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Original article

Hepatorenal Toxicity of Different Doses of Ketorolac Administration in Adult Male Rats: A Preclinical Study

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SUMMARY

Background/Aim. Ketorolac is a potent non-steroidal anti-inflammatory drug (NSAID) that can inhibit cyclooxygenase activity and prostaglandin synthesis, thereby reducing pain and inflammation. The aim of this study was to investigate the hepatorenal toxicity of ketorolac administration in adult male rats.
Methods. Twenty-four adult male Wistar rats were randomly assigned to three groups (n = 8 per group): a control group receiving normal saline (1 mL/kg), a low-dose ketorolac group (10 mg/kg), and a high-dose ketorolac group (20 mg/kg). The animals were maintained under standard housing conditions for three weeks after the last treatment. Blood samples were collected under anesthesia, and serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine (Cr) were measured using commercial kits and a BT 1000 Biotectica analyzer.
Results. Compared to the control group, the low-dose ketorolac group did not show a significant increase in ALT and AST levels, but the high-dose ketorolac group exhibited a significant elevation in these hepatic enzymes ($P < 0.05$). Both the low-dose and high-dose ketorolac groups demonstrated a significant increase in BUN and Cr levels compared to the control group, with the high-dose group showing a more pronounced elevation in these renal parameters ($p < 0.05$).
Conclusion. The findings of this study suggest that high-dose ketorolac administration can induce hepatotoxic and nephrotoxic effects, as evidenced by the increased levels of liver and kidney function markers in adult male rats. These results highlight the importance of careful monitoring and dose optimization when using ketorolac in clinical settings.

Keywords: **ketorolac, hepatorenal toxicity, kidney, liver, rat**

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INTRODUCTION

Ketorolac is a powerful non-steroidal anti-inflammatory medication that is extensively utilized for the treatment of moderate to severe pain (1, 2). As an inhibitor of cyclooxygenase (COX) enzymes, ketorolac blocks the synthesis of pro-inflammatory prostaglandins, thereby reducing pain and inflammation (3-4). While the analgesic and anti-inflammatory properties of ketorolac make it a valuable therapeutic option, non-steroidal anti-inflammatory drugs (NSAIDs) in general are known to carry risks of adverse effects, particularly involving the gastrointestinal, cardiovascular, and renal systems (5-7). The hepatotoxic and nephrotoxic potential of ketorolac has been a topic of concern in clinical practice. Several case reports and observational studies have documented instances of ketorolac-induced liver injury and acute kidney injury, often in the setting of prolonged administration or pre-existing comorbidities (8-11). However, the precise dose-dependent nature of ketorolac's hepatorenal toxicity has not been extensively characterized in controlled preclinical investigations.

Animal models, such as the adult male rat, provide a valuable platform to systematically evaluate the toxicological profile of pharmaceutical agents under standardized experimental conditions (12, 13). By employing this approach, researchers can elucidate the threshold doses at which ketorolac may exert detrimental effects on the liver and kidneys, thereby informing safer clinical use of this non-steroidal anti-inflammatory drug (NSAID). The present study aimed to investigate the dose-dependent hepatorenal toxicity of ketorolac administration in an adult male rat model.

METHODS

Study design and animal grouping

This was a controlled preclinical study that examined the dose-dependent hepatic and renal toxicity of ketorolac in an adult male rat model. The study included 24 adult male Wistar rats weighing 200-250 grams. The animals were randomly assigned to three groups (n = 8 per group), using a computer-generated randomization scheme. The control group (C) received 1 mL/kg of normal saline; the low-dose ketorolac group (LDK) received 10 mg/kg of ketorolac, whereas high-dose ketorolac group (HDK) received 20 mg/kg of ketorolac.

Animal housing and care

The experimental animals were housed in a regulated environment within the animal research facility, which was maintained at a temperature of 24 ± 2 degrees Celsius and operated on a 12-hour light/dark cycle. The rats had ad libitum access to typical rodent diet and drinking water for the full length of the study.

Drug administration and sample collection

The assigned treatments were administered daily via oral gavage for three weeks. One week after the last dose, the animals were anesthetized, and blood samples were collected via cardiac puncture using sterile syringes. The blood samples were permitted to coagulate, after which they were centrifuged at 1500 revolutions per minute for 10 minutes to separate the serum component. The serum samples were then stored at a temperature of -20 degrees Celsius until subsequent analysis could be performed.

