J Renal Inj Prev. 2020; 9(4): e30.

http://journalrip.com doi: 10.34172/jrip.2020.30

Journal of Renal Injury Prevention

Nonsteroidal anti-inflammatory drug induced acute kidney injury; A review and case study

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ARTICLE INFO

Article Type:
Review

Article History:
Received: 10 May 2020
Accepted: 1 June 2020
Published online: 13 June 2020

Keywords:
Acute kidney injury, Kidney, Nonsteroidal anti-inflammatory drug, Prevention, Renal, Renal failure

ABSTRACT

Introduction: The use of nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly therapeutic classes and are responsible for ten percent of medications dispensed annually. Twelve percent of individuals currently report taking a NSAID daily. Renal injury caused by these agents can present in various forms, resulting from either acute or chronic use. Historically approximately five percent of patients initiated on NSAIDs experience a kidney-related adverse event. Drug-induced renal injury accounts for twenty percent of episodes of acute kidney injury (AKI). Patients requiring renal replacement therapy (RRT) have experienced an increased length of stay with associated healthcare costs per incident. The adverse effects of NSAIDs contribute to a significant economic burden, both to the patient and to the healthcare system.
Methods: A medical literature review was composed.
Results: Numerous risk factors contribute to the development of drug-induced renal injury and disease. Patient specific factors include volume depletion and comorbid conditions. External risk factors such as use of high-risk medications and diagnostic contrast dyes contribute to the increased risk. Implementation of risk mitigation and educational strategies targeting healthcare professionals has the potential to decrease negative clinical and economic outcomes.
Conclusion: Healthcare providers' understanding of the pathophysiology, diagnostic criteria, and risk factors associated with AKI is vital to improve patient outcomes. Proactively screening high risk patients and utilizing appropriate mitigation strategies contributes to limiting the incidence and severity of injury. When the use of NSAIDs cannot be avoided, utilization of lower doses may be a suitable alternative.

Implication for health policy/practice/research/medical education:
The research discussed in the manuscript aimed to describe the significance and mechanism of nonsteroidal anti-inflammatory drug induced (NSAID) acute kidney injury (AKI). We found that an accurate diagnosis and implementation of mitigation strategies to limit patients' risk factors and exposure to NSAIDs has the potential to limit the incidence of AKI.

Please cite this paper as: Sabatino D, Tillman M, Pawasauskas J, Brothers T. Nonsteroidal anti-inflammatory drug induced acute kidney injury; A review and case study. J Renal Inj Prev. 2020; 9(4): e30. doi: 10.34172/jrip.2020.30.

Review

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed medications and are responsible for upwards of ten percent of all medications dispensed annually in the United States. One in every eight individuals currently reports taking an NSAID daily (1,2). The anti-inflammatory and analgesic effects of NSAIDs have been routinely utilized in clinical practice over the last seventy years (3,4). These agents are routinely administered for the myriad of conditions in which they are effective; including arthritis, fever, and pain (5). Furthermore, the over-the-counter availability and affordable cost of these agents lends to their ease of access.

Patients treated with NSAIDs may be at an increased risk for renal injury. NSAID-induced renal injury can present in various forms, resulting from either acute or chronic use. A correlation between NSAID-use and acute kidney injury (AKI) in an acute care setting is routinely encountered (6). Furthermore, studies have historically found that approximately five percent of patients initiated

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on NSAID therapy experience a kidney-related adverse event (7-9). In a prospective community based study, elderly patients over the age of 66 were assessed for correlations between NSAID use and the progression of chronic kidney disease (CKD). Progression to CKD was defined as a greater than 15 mL/min decline in glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) equation formula. The MDRD equation accounts for age, race, sex, and serum creatinine. (10). In this population, 26% of the total cohort developed CKD (11). The risk of injury can be observed with the use of either a non-selective cyclooxygenase inhibitor, such as naproxen and ibuprofen, or with a selective cyclooxygenase inhibitor, such as meloxicam or celecoxib (12). The risk of NSAID-induced AKI in various populations is 3.3%; however, a higher incidence appears to occur in individuals over the age of sixty, as well as in patients previously diagnosed with CKD (13-18).

The adverse effects of NSAIDs contribute to a significant economic burden, both to the patient and to the healthcare system. AKI has been associated with increased length of hospitalization of 3.2 days with an associated cost of $7933 per incident (19). Patients who experienced stage five CKD requiring renal replacement therapy (RRT), experienced an increased length of stay of 11.5 days, with an associated cost of $42 077 per incident (20). Therefore, strategies aiming to decrease the incidence of AKI may decrease overall healthcare expenditures and protect patients from unnecessary, avoidable risk.

