

## **Biochemical and histopathological effect of ketorolac on liver and kidney of local male rabbits**

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### **Abstract**

Ketorolac is anti-inflammatory analgesic drug which have high activity to reduce pain, used in rabbits, primary in ocular operation. In current study, the aim of it to obvious the biochemical and histopathological effect caused by ketorolac on liver and kidney of the rabbits. Thirty local male rabbits were used, the rabbits divided equally and randomly into three groups, first control group, second group and third group ,each group consist of ten rabbits and the study continuous for 14 days. The Biochemical result of this study revel normal value in first control group, the second and third group showed significant increase in the liver enzyme, creatinine, bilirubin and nitrogen urea. Histopathological changes showed normal histological structures of liver and kidney in control group. Liver in second group showed cellular necrosis and hemorrhage at 15 mg/kg of ketorolac, while injection of 30 mg/kg in third group, the liver showed complete destruction of cell membrane. Kidney in second group showed hemorrhage at 15 mg/kg of ketorolac while injection of 30 mg/kg of ketorolac in third group, the kidney showed glomerular atrophy, bowman space dilation, collapsed tuft, degenerated tubules and cellular necrosis.

**Keyword: ketorolac, analgesic, liver, rabbits, biochemical study.**

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## Introduction

With the development of more surgical operation in the animal medicine, it is necessary to needed analgesic has ideal properties characterized by high interest with low side effect on the body. Main surgical operation with high pain deals with opioids to reduce pre and post-operative pain but this lead to presence of other problems related with side effect of these analgesic drug such as sedation, nausea, constipation and dependence. NSAIDs become alternative of opioids like ketorolac because of high efficiency with the pain with low damage to cellular tissue in contrast with other analgesia and the anti-inflammatory action depend upon inhibition COX enzyme which diminish PGF2 and prevent pain (1). Ketorolac or trade names Toradol, is a NSA drug used to reduce pain. It is suitable for use in cases of moderate to severe pain, especially for a period not exceeding six days. The medication is taken orally and nasally, or by intravenous or intramuscular injection, and is available as eye drops (2). Ketorolac is nonsteroidal anti-inflammatory analgesic drug, cyclooxygenase inhibitors, good tissue absorption, used for analgesic moderate to severe pain, and is generally not given for more than 5 days because of the potential for renal damage associated with its use. The drug is active when given with

## Material and methods

**Drug:** Ketorolac (15 and 30mg/kg) ampule was obtained from Baxter health corporation, India.

**Animal and experimental design:** Thirty local male rabbits were used in current experimental study, weight (1300-1500gm) and (10-12 month) of age. The study started after two weeks of suitable environment

paracetamol to reduce pain in infants due to does not suppress their breathing unlike opioids. Ketorolac is given in combination with opioid medications to relieve pain, and is also used to treat idiopathic pericarditis based on its anti-inflammatory effect (3). Repeated use of ketorolac may result in the accumulation of toxic substances in various body tissues, which leads to an increase in the appearance of its side effects, and this causes damage to body tissues such as the liver and kidneys (4). Ketorolac causes toxicity in the eye of rabbits when used as intravitreal injections (5). The more previous study about ketorolac when used as eye drops analgesic but the absorption may occur via conjunctiva or nasal mucus membrane to systemic circulation and cause unsuitable side effect in animal with chronic diseases (6). The primary uses of ketorolac for reduce ocular pain, prevent of eye infection, ocular edema. In rabbits, ketorolac used widely in ocular analgesia and prevent eye infection with low doses and long duration of action (7). For the important of this analgesic drug and because of severity of toxicity, this study aim to study the biochemical and histopathological changes in liver and kidney of ketorolac in local male rabbits.

undergo the rabbits. Animals divided into three groups, each group consist of 10 animals as the following:

- 1- First control group: injected daily with 1 ml of physiological normal saline (0.9% of NaCl solution) for 14 days.
- 2- Second group: injected daily with 15 mg/kg of ketorolac for 14 days.

3- Third group: injected daily with 30 mg/kg of ketorolac for 14 days.

**Biochemical analysis:** Blood samples obtained from rabbits ears collected in clean dry tubes and centrifuged to prepare serum for procedures of liver and kidney function. The liver function including aminotransferase (ALT), aspartate aminotransferase (AST) and serum alkaline phosphatase (ALP) in addition to calculate the bilirubin (8). Kidney functions including determining of creatinine and blood urea nitrogen (9).

## Result

### Biochemical results

Group 1 showed normal value of the liver function tests while there are significant increase of ALT and AST in second and third group (Table 1). Also there are significant increase in alkaline phosphates & bilirubin in second and third group with become normal in the control group (Table 2),

**Statistical analysis :** mean standard deviation used for this data in current study, SPSS program version 19 analyzed it and the Data were considered statistically significant with  $P \leq 0.05$  (10).

**Histopathological examination:** After the end of current study, the animal sacrificed , liver and kidney samples were preserver in 10% formalin for histopathological procedures (11),(12).