Biochemical analyses

Serum levels of the following parameters were measured using commercial kits (Pars Azmoun, Iran) and a BT 1000 Biotectica auto-analyzer: AST, ALT, BUN, Cr.

Ethical considerations

The study was approved by the Ethics Committee of the university (IR.SHMU.REC.1397.113). The guidelines for the Care and Use of Laboratory Animals were followed. Only male animals were used in the study to eliminate potential confounding factors related to pregnancy.

Statistical analysis

Normality of the continuous variables was assessed using the Shapiro-Wilk test. One-way ANOVA compared mean liver and kidney function parameters across the three groups, with post-hoc LSD analysis identifying significant differences. P-

values less than 0.05 were considered statistically significant.

RESULTS

The mean weight of rats in the C group was 212.37 ± 11.01 g, in the LDK group it was 212.12 ± 3.79 g, and in the HDK group it was 214.5 ± 3.96 g, with no statistically significant difference among the three groups (p = 0.63).

Liver function markers

The AST and ALT levels are presented in Figure 1. One-way ANOVA revealed a statistically significant difference in mean AST (F (2.21) = 15.72, p < 0.001) and ALT (F (2.21) = 18.84, p < 0.001) levels across the three groups. Post-hoc analysis using the LSD test showed that the mean ALT level in the C group was 24.12 U/L, 39.16 U/L in the LDK group, and 78.25 U/L in the HDK group. Compared to the C group, the ALT level in the HDK group was significantly higher (p < 0.001). Similarly, the mean AST level in the C group was 28.32 U/L, 44.23 U/L in the LDK group, and 93.55 U/L in the HDK group. Compared to C group, the AST level was significantly elevated in the HDK group (p < 0.001). There were no statistically significant differences in AST or ALT levels between the LDK and C groups.

