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Case Report

Self-induced Anuria with Diclofenac: An Interesting Case of "Quadruple Whammy" Acute Kidney Injury

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ABSTRACT

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of drugs widely prescribed and used worldwide. Patients taking NSAIDs, including diclofenac, should be aware of its potential nephrotoxic effects. However, the rapid onset of acute kidney injury (AKI) after a single dose of diclofenac is considered a very rare side effect.

Case Presentation: We present a 66-year-old woman with habitual self-induced anuria with the chief complaint of shoulder pain due to falling down. The patient presented with various co-morbid conditions, including hypertension, type 2 diabetes, tricuspid valve repair, and aortic valve replacement. She rapidly developed anuria after receiving a single dose of diclofenac over the previous two days of admission. Creatinine and BUN exhibited a significant rise in laboratory tests. During hospitalization, the consumption of NSAIDs was prohibited and losartan and furosemide were discontinued. Moreover, phenacetin was used to relieve pain instead. Luckily, after two days of hospitalization, urine output returned to normal levels. Additionally, creatinine and BUN levels gradually decreased to baseline values.

Conclusion: To the best of our knowledge, we described a rare case of diclofenac-induced AKI presenting with anuria, a complete cessation of urine flow, in a patient with no previous kidney complications. This case can be explained by the phenomenon known as "quadruple Whammy," which involves the concurrent use of NSAIDs, ARBs, and diuretics in the setting of hypovolemia.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of drugs used to control pain, fever, and other inflammatory processes. NSAIDs are particularly effective for muscle pain, arthritic conditions, dysmenorrhea, pyrexia, gout, and migraines. They are also beneficial as opioid-sparing agents in some cases of acute trauma [1].

The therapeutic effects of NSAIDs are based on their inhibition of prostaglandin (PG) synthesis by blocking the cyclooxygenase (COX) pathway. The inhibition of PG is a double-edged sword, exerting harmful consequences on most organs. The kidney is one of the major organs adversely affected by NSAIDs. Since prostaglandins play important protective roles in the kidneys, the inhibition of prostaglandin synthesis can lead to complications, such as acute kidney injury (AKI), sodium retention, and its consequences, like hypertension, edema, hyperkalemia, papillary necrosis, interstitial nephritis, nephrotic syndrome, and renal dysgenesis. Fortunately, most of these complications are reversible. Pre-renal AKI resolves after NSAID discontinuation, and interstitial nephritis and nephrotic syndrome also respond well to NSAID withdrawal, with or without a short course of steroids [2, 3].

Diclofenac is a class of medications called NSAIDs approved by the Food and Drug Administration (FDA). It is beneficial in alleviating acute and chronic pains associated with inflammatory conditions, particularly those involving the musculoskeletal system, such as osteoarthritis and rheumatoid arthritis [4]. The prevalence of renal complications among NSAID users has been reported to be approximately 27.88%. Diclofenac consumption is associated with decreased renal perfusion, leading to the development of AKI [5, 6].

Anuria is another complication observed in recipients of this drug. According to a phase IV clinical trial by the FDA in August 2022, of 32,785 people taking diclofenac, 73 (0.22%) had anuria, of whom 59.15% were women and 44.93% were 60 years of age or older. Of all cases with anuria, 61.54% had been using the drug for less than one month, whereas 38.46% had been receiving the drug for 1-2 years. The fact that a single dose of diclofenac in a very short period gives rise to diclofenac-induced anuria remains controversial [7].

Here, we report a 66-year-old woman with normal baseline kidney function who presented with self-induced anuric AKI after only a single dose of diclofenac sodium.

Case Report

A 66-year-old obese woman was admitted to the emergency department of Loghman Hakim Hospital in Tehran. The main complaint of our patient was shoulder pain following a fall down the stairs at home. During medical history-taking, we noticed that the patient had been anuric for the past 2 days. Interestingly, she did not seem concerned about her anuria.

On the day before admission, two 25 mg tablets of diclofenac were taken by the patient early in the morning to prevent urine production while traveling by car. Additionally, she restricted fluid intake. “I always follow this regimen for traveling”, she said.

