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Toxic Effects of Morphine on the Kidneys in Domestic Rabbits

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Abstract Morphine is a drug that belongs to a group of drugs called opioid analgesics or narcotics. This study was conducted to evaluate the effect of Morphine is toxic to kidney tissue in domestic rabbits. 21 male domestic rabbits were used in this study. They were divided into three groups: the first (control) was injected with distilled water, the second and third groups, each group containing 7 rabbits, were injected with morphine subcutaneously for 35 days. The results confirmed the presence of degenerative changes represented by vascular congestion in some blood vessels, contraction of the glomerulus and expansion of Bowman's space, in addition to the separation of some tubular cells from the basement membrane. It was an infiltration of the inside of the tubular lumen and the spread of tubular cell necrosis with the appearance of edema. The results confirmed the effect of morphine on the average diameters of the glomeruli, with significant differences.

Key Words Bowman Space, Domestic Rabbit, Kidneys, Morphine, Toxic

INTRODUCTION

Morphine is a drug belonging to a group of drugs called opioid painkillers or drugs, which is an opium derivative extracted from the unripe seeds of the opium poppy plant [1]. Morphine relieves severe and moderate pain because of injuries, surgeries, heart attacks or chronic diseases including cancer and it is additionally used as a preoperative treatment to reduce the level of alertness and anxiety [2]. It was first extracted within the city of Paderborn in Germany in the fall of 1803 by Fredrick Sertürner and called it morphine ratio. To the ancient Greek god of dreams Morpheus. Morphine contains in its chemical structure an aromatic ring representing the nucleus of phenanthrene [3]. This ring is connected to several hydrogen coals that take the shape of a boat and stop with the element nitrogen connected to the root of an instance known as piperidine. Studies show that the phenol ring and the piperidine ring are responsible for pain relief events and add to it a penta-ring and hydroxyl radicals (4) was initially used as an analgesic substance, but then it was proven that it can cause addiction and is considered an epidemic of materials Opioids are a public health crisis with inside the United States [5,6,7] and the high dose of Morphine slows the respiratory tract speed, leading to hypoxia and demise, hypotension, drowsiness, vomiting, constipation, severe cough, urinary retention and opioids exert their harmful effects on breathing through activating beta-opioid receptors [8,9]. Oxidative stress and free radicals rise due to the use of morphine [10]. Opioids decrease kidney function by diminishing the renal plasma flow with the drift [11]. The liver and the kidneys are the major organs of metabolism and toxin excretion through urine and feces [12]. This way, the majority of foreign chemicals introduced into the body, such as drugs, are metabolized by hepatocytes and eliminated by renal cells. It is even likely that in the process of metabolism, waste products damage liver and renal cells [13]. Morphine has commercial names, including Oramorph, Cefridol, Morcap and Zomorph [14]. The kidney is the most important part of the urinary device consisting of kidneys, ureters, urinary bladder and urethra The kidneys are characterized in different vertebrates being of similar basic tissue structure in addition to the similarity of the function may be lobed or smooth and different in terms of location and glomeruli and tubules and the degree of complexity and arrangement [15]. The kidney is a glandular organ and there is a pair of them on both sides of the spine and connected to the dorsal wall of the abdomen and their natural color is red-brown that modifications because of the disease and chemicals carried within the blood and its shape as a bean [16].

The structural and functional unit of the mechanism is known as nephrons and there are with inside the human college about (1-1.5) million nephrons in animals, their numbers increase or lower depending on the size and type of animal [17].

Despite the extensive use of morphine as a critical analgesic in medical treatments, limited studies have explored its specific toxic effects on kidney tissues, particularly in animal models such as rabbits. Although earlier studies have largely described systemic effects of opioids, detailed studies of the dose-dependent changes in renal tissue morphologically and functionally are not available. The role of morphine in inducing glomerular degeneration, vascular congestion, tubular cell necrosis and basement membrane detachment has not been thoroughly documented, leaving a gap in understanding the underlying mechanisms of morphine-induced renal toxicity. Moreover, the physiological long-term consequences like weight loss and disruption in metabolism brought about by morphine exposure are not given prominence in existing research.