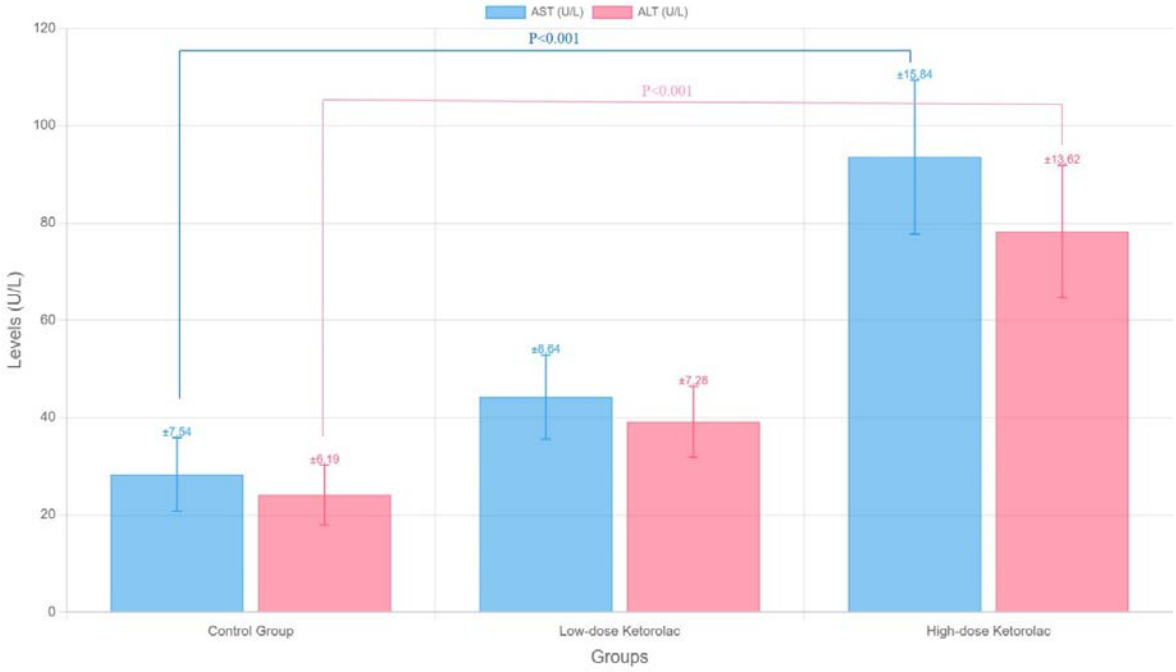

Figure 1. *Serum AST and ALT levels in the three groups*

Kidney function markers

The serum levels of BUN and Cr are shown in Figure 2. One-way ANOVA demonstrated significant differences in mean BUN (F (2.21) = 22.41, p < 0.001) and Cr (F (2.21) = 19.76, p < 0.001) across the three groups. Post-hoc analysis using the LSD test revealed that the mean BUN level in the C group was 16.14 mg/dL, 41.15 mg/dL in the LDK group, and 79.36 mg/dL in the HDK group. Both the LDK group and the HDK group had significantly higher BUN levels compared to the C group (p < 0.001). Additionally, the BUN levels were observed to be significantly elevated in the HDK treatment group in comparison to the LDK group (p = 0.002). The mean Cr level in the C group was 0.21 mg/dL, 0.42 mg/dL in the LDK group, and 0.96 mg/dL in the HDK group. Both the LDK group and the HDK group had significantly higher Cr levels compared to the C group (p < 0.001). Additionally, the HDK group exhibited significantly higher Cr levels compared to the LDK group (p = 0.005).

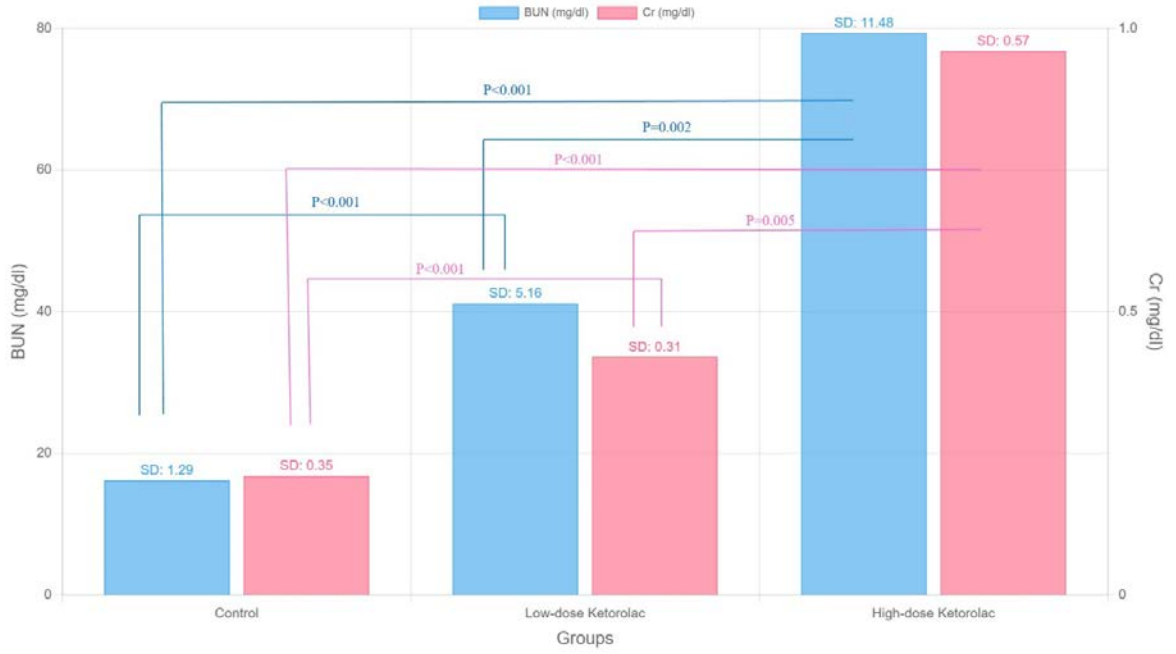

Figure 2. *Serum BUN and creatinine levels in the three groups*

DISCUSSION

The present study provides important insights into the hepatorenal toxicity of ketorolac, a commonly prescribed NSAID, in an adult male rat model. The results demonstrate that HDK administration significantly impairs both liver and kidney function, while LDK primarily affects renal parameters. A significant increase in serum AST and ALT levels observed in the HDK group compared to the C group is a clear indicator of hepatocellular injury. Liver enzymes such as AST and ALT are released into the bloodstream upon damage or dysfunction of hepatocytes, the primary functional cells of the liver (14-16). The observed elevation in these biomarkers suggests that HDK exposure can lead to disruption of the structural and functional integrity of hepatic tissue, potentially through mechanisms involving oxidative stress, mitochondrial dysfunction, and inflammatory responses (17-20). The lack of significant changes in liver enzymes between the control group and the LDK group implies that the lower dose of the drug may not be sufficient to induce overt hepatic toxicity in this animal model. This finding is consistent with the known dose-dependent nature of NSAID-induced liver injury, where higher doses are more likely to trigger hepatocellular damage (21-28). The observed differential effects on liver function between the low and high-dose groups highlight the importance of considering the appropriate dosage when evaluating the safety and tolerability of ketorolac in both preclinical and clinical settings.

