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The Impact of Common Analgesics on Kidney Function: An Experimental Study on Rats

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Abstract

This experimental study aimed to evaluate the nephrotoxic and hepatotoxic effects of ibuprofen in male Wistar rats, which is a widely used nonsteroidal anti-inflammatory drug (NSAID). The animals were divided into two groups: a control group and a treatment group that received 800 mg/day ibuprofen orally for 12 consecutive days. Biochemical analysis demonstrated a statistically significant increase ($p < 0.01$) in the serum urea and creatinine levels in the ibuprofen-treated group, indicating impaired renal function. Additionally, liver enzymes ALT and AST were markedly elevated, suggesting hepatic injury. Histopathological examination of the kidney tissues revealed pronounced structural damage, including glomerular atrophy, tubular necrosis, vacuolation of tubular cells, and congestion of interstitial blood vessels. These findings provide strong evidence that high-dose, short-term administration of ibuprofen can lead to considerable functional and structural damage in both the kidneys and liver. This study highlights the necessity of cautious ibuprofen use, especially in individuals with pre-existing renal or hepatic conditions, and calls for increased awareness of the potential risks associated with unsupervised NSAID consumption.

Key Words: Ibuprofen, Kidney function, NSAIDS, Histopathological changes, Wistar Rats.

1. Introduction

Ibuprofen, a propionic acid derivative, and acetaminophen, an aniline derivative, are nonsteroidal anti-inflammatory drugs (NSAIDs) mainly used for their antipyretic, anti-inflammatory, and analgesic properties (Rainsford, 2009). Its mechanism of action is the inhibition of cyclooxygenase enzyme (COX) to reduce prostaglandin (PG) production, so that the PG-mediated inflammatory response can be weakened (Prusakiewicz et al., 2009). Although both COX isoforms are found in the kidneys, their effects on renal function are diametrically opposite; hence, the specific NSAID used may have varying effects on renal function. It has been proposed that blocking COX-1 increases natriuresis and lowers

blood pressure, whereas blocking COX-2 might cause water and sodium retention and raise blood pressure (Qi et al., 2002).

The primary area of the kidneys where water, salt, and chloride are reabsorbed is known to be the renal medulla. One possible explanation for the effects of COX-2 inhibition, such as water and sodium retention, is the lower levels of medullary PGE2. It has been suggested that PGs created by COX-2 are vasodilators that help preserve renal blood flow that has been compromised by vasoconstrictors such as noradrenaline or angiotensin II (Khan et al. 2019). Additionally, a mouse study revealed that COX-1 inhibition decreased the quantity of PGs in the renal cortex, medulla, and aorta, whereas COX-2 inhibition decreased PGs solely in the renal medulla (Qi et al., 2002).

As first-line antipyretic and analgesic drugs, they have been widely used for a long time, not only as prescription drugs but also as over-the-counter medications (Gimenez-Bastida, 2019; Lucas, 2019).

Acute interstitial nephritis with hematuria, proteinuria, and sometimes nephrotic syndrome has been reported in humans, and the long-term use of nonsteroidal anti-inflammatory drugs has caused renal papillary necrosis and other abnormal renal pathologies in animals (Li et al., 2001). A second form of renal toxicity has been observed in patients with pre-renal conditions, leading to a reduction in renal blood flow or blood volume, in which renal prostaglandins play a supportive role in the maintenance of renal perfusion.

NSAIDs can also increase the risk of hyperkalemia. NSAIDs should be used in patients undergoing dialysis (Adams et al., 1970). With nonsteroidal anti-inflammatory treatment, there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure, in elderly patients, or in patients receiving concomitant therapy with angiotensin-II receptor antagonists, adrenergic blockers, angiotensin-converting enzyme inhibitors, or diuretics. Patients at risk should be monitored periodically during long-term therapy (Angita Pharma, Inc., 2020).

This study aimed to measure biochemical and histological alterations in the kidney to assess the harmful effects of ibuprofen.

2. Materials and Methods

Materials: Brufen pills were obtained from Egyptian Pharmaceutical Suppliers. Ibuprofen was the active component. Two Ibuprofen pills, each containing 400 mg of medication, were ground in a glass mortar, combined with 50 ml of distilled water, placed in a glass beaker, and administered orally as an aqueous suspension. To ensure that the medication was distributed evenly to the animals, it was shaken constantly while being administered. Each day, the animals were checked for clinical symptoms in their enclosures (Aprioku et al., 2014).