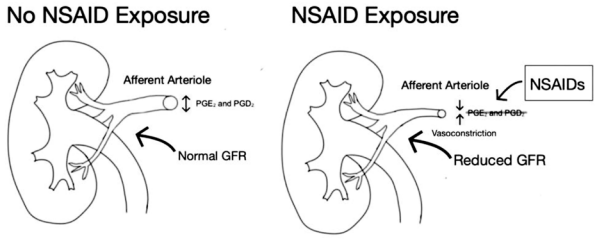
Pathophysiology of AKI

The two primary mechanisms attributed to NSAID-induced renal injury are well described in literature. The first mechanism proposes an inhibitory effect on prostaglandin synthesis. Physiologically prostaglandins, mainly prostacyclins, (PGE_2 and PGD_2), vasodilate the afferent arteriole, thereby increasing renal perfusion, with distribution of the cortex flow to the nephrons in the renal medullary region. The vasodilation in turn interacts with the renin-angiotensin-aldosterone system and the sympathetic nervous system to ensure adequate perfusion to the renal system. NSAIDs use can result in afferent renal arteriole vasoconstriction, ultimately leading to acute renal injury (20,21). The second NSAID-induced renal injury mechanism can be defined as acute interstitial nephritis (AIN). AIN is an immune-mediated response which may be induced by chronic NSAID exposure. Impaired perfusion occurs due to a localized inflammatory response and edema of the renal interstitium leading to renal cellular injury (22). In conjunction with patient-specific risk factors, an increased risk for AKI can occur (Figure 1).

Although the temporal relationship of kidney related injury due to NSAID exposure may vary between individuals, a decline in renal function commonly occurs within 3-7 days (11). During this time, maximum prostaglandin synthesis inhibition occurs, allowing practitioners to commonly observe a decrease in urine output, a rise in serum creatinine (SCr), or both (20). A retrospective cohort study examined the time from initial NSAID therapy to a rise in SCr, where twelve female subjects were given ibuprofen 800 mg three times daily for 11 days. Of these twelve patients, three required discontinuation of NSAID therapy due to an increase in SCr by 1.5 mg/dL prior to day 8 of therapy. In this small sample size, 25% of participants experienced AKI within 3-7 days, which routinely correlates to the time required to observe a decrease in renal function associated with the administration of an NSAID (23,24).

A higher incidence of AKI is typically observed during the first month of NSAID therapy. This may be attributed to the prostaglandin synthesis pathway (25). Prostaglandins are not regularly stored in the body and are synthesized when inadequate amounts are available for their primary role of vasodilation to the afferent arteriole. Over the course of long term NSAID therapy, prostaglandin synthesis is regulated to ensure adequate renal perfusion (26).

Frequent episodes of AKI can predispose a patient to the development of CKD (23). Following an AKI event, maladaptive formations can occur. These formations include fibrosis, vascular rarefaction, tubular loss, glomerulosclerosis, and chronic interstitial inflammation, all of which can lead to chronic renal insufficiency and potentially end-stage renal disease (ESRD) necessitating RRT (27,28). The association between AKI and the development of CKD has become more prominent as researchers have identified AKI to be an independent risk factor for both the progression to ESRD and increased mortality (27). Elderly patients who experienced a SCr increase of 0.1 mg/dL during hospitalization were found to be 1.45 times more likely to progress to ESRD than patients who did not (27). This risk increases to approximately



- In the non-NSAID exposure kidney pictorial, the afferent arteriole is adequately dilated by prostaglandins (PGE_2 and PGD_2).
- This dilation of the afferent arteriole allows for adequate renal blood perfusion.
- The kidney is able to maintain necessary filtration processes.

- In the NSAID exposure kidney pictorial, the afferent arteriole is vasoconstricted due to prostaglandin (PGE_2 and PGD_2) inhibition.
- This vasoconstriction of the afferent arteriole restricts renal blood perfusion.
- This kidney is unable to maintain necessary filtration processes.

Figure 1. Mechanism of NSAID induced AKI.

double when SCr increases by 0.2 mg/dL. An increase in mortality has also been associated with increased SCr during hospitalization. A rise in SCr by 0.1 mg/dL or 0.3 mg/dL has been further associated with an increased risk in mortality by 14% to 26%, respectively (27).