Regarding the assessment of renal function, the present study demonstrated that both LDK and HDK groups exhibited significantly elevated levels of BUN and creatinine, two well-established biomarkers of kidney injury and dysfunction. Moreover, the HDK group exhibited even greater increases in BUN and creatinine compared to the LDK group, indicating a dose-dependent nephrotoxic effect of the drug. The observed elevations in BUN and creatinine levels are consistent with the known nephrotoxic potential of NSAIDs, including ketorolac (29-36). The underlying mechanisms by which ketorolac can impair renal function are multifaceted and involve disruptions in the homeostasis of renal blood flow, glomerular filtration, and prostaglandin synthesis (37-39). Specifically, ketorolac's inhibition of cyclooxygenase (COX) enzymes, which play a critical role in the regulation of renal hemodynamics and electrolyte balance, can lead to vasoconstriction, reduced glomerular filtration rate, and impaired urine output, ultimately resulting in the accumulation of waste products such as BUN and creatinine (40-42).

The dose-dependent nature of the renal effects observed in this study suggests that the degree of

ketorolac-induced nephrotoxicity is closely related to the administered dose. This finding is particularly important, as it highlights the need for careful dosage selection and monitoring when prescribing ketorolac, especially in patients with pre-existing renal impairment or those at higher risk of developing NSAID-associated kidney injury. The underlying mechanisms responsible for the hepatorenal toxicity of ketorolac are not entirely clear, and several potential biological pathways have been hypothesized to explain this observed phenomenon. One key mechanism involves the induction of oxidative stress and inflammatory responses by ketorolac, which can lead to cellular damage and dysfunction in both the liver and kidneys (42, 43). Ketorolac's inhibition of prostaglandin synthesis may also play a role, as prostaglandins are crucial mediators of renal blood flow, glomerular filtration, and tubular function (44). Additionally, ketorolac and its metabolites may directly interact with cellular components, such as mitochondria, and disrupt essential metabolic pathways, contributing to the observed hepatic and renal toxicity (43). The interplay between these various mechanisms, including oxidative stress, inflammation, and metabolic disturbances, likely contributes to the overall hepatorenal toxicity profile of ketorolac.

This study has several limitations that should be acknowledged. First, the investigation was limited to two specific doses of ketorolac (10 mg/kg and 20 mg/kg), which may not fully capture the complete dose-response relationship. Including additional intermediate and lower doses could provide a more comprehensive understanding of the threshold for hepatorenal toxicity. Second, while biochemical markers of liver and kidney function were assessed, no histopathological analyses were conducted to confirm cellular-level changes or identify specific patterns of tissue injury. Such data could provide deeper mechanistic insights into the toxic effects of ketorolac. Finally, this preclinical study was conducted in a controlled laboratory environment, which may not fully replicate the complex clinical scenarios encountered in human patients, particularly those with comorbidities or concurrent medication use.

CONCLUSION

In conclusion, the present study provides compelling evidence that HDK administration can induce significant hepatotoxicity, as evidenced by the elevated serum levels of liver enzymes AST and ALT. Furthermore, both LDK and HDK groups exhibited dose-dependent renal toxicity, as indicated by the increased BUN and creatinine levels. These findings underscore the importance of carefully considering the potential hepatorenal side effects associated with ketorolac therapy and the need for appropriate dosage adjustments and close monitoring in clinical settings, especially in patients with pre-existing liver or kidney disorders. Future studies exploring the underlying molecular mechanisms and exploring potential protective strategies may help elucidate the complex pathways involved in ketorolac-induced hepatorenal toxicity.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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References

1. Forestell B, Sabbineni M, Sharif S, et al. Comparative Effectiveness of Ketorolac Dosing Strategies for Emergency Department Patients With Acute Pain. Ann Emerg Med 2023; 82:615-23. https://doi.org/10.1016/j.annemergmed.2023.04.011

2. Marzuillo P, Calligaris L, Amoroso S, Barbi E. Narrative review shows that the short-term use of ketorolac is safe and effective in the management of moderate-to-severe pain in children. Acta Paediatr 2018; 107:560-67. https://doi.org/10.1111/apa.14189