Study Objective

The present study aims to analyze the toxic effects that are generated by morphine on local rabbit kidney tissues (Oryctolagus cuniculus) using thorough histopathological and physiological evaluations. The experiment explores dose-related changes in renal morphology like glomerular decrease, widening of Bowman's space, vascular engorgement and tubular necrosis after administering morphine subcutaneously for 35 days in doses of 30 mg and 60 mg. Also, the research investigates the impact of morphine on weight and health to reveal systemic effects and changes in metabolism induced by chronic opioid treatment.

This research presents new information regarding the individual histopathological alterations resulting from chronic morphine exposure in renal tissue, a facet of interest not extensively explored through earlier research. While the majority of studies were founded on the renal effects of opioids, this research significantly identifies dose-dependent renal toxicity, including glomerular tightening, necrosis in tubular cells and basement membrane disassociation. Apart from that, the research closes the gap between exposure to morphine and its physiological effects, like marked loss in weight and change in behavior and provides an exhaustive account of the influence of morphine on tissue structure and health.

Working methods

The research was carried out on 21 adult male local rabbits of 1-1.96 kg, bought from local markets in Diyala. The rabbits were kept in a farm under normal conditions in cages with dimensions of 150 × 70 × 50 cm, raised 25 cm above the floor with wire mesh to ensure hygiene and ventilation. The rabbits were divided into three groups and in each group, there were 7 rabbits. The control group was the first group and received a subcutaneous injection of distilled water. The second group was administered a subcutaneous injection of 30 mg of morphine and the third group was given 60 mg of morphine. The injection schedule was repeated for 35 consecutive days to study the morphine exposure effect. All rabbits were sacrificed at the end of the experiment. Rabbit kidneys were carefully dissected and placed in formalin solution for histological analysis [18]. Tissue sections were handled according to routine histopathological protocols to study morphological alterations of kidney tissues. Body weights of the rabbits treated with morphine were also measured pre-experiment and post-experiment to study the effects of morphine on growth and metabolism.

RESULTS

Phenotypic Modifications

The study revealed that rabbits exposed to morphine exhibited several adverse phenotypic changes, including fatigue, lethargy, reduced movement and decreased food intake. Additional symptoms, such as itching, slow breathing and aggression, were particularly evident in the group treated with 60 mg of morphine. The narcotic effect of morphine appears to intensify with increased doses, contributing to more pronounced behavioral changes. The results also demonstrated a significant decrease in body weight across the experimental groups treated with morphine compared to the control group. Rabbits in the 30 mg and 60 mg treatment groups experienced a notable reduction in their mean body weights, as shown in Table 1, with differences statistically significant at the 0.05 level.

These factors collectively underline the significant physiological burden imposed by prolonged morphine exposure, particularly at higher doses. Table 1 summarizes the effect of morphine on the mean body weight of rabbits across three groups: the control group, the 30 mg morphine group and the 60 mg morphine group. The control group exhibited the highest mean body weight (1.37±0.11µm), indicating normal growth and health conditions. In contrast, rabbits treated with 30 mg of morphine showed a significant decrease in mean body weight (0.92±0.09µm) and this reduction was statistically significant ($p \leq 0.05$). The 60 mg group demonstrated the most severe effect, with body weight dropping further, although no standard error is recorded in this table. The mean weight across all 21 rabbits was 0.92±0.43µm.