Recent epidemiologic data suggests that approximately 700 000 patients in the United States are receiving RRT annually, which accounts for 0.2% of the population (28). Mortality estimates indicate that the five-year survival rate for patients on hemodialysis is approximately 65% and the death rate for those receiving any form of RRT is approximately 240 patients per day (29,30). The annual per patient cost for one year of hemodialysis is approximately $90 000, which translates to 28 billion US healthcare dollars spent annually (31).

Diagnosis

Diagnosis of AKI is challenging and imperfect due to the limitations of renal biomarkers, such as serum creatinine, blood urea nitrogen, urinary albumin/protein, and volume excretion. Three suggested AKI classification systems have been utilized (2004 RIFLE, 2007 AKIN and KDIGO 2012), each proposing different criteria in the diagnosis of AKI (32,33) (Table 1).

The RIFLE (risk, injury, failure, loss, and end-stage) criteria utilizes SCr and urine output for diagnosis. These criteria have been extensively evaluated in the adult critical care population who had experienced a reduction in kidney function (34). Limitations of the RIFLE criteria include the dependence of obtaining a baseline SCr value and the absence of consensus indicating when RRT is indicated (32).

In 2004, the AKIN (Acute Kidney Injury Network) criteria were developed to address the RIFLE criteria's shortcomings. AKIN criteria differ from the RIFLE criteria in several specific ways. RIFLE criteria are defined as an increase in SCr by 50% or greater from baseline within 7 days, while the AKIN criteria recommend 48 hours. The AKIN classification defines AKI as an increase in SCr by 0.3 mg/dL and greater from baseline or an increase in SCr by 50% or greater from baseline within 48 hours. AKIN further avoids utilizing GFR as a marker of AKI, as there is currently no reliable method to measure GFR and estimated glomerular filtration rates are unreliable in the setting of AKI (35-37). Lastly, AKIN criteria include recommendations pertaining to RRT indication based upon staging (32,38).

In 2012 the third staging system termed the Kidney Disease: Improving Global Outcomes (KDIGO) was created to incorporate both the RIFLE and AKIN criteria into one staging system. This is accomplished by observing creatinine changes over a 48-hour period as well as a decline in renal function over 7 days (32). Currently, KDIGO criteria is considered the gold standard for AKI diagnosis (32,39) (Table 2).

Risk factors

Risk factors play a key role in determining which patients are more prone to experiencing NSAID-induced AKI. Some of these risk factors include impaired perfusion to the kidneys, such as heart failure, volume depletion, infection, CKD, blood pressure altering medications, contrast dyes and nephrotoxic chemotherapeutic agents (40). Obstruction of the urinary tract associated with AKI can largely be attributed to nephrolithiasis and various oncologic conditions involving the genitourinary tract (41). A study evaluating the incidence of AKI in critically ill patients with specific and/or similar comorbid disease states that impair renal blood flow found that 20.4% of patients with heart failure, 54.7% of patients with sepsis, and 23.9% of patients with CKD developed AKI (42).

Numerous agents have also been commonly associated with AKI in the acute care setting, namely aminoglycosides, beta-lactam antibiotics, NSAIDs, angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), and diagnostic

Table 1. RIFLE, AKIN, and KDIGO AKI dagnosis criteria (32)

	RIFLE	AKIN	KDIGO
AKI diagnosis	SCr increase ≥ 50% within 7 days	SCr increase ≥ 0.3 mg/dL **(OR)** increase ≥ 50% within 48 hours	SCr increase ≥ 0.3 mg/dL within 48 hours **(OR)** Increase ≥ 50% within 7 days
Staging criteria	**Risk** ≥ 1.5 times baseline **Injury** ≥ 2 times baseline **Failure** ≥ 3 times baseline **(OR)** ≥ 0.5 mg/dL increase to at least 4.0 mg/dL	**1** SCr increase ≥ 0.3 mg/dL **(OR)** Increase 1.5-1.9 times baseline **2** 2-2.9 times baseline **3** ≥ 3 times baseline **(OR)** ≥ 0.5 mg/dL increase to at least 4.0 mg/dL **(OR)** Initiation of RRT	**1** SCr increase ≥ 0.3 mg/dL within 48 hours **(OR)** 1.5-1.9 times baseline **2** 2-2.9 times baseline **3** 3 times baseline **(OR)** Increase to at least 4.0 mg/dL **(OR)** Initiation of RRT