It is also noteworthy that three years ago, she underwent aortic valve replacement with a prosthetic valve and pulmonary valve repair. Her laboratory test results from the last month showed normal blood urea nitrogen (BUN) (33 mg/dL) and creatinine (Cr) (0.7 mg/dL) levels. A 15-year history of diabetes mellitus, well-controlled hypertension (120/70 mm Hg with medication), and osteoarthritis of both knees were other complications for the patient. Her daily medications were losartan 50 mg twice a day, furosemide 20 or 40 mg every morning, levothyroxine 150 µg daily, metformin 500-1000 mg daily, warfarin 5 mg daily, diltiazem 30 mg twice daily, and lovastatin 20 mg daily. She also occasionally took 25 mg of diclofenac sodium for knee pain. She mentioned that with each diclofenac pill, her blood pressure increased, her urine output stopped for 24 hours, and after 48 hours, her urine volume gradually returned to normal.

On admission, the patient was conscious and oriented and had no symptoms other than anuria and left arm pain. Physical examination revealed extensive ecchymosis around the left shoulder. Her blood pressure (BP), respiratory rate (RR), pulse rate (PR), and body temperature (BT) were 160/90, 16/min, 90/min, and 37.2°C, respectively. Laboratory findings are summarized in Table 1.

Imaging showed an intra-articular fracture of the left humerus. Kidney and urine ultrasound revealed an empty bladder and normal kidney size without any stones or hydronephrosis.

Losartan and furosemide were promptly discontinued upon admission, and all NSAIDs were prohibited. Phenacetin was administered to manage arm pain.

Table 1. Labratory data during 7 days of admission

Parameter	Day							
	Admission	1	2	3	4	5	6	7
BUN (mg/dL)	71	114	121	96	55	45	30	26
Creatinine (mg/dL)	2.8	2.8	2.1	1.4	0.7	0.7	0.7	0.7
Potassium (mEq/L)	4.5	5.2	4.9	4.4	4.5	4.4	4.3	4.2
Creatine phosphokinase (CPK) (IU/L)	798	776	672	699	619	290	156	100
Phosphate	7	7.2		4.8	3.3	3.2	3.3	3.2
HCO_3	16	17.8	26.4	19.8	21.4	23.2	23.4	22.2
Lactate	41			24				

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From the second day of hospitalization (the fourth day of taking diclofenac sodium 50 mg), urine output gradually improved and returned to normal after two days. As indicated in Table 1, BUN and Cr levels also returned to baseline values, and blood pressure normalized accordingly.

Discussion

NSAIDs are responsible for 25% of adverse drug effects worldwide. The kidney is one of the major organs that can be adversely affected by NSAIDs and selective Cox-2 inhibitors, but renal complications are less quantified than gastrointestinal and cardiovascular effects [8, 9].

A systematic review and meta-analysis estimated the pooled odds ratio of AKI to current NSAID exposure in the general population to be 1.73, which was higher in the elderly (2.51) and patients with chronic kidney disease (1.12-5.25) [9]. The incidence of AKI is unclear concerning specific formulations of NSAIDs, except in some case reports, although all cases have some comorbidities [3, 10-12].

Diclofenac is one of the most prescribed NSAIDs in the world, with a reported incidence of anuria to be 0.13% according to a phase 4 FDA clinical trial. Almost all patients were on medication for less than one month, 58% were female and 71% were 60 years or older [7].

The occurrence of hemodynamically induced AKI following NSAIDs (nonselective or coxibs) is dose- and duration-dependent, and it escalates with comorbidities such as hypertension, heart failure, diabetes mellitus, hypovolemia, older age, preexisting CKD, and co-ingestion with other nephrotoxic drugs [3, 13].

The term “triple whammy” was first introduced by Merlin C. Thomas in 2000, and refers to the simultaneous use of angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), diuretics, and NSAIDs, or selective cox-2 inhibitors [14-17].

