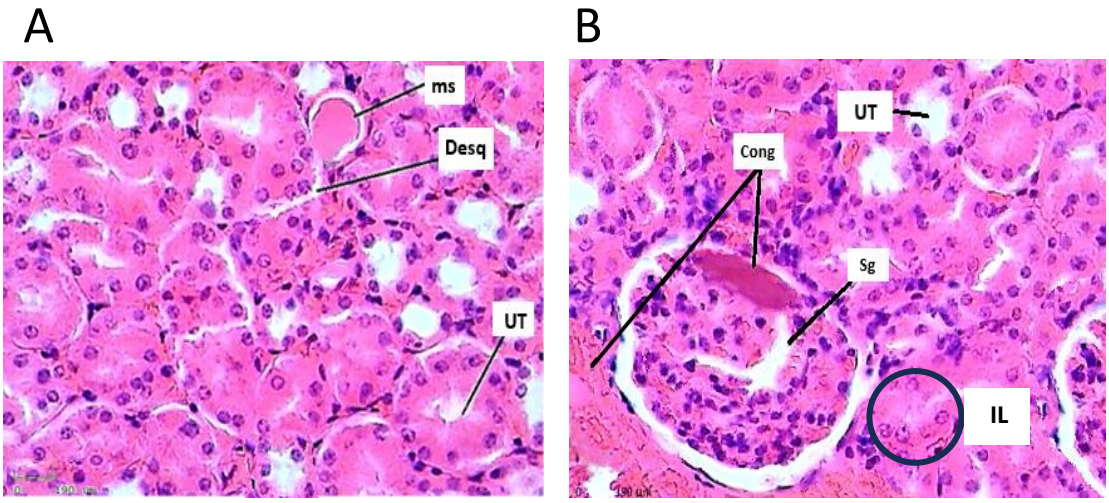


Figure. 5: Histopathological examination of kidney following administration of 1 mg/kg Loperamide. (A) Cross-section of the kidney showing urinary tubules (UT), desquamation (Desq.), and mucous material (MS). (B) Cross-section showing a segmented glomeruli (Sg) and vascular congestion (Cong.) and lymphocytic infiltration (IL) (H&E 40X).

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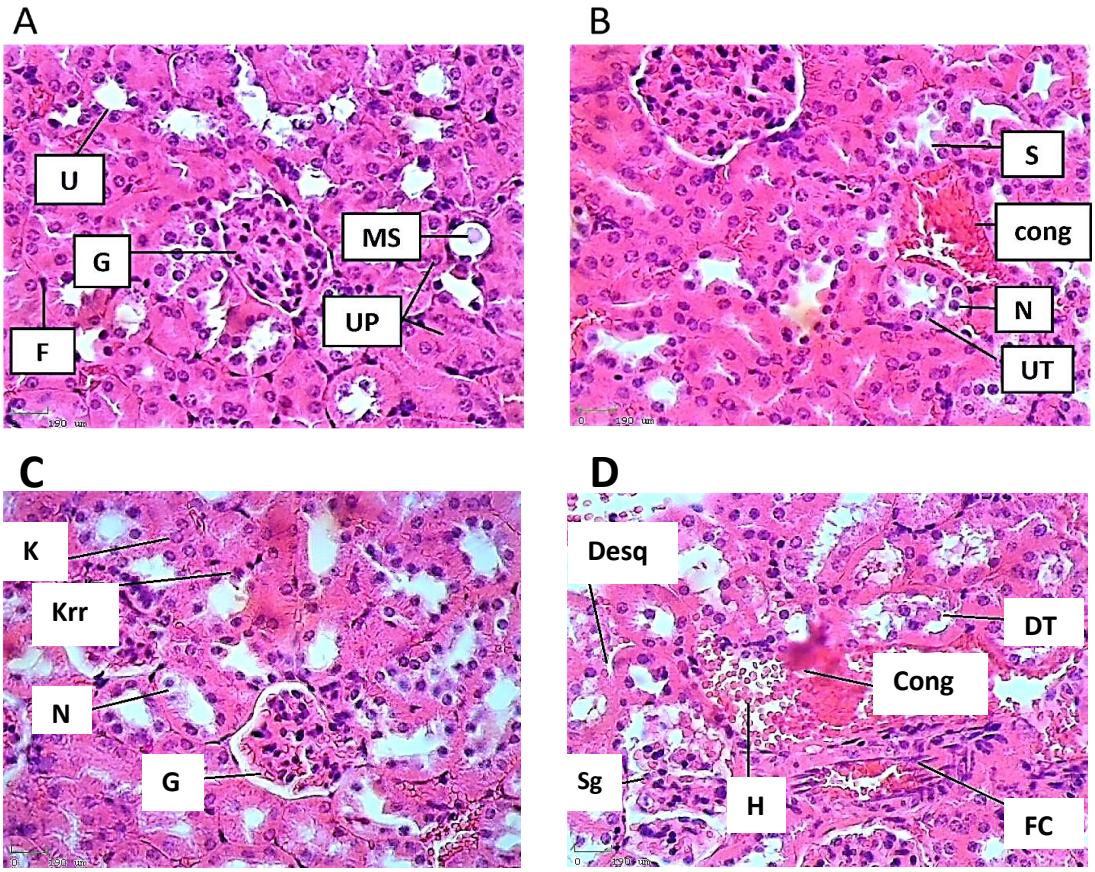