3. Maslin B, Lipana L, Roth B, et al. Safety Considerations in the Use of Ketorolac for Postoperative Pain. Curr Drug Saf 2017; 12:67-73. https://doi.org/10.2174/1574886311666160719154420

4. Butcher B, Hutchings E, Fazekas B, et al. Opioid-sparing effects of ketorolac in palliative care patients receiving opioids for chronic cancer-related pain: A systematic literature review. Palliat Med 2022; 36:71-80. https://doi.org/10.1177/02692163211045310

5. Vonkeman HE, van de Laar MA. Nonsteroidal anti-inflammatory drugs: adverse effects and their prevention. Semin Arthritis Rheum 2010; 39:294-312. https://doi.org/10.1016/j.semarthrit.2008.08.001

6. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly. Aging Dis 2018; 9:143-50. https://doi.org/10.14336/AD.2017.0306

7. Ribeiro H, Rodrigues I, Napoleão L, et al. Non-steroidal anti-inflammatory drugs (NSAIDs), pain and aging: Adjusting prescription to patient features. Biomed Pharmacother 2022; 150:112958. https://doi.org/10.1016/j.biopha.2022.112958

8. Cao YL, Tian ZG, Wang F, et al. Characteristics and clinical outcome of nonsteroidal anti-inflammatory drug-induced acute hepato-nephrotoxicity among Chinese patients. World J Gastroenterol 2014; 20:13956-65. https://doi.org/10.3748/wjg.v20.i38.13956

9. Mariano F, Cogno C, Giaretta F, et al. Urinary protein profiles in ketorolac-associated acute kidney injury in patients undergoing orthopedic day surgery. Int J Nephrol Renovasc Dis 2017; 10:269-74. https://doi.org/10.2147/IJNRD.S137102

10. Othman AI, Abdel-Ghaffar A, Mahmoud AM. Ketorolac- and warfarin-induced renal toxicity: ultrastructural and biochemical study. J Basic Appl Zool 2019; 80: 1-9. https://doi.org/10.1186/s41936-019-0106-2

11. Bories M, Bacle A, Gilardi H, Le Corre P. Risk of acute kidney injury by initiation of non-steroidal anti-inflammatory drugs in hospitalised patients treated with diuretics and renin-angiotensin-aldosterone system inhibitors. Eur J Hosp Pharm 2022; 29:359-61. https://doi.org/10.1136/ejhpharm-2020-002550

12. Domínguez-Oliva A, Hernández-Ávalos I, Martínez-Burnes J, et al. The Importance of Animal Models in Biomedical Research: Current Insights and Applications. Animals (Basel) 2023; 13:1223. https://doi.org/10.3390/ani13071223

13. Jota Baptista CV, Faustino-Rocha AI, Oliveira PA. Animal Models in Pharmacology: A Brief History Awarding the Nobel Prizes for Physiology or Medicine. Pharmacology 2021; 106:356-68. https://doi.org/10.1159/000516240

14. Kalas MA, Chavez L, Leon M, et al. Abnormal liver enzymes: A review for clinicians. World J Hepatol 2021; 13:1688-98. https://doi.org/10.4254/wjh.v13.i11.1688

15. McGill MR. The past and present of serum aminotransferases and the future of liver injury biomarkers. EXCLI J 2016; 15:817-28.

16. Youssef EM, Wu GY. Subnormal Serum Liver Enzyme Levels: A Review of Pathophysiology and Clinical Significance. J Clin Transl Hepatol 2024; 12:428-35. https://doi.org/10.14218/JCTH.2023.00446

17. Sriuttha P, Sirichanchuen B, Permsuwan U. Hepatotoxicity of Nonsteroidal Anti-Inflammatory Drugs: A Systematic Review of Randomized Controlled Trials. Int J Hepatol 2018; 2018:5253623. https://doi.org/10.1155/2018/5253623

18. Rostom A, Goldkind L, Laine L. Nonsteroidal anti-inflammatory drugs and hepatic toxicity: a systematic review of randomized controlled trials in arthritis patients. Clin Gastroenterol Hepatol 2005; 3:489-98. https://doi.org/10.1016/S1542-3565(04)00777-3

