The Intraperitoneal-Ketoprofen-Histopathological Induced Alterations in the Wistar Rat Kidneys

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Abstract

The current-focused study was carried out to generate a data profile about expected changes that could be induced in the kidneys of rats due to the use of intraperitoneal ketoprofen (KP). The study involved using 24 adult male Wistar rats sorted randomly into four groups (six animals per group). One group was treated as a control group, C, which was supplied with distilled water (DW) only. The remaining animals were presented as (50KP), (25KP), or (12.5KP) groups that received 50mg/kg.b.w., 25mg/kg.b.w., or 12.5mg/kg.b.w., respectively, of KP. The experiment was continued for 70 days, and the kidney tissue samples were collected from the scarified animals at the end of day 70 of that experiment. The kidney tissues of the 50KP animals revealed dilation of the tubules throughout the outer strip of the outer medulla with necrosis and sloughing of the epithelial cells of the proximal convoluted tubules (PCTs). However, the 25KP group suffered lesser grades of epithelial-cell sloughing of the PCTs with lower levels of dilation of tubules than those recorded in the 50KP group. On the other hand, the kidney tissues of the 12.5KP group showed only dilation in the PCTs. The present experimental data unveil the side effects generated by the use of the intraperitoneal KP in the examined rat kidneys which should be used as a launching set of information for better use or further study this drug and its side effects in human patients.

Keywords*: Ketoprofen, renal failure, side effects.*

Introduction

KP is an anti-inflammatory, anti-pyretic, analgesic derivative of propionic acid with non-steroidal anti-inflammatory (NSAID) therapeutic properties. KP reduces cyclooxygenase I and II enzyme activity, which contributes to a reduction in prostaglandin and thromboxan precursor production. As a consequence, the decline in prostaglandin production triggers the therapeutic potential of ibuprofen via the enhancement of prostaglandin synthase. The production of A2 thromboxane by thromboxane synthases, which prevent the accumulation of platelets, is also decreased with KP [(1)]. KP is the 11th most popular in Italy with 206 records for 2008, of which some 30 percent is extreme, based on a survey of random cases of adverse outcomes. A maximum of 13 percent of reported data were in the aspect of pediatric patients (under 18 years of age), even in the age group (under six years old) of off-label medication use. The 2012 evidence is not fully accessible; however, unofficial statistics show that KP was implicated in 560 adverse drug reactions, of which 31 percent were seriously affected [(2,3)].

KP records are that because of the unwise consumption of KP in the world countries despite multiple warnings about hepatotoxicity compared to other NSAIDs such as nimesulide. The KP's reported adverse events contain peripheral edema as a cardiovascular response, central responses such as drowsiness, headache, etc., dermatological responses including skin sensitiveness and photosensitization, blood based responses e.g. edema, platelet malfunction, etc., kidney, elevation of enzymes in the liver, gastrointestinal reactions for example vomiting, diarrhea, gastric ulcer and bleeding, etc. Additional studies have

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shown at least intermittent serum aminotransferase elevations ranging between one percent and two percent of the patients receiving KP. Even with product continuity, these can be overcome. For less than one percent of cases, reported elevations of aminotransferase (more than threefold increased) exist. It is very unusual that liver damage with KP jaundice is clinically evident and only few cases have been recorded. The latency to onset of the symptoms is a quick process, sometimes appear within a few days. The trends of enzyme changes differ between hepatocellular and cholestatic. In some instances, immunoallergic symptoms (low level fever, rash) are observed, but are not usually prevalent and self-antibody development is uncommon [4,5].

The performance of adverse KP effects on the kidney have not been comprehensively studied from the prospective of tissue damages. According to that, the current-focused study was carried out to generate a data profile about expected changes that could be induced in the kidneys of rats due to the use of intraperitoneal KP.