Male Wistar rats were used as experimental animals. For the investigation, 120 g weights acquired from the Theodor Bilharz Research Institute in Giza, Egypt, were utilized. Rodents were provided regular rodent feed and had unrestricted access to tap water. They were handled in compliance with international guidelines for the Care and Use of Laboratory Animals and kept at a room temperature of 28.0±2.0°C with natural illumination.

Experimental methodology: The rats were divided into two groups, each of which contained six animals kept in the animal house of the Faculty of Education at Ain Shams University in Cairo, Egypt. Each group was given free access to food and water, and the animals were given medication for 12 days in a row as follows:

• Ibuprofen group: For 12 days, they received 0.2 ml of the medication daily.

•Control group: nothing was provided to them (only food and beverages).

Every day, the animals were monitored for clinical symptoms in their cages. The animals were put to sleep with chloroform at the end of the 12-day trial, and their blood was drawn using needles and stored in tubes.

Determination of biochemical parameters: A cardiac puncture was performed to obtain clotted blood from which serum was extracted. Key serum biochemical indicators such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined using Sigma diagnostics. Serum creatinine, a result of muscle metabolism, whose increased levels indicate impaired renal excretion, is used to assess kidney function. Blood urea nitrogen (BUN) is another filtration marker obtained from protein breakdown; however, extrarenal effects reduce its selectivity. A more thorough measure of the kidney's filtering ability is provided by the Estimated Glomerular Filtration Rate (eGFR), which is determined using creatinine level, age, sex, and occasional race. Overall, these metrics provide important information about the functioning of the kidneys.

Preparation of histopathological slides: Following kidney isolation in 10% formalin, tissue slides were prepared, and histological examinations were performed (Aziz et al., 2018).

Statistical analysis:

The t-test was used to analyze all data to identify the cause of a significant effect. Mean ± St. D. was used to express the results, with $p<0.05$. considered a significant difference from the control.

3. Results

Effect of ibuprofen on serum ALT and AST levels in rats: The results indicated a significant difference ($p<0.01$) in the serum levels of ALT (33.41 and 149.39) between the two groups, as well as a significant increase ($p<0.01$) in the serum levels of AST (43.467 and 157.5), with the highest levels in the ibuprofen group when compared with the control group (Table 1 and Figure 1).

Table 1: Mean and standard deviation of the liver function (ALT and AST) of control and Ibuprofen groups of male rats

Groups	Control		Ibuprofen	
	Mean	St. D.	Mean	St. D.
ALT	33.41	±0.835	149.39 *	±1.5
AST	43.467	±0.828	157.5 *	±2.65

*The mean difference is highly significant at $p<0.01$ level. St. D.: Standard deviation, ALT: Alanine aminotransferase, AST: Aspartame aminotransferase

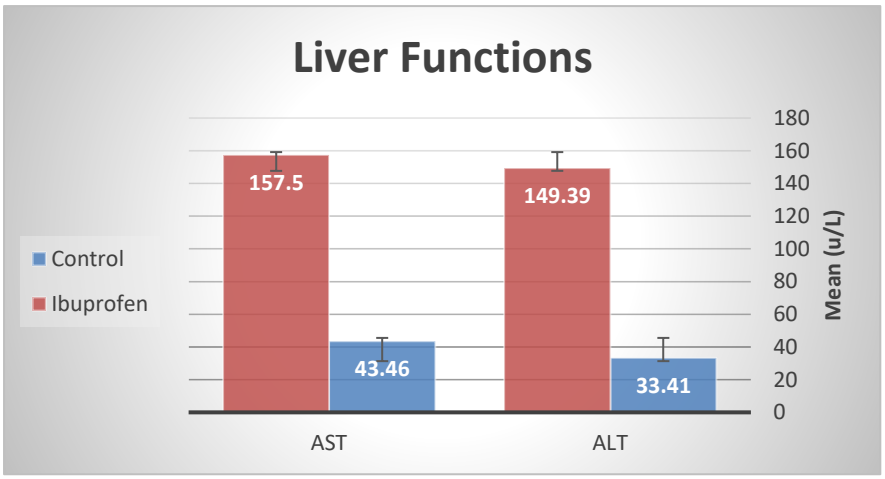

Figure 1: Histogram presents the mean of ALT and AST in the blood serum of control and ibuprofen groups of male rats

Effects of Ibuprofen on Rat Serum Creatinine and Urea Levels:

The ibuprofen group's serum levels of Creatinine (0.68 and 2.47) and Urea (20.44 and 52.86) were significantly higher ($p<0.01$) than those of the control group (Table 2 and Figure 2).