19. Lapeyre-Mestre M, de Castro AM, Bareille MP, et al. Non-steroidal anti-inflammatory drug-related hepatic damage in France and Spain: analysis from national spontaneous reporting systems. Fundam Clin Pharmacol 2006; 20:391-5. https://doi.org/10.1111/j.1472-8206.2006.00416.x

20. Rivera-Espinosa L, Muriel P, Ordaz Gallo M, et al. Ketorolac pharmacokinetics in experimental cirrhosis by bile duct ligation in the rat. Ann Hepatol 2003; 2:175-81. https://doi.org/10.1016/S1665-2681(19)32130-1

21. Lu W, Cheng F, Jiang J, et al. FXR antagonism of NSAIDs contributes to drug-induced liver injury identified by systems pharmacology approach. Sci Rep 2015; 5:8114. https://doi.org/10.1038/srep08114

22. Bessone F. Non-steroidal anti-inflammatory drugs: What is the actual risk of liver damage? World J Gastroenterol 2010; 16:5651-61. https://doi.org/10.3748/wjg.v16.i45.5651

23. Donati M, Conforti A, Lenti MC, et al. Risk of acute and serious liver injury associated to nimesulide and other NSAIDs: data from drug-induced liver injury case-control study in Italy. Br J Clin Pharmacol 2016; 82:238-48. https://doi.org/10.1111/bcp.12938

24. Lacroix I, Lapeyre-Mestre M, Bagheri H, et al. Nonsteroidal anti-inflammatory drug-induced liver injury: a case-control study in primary care. Fundam Clin Pharmacol 2004; 18:201-6. https://doi.org/10.1111/j.1472-8206.2004.00224.x

25. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. Mayo Clin Proc 2014; 89:95-106. https://doi.org/10.1016/j.mayocp.2013.09.016

26. Soleimanpour M, Imani F, Safari S, et al. The Role of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in the Treatment of Patients with Hepatic Disease: A Review Article. Anesth Pain Med 2016; 6:e37822. https://doi.org/10.5812/aapm.37822

27. Rubenstein JH, Laine L. Systematic review: the hepatotoxicity of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2004; 20:373-80. https://doi.org/10.1111/j.1365-2036.2004.02092.x

28. Aithal GP, Day CP. Nonsteroidal Anti-Inflammatory Drug-Induced Hepatotoxicity. Clinics in Liver Disease 2007; 11: 563-75. https://doi.org/10.1016/j.cld.2007.06.004

29. Ingrasciotta Y, Sultana J, Giorgianni F, et al. Association of individual non-steroidal anti-inflammatory drugs and chronic kidney disease: a population-based case control study. PLoS One 2015; 10:e0122899. https://doi.org/10.1371/journal.pone.0122899

30. Ungprasert P, Cheungpasitporn W, Crowson CS, Matteson EL. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: A systematic review and meta-analysis of observational studies. Eur J Intern Med 2015; 26:285-91. https://doi.org/10.1016/j.ejim.2015.03.008

31. Lafrance JP, Miller DR. Selective and non-selective non-steroidal anti-inflammatory drugs and the risk of acute kidney injury. Pharmacoepidemiol Drug Saf 2009; 18:923-31. https://doi.org/10.1002/pds.1798

32. Hörl WH. Nonsteroidal Anti-Inflammatory Drugs and the Kidney. Pharmaceuticals (Basel) 2010; 3:2291-321. https://doi.org/10.3390/ph3072291

33. Galli G, Panzetta G. Case report: reversible acute renal failure following therapy with both ketorolac (non-selective non-steroidal anti-inflammatory drug NSAID) and celecoxib (COX-2 selective) in the same patient. G Ital Nefrol 2002; 19:199-203.

34. Brater DC. Anti-inflammatory agents and renal function. Semin Arthritis Rheum 2002; 32:33-42. https://doi.org/10.1053/sarh.2002.37216

35. Dixit M, Doan T, Kirschner R, Dixit N. Significant Acute Kidney Injury Due to Non-steroidal Anti-inflammatory Drugs: Inpatient Setting. Pharmaceuticals (Basel) 2010; 3:1279-85. https://doi.org/10.3390/ph3041279

36. Perazella MA, Buller GK. NSAID nephrotoxicity revisited: acute renal failure due to parenteral ketorolac. South Med J 1993; 86:1421-4. https://doi.org/10.1097/00007611-199312000-00025

37. Drożdżal S, Lechowicz K, Szostak B, et al. Kidney damage from nonsteroidal anti-inflammatory drugs-Myth or truth? Review of selected literature. Pharmacol Res Perspect 2021; 9:e00817. https://doi.org/10.1002/prp2.817