Figure. 6: Histopathological examination of kidney sections following administration of 3 mg/kg of Loperamide. A) Cross-section of the kidney showing urinary tubules (U), glomerular atrophy (G), fibrocytes (F), mucoid material (MS), and an upper closed nephron tubule (UP). B) Kidney section showing tubular necrosis (N), vascular congestion (Cong.), cellular detachment (Sc), and urinary tubules (UT). C) Cross-section of the kidney showing karyolysis (K), karyorrhexis (Krr), necrosis (N), and glomerular atrophy (G). D) Cross-section of the kidney showing desquamation (Desq.), segmented glomeruli (Sg), haemorrhage (H), congestion (Cong.), fibrocytes (Fc), and damaged tubules (DT) (H&E 40X).

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Discussion

Loperamide (Imodium) is an agonist of μ-opiod receptors that increases their peristalsis in the gut, reduced intestine content, and result in a higher absorption of water and ions by inhibiting intestinal contractions and causing in increase in intestinal transit period (2,10,15). The common side-effects of this compound are bloating and constipation with reports of cardiovascular toxicity and other life-threatening side effects (1-3,15-18). Plasma loperamide administration concentration is highest after 5 hours of capsule intake and 2.5 hours after the liquid. While Loperamide Distribution based on research literature occurs by plasma protein binding which is about 95% while its elimination half-life is 10.8 hours with a range of 9.1 to 14.4 hours. Excretion of the unchanged Loperamide and its metabolites occurs through the feces (1-5). The common side-effects of this drug include headache, vomiting, bloating, and constipation with reports of cardiovascular toxicity (17). Even though Loperamide is generally well tolerated at recommended therapeutic doses, its use could be associated with these side-effects especially after prolonged use or abuse.

General loperamide effects on various tissues and organs included in vitro and animal studies have shown that Imodium (loperamide hydrochloride) slows down intestinal motility, hence, affecting the movement of water and electrolyte in the bowel. Loperamide binds to the opiate receptor in the gut wall. Furthermore, it inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis (4). There has also been a connection between anti-diarrheal medication and liver/ kidney abnormalities such as liver abscesses following the treatment of gastroenteritis episodes with these drugs in patients (16), and loperamide has been specifically associated with respiratory depression and serious cardiac problems such as cardiotoxicity and death (17-21). Various substances of E. coli increase intracellular cyclic nucleotides that result in the opening of mucosal chloride channels initiating the loss of chloride followed by sodium and water into the intestinal lumen. On isolated tissue loperamide has been shown to reduce the chloride loss associated with these substances and castor oil. Orally administered Loperamide blocks castor oil-induced diarrhea in rats and has an ED50 value of 0.15 mg/kg (1 hour). With a rapid and long-lasting antidiarrheal action. Loperamide has also been shown to decrease secretion caused by E. coli enterotoxin both in vivo and in vitro (2).