Table 2: Mean and standard deviation of the Kidney Function (Creatinine and Urea) of control and ibuprofen groups of male rats.

Groups	Control		Ibuprofen	
	Mean	St. D.	Mean	St. D.
Creatinine	0.68	±0.07	2.47*	±0.155
Urea	20.44	±0.61	52.86*	±2.39

*The mean difference is highly significant at $p<0.01$ level. St. D. Standard deviation.

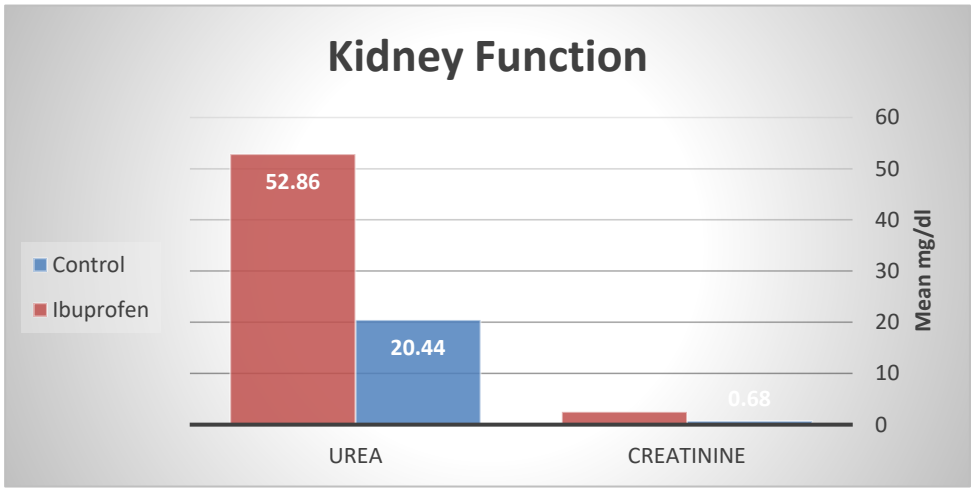

Figure 2: Histogram presents the mean creatinine and urea levels in the blood serum of male rats in the control and ibuprofen groups.

Effects of ibuprofen on the histological structure of rat kidneys:

Normal renal architecture with glomeruli, Bowman's space, renal tubules, and tubular cells was found by histological examination of the normal kidneys of the control group (Figs. 3 and 4).

However, the ibuprofen group displayed histological changes, such as renal tubule necrosis, tubular cell vacuolation, glomerular atrophy, and interstitial blood vessel congestion (Figs. 5 and 6).

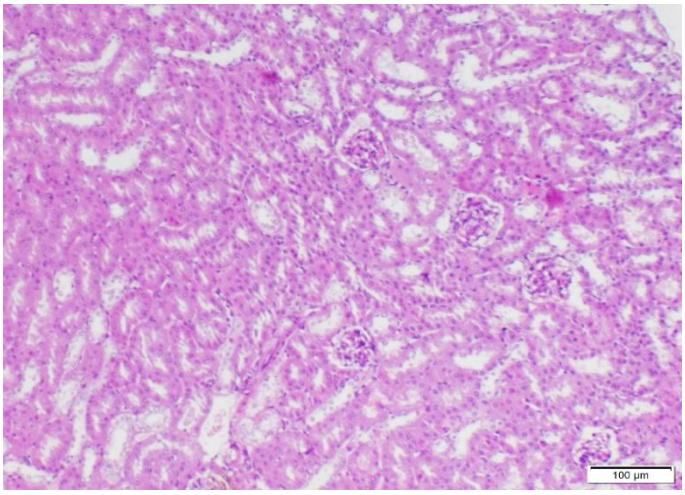

Figure 3: Control group showing normal renal architecture with glomeruli, Bowman's space, renal tubules, and tubular cells. (x100, H&E).