Materials and Methods

Animals and experimental design

The study involved using 24 adult male Wistar rats, weighed at 175-250gm with 10-14 weeks of age, sorted randomly into four groups (six animals per group) that lived in a housing under 22-25°C. One group was treated as a control group, C, which was supplied with distilled water (DW) only. The remaining animals were presented as (50KP), (25KP), or (12.5KP) groups that received 50mg/kg.b.w., 25mg/kg.b.w., or 12.5mg/kg.b.w., respectively, of KP. The experiment was continued for 70 days, and the kidney tissue samples were collected from the scarified animals at the end of day 70 of that experiment.

Kidney tissue preparation

Ten percent formalin was used for fixing the tissue specimens for two hours that was followed by a 30-minute-DW based removal step of the fixative. Then, a series of alcohol concentrations at (70% for 30mins, 90% for 60mins, and 100% as two cycles for 60mins per cycle) was used to dehydrate the tissues followed by a 50%:50% of alcohol to xylene immersing step for clearing the tissues for 60mins. After that, the tissues were immersed in a pure xylene for 90mins. Later, molten paraffin wax was used to impregnate the tissues followed by embedding and blocking out those tissues. Paraffin based sections at 4 to 5um were hematoxylin- and eosin-stained. The tissue sections were prepared according to [6–8].

Results

The kidney tissues of the 50KP animals revealed dilation of the tubules throughout the outer strip of the outer medulla with necrosis and sloughing of the epithelial cells of the PCTs, figure 1.

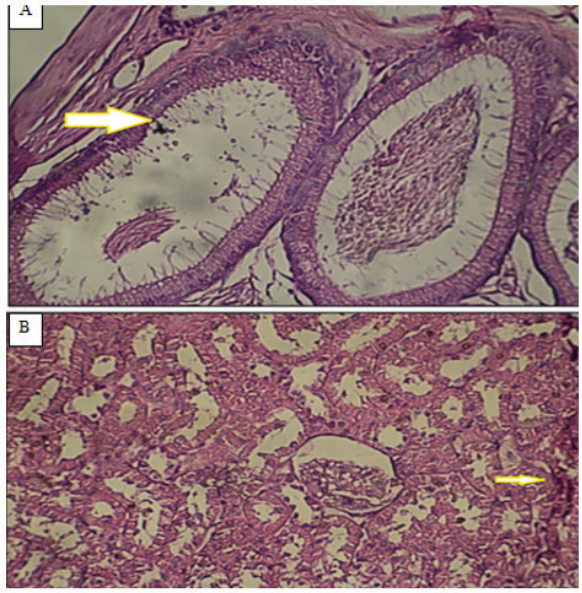

Figure 1: Rat kidney histopathological changes after intraperitoneal ketoprofen treatment at 50mg/kg.b.w. for 70 days. A. Dilation of the tubules throughout the outer strip of the outer medulla, (H&E) Stain.400X. B. Necrosis and sloughing of the epithelial cells of the proximal convoluted tubules. (H&E) Stain.200X.

However, the 25KP group suffered lesser grades of epithelial-cell sloughing of the PCTs with lower levels of dilation of tubules than those recorded in the 50KP group, figure 2.