The damaging toxic effect of high dose Loperamide was also observed in other statistical studies by the (CNITV) that was in agreement with this study showing 13/40 episodes of canine poisoning by loperamide; the average dose ingested by affected dogs was 0.9 mg/kg. they were treated but in severe cases with coma and respiratory distress naloxone (10). Other reports agreed with this study in the fatal Toxicity of Loperamide when exceeded normal therapeutic doses, according to (2) claim about 10 enquiries per year about ingestion of products containing loperamide by dogs in which a 6-week-old puppy died after a dose of 14.3 mg/kg, whereas all other dogs survived (2,8).

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General observations of the treated groups in this study included changes in animal behavior such as low activity, isolation that is possibly associated to depressive activity and an increase in overall breathing rate in mice treated at a high-dose relative to the control group. Histopathological examination in this study reveals marked structural alterations in both the kidney and liver specifically at high-doses of loperamide intake. This study was designed to closely investigate the effects of higher than recommended dose intake of loperamide on the hepatic and renal tissue as few studies were found regarding this. This study was used to investigate the effects of repetitive recommended and high exposure of loperamide intake on the renal and hepatic tissue for prolonged period of time (21 days) as very limited studies investigated these effects and only a narrow literature was found on kidney and liver associated to loperamide induced damage.

In the liver, hepatic injury and disruption following loperamide daily dosage intake of 6 mg/kg (3 mg/kg twice a day) in young adult mice resulted in disruptive effects on the hepatic tissue such as hepatocellular necrosis, pyknosis, and karyolysis indicating severe cellular effects resulting in irreversible hepatocellular damage. Additionally, the presence of vascular congestion with partial haemolysis suggests hepatic microcirculation damage. That were in agreement with studies that reported hepatic tissue damage and increase in hepatic bile activity following the treatment with 5 mg/kg per day for two weeks. Furthermore, other reports stated loperamide reduced intestinal secretion in mice, consequently effecting intestinal activity (21). These finding are also consistent with previous research which observed changes in absorption/secretion of ion permeability of the mucosal surface are correlated to the presence of endotoxins, prostaglandins, hormones and other substances, resulting in secretory diarrhea (2). This study was in agreement with other reports in patients abusing loperamide hydrochloride recommended intake resulted in cell damage, and/or necrosis leading to sudden death (2,5,13,19), ventricular arrhythmias and cardiac arrest, syncope and respiratory depression in patients less than 2 years old (8). This was also in agreement with a study of a 25-year-old woman suffering from puzzling abdominal pain, sinus rhythm, intra-ventricular conduction defect and acute respiratory failure for several weeks. After several assessment and inducing toxicology testing it showed a markedly elevated blood loperamide level of 32 ng/mL indicating drug abuse (9).

In the kidney, the main lesions found after high-dose intake included cellular morphology damage, narrowing of the tubular lumen, necrosis and nuclear alterations such as pyknosis, karyorrhexis and karyolysis; furthermore, intratubular congestion and focal glomerular atrophy were observed. These abnormalities could possibly result in impairment of of tubular reabsorption and flow, thus affecting renal function integrity. Altogether, these findings indicate renal injury from cellular degeneration to irreversible cell damage. These findings were in agreement with previous research that examined the metabolic changes in SD rats following loperamide intake and found alteration in kidney-related biochemical parameters, specifically a reduction in creatinine levels and possible indication of toxicity in both the liver and kidney. However, measured kidney function biomarkers including blood urea nitrogen (BUN) and creatinine and found no significant change in BUN levels but a decrease in creatinine levels indicating loperamide renal effects (22). This study included the use of