Table 3 showed normal value of creatinine with significant increase in second and third group.

The kidney functions showed significant increase in the blood urea in second and third group while the first group showed normal value of blood urea (Table 4).

**Table 1: AST and ALT Level Under Effect Of Ketorolac After 14 Days.**

Groups	AST (IU/L)	ALT(IU/L)
Group 1 (n=10)	33.6±1.6	122±1.5
Group 2 (n=10)	65.41±1.25	210.85±1.50
Group 3 (n=10)	75.80±1.15	235.65±2.50

SD,  $P < 0.01$  highly significant

**Table 2 :ALP and Bilirubin Level Under Effect Of Ketorolac After 14 Days.**

Groups	ALP(IU/L)	Bilirubin
Group 1 (n=10)	48.3± 0.20	0.11± 0.05
Group 2 (n=10)	73.3± 0.19	0.60± 0.05
Group 3 (n=10)	84.7± 85.2	0.75± 0.01

SD,  $P < 0.01$  highly significant



**Table 3 : Creatinine Level Under Effect Of Ketorolac After 14 Days.**

Groups	creatinine level(mg/dl)
Group 1 (n=10)	0.45±0.15
Group 2 (n=10)	0.65±0.25
Group 3 (n=10)	0.55±0.30

SD, P < 0.01 highly significant

**Table 4 : Blood Urea Level Under Effect Of Ketorolac After 14 Days.**

Groups	Blood urea level(mg/dl)
Group 1 (n=10)	35.3±22.5
Group 2 (n=10)	45.7±5.7
Group 3 (n=10)	52.5±1.5

SD, P < 0.01 highly significant

### Histopathological results

Control group showed normal histological structures of the liver (figure 1), second group when injected 15 mg/kg of ketorolac daily for two weeks, liver showed cellular necrosis and hemorrhage (figure 2) and injection of 30 mg/kg of ketorolac daily for two weeks, liver showed complete necrosis of cellular membrane (figure 3).

Kidney in control group showed normal histological of glomeruli, renal tubules and other structures (figure 4), second group when injected 15 mg/kg of ketorolac daily for two weeks, kidney showed hemorrhage of glomeruli (figure 5) and injection of 30 mg/kg of ketorolac daily for two weeks, kidney showed glomeruli atrophy, bowman space dilation, collapsed tuft, degenerated tubules and cellular infarction (figure 6).

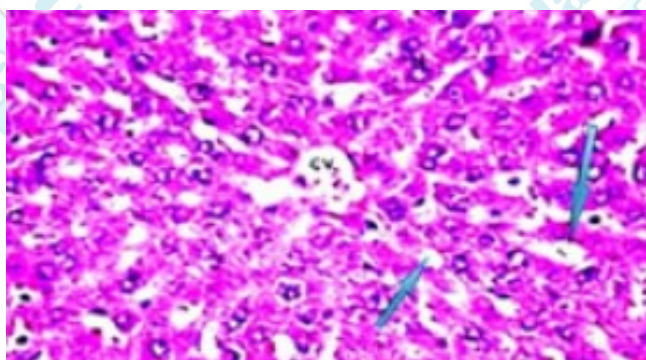


Figure 1. photomicrograph of liver (control group), showed normal hepatocyte and central vein (H&E. 40.X).

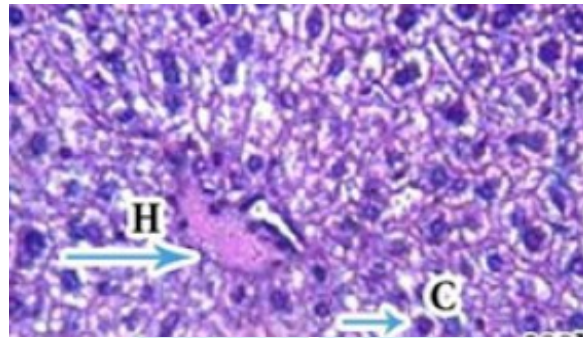


Figure 2. photomicrograph of liver (second group) at 15 mg/kg of ketorolac showed cellular necrosis (C), and hemorrhage (H), (H&E. 40.X).

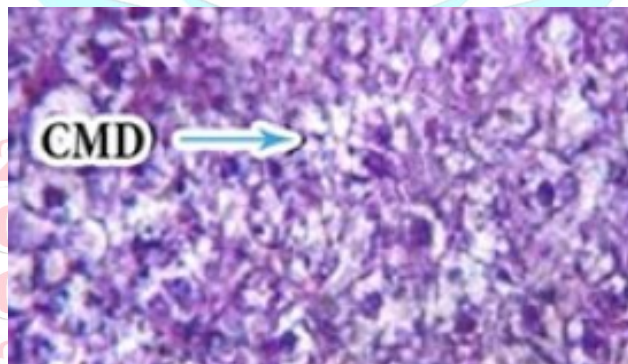


Figure 3. photomicrograph of liver (third group) at 30 mg/kg of ketorolac showed cellular membrane destruction (CMD), (H&E. 40.X).