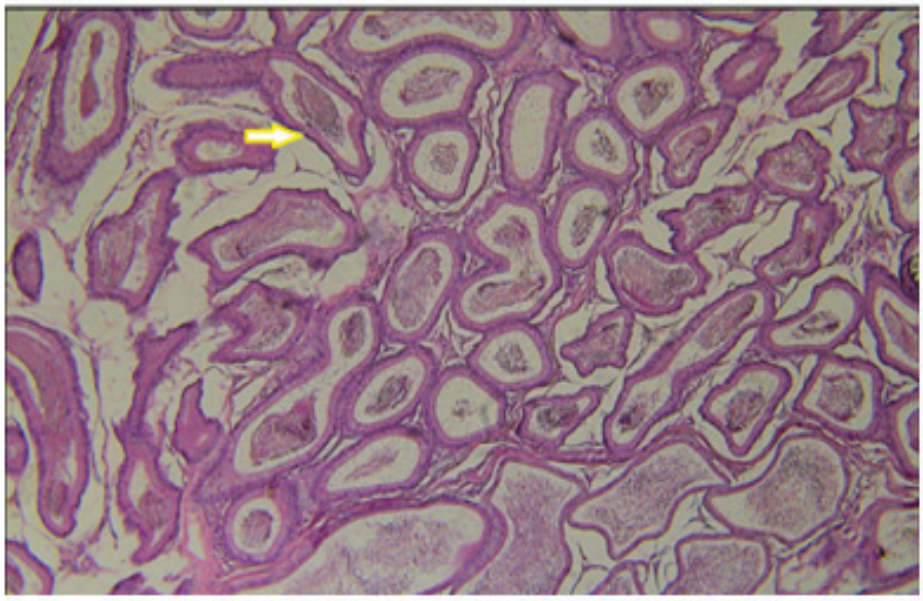

Figure 2: Rat kidney histopathological changes after intraperitoneal ketoprofen treatment at 25mg/kg.b.w. for 70 days. Changes are shown, here, as Lesser grades of epithelial-cell sloughing of the proximal convoluted tubules and lower levels of dilation of tubules than those recorded in the 50KP group. (H&E) Stain.200X.

On the other hand, the kidney tissues of the 12.5KP group showed only dilation in the PCTs, figure 3. The KP group kidney tissues were compared to each other and with the control group, figure 4.

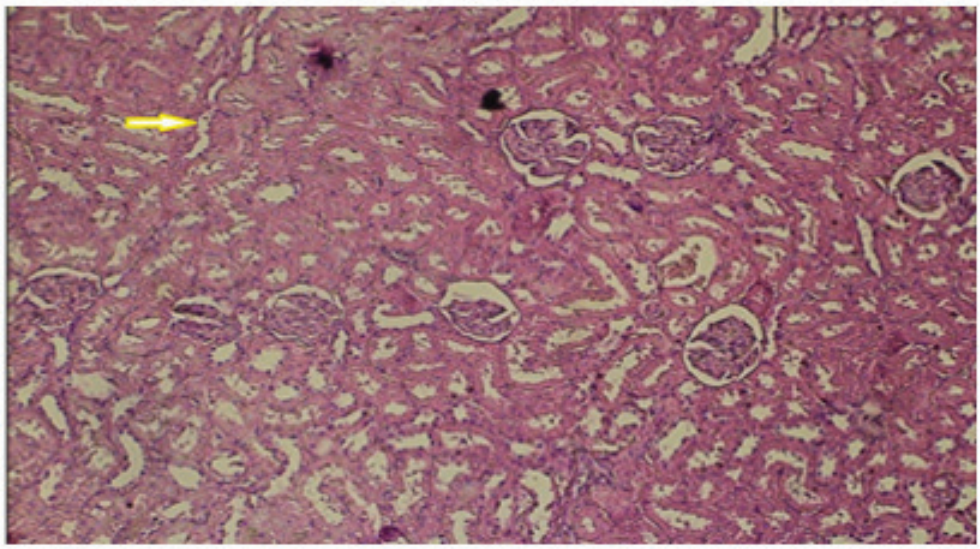

Figure 3: Rat kidney histopathological changes after intraperitoneal ketoprofen treatment at 12.5mg/kg.b.w. for 70 days. Only dilation in the proximal convoluted tubules is shown. (H&E) Stain.200X.