38. Hall ST, Mangram AJ, Barletta JF. Identification of Risk Factors for Acute Kidney Injury from Intravenous Ketorolac in Geriatric Trauma Patients. World J Surg 2022; 46:98-103. https://doi.org/10.1007/s00268-021-06320-z

39. Aitken HA, Burns JW, McArdle CS, Kenny GN. Effects of ketorolac trometamol on renal function. Br J Anaesth 1992; 68:481-5. https://doi.org/10.1093/bja/68.5.481

40. Waterbury LD, Silliman D, Jolas T. Comparison of cyclooxygenase inhibitory activity and ocular anti-inflammatory effects of ketorolac tromethamine and bromfenac sodium. Curr Med Res Opin 2006; 22:1133-40. https://doi.org/10.1185/030079906X112471

41. Takahashi K, Patel AK, Nagai S, et al. Perioperative Ketorolac Use: A Potential Risk Factor for Renal Dysfunction After Live-Donor Nephrectomy. Ann Transplant 2017; 22:563-9. https://doi.org/10.12659/AOT.904762

42. Freedland SJ, Blanco-Yarosh M, Sun JC, et al. Effect of ketorolac on renal function after donor nephrectomy. Urology 2002; 59:826-30. https://doi.org/10.1016/S0090-4295(02)01514-5

43. Buckley MM, Brogden RN. Ketorolac. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1990; 39:86-109. https://doi.org/10.2165/00003495-199039010-00008

44. Macario A, Lipman AG. Ketorolac in the era of cyclo-oxygenase-2 selective nonsteroidal anti-inflammatory drugs: a systematic review of efficacy, side effects, and regulatory issues. Pain Med 2001; 2:336-51. https://doi.org/10.1046/j.1526-4637.2001.01043.x

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Toksičnost različitih doza ketorolaka u jetri i bubrezima odraslih pacova muškog pola: pre-klinička studija

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SAŽETAK

Uvod/Cilj. Ketorolak je potentni nesteroidni antiinflamatorni lek (engl. *nonsteroidal anti-inflammatory drug* – NSAID) koji može inhibirati aktivnost ciklooksigenaze i sintezu prostaglandina, čime smanjuje bol i upalu. Cilj ove studije bio je da istraži hepatorenalnu toksičnost primene ketorolaka kod odraslih pacova muškog pola.

Metode. Dvadeset i četiri odrasla pacova muškog pola soja Wistar nasumično su podeljena u tri grupe (n = 8 po grupi): kontrolnu grupu koja je primala fiziološki rastvor (1 mL/kg), grupu koja je dobijala nisku dozu ketorolaka (10 mg/kg) i grupu koja je dobijala visoku dozu ketorolaka (20 mg/kg). Životinje su čuvane pod standardnim uslovima tri nedelje nakon poslednjeg tretmana. Uzorci krvi su uzeti dok su pacovi bili pod anestezijom, a nivoi alanin aminotransferaze (ALT), aspartat aminotransferaze (AST), uree u krvi (engl. *blood urea nitrogen* – BUN) i kreatinina (Cr) mereni su komercijalnim kompletima i analizatorom BT 1000 *Biotectica*.

Rezultati. U poređenju sa kontrolnom grupom, grupa koja je primala nisku dozu ketorolaka nije pokazala značajan porast nivoa ALT-a i AST-a, dok je grupa koja je primala visoku dozu ketorolaka pokazala značajan porast ovih hepatičnih enzima ($p < 0,05$). I u grupi sa niskom dozom i u grupi sa visokom dozom ketorolaka zabeležen je značajan porast nivoa BUN-a i Cr-a u poređenju sa kontrolnom grupom. U grupi koja je dobijala visoku dozu ketorolaka porast ovih renalnih parametara bio je izraženiji ($p < 0,05$).

Zaključak. Rezultati ove studije ukazali su na to da primena visoke doze ketorolaka može imati hepatotoksične i nefrotoksične efekte; to je potvrdilo zabeleženo povećanje nivoa markera funkcije jetre i bubrega kod odraslih pacova muškog pola. Ovakvi rezultati ističu važnost pažljivog praćenja i optimizacije doza prilikom primene ketorolaka u kliničkim uslovima.

Ključne reči: **ketorolak, hepatorenalna toksičnost, bubrezi, jetra, pacov**