The Group Injected with 30mg Morphine

Figure 1 shows a transverse section of the kidney tissue from rabbits treated with 30 mg/kg of morphine for 35 days, stained with hematoxylin and eosin (H&E) at 10X magnification. The histological examination reveals notable pathological changes, including vascular congestion, expansion

Table 1: Effect of morphine on Mean body weight/µm

Groups	No	Mean±Std. error
Control	7	1.37±0.11*
30 mg	7	0.92±0.09*
60 mg	7	60 mg
Total	21	0.92 0.43

*Differences are statistically significant at the 0.05 level

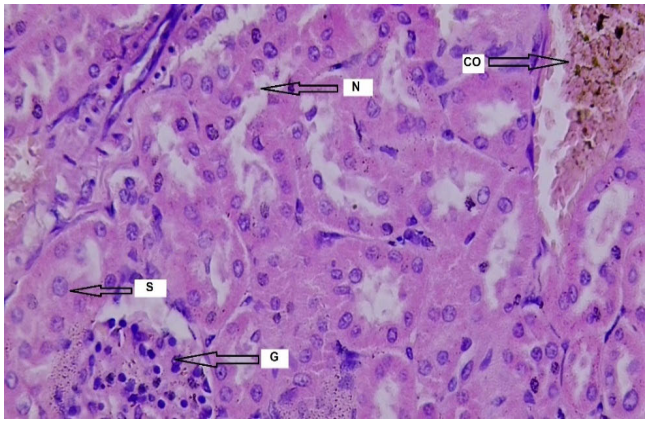

Figure 1: Transverse section with inside the kidney of rabbits of the group treated with a concentration of 30 mg/kg of morphine for 35 days showing G glomerulus, S cell expansion, N tubule cell necrosis, CO hematogenesis (H&E 10X)

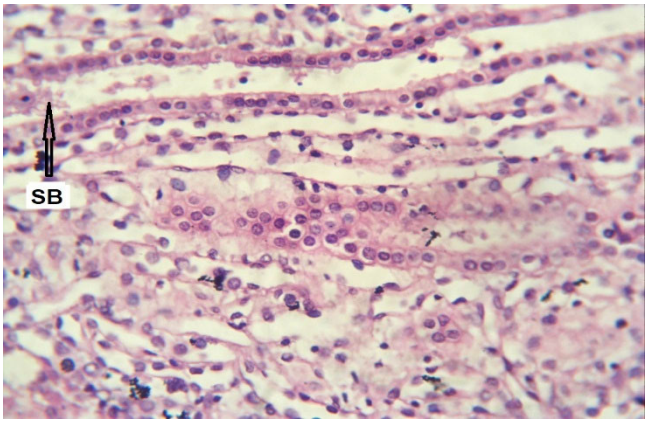

Figure 3: Cross-sectional section with inside the kidney of rabbits from the treatment group with a dose of 30 mg/kg of morphine for 35 days presents SB separation of some tubule cells from the basement membrane

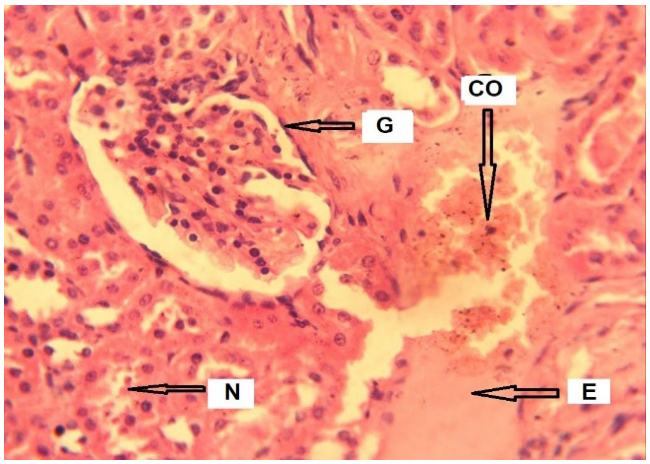

Figure 2: Transverse section with inside the kidney of group treated rabbits of a concentration of 30 mg/kg of morphine for 35 days showing G glomerulus, E edema, N tubule cell necrosis and CO hematological congestion