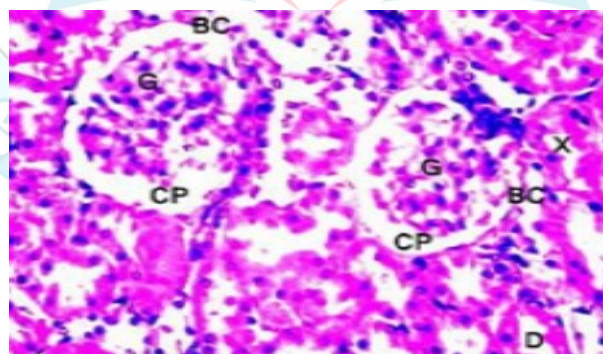


Figure 4. photomicrograph of kidney (control group), showed bowman capsule (BM), normal glomeruli histological appearance (G), normal cuboidal epithelium (CP), (H&E. 40.X).

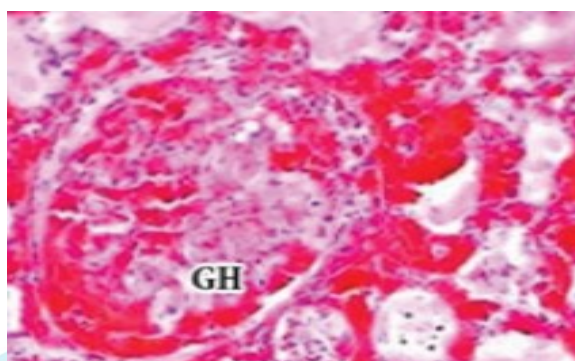


Figure 5. photomicrograph of kidney (second group) at 15 mg/kg of ketorolac showed glomeruli hemorrhage (GH), (H&E. 40.X).

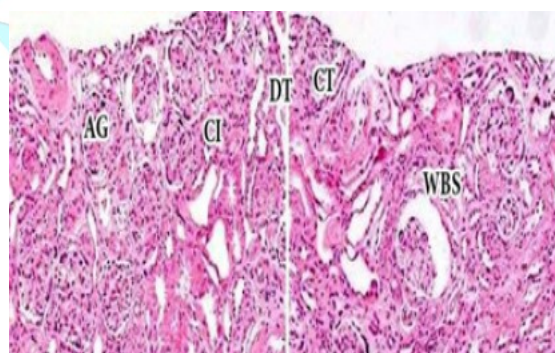


Figure 6. photomicrograph of kidney (third group) at 30 mg/kg of ketorolac showed collapsed tuft (CT), degenerated tubules (DT), widely bowman space dilation (WBC) atrophy of glomeruli (AG) in addition to cellular inflammatory cells infiltrations (CI), (H&E. 20.X).

## Discussion

Currently, analgesic are taken continuously and without medical advice in different parts of the world (13). After that, ketorolac was used to reduce pain after surgical operations. It was mainly used in eye surgeries as an alternative to many medications because it has a rapid action and lasts for a considerable period of time compared to opioids (7). Because of the excessive use of analgesic drugs among the world's population, the current study aimed to identify biochemical and histopathological changes caused by ketorolac in liver and kidney of local male rabbits. In this study the injection of 15 and 30mg/kg of ketorolac revel

increase in ALT,AST after long administration of it, this resemble other study when used of combination of diclofenac and ketorolac in rabbits (14). Significant increase in ALT and AST also recorded and resemble to the other study used ketorolac as liquid suppository (15). The value of ALT,AST,ALP showed significant increase in liver function parameter and this resemble to other study used the analgesic in many doses in rabbits (16). Also there is increase in creatinine, bilirubin and blood urea as kidney function test which resemble to other study showed increase in same parameter when used of ketorolac in dogs and rats (17). The histopathological changes in



liver revealed cellular necrosis and hemorrhage at 15 mg/kg of ketorolac, at 30 mg/kg, liver showed complete destruction of cellular membrane, this signs resemble to other study used of ketorolac under isofluran anaesthesia in rabbits (14). Kidney in second and third group showed hemorrhage of glomeruli, glomerular atrophy, bowman capsule dilation and collapsed tuft, this histopathological changes reveal

### Conclusion

The current study showed the ketorolac have good analgesic properties but when increase doses of it lead to changes in liver and kidney function in addition to hepatotoxicity and nephrotoxicity.

toxic natural of ketorolac on the kidney because of excretion of it by the kidney caused dysfunction of kidney (18), these previous signs sure by increase of kidney parameter tests (creatinine, blood urea) in second and third group (19). Above study may be aggrment with other study reported hepatotoxicity and nephrotoxicity occur by ketorolac (20).

### Recommendation

Ketorolac have good analgesic properties and widely used but the used of it under control and identify the patient or in veterinary uses about advantage and disadvantage in addition to monitor the liver and kidney function, also there is necessary to study the effect of this drug by other tests.

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