The importance of the triple whammy lies in the fact that prescribing a combination of these three classes of drugs can lead to AKI, with an even higher risk when taken by patients with pre-existing CKD (quadruple whammy) [15]. This is likely the crucial point in our case, explaining how a single tablet of diclofenac can induce anuria and AKI.

Both ACE-I/ARB, diuretics, and NSAIDs can individually cause AKI, and the presence of other risk factors can exacerbate kidney damage. ACE-I and ARB dilate efferent renal arterioles but fail to compensate for glomerular filtration rate (GFR) in the presence of hypovolemia or afferent vasoconstriction. Diuretics induce a hypovolemic state and diminish renal blood flow (RBF), leading to prerenal AKI. NSAIDs, on the other hand, constrict renal arterioles, further reducing RBF and GFR [15, 18]. NSAIDs also diminish the local production of PGs, which are responsible for the compensatory vasodilatory effects. This is particularly significant in individuals with upregulated RAAS (hypovolemic patients, ARB or ACE-I users, etc.), as those reliant on the vasodilatory effects of PGs to maintain the hemodynamic integrity of the kidney. Thus, inhibition of PGs by NSAIDs leads to severe afferent vasoconstriction and GFR reduction [2].

The main questions are as follows: 1) How many doses should be taken to develop AKI? 2) How many days after triple whammy therapy does kidney damage occur?

NSAIDs exert their anti-inflammatory and adverse effects by inhibiting prostaglandin-endoperoxide synthase-2 (PGHS-2) and prostaglandin-endoperoxide synthase-1 (PGHS-1), respectively. Therapeutic effects often require significant suppression of prostaglandins. In the case of diclofenac, even therapeutic doses can lead to toxicity; as inhibition of 80% of PGHS-2 occurs, approximately 70% of PGHS-1 has already been inhibited at the given concentration of the drug [19].

In our case, urination ceased after adding 25 mg of diclofenac to a "double whammy" containing an ARB and a diuretic. Additionally, intentional dehydration during travel may be another triggering factor, referred to as a "quadruple whammy".

Several studies have assessed the risk of AKI after a triple whammy, showing that the highest risk occurs within the first 30 days and then decreases [14-20]. Only a 2022 Japanese study reported the time to onset of AKI [18]. According to this study, the median time to AKI onset after NSAID administration was less than two weeks, which was different from the time to anuria onset in our case. Anuria often occurred intentionally when the patient preferred to be anuric. A significant finding of our study was that NSAID-induced AKI occurred despite normal baseline renal function, which is unusual compared to previous reports of NSAID-induced AKI in healthy adults versus CKD patients [8]. Perhaps in our case, given pre-existing diabetes and hypertension, there was some subclinical kidney damage that should be kept in mind in similar cases.

Conclusion

The case is unique in several aspects: It is the first reported case of complete cessation of urination following oral administration of a diclofenac tablet, the first case of hemodynamically induced AKI occurring in a person with at least one clinically healthy kidney, and ultimately, the pioneering case of habitual self-induced anuria.

We would explain this event as a "quadruple whammy" with co-ingestion of three culprit agents: NSAIDs, ARB, and diuretic in the setting of hypovolemia.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them. A written consent has been obtained from the subjects. Principles of the Helsinki Convention was also observed.

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Authors' contributions

Study design: Legha Lotfollahi; Preparing the original draft: Melika Golmohammadi; Review and editing: Melika Golmohammadi and Legha Lotfollahi; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

References

[1] Ghlichloo I, Gerriets V. Nonsteroidal anti-inflammatory drugs (NSAIDs). Treasure Island: StatPearls; 2022. [Link]

[2] Klomjit N, Ungprasert P. Acute kidney injury associated with non-steroidal anti-inflammatory drugs. European Journal of Internal Medicine. 2022; 101:21-28. [DOI:10.1016/j.ejim.2022.05.003] [PMID]

[3] Dhanvijay P, Misra AK, Varma SK. Diclofenac induced acute renal failure in a decompensated elderly patient. Journal of Pharmacology & Pharmacotherapeutics. 2013; 4(2):155-7. [DOI:10.4103/0976-500X.110916] [PMID] [PMCID]