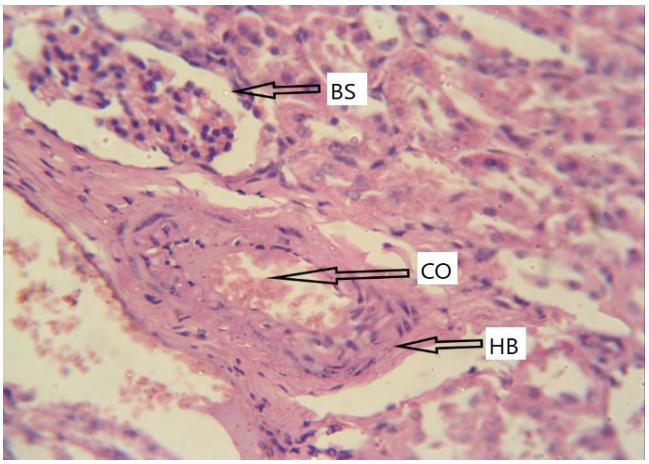

Figure 4: Cross-section with inner kidney of a group of rabbits treated with a 60 mg/kg dose of morphine for 35 days with HB vascular wall hyperplasia, BS Bowman space, CO hemocongestion (H&E 10X)

Table 2: Effect of morphine on mean glomeruli/µm

Groups	No	Mean±Std. error
Control	7	87.16±6.55
30 mg	7	75.54±5.09**
60 mg	7	52.42±4.49*
Total	21	71.70±4.39

*Marked differences with the control group at 0.05 likelihood, **Marked differences between treatment groups at 0.05 likelihood

of renal tubular cells and necrosis. The labeled regions highlight significant damage to the renal tubules, with areas marked N indicating tubular cell necrosis, characterized by cell swelling, disintegration and loss of structural integrity.

Figure 2 presents another transverse section of the kidney tissue of rabbits treated with 30 mg/kg of morphine for 35 days, stained similarly at 10X magnification. The section highlights additional pathological features, including glomerular contraction (G), edema (E), tubular cell necrosis (N) and hematological congestion (CO). The glomerulus appears severely contracted, suggesting a decline in glomerular cell function and structural integrity. This contraction is associated with Bowman's space expansion, which disrupts the glomerular filtration process and signifies significant glomerular damage. The edema, marked as E, indicates fluid accumulation in the renal tissue, a common response to cellular injury and oxidative stress.

The Group Injected with 60mg Morphine

Figure 3 illustrates a cross-sectional view of the kidney tissue from rabbits treated with 30 mg/kg of morphine for 35 days, highlighting significant histopathological changes. The region labeled SB shows the separation of some tubular epithelial cells from the basement membrane, which is a hallmark of severe renal damage. This separation is a consequence of cellular swelling, which occurs due to the toxic effects of morphine.

Figure 4 displays a cross-sectional view of kidney tissue from rabbits treated with a higher concentration of morphine

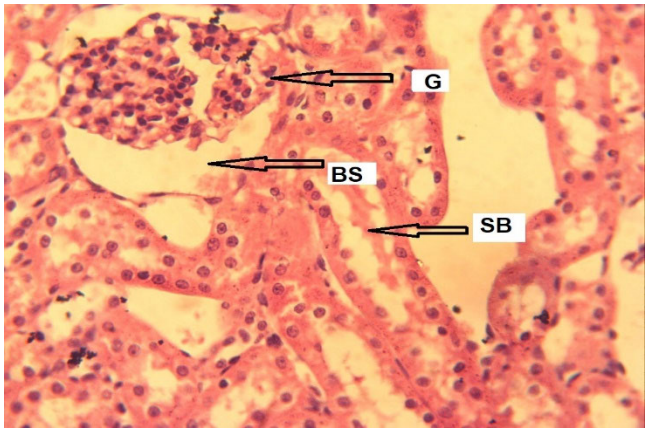

Figure 5: Cross-section with inside kidney of rabbits belonging to the group that was treated with a dose of 60 mg/kg of morphine for 35 days, where G glomerulus, SB separation of tubule cells and the basement membrane, BS Bowman space (H&E 10X)

(60 mg/kg) for 35 days, stained with hematoxylin and eosin (H&E) at 10X magnification. The section highlights critical pathological changes, including HB vascular wall hyperplasia, BS Bowman space expansion and CO hemocongestion. Hyperplasia of the vascular wall (HB) is an increase in blood vessel wall thickness resulting from long-term morphine intake. Hyperplasia of the vascular wall interferes with blood flow and leads to reduced oxygenation and delivery of nutrients to renal tissue, enhancing hypoxia and cell injury.

