Nonsteroidal Anti-inflammatory Drug (NSAID) Toxicity in Emergency Room

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Abstract

Nonsteroidal anti-inflammatory medicines, collectively referred to as NSAIDs in academic context, exhibit chemical diversity while concurrently manifesting comparable therapeutic and harmful effects. All pharmaceutical substances under this particular category function by diminishing inflammation, alleviating pain, and reducing fever by means of inhibiting enzymes responsible for the creation of endoperoxides, often referred to as cyclooxygenase (COX) enzymes. The two cyclooxygenase isozymes, COX-1 and COX-2, are responsible for the conversion of arachidonic acid into its endoperoxide metabolites. These metabolites include prostacyclin, prostaglandins, and thromboxane, each exhibiting a wide range of biological activities such as inflammation, regulation of smooth muscle tone, and promotion of thrombosis. The COX-1 enzyme is consistently produced and is recognized as the main provider of prostanoids required for maintaining physiological balance, such as safeguarding the stomach epithelium. In contrast, the COX-2 enzyme is capable of being induced, leading to a substantial increase in the synthesis of prostanoids in circumstances characterized by stress and inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) may induce toxicity via the same pharmacological mechanisms that contribute to their therapeutic efficacy. This review aims to discuss NSAIDs toxicity in details, its symptoms, and possible management in the emergency room.

Keywords: NSAIDs, toxicity, emergency room, management

Introduction:
Nonsteroidal anti-inflammatory medicines (NSAIDs), collectively referred to as such in academic discourse, exhibit chemical diversity while concurrently manifesting comparable therapeutic and harmful effects. All medications belonging to this particular family function by inhibiting the activity
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The toxicity of NSAIDs is a significant concern in the management of acute overdose cases. Acetaminophen, either as a standalone medication or as part of combination products, emerged as the predominant substance implicated in poisoning scenarios where acetaminophen emerges as the predominant substance implicated in poisoning.

The majority of NSAIDs are generated from organic acids and exhibit fast absorption from the gastrointestinal (GI) tract. These pharmaceutical substances undergo significant hepatic metabolism and are eliminated from the body by glomerular filtration and tubular secretion. Due to the aforementioned factors, NSAIDs are generally considered to be contraindicated in individuals who have significant hepatic and renal impairment. Due to their high affinity for plasma proteins, NSAIDs have a propensity to concentrate efficiently and expeditiously in sites of inflammation, hence facilitating prompt analgesic efficacy within a time frame of 30 to 60 minutes [2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used as both over-the-counter and prescription medications for the purpose of alleviating pain and reducing fever, due to their established safety and efficacy. According to estimates, a total of 14 million individuals in the United States who are aged 45 and over engage in daily use of NSAIDs. The United States Centers for Disease Control and Prevention (CDC) anticipates a significant increase in the use of this category of drugs as the population continues to age, which will correspond to the projected growth in the prevalence of painful disorders, including osteoarthritis and inflammatory diseases. It is thus unsurprising that the incidence of adverse events linked to the usage of NSAIDs is also expected to increase. Prior research has shown that medication toxicity accounts for around 5% to 7% of hospital admissions, with non-aspirin NSAIDs being responsible for approximately 11% to 12% of such hospitalizations [11-12].

According to the 2009 Annual Report of the National Poison Data System (NPDS) by the American Association of Poison Control Centers, analgesics were found to be the predominant medication category involved in acute overdose cases among adult patients, accounting for 10% of such incidents. In pediatric patients, analgesics ranked as the second most prevalent drug category, comprising 9% of reported cases.

Acetaminophen, either as a standalone medication or as part of combination products, emerged as the prevailing analgesic in cases of acute overdose, accounting for 42% of recorded incidents. Nonsteroidal anti-inflammatory drugs NSAIDs were responsible for 33% of the documented instances of acute ingestion involving analgesics. Ibuprofen is the predominant NSAID used in cases of overdose, accounting for around 81% of such incidents. Naproxen, on the other hand, constitutes approximately 11% of reported NSAID overdose cases. The aforementioned data has shown little changes throughout the course of the last ten years. In the United Kingdom, there exists a comparable scenario where acetaminophen emerges as the predominant substance implicated in poisoning inquiries made to the National Poisons Information Service telephone service (accounting for 10.2% of telephone calls) as well as accesses to the online TOXBASE database (representing 6.3% of accesses). Ibuprofen, an NSAID, is the second most often seen agent, accounting for 4.7% of telephone queries and 3.7% of TOXBASE accesses. The toxicity of NSAIDs can give rise to various adverse effects, including gastrointestinal (GI) bleeding, hypertension, hepatotoxicity, and renal damage. In cases of acute NSAID overdose, symptoms are typically absent or exhibit minimal GI manifestations.

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However, complications associated with toxicity may manifest as anion gap metabolic acidosis, coma, convulsions, and acute renal failure [13, 14].