[4] Alfaro, R. A, Davis D.D. Diclofenac. Treasure Island: StatPearls; 2022. [Link]

[5] Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: An update of gastrointestinal, cardiovascular and renal complications. Journal of Pharmacy & Pharmaceutical Sciences. 2013; 16(5):821-47. [DOI:10.18433/J3VW2F] [PMID]

[6] Chatterjee S, Dureja GP, Kadhe G, Mane A, Phansalkar AA, Sawant S, et al. Cross-Sectional study for prevalence of non-steroidal anti-inflammatory drug-induced gastrointestinal, cardiac and renal complications in India: Interim report. Gastroenterology Research. 2015; 8(3-4):216-21. [DOI:10.14740/gr658w] [PMID] [PMCID]

[7] eHealthMe. Anuria in diclofenac-How severe and when it was recovered? [Internet]. 2022 [Updated 2024 May 1]. Available from: [Link]

[8] Zhang X, Donnan PT, Bell S, Guthrie B. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: Systematic review and meta-analysis. BMC Nephrology. 2017; 18(1):256. [DOI:10.1186/s12882-017-0673-8] [PMID] [PMCID]

[9] 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. European Journal of Internal Medicine. 2015; 26(4):285-91. [DOI:10.1016/j.ejim.2015.03.008] [PMID]

[10] Chandana C, Anusha S, Kavya HB. Diclofenac induced rapidly progressive renal failure in elderly patient-A case report. Indian Journal of Pharmacy Practice. 2022; 15(4):315-7. [DOI:10.5530/ijopp.15.4.56]

[11] Tomaszewski M, Zukowska-Szczechowska E, Zywiec J, Grzeszczak W. Transient anuria in a patient with chronic renal failure and liver affection after a single oral dose of diclofenac. Nephron. 2001; 88(3):287-8. [DOI:10.1159/000046009] [PMID]

[12] Shohaib S. Injection of diclofenac precipitating oliguric acute renal failure in a patient with kidney myeloma. Nephron. 2000; 85(1):96. [DOI:10.1159/000045639] [PMID]

[13] Naughton CA. Drug-induced nephrotoxicity. American Family Physician. 2008; 78(6):743-50. [Link]

[14] Hanim Islahudin F, Cheah HM. Beware of triple whammy. Malaysian Journal of Pharmacy 2022; 8(1):38-41. [DOI:10.52494/OPCN8135]

[15] Prieto-García L, Pericacho M, Sancho-Martínez SM, Sánchez Á, Martínez-Salgado C, López-Novoa JM, et al. Mechanisms of triple whammy acute kidney injury. Pharmacology & Therapeutics. 2016; 167:132-45. [DOI:10.1016/j.pharmthera.2016.07.011] [PMID]

[16] Loboz KK, Shenfield GM. Drug combinations and impaired renal function-The 'triple whammy. British Journal of Clinical Pharmacology. 2005; 59(2):239-43. [DOI:10.1111/j.0306-5251.2004.2188.x] [PMID] [PMCID]

[17] Thomas, MC. Diuretics, ACE inhibitors and NSAIDs--the triple whammy. The Medical Journal of Australia. 2000; 172(4):184-5. [DOI:10.5694/j.1326-5377.2000.tb125548.x]

[18] Kunitsu Y, Hira D, Morikochi A, Ueda T, Isono T, Morita SY, et al. Time until onset of acute kidney injury by combination therapy with "triple whammy" drugs obtained from Japanese Adverse Drug Event Report database. Plos One. 2022; 17(2):e0263682. [DOI:10.1371/journal.pone.0263682] [PMID] [PMCID]

[19] Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochemical Pharmacology. 2020; 180:114147. [DOI:10.1016/j.bcp.2020.114147] [PMID] [PMCID]

[20] Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: Nested case-control study. BMJ. 2013; 346:e8525. [DOI:10.1136/bmj.e8525] [PMID] [PMCID]