Table 2. KDIGO Staging Criteria (39)

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline **(OR)** ≥0.3 mg/dL (≥ µmol/l) increase	<0.5 mL/kg/h for 6 hours
2	2.0-2.9 times baseline	<0.5 mL/kg/h for 12 hours
3	3.0 times baseline **(OR)** increase in serum creatinine to ≥4 mg/dL **(OR)** Initiation of renal replacement therapy	<0.3 mL/kg/h for ≥ 24 hours **(OR)** Anuria for ≥ 12 hours

contrast dye (43). A study evaluating 360 critically ill patients receiving aminoglycoside therapy noted that 58% developed AKI (44). Baseline GFR were similar in both patient cohorts despite one cohort developing AKI. Of note, within the AKI cohort, diabetes and hypotension were more prevalent, suggesting these conditions may have contributed to the high incidence of AKI (45). Another study evaluated 424 patients to determine the incidence of AKI associated with the use of anti-infective medications. AKI developed in 17.9% of the sample and was largely associated with the use of aminoglycosides and beta-lactam antibiotics (7) .

The use of ACE-I/ARB therapy is associated with an increased risk of developing AKI (45). In a study comparing the effects of telmisartan 80 mg daily, ramipril 10mg daily and combination therapy evaluated 25,620 patients. The secondary outcome, observing the risk of renal dysfunction in telmisartan and ramipril was determined as 2.21% and 2.03%, respectively (46). This risk of AKI significantly increases in the presence of a diuretic of NSAID. A retrospective cohort study assessed patients on antihypertensive therapy with an ACE-I/ARB, a diuretic and NSAID therapy. At a mean follow-up period of 5.9 years, patients receiving the three-agent regimen were found to have a 1.31 increased relative risk in developing AKI. Of importance, the majority of AKI occurred during the first month of therapy (47).

Contrast dye has been associated with an 11% risk of developing AKI in the emergency setting (48). However, there is large variability in the incidence of contrast-induced AKI due to the heterogeneity in health status of these patients. In non-emergent elective procedures, contrast-induced AKI was observed in less than 1% of patients (49). The prevalence increased to 4% when contrast dye was used in patients with CKD (50). In a study by Manske et al, the utilization of low volume contrast, defined as <5 mL/kg per SCr, was found to be less nephrotoxic (51).

The duration and dose of NSAID therapy should also be considered when assessing the patient's risk of developing AKI. Although an exact cumulative dose placing an individual at risk for NSAID-induced AKI is unknown, research has suggested an associated increased risk when NSAID exposure continues over multiple days. The relationship between NSAIDs and AKI is due to a combination of higher doses and multiple patient-specific risk factors that are present (52). A case-control study that reviewed 306 hospital records of the general population who received at least one NSAID prescription and developed AKI over a five-year period (53) A higher incidence of AKI was observed during the first month of high NSAID use compared to months of sustained use (53).

It is the role of healthcare providers to proactively screen patients for potential risk of NSAID induced AKI due to their current illness, comorbidities, and medication regimens.

Mitigation strategies

The primary mitigation strategy should primarily focus on prevention and risk reduction initiatives. A risk-benefit analysis should be performed prior to prescribing an NSAID, particularly in patients with one or more known risk factors. It has been suggested to minimize both the dosage and duration of therapy in patients with an estimated CrCl <60 mL/min (54).

Healthcare provider education on safe and effective NSAID use remains a key component to further minimize kidney related injury. Some institutions have utilized a new model of training titled 'empowering education'. This approach matches the educational efforts with the information gaps of the medical staff to increase the desire to learn while also improving patient safety and outcomes (55).

Initiatives led by educators targeting prescribers caring for patients with kidney function altering disease states (i.e. heart failure) should be advised on the risks associated with NSAID use. A cross-sectional study observed the avoidance of NSAID therapy in patients diagnosed with CKD. A total of 12,065 adults completed a questionnaire to evaluate the use of NSAIDs based on the patient's kidney function. The questionnaire concluded that 10.2% of patients with moderate-to-severe CKD had a prescription for an NSAID and 66.1% of patients with CKD had been taking an NSAID for one year or longer (54). Healthcare provider education is imperative to decrease the risk of patients developing AKI and possible further kidney complications.