Figure 5 is a cross-sectional image of kidney tissue in the same rabbits that were administered 60 mg/kg morphine for 35 days stained with H&E at 10X. The figure demonstrates profound morphology changes in the renal structures G glomerulus, BS Bowman space and SB separation of tubule cells and basement membrane. The glomerulus reflects contraction and cellular degeneration, which illustrates compromised glomerular function. This structural injury disrupts kidney filtration and compromises its solute and fluid balance. BS Bowman space is grossly dilated, a result of glomerular contraction and disruption of cellular integrity. The combined effects of glomerular contraction, Bowman space expansion and tubular cell separation highlight the extent of renal damage caused by prolonged exposure to high doses of morphine.

Table 2 shows the effect of morphine administration on the mean glomerular diameter in rabbits across three groups: the control group, the 30 mg morphine group and the 60 mg morphine group. The control group, which received no morphine, exhibited the largest mean glomerular diameter (87.16±6.55µm), indicating healthy and intact kidney function. In contrast, the mean glomerular diameter significantly decreased in the groups treated with morphine. For the 30 mg morphine group, the mean diameter was reduced to 75.54±5.09µm and for the 60 mg group, it further decreased to 52.42±4.49 µm. These reductions are statistically significant, as indicated by the symbols (** and *), highlighting the dose-dependent impact of morphine toxicity on glomerular size.

DISSCUSION

The decline in body weight may be attributed to the impact of morphine on metabolic processes, which disrupt normal kidney functions and cause systemic stress [19]. The observed phenotypic modifications also indicate the broader toxic effects of morphine beyond the kidneys. Metabolic disorders caused by morphine's influence on vital organs contribute to the observed symptoms and weight loss [20]. Morphine's interference with digestive enzymes reduces the animals' capacity to metabolize food efficiently, leading to malnutrition and a subsequent decline in physical health [21]. Tubule cell necrosis results from the accumulation of fluid and cellular debris due to morphine toxicity [22]. The region marked S corresponds to tubular epithelial cell expansion, which occurs as a result of intracellular fluid buildup and swelling [23]. These changes are indicative of renal cell injury, consistent with oxidative stress and disrupted cellular metabolism caused by morphine exposure, The marked contraction of the glomerulus, denoted by G, with an expanded Bowman's space. This contraction points to significant degeneration and loss of glomerular cells, impairing the kidney's filtration capacity. The vascular region labeled CO highlights hematological congestion, where blood accumulates in the vessels due to impaired circulation, caused by the toxic effects of morphine [24]. Morphine induces oxidative stress that disrupts cellular metabolism and causes the accumulation of intracellular fluid, leading to swelling and detachment of the cells. The resulting blockage of the tubule lumen impedes normal renal function, particularly the reabsorption and secretion processes, which are vital for maintaining fluid and electrolyte balance [25]. Furthermore, the cellular necrosis observed can be attributed to calcium deposition and mitochondrial dysfunction, both of which are exacerbated by oxygen deficiency [26]. Morphine toxicity disrupts renal blood flow, reducing oxygen supply to tubular cells [27]. This hypoxia impairs the mitochondria's ability to produce energy, leading to cell death [28]. The necrotic cells and cellular debris further accumulate within the tubular lumen, exacerbating blockages and contributing to the deterioration of kidney function [29]. The decrease in glomerular diameter reflects glomerular contraction and degenerative changes induced by morphine, which impair the kidneys' filtration ability. The contraction of glomeruli results from cellular damage, including necrosis and oxidative stress, which disrupts the structural integrity of glomerular cells. The severity of these changes is greater in the 60 mg group, demonstrating that higher doses of morphine exacerbate renal damage, these pathological changes indicate that prolonged morphine exposure causes progressive damage to the renal tubular epithelium, ultimately compromising the structural and functional integrity of the kidneys [30]. The most glaring pathological alteration is the SB separation of the basement membrane from tubular epithelial cells. It is