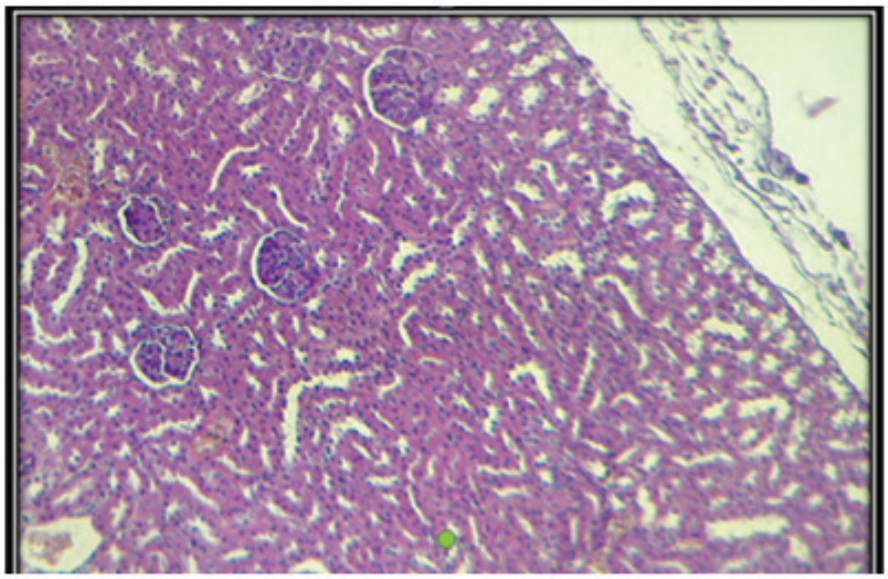

Figure 4: Normal cortical tubules and glomeruli of rat treated with distilled water within normal limits. (H&E) Stain.100X.

Discussion

Ketoprofen is a NSAID agent that is used for treating cases mediated by an inflammatory, fever, and/or pain process. The use of the drug as a therapeutic compound has been faced with a wide range of difficulties presented by the appearance of various adverse effects such as peripheral edema and platelet malfunction, drowsiness and headache, skin sensitiveness and photosensitization, and gastric ulcer and bleeding due to cardiovascular, central, dermatological, and gastrointestinal reactions, respectively, [9–13]. The adverse KP changes occurred in the kidney have not been fully sorted out. Therefore, the current work was conducted to characterized any histopathological alterations that could happen as responses to the use of KP in three concentrations.

The outcomes of the study unveiled that intraperitoneal ketoprofen treatment at 50mg/kg.b.w. for 70 days demonstrated dilation of the tubules throughout the outer strip of the outer medulla and necrosis and sloughing of the epithelial cells of the PCTs. Ingrasciotta *et al.*, [14] has found that using NSAID drugs such as oxicams, ketorolac, meloxicam, and piroxicam was positively correlated with the increased risk of developing chronic kidney disease (CKD). It has been suggested that utilizing ketorolac may induce CKD with a subclinical property due to acute renal damages [14]. This indicates an agreement with current findings that revealed the adverse effects encouraged by the use of the NSAID, KP, in the studied rats. The adverse effects of the KP use in humans can be inferred from a case report of a Turkish woman who received a topical treatment of KP as two times daily for five days who revealed increases in the levels of serum creatinine and urea which suggested an acute renal failure condition in this women [15]. The use of KP in pregnant women especially a short time before delivery has been found to increase the risk of renal dysfunction in the neonates [3]. The systemic-NSAID based kidney damages can be induced via acute interstitial nephritis due to a dose-independent allergic mechanism with cyclooxygenases 1- and 2-non-selective disruption causing an acute renal failure with reversed functions of the affected tissues [15].

However, those damages in the rat kidneys were correlatively decreased as the KP concentration was reduced. This was completely seen with groups 25KP and 12.5KP that showed lower grades of kidney tissue changes suggesting safer use of the KP with reduced concentrations. It has been recognized that using low doses of KP in children had led to the development of low rates of intense adverse effects with only nausea and vomiting [3].

The present experimental data unveil the side effects generated by the use of the intraperitoneal KP in the examined rat kidneys which should be used as a launching set of information for better use or further study this drug and its side effects in human patients.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER in Iraq

Conflict of Interest: Non

Funding: Self-funding

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