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chloroform vapor for euthanasia in accordance with the laboratory procedure with which the researcher was trained in at the time of the experiment. The control group underwent a similar procedure as to treated groups and showed no apparent histopathological alteration in both organs. Even though the histopathological findings clearly demonstrate the hepatic and renal alterations and cell effects following repeated high-dose of loperamide exposure, quantitative statistical analysis of histological lesions is needed. Furthermore, this study was limited due to the absence of biochemical parameters such as determination of Alanine aminotransferase (ALT), Aspartate Aminotransferase (AST) and Alkaline phosphate tests which would have given clear quantitative data on liver cell injury and bile duct/liver function abnormalities. While performing creatinine and blood urea nitrogen (BUN) tests would have given evidence on kidney function, filtration, and urea metabolism and should be further studied in future experiments.

Conclusion

Although Loperamide has a well-established clinical safety report at therapeutic doses, the results indicated that the abuse of this medicine at higher than recommended intake is associated with several hepatic and renal effects. This study concludes the association between loperamide therapeutic dose intake and possible renal and hepatic effects such as necrosis and partial congestion haemolysis. This study also indicates the connection between high-dose of loperamide administration and several histopathological alterations in the liver and kidney, including vascular congestion, nuclear pyknosis, necrosis and karyorrhexis with appearance of haemorrhagic alterations in addition to hepatic and renal cell necrosis. These morphological changes provide evidence of hepatic and renal injury following high-dose loperamide intake and further pharmacological characteristics should be taken into consideration.

DECLARATIONS

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Competing interests statement

The author declares no conflict of interest, financial or otherwise, that affected on the results or interpretation of this research.

Ethics statement

The author confirms that this research follows the journal's Attached Ethic Approval guidelines and policies as noted on the journals author guidelines page, and approved by the

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Ethical Committee of Scientific Research (ECSR), Faculty of Education for Pure Sciences (TU; No.2026.14).

Author contributions

Asraa Abed Thiyab was responsible for conceptualization, methodology, data analysis, interpretation of results, and writing and revision of the manuscript. The author approved the final version of the manuscript.

References

1. Apotex Inc. Loperamide: loperamide hydrochloride tablets USP 2 mg: oral antidiarrheal agent [Internet]. Weston (ON): Apotex Inc.; 2012 Jan 6 [cited 2026 Nov 1]. 31 p. Available from: https://pdf.hres.ca/dpd_pm/00015415.PDF
2. Barakat M, Akour A, Malaeb D, et al. Perspectives of and experience toward the abuse of antidiarrheal drug (loperamide) among community pharmacists: a cross-sectional study. Int J Environ Res Public Health. 2023;20(14):6400. doi:10.3390/ijerph20146400.
3. Berger SI, Ma'ayan A, Iyengar R. Systems pharmacology of arrhythmias. Sci Signal. 2010;3(118). doi:10.1126/scisignal.2000723.
4. Tan CC, Ting USL, Khoo ZX, et al. Cytotoxic effects of opiate agonist loperamide hydrochloride on human oral cancer cells—an in vitro study. Explor. Med. 2025; 6:1001301. doi:10.37349/emed.2025.1001301.
5. Lei Z, Rong H, Yang Y, et al. Loperamide induces excessive accumulation of bile acids in the liver of mice with different diets. Toxicology. 2022;477:153278. doi:10.1016/j.tox.2022.153278.
6. Enakpene EO, Riaz IB, Shirazi FM, et al. The long QT teaser: loperamide abuse. Am J Med. 2015;128(10):1083-1086. doi:10.1016/j.amjmed.2015.05.019.
7. Hugnet C, Cadore JL, Buronfosse F, et al. Loperamide poisoning in the dog. Vet Hum Toxicol. 1996;38(1):31-33. PMID:8825747.
8. Lu HR, Damiano BP, Kreir M, et al. The potential mechanisms behind loperamide-induced cardiac arrhythmias associated with human abuse and extreme overdose. Biomolecules. 2023;13(9):1355. doi:10.3390/biom13091355.
10. Yakubu MT, Adams MD. HPLC profile, biochemical and histoarchitectural changes in loperamide-induced constipated Wistar rats after oral administration of aqueous extract of Cnestis ferruginea (Vahl ex DC) roots. Pharmacol Res Nat Prod. 2025;6:100144. doi:10.1016/j.prenap.2025.100144.
11. Riviere J, Papich M, Adams H. Veterinary pharmacology and therapeutics. 9th ed. Hoboken (NJ): Wiley-Blackwell; 2011.