Furthermore, NSAIDs can induce damage to the GI tract by inhibiting the production of gastric mucosa through the inhibition of COX-1. Nephrotoxicity is also a potential consequence of NSAID usage due to the reduction of prostaglandin levels, which are crucial for the vasodilation of renal arterioles. Lastly, neurologic toxicity may present as drowsiness, confusion, nystagmus, blurred vision, diplopia, headache, and tinnitus [15, 16].

A review of Ibuprofen, Acetaminophen, and Aspirin toxicity in adults showed that the misuse of over-the-counter drugs, which are often considered to be harmless, may lead to significant consequences. Ibuprofen, acetaminophen (APAP), and acetylsalicylic acid (ASA) are among the frequently used over-the-counter drugs, both individually and as constituents in combination pharmaceutical formulations. The prompt emphasizes the crucial importance of the clinician's ability to identify the indicators and manifestations of acute ingestion, and promptly provide the appropriate course of therapy. Furthermore, a significant number of the indicators and manifestations of acute NSAID poisoning may not be immediately apparent upon the first arrival of the toxic patient at the emergency room. Therefore, it is essential for the physician to predict the potential consequences after the diagnosis in order to promptly implement suitable therapies for patients experiencing acute toxicity. This is crucial for delivering comprehensive and high-quality patient care inside the emergency department [17].

NSAID Toxicity: An Overview

NSAIDs exhibit mild acidity and have a high degree of protein binding, exceeding 90%. Additionally, they possess a very small volume of distribution, estimated to be about 0.1-0.2 L/kg. The process of metabolism mostly takes place in the liver by oxidation and conjugation, although a little portion of the parent NSAID is eliminated through the kidneys, accounting for less than 10%–20% of the total [16,18]. The half-life of different medications exhibits variability, with ibuprofen, diclofenac, and mefenamic acid, having an estimated half-life of 2 hours, indomethacin having a half-life of 4 hours, and naproxen having a half-life of up to 15 hours [16].

The primary cause of toxicity in cases of NSAID overdose seems to be the excessive suppression of COX-1 and the concomitant decrease in prostaglandin production. The occurrence of metabolic acidosis in cases of severe NSAID toxicity is not attributed to the inhibition of COX, but rather to the buildup of acidic metabolites. The gastrointestinal, renal, and CNS are most impacted, both during therapeutic administration and in cases of acute overdose [19].

Gastrointestinal adverse effects manifest via two distinct processes. The suppression of prostaglandins leads to a decrease in the synthesis of mucus and bicarbonate, a reduction in stomach blood flow, and an enhancement in acid production. NSAIDs have been identified as having direct cytotoxic effects on the stomach mucosa. Chronic use of this substance leads to the manifestation of gastrointestinal symptoms, which may vary from feelings of nausea and moderate pain in the upper abdomen to the development of ulcers in the stomach or duodenum, and even gastrointestinal bleeding. The gastrointestinal manifestations seen in cases of acute overdose may be attributed to these pathways as well [16].

The renal arterioles are affected by the vasodilatory actions of prostaglandins, leading to nephrotoxicity in both therapeutic usage of NSAIDs and NSAID overdose. NSAID nephrotoxicity is improbable to manifest at therapeutic levels in individuals who possess normal physiological regulation of renal blood flow, given the little contribution of prostaglandins in maintaining renal blood flow. Nevertheless, in individuals experiencing a decrease in fluid volume inside their blood vessels (such as those who have vomited excessively due to an overdose) or those with elevated levels of angiotensin (such as patients with heart failure or cirrhosis), the role of prostaglandins in ensuring sufficient blood flow to the kidneys becomes more prominent. Prostaglandins have been shown to have negative effects on the preservation of glomerular filtration rates in patients, potentially leading to the development of renal failure upon their suppression. Chronic use has also been associated with the development of interstitial nephritis [20].

High anion gap metabolic acidosis is a condition that is seen in cases of excessive use of NSAIDs. This condition arises as a result of the buildup of acidic metabolites. Vomiting and alcohol use might further aggravate acidosis. The suppression of COX-1 activity also has an impact on the process of platelet aggregation, as it leads to a decrease in the production of thromboxane-A2, affecting this physiological mechanism. The aforementioned scenario has significant ramifications for patients who
are undergoing simultaneous treatment with anticoagulant or antiplatelet medications. However, it is important to note that there is a theoretical possibility of heightened risk of bleeding in cases of acute overdose. Various hematological abnormalities have been documented in isolated case reports subsequent to acute overdose incidents; nevertheless, these findings are mostly considered to be idiosyncratic in nature [18, 21].