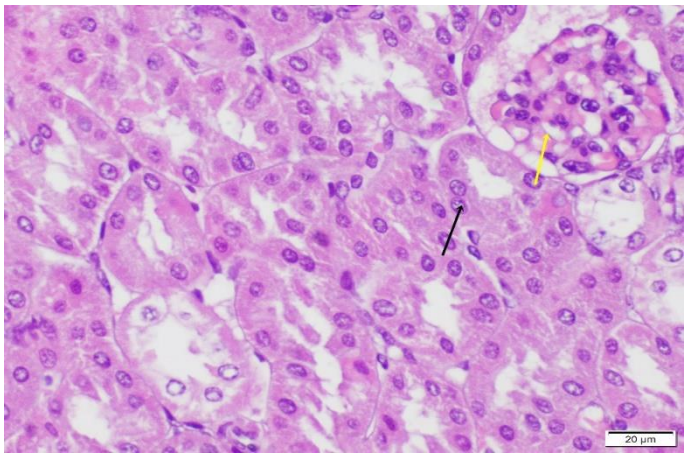

Figure 4: Control group showing normal renal architecture with glomeruli, Bowman's space (yellow arrow), renal tubules, and tubular cells (black arrow). (x400, H&E).

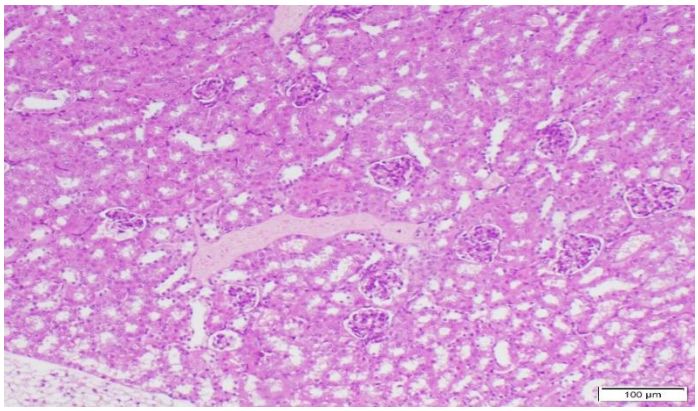

Figure 5: Ibuprofen group showing atrophy of glomeruli, necrosis of renal tubules, vacuolation of tubular cells, and congestion of interstitial blood vessels. (x100, H&E).

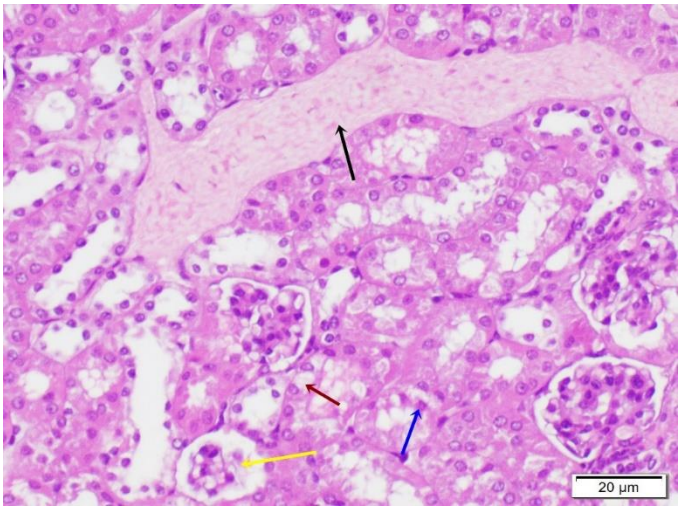

Figure 6: Ibuprofen group showing atrophy of glomeruli (yellow arrow), necrosis of renal tubules (blue arrow), vacuolation of tubular cells (brown arrow), and congestion of interstitial blood vessels (black arrow). (x400, H&E).

4. Discussion

Ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID) for pain relief, acts as a non-selective cyclooxygenase (COX) inhibitor. Although commonly prescribed, prolonged or high-dose use has been linked to adverse renal outcomes. Biochemical alterations observed in this study suggest impaired kidney and liver function, as evidenced by the elevated levels of key biomarkers (Razzaq & Aboshnin, 2023).