due to swelling and necrosis of the cells that have resulted from morphine, a byproduct of hypoxia and mitochondrial damage. The detachment of cells disrupts the renal tubules' structural and functional integrity, leading to luminal blockages and impaired reabsorption processes [31] The labeled N highlights necrotic tubular cells, which appear swollen, fragmented and disorganized, confirming morphine-induced damage to the renal tubular epithelium. Necrosis in renal tubules disrupts the reabsorption and excretion processes, contributing to renal dysfunction [32]. The region marked CO shows pronounced hematological congestion, where blood accumulates in the capillaries and vessels due to impaired circulation and vascular integrity, This congestion further exacerbates tissue injury by limiting oxygen and nutrient delivery to renal cells, creating hypoxic conditions, The findings collectively indicate that morphine toxicity triggers oxidative stress, leading to edema, necrosis and significant disruption of renal tissue structure and function [11].BS Bowman's space expansion is an important feature. It is an expansion due to glomerular degeneration or reduction of the glomerular cells, hence resulting in expansion of the surrounding Bowman space, hemocongestion is proof of disturbed blood flow, usually a result of the morphine-induced vascular damage and hyperplasia, All such pathological changes combined with vascular wall hyperplasia, Bowman space elongation and hemocongestion are indicative of the strong dose-dependent effect of morphine on renal structure and function, delineating the hazards of prolonged exposure to excessive morphine levels [33] The glomerular injury affects the filtration capability of the kidney, an important process in homeostasis maintenance. The CO hemocongestion is also evident, with visibility of blood congestion within the renal vessels [34].

CONCLUSIONS

The present study was initiated to investigate the toxic effects of morphine on kidney tissues in domestic rabbits (*Oryctolagus cuniculus*), considering the widespread use of opioids for pain management and their potential adverse impacts on organ systems. Previous research has highlighted the systemic effects of morphine; however, its specific impact on renal structure and function remains underexplored. The need for this study arises from concerns regarding the dose-dependent nature of morphine toxicity, which could compromise kidney health over prolonged use.

The findings demonstrate that prolonged morphine administration induces significant renal damage, as evidenced by vascular congestion, tubular cell necrosis and the detachment of epithelial cells from the basement membrane. These structural changes reflect severe impairment of renal function, driven by hypoxia, mitochondrial dysfunction and oxidative stress. Notably, morphine toxicity also caused the accumulation of fluid within cells, leading to cell swelling and blockage of the tubule lumen. The observed dose-dependent changes in glomerular morphology, with significant reductions in glomerular diameter in the 30 mg and 60 mg morphine-treated groups. The contraction of glomeruli and expansion of Bowman's space in the experimental groups point to progressive damage to the renal filtration units. These changes impair glomerular function, which is essential for the regulation of fluid and electrolyte balance. The higher dose group (60 mg) exhibited more severe degenerative changes, reinforcing the correlation between morphine dose and renal toxicity.

Behavioral and physiological observations further confirmed the systemic impact of morphine. Rabbits in the 60 mg group displayed lethargy, fatigue, reduced appetite and significant weight loss. These symptoms are linked to renal dysfunction and morphine-induced metabolic disruptions, including decreased digestive enzyme secretion. The resulting malnutrition and reduced energy balance suggest that morphine toxicity extends beyond renal damage, impacting health. In conclusion, this study highlights the significant risks associated with prolonged morphine administration, particularly at higher doses. Further research is recommended to identify protective strategies and alternative treatments to mitigate opioid-induced renal toxicity.

Ethical Statement

Ethical clearance has been taken from the Institutional Ethical Committee.

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