The concomitant use of NSAIDs and radiocontrast dye has the potential to increase the risk of AKI (56). In a retrospective cohort study that reviewed preventative strategies implemented to avoid radiocontrast AKI, one in every twelve patients reviewed were still prescribed an NSAID. Only one case of NSAID discontinuation occurred on the day prior to the procedure. This lack of

provider awareness and medication regimen modification may be due to the lack of formal guidelines available (44). Practitioners are recommended to utilize risk assessment tools, such as the age, creatinine, and left ejection fraction (ACEF) scoring tool, to predict the risk of developing contrast induced AKI. The ACEF risk scoring tool accounts for the patients age, creatinine, and left ventricular ejection fraction to predict risk of contrast induced AKI (57). A study identified patient risk factors for contrast induced AKI (age greater than 75, diabetes mellitus, chronic congestive heart failure, acute pulmonary edema, hypotension, anemia, and CKD) by using multivariate logistic regression. Each of these risk factors were then stratified with an integer to obtain a patient's cumulative risk score (56). A score of less than or equal to five was associated with a 7.5% risk of contrast induced AKI and a 0.04% risk of dialysis (low risk) (45). In comparison, a score of 16 or greater yielded a 57% risk of developing AKI and 13% risk of needing dialysis treatment (high risk) (45). Until guidelines for the use of radiocontrast dye become available, prescriber education on utilizing contrast induced AKI risk assessments tools is advised to minimize the risk of developing AKI.

Once an event of AKI has been identified, prompt management is essential to minimize the extent of injury (58). A stepwise approach to management should be utilized. First, the offending agent should be discontinued with the goal of returning the kidney to baseline function. Next, volume status should be assessed with the goal to minimize intravascular depletion. In severe cases of NSAID-related AKI marked by profound acid-base or electrolyte imbalances, RRT may be warranted. Despite NSAID use being commonly associated with AKI, severe injury necessitating RRT is common and has been suggested to be as high as 8% (59) (Table 3).

Case vignette

A 55-year old male was admitted to a community hospital for the primary treatment of acute alcohol withdrawal. His past medical history included primary essential hypertension, chronic foot pain, opioid use disorder (OUD), nicotine dependence, and chronic alcohol use disorder. His outpatient medication regimen includes amlodipine 5 mg orally daily, buprenorphine-naloxone 24 mg-6 mg orally daily, citalopram 20 mg orally daily, hydroxyzine 50mg orally every six hours as needed for anxiety, thiamine 200 mg orally daily, and mirtazapine 30mg orally at night. The patient further admitted to the illicit use of clonazepam and alprazolam three to four times per week. Initial laboratory findings revealed an elevated serum creatinine of 1.4 mg/dL despite having adequate urine output of 1.17 mL/kg/h.

The patient was prescribed a liberal diet upon admission. The initial serum creatinine reading was obtained on the first day of admission and resulted at 1.4 mg/dL. Due to the confounding diagnosis of OUD, opioid analgesics were avoided. The patient was initiated on ibuprofen 800 mg every eight hours as needed for pain and acetaminophen 650 mg every six hours as needed for pain on the second day when he received one dose of each medication. The patient received ibuprofen daily beginning on day 2, with intermittent doses of ketorolac (60 mg IM) and acetaminophen 650 mg, and additionally on the eighth day of admission. Repeated serum creatinine values were 1.4 mg/dL and 1.3 mg/dL on days 4 and 6 of admission. On days 5 through 9 of hospitalization, a gradual decline in urine output was observed (Figure 2).

Case assessment and evaluation

In this patient, a multimodal, stepwise pain approach, with the use of NSAIDs, acetaminophen, gabapentin, and buprenorphine were employed. The pain management approach utilized relied largely upon the use of NSAID agents for episodes of breakthrough pain, due to his history of substance use disorder. Eliminating opioids as a therapeutic option for treating acute pain limits the alternatives available, and NSAIDs were considered a safe and efficacious option. The patient was maintained on buprenorphine-naloxone and gabapentin daily, in combination with ibuprofen, ketorolac, and on several

Table 3. AKI Risk Factors and Mitigation Strategies

AKI Risk Factors	Mitigation Strategies
Conditions that impair renal blood flow; volume depletion, CKD, CHF, sepsis	Patient counseling by healthcare providers to ensure safe use of OTC NSAID medications and minimize NSAID polypharmacy (54,55).
Cardiovascular medications; ACE-inhibitors, ARBs	Ensure benefits of nephrotoxic agents outweigh the risks of adverse outcomes prior to initiation therapy (54).
NSAID medications	Minimize NSAID exposure in an inpatient setting when cardiovascular risk factors are present (54).
Radiocontrast dye	Increase provider awareness of the interaction to avoid the combinations of NSAID medications and radiocontrast dye (45,56).
Anti-infective medications (beta-lactams, aminoglycosides)	Be able to identify and manage episodes of AKI. Management includes discontinuation of the offending agent and volume status assessment/correction. RRT may be considered in severe cases (58,59).