The serum levels of ALT (33.41 vs. 149.39) and AST (43.467 in the control group vs. 157.5 in the ibuprofen group) were found to be significantly elevated ($p<0.01$) in the current investigation, and the ibuprofen group exhibited significantly higher values. Similarly, the ibuprofen group had significantly higher ($p<0.01$) serum creatinine (0.68 vs. 2.47) and urea (20.44 vs. 57.99) levels than the control group. Significant degradation in the hepatic and renal tissues of ibuprofen-treated rats was further supported by histological analysis (Aprioku et al., 2014; Klomjit & Ungprasert, 2022).

Direct nephrotoxicity, immune-mediated harm from the accumulation of antigen-antibody complexes in glomeruli, and hemodynamic consequences from COX inhibition, which lowers prostaglandin synthesis, are some of the mechanisms by which ibuprofen can cause kidney damage. This suppression causes vasoconstriction of renal tubules, which lowers the glomerular filtration rate (GFR) and renal blood flow (RBF), ultimately resulting in tubular injury (Shao et al., 2021).

Owing to these mechanisms, patients using ibuprofen are at an increased risk of kidney failure and require close monitoring to avoid further damage (Gul et al., 2018).

Farquhar, W. B. et al. (1999) stated that acute renal failure has also been linked to more severe liver damage, and that the rapid decline of both liver and kidney functions can sometimes result in the patient's death.

5. Conclusion

Ibuprofen administration resulted in significant disruption of liver and kidney function, as reflected by elevated biochemical markers and tissue damage. These findings underscore the importance of cautious use and regular monitoring to mitigate the risk of acute organ failure.

6. References

Adams SS, Bough RG, Cliffe EE, Dickinson W, Lessel B, McCullough KF, et al. (1970). Pharmacology, metabolism, and toxicity of ibuprofen. Rheumatol Phys Med, 10 (Suppl 10), 9-26.

Adams SS, Bough RG, Cliffe EE, Lessel B, Mills RFN (1969). Absorption, distribution, and toxicity of ibuprofen. Toxoicol Appl Pharmacol, 15,310-330.

Angita Pharma Inc. (2020). Ibuprofen Tablets USP: Product monograph. Angita Pharma Inc (page 6,7,8).

Aprioku, J. S., Nwidu, L. L., and Amadi, C. N. (2014). Evaluation of the toxicity profile of ibuprofen in Wistar albino rats. American Journal of Biomedical Sciences, 6(1), 32-40. https://doi.org/10.5099/aj140100032

Aziz DN, Ouda HM, and Ubaid MM (2018). Comparing the Toxic Effects of Nonsteroidal Anti-Inflammatory Drugs (Celecoxib and Ibuprofen) on Heart, Liver, and Kidney in Rats. Asian Journal of Pharmaceutical and Clinical Research, p 482-483.

Farquhar, W. B., Morgan, A. L., Zambraski, E. J., & Kenney, W. L. (1999). Effects of acetaminophen and ibuprofen on renal function in stressed mice. Journal of Applied Physiology, 86(2), 598–604. https://journals.physiology.org/journal/jappl

Fitzpatrick FA & Wynalda MA (1976). In Vivo suppression of prostaglandin biosynthesis by non-steroidal anti-inflammatory agents. Prostaglandin,12,1037-1051.

Giménez-Bastida J. A., Boeglin W. E., Boutaud O., Malkowski M. G., Schneider C. (2019). Residual Cyclooxygenase Activity of Aspirin-Acetylated COX-2 Forms 15 R-Prostaglandins that Inhibit Platelet Aggregation. FASEB J., 33 (1), 1033–1041. 10.1096/fj.201801018R - DOI - PMC - PubMed

Gul, A., Qamar, K., Hussain, T. (2018). Protective effects of commercial green tea on ibuprofen-induced glomerular atrophy in the kidneys of adult rats. Journal of the College of Physicians and Surgeons Pakistan, 28(9), 659–662.

Guseibat, T. A., Elturshani, O. M., Mohamed, F. A., Eltarhouni, A. A. (2022). Histopathological changes in the kidney tissues of mice following ibuprofen treatment. Libyan Journal of Basic Sciences, 16(1), 1-11. https://doi.org/10.58172/75 .