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https://creativecommons.org/licenses/by-sa/4.0/

12. Bancroft JD, Suvarna SK, Layton C. Bancroft's theory and practice of histological techniques. 7th ed. London: Elsevier; 2013.

13. Drugs.com; 2015 [cited 2015 Aug 25]. Available from: [https://www.drugs.com/monograph/loperamide-hydrochloride.html] (https://www.drugs.com/monograph/loperamide-hydrochloride.html)

14. Gong XW, Xu YH, Chen XL, et al. Loperamide, an antidiarrhea drug, has antitumor activity by inducing cell apoptosis. Pharmacol Res. 2012;65(3):372-378. doi:10.1016/j.phrs.2011.11.007.

15. Olofinsan KA, Ajala-Lawal RA, Ajiboye TO. Loperamide-induced cardiotoxicity in rats: evidence from cardiac and oxidative stress biomarkers. J Biochem Mol Toxicol. 2019;33(4). doi:10.1002/jbt.22278.

16. Thomas T, Egbuzuo U, Laiyemo AO. Link between anti-diarrheal medications and liver abscesses. Am J Gastroenterol. 2017;112(Suppl 1). doi:10.14309/00000434-201710001-02247.

17. Gottlieb S. Emerging issues of misuse and abuse of OTC loperamide challenge FDA to address a new turn in the opioid addiction crisis, while maintaining access for patients [Internet]. Silver Spring (MD): US Food and Drug Administration; 2018 May 9 [cited 2026 Oct 15]. Available from: https://blogs.fda.gov/fdavoice/index.php/2018/05/emerging-issues-of-misuse-and-abuse-of-otc-loperamide-challenge-fda-to-address-a-new-turn-in-the-opioid-addiction-crisis-while-maintaining-access-for-patients/

18. Akel T, Bekheit S. Loperamide cardiotoxicity: a brief review. Ann Noninvasive Electrocardiol. 2018;23(2). doi:10.1111/anec.12505.

19. Killinger JM, Weintraub HS, Fuller BL. Human pharmacokinetics and comparative bioavailability of loperamide hydrochloride. J Clin Pharmacol. 1979;19(4):211-218. doi:10.1002/j.1552-4604.1979.tb01654.x.

20. Eggleston W, Clark KH, Marraffa JM. Loperamide abuse associated with cardiac dysrhythmia and death. Ann Emerg Med. 2017;69(1):83-86. doi:10.1016/j.annemergmed.2016.03.047.

21. Qiu B, Zhu L, Zhang S, et al. Prevention of loperamide-induced constipation in mice and alteration of 5-hydroxytryptamine signaling by *Ligilactobacillus salivarius* Li01. Nutrients. 2022;14(19):4083. doi:10.3390/nu14194083

22. Kim JE, Lee YJ, Kwak MH, et al. Metabolomics approach to serum biomarker for loperamide-induced constipation in SD rats. Lab Anim Res. 2014;30(1):35-43. doi:10.5625/lar.2014.30.1.35.

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