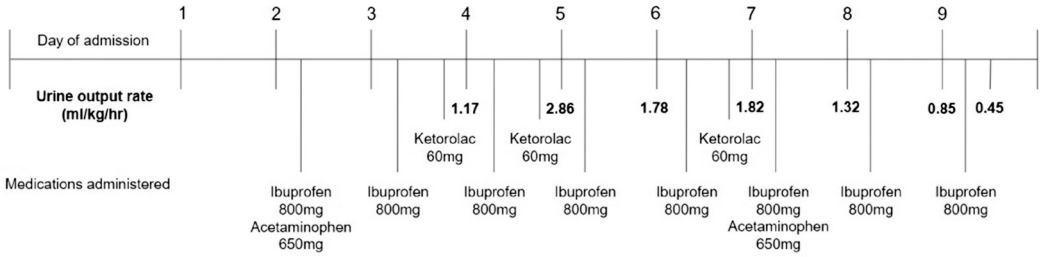


Figure 2. Hospital course depicting urine output in relation to medications administered.

occasions acetaminophen, when additional analgesia was required.

Despite the complexity of treating his acute pain, strategies to minimize the risk of injury should have been utilized. AKI risk assessment begins with identification of pertinent risk factors predisposing a patient for experiencing an episode of AKI. This patient had multiple risk factors including hypertension and tobacco use, both of which increase his risk of kidney injury. Each of these factors can result in reduced perfusion of renal parenchyma. The patient further had evidence of renal impairment upon admission, evidenced by an elevated serum creatinine of 1.4 mg/dL. Throughout his hospital admission, the patient received the maximum dosage of both NSAID medications; 800 mg oral doses of ibuprofen and 60 mg intramuscular injections of ketorolac. Initiation at lower doses (ibuprofen 200 mg and ketorolac 15 mg) could have minimized renal injury while managing acute pain. Lastly, the incorporation of analgesic modes such as acetaminophen for would further minimize the potential for NSAID exposure.

When approaching pain management, multiple factors should be considered in selecting the safest and most efficacious agent. Numerous pain medications are readily available with varying mechanisms of action. which makes choosing the right mechanisms for each situation highly important. When utilizing NSAID medications, providers must recognize the renal implications of their mechanism of action, side effect profile, and potential for long term consequences. Prescribers should identify characteristics that may predispose a patient to adverse effects, recognize biological markers that may indicate when an adverse reaction is occurring, and be readily available to modify the pharmacotherapeutic regimen to minimize the risk of negative outcomes.

Conclusion

Our findings suggest that NSAID induced AKI is a complex process that has wide inter patient variability. The mechanism of injury varies based on acute or chronic use of NSAIDs. The presentation of disease differs depending on patient-specific risk factors, such as volume depletion, comorbid conditions, use of high-risk medications, or concomitant diagnostic contrast dye. Healthcare providers' understanding of the pathophysiology, diagnostic criteria, and risk factors associated with AKI is vitally important to improve clinical outcomes. Proactively screening high risk patients and utilizing appropriate mitigation strategies, such as adequately hydrating patients and limiting NSAID exposure to the lowest dose for the shortest period of time. As illustrated by the case vignette, AKI can be precipitated through the use of a typical NSAID regimen, demonstrating the importance of proper risk factor management. Practitioners should also limit use of NSAIDs in patients with cardiovascular disease or in patients undergoing diagnostic evaluation with contrast dyes. Implementation of risk mitigation strategies and educational strategies targeting healthcare professionals has the potential to decrease negative clinical and economic outcomes.

Authors' contribution

DS researched and developed the manuscript. DS created Figure 1, Table 1, and Table 2. MT researched and developed manuscript. MT created Table 3 and Figure 2. JP and TB reviewed, edited, and provided intellectual concepts for the manuscript and verified the analytical methods. All authors approved the final version for publication.

Conflicts of interest

JP is consultant to Heron Therapeutics and Mallinckrodt Pharmaceuticals and Speakers' Bureau for Mallinckrodt Pharmaceuticals.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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