Khan S, Andrews KL, Chin-Dusting JPF (2019). Cyclo-oxygenase (COX) inhibitors and cardiovascular risk: are non-steroidal anti-inflammatory drugs really anti-inflammatory? Int J Mol Sci, 20, 4262. [DOI] [PMC free article] [PubMed] [Google Scholar]

Klomjit, N. and Ungprasert, P. (2022). Acute kidney injury associated with non-steroidal anti-inflammatory drugs. European Journal of Internal Medicine, 101, 21–28. https://doi.org/10.1016/j.ejim.2022.05.003

Li Z. (2001). Analysis of 14 cases of renal failure caused by long-term ibuprofen use, Guangxi Med. (06), 14-15.

Lucas GNC, Leitão ACC, Alencar RL, Xavier RMF, Daher EF, Silva Junior GBD (2019). Pathophysiological aspects of nephropathy caused by non-steroidal anti-inflammatory drugs. J Bras Nefrol, Jan-Mar;41(1),124-130. Doi: 10.1590/2175-8239-JBN-2018-0107. Epub 2018 Sep 21. PMID: 30281062; PMCID: PMC6534025.

Prusakiewicz JJ, Duggan KC, Rouzer CA, Marnett LJ (2009). Differential sensitivity and mechanism of inhibition of COX-2 oxygenation of arachidonic acid and 2-arachidonoylglycerol by ibuprofen and mefenamic acid. Biochemistry, 48, 7353-7355.

Qi Z, Hao C-M, Langenbach RI, et al (2002). Opposite effects of cyclooxygenase-1 and -2 activity on the pressor response to angiotensin II. J Clin Invest, 110,61-69.

Rainsford K. (2009). Ibuprofen pharmacology, efficacy and safety. Inflamm Pharmacol,17, 275-342.

Razzaq, S. A., & Aboshnin, Z. A. (2023). Amelioration of ibuprofen induced hepato-renal injury: Biochemical and histological study in rats. Journal of Chemical Health Risks, 13(4), 539–546. http://www.jchr.org

Shao, Q.-h., Yin, X.-d., Liu, H.-x., Zhao, B., Huang, J.-q., & Li, Z.-l. (2021). Kidney injury following ibuprofen and acetaminophen administration: A real-world analysis of post-marketing surveillance data. Frontiers in Pharmacology, 12, 750108. https://doi.org/10.3389/fphar.2021.750108

تأثير المسكنات الشائعة على وظائف الكلى: دراسة تجريبية على الجرذان

المستخلص العربي والتوصيات:

هدفت هذه الدراسة التجريبية إلى تقييم التأثيرات السمية الكلوية والكبدية للإيبوبروفين على ذكور فئران ويستار وهو دواء مضاد للالتهاب غير الستيرويدي واسع الاستخدام. قُسمت الحيوانات إلى مجموعتين: مجموعة ضابطة ومجموعة علاجية تناولت 800 ملغم/يوميًا من الإيبوبروفين عن طريق الفم لمدة 12 يومًا متتاليًا. أظهر التحليل الكيميائي الحيوي زيادة كبيرة إحصائيًا ($p < 0.01$) في مستويات اليوريا والكرياتينين في مصل الدم في المجموعة المعالجة بالإيبوبروفين، مما يشير إلى ضعف وظائف الكلى. بالإضافة إلى ذلك، كانت إنزيمات الكبد ALT و AST مرتفعة بشكل ملحوظ، مما يشير إلى إصابة الكبد. كشف الفحص المرضي النسيجي لأنسجة الكلى عن تلف بنيوي واضح، بما في ذلك ضمور كبيبي ونخر أنبوبي وتخلخل في الخلايا الأنبوبية واحتقان الأوعية الدموية الخلالية. تقدم هذه النتائج دليلاً قوياً على أن تناول جرعة عالية وقصيرة الأمد من الإيبوبروفين يمكن أن يؤدي إلى ضرر وظيفي وهيكلي كبير في كل من الكلى والكبد. وتسلط هذه الدراسة الضوء على ضرورة توخي الحذر في استخدام الإيبوبروفين، خاصةً لدى الأفراد الذين يعانون من مشاكل كلوية أو كبدية موجودة مسبقاً، وتدعو إلى زيادة الوعي بالمخاطر المحتملة المرتبطة باستهلاك مضادات الالتهاب غير الستيروئيدية غير الخاضعة للإشراف.