The majority of NSAID exposures are characterized by mild-to-moderate ingestions, resulting in low levels of symptom severity. These symptoms mostly present as general gastrointestinal disturbances, including nausea and vomiting. Additionally, slight abnormalities in blood chemistry and electrolyte levels may be seen, although these often recover quickly with appropriate supportive treatment. In cases of significant consumption, some individuals may experience a change in their level of awareness that may lead to a state of coma. This is often accompanied by a gradual and occasionally resistant metabolic acidosis, as well as the development of multisystem organ failure. Seizures may be implicated and exhibit heightened occurrence in certain categories of NSAIDs such as pyrazolones and fenamates (for example, phenylbutazone and mefenamic acid, respectively). Typically, other NSAIDs exhibit lower levels of toxicity compared to the aforementioned ones. Ingestions of ibuprofen at doses equal to or below 100 mg/kg normally result in mild symptoms, since it is the most commonly used NSAID. Life-threatening circumstances are generally not seen until ibuprofen ingestions reach or exceed 400 mg/kg [22].

Aside from these independent toxicities, NSAIDs may also result in adverse effects when taken concurrently with numerous other drugs. As a result of their pharmacokinetics, NSAIDs may interact with other high plasma protein-bound drugs, displacing them and leading to an increase in the free serum concentration of these drugs. Drugs with narrow therapeutic windows, such as warfarin or phenytoin, can theoretically reach toxic levels when displaced in this manner. Additionally, NSAIDs may increase the toxicity of drugs that are dependent on renal clearance (such as lithium) or hepatic metabolism because some NSAIDs reduce renal perfusion and inhibit cytochrome P450 (CYP) enzymes or glucuronidation [2].

Other notable drug interactions occur during concurrent use of NSAIDs and antihypertensives, anticoagulants and antiplatelets, selective serotonin receptor inhibitors (SSRIs), and substances that injure GI mucosa. The effects of many antihypertensives are diminished due to the ability of NSAIDs to reduce natriuresis. Besides decreased efficacy, specific use of NSAIDs with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may exacerbate potassium retention, known to have significant cardiac consequences. Simultaneous use of NSAIDs and anticoagulants or antiplatelets can result in an increased risk of bleeding due to reduced platelet aggregation. Bleeding risk is also similarly increased with concomitant use of SSRIs and NSAIDs, as serotonin is one of many substances taken up by and released from platelets to stimulate aggregation and hemostasis. Lastly, the risk of peptic ulcer disease or a GI bleed is markedly increased when NSAIDs are ingested in combination with alcohol or glucocorticoids which inhibit the activation of the arachidonic acid precursor phospholipase A2 [23-26].

Emergency Room Response to NSAID Toxicity:

The management of acute poisoning caused by NSAIDs primarily involves providing supportive and symptomatic care. In the emergency room, the response to NSAID toxicity involves a multi-faceted approach. The first step is to ensure that the patient is stable and their vital signs are within normal limits. This includes assessing their heart rate, blood pressure, and oxygen saturation levels. Next, prompt decontamination is vital to prevent further absorption of the NSAID and minimize its toxic effects. This may involve gastric lavage or administration of activated charcoal to absorb the drug in the gastrointestinal tract [27].

Initial stabilization consists of securing the airway, breathing, and circulation (ABCs). For gastrointestinal (GI) decontamination, syrup of ipecac is no longer recommended and should not be administered for NSAID overdose under any circumstances. If the patient has no clinical evidence of a perforated viscus, decontaminate with activated charcoal (AC). The patient must be able to protect the airway (eg, normal mental status, preserved gag reflex, absence of vomiting) in order to prevent aspiration of charcoal. Activated charcoal may not be warranted in patients presenting later than 1-4 hours post ingestion. No evidence exists that empiric administration of activated charcoal in drug overdose improves clinical outcome. Orogastric lavage may be indicated in massive overdoses after recent exposure, especially in the patients who are intubated. No specific antidotes for NSAID poisoning exist. Patients with significant toxicity who develop severe acidosis may require supportive treatment with intravenous sodium bicarbonate. Intravenous fluid administration is crucial to maintain

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hydration and support kidney function. This helps to flush out the toxic substances and prevent kidney injury. Additionally, it is important to closely monitor the patient's gastrointestinal symptoms and initiate appropriate interventions to address them. For patients experiencing abdominal pain and nausea, medications such as antiemetics and antacids may be administered to alleviate discomfort and reduce the risk of further complications [22, 28, 29].

Hemodialysis may be seen as a potential therapeutic intervention for the amelioration of profound acidosis. Acute renal failure often resolves within a few days. Urinary alkalization and forced diuresis do not play a significant role in the management of NSAID toxicity or overdose. The administration of sodium bicarbonate for the treatment of metabolic acidosis is contingent upon the underlying cause and individual patient attributes. It is essential to closely monitor the patient's volume status and renal function throughout the process of hydration in order to prevent iatrogenic problems. This is especially crucial for patients who have had adverse medication responses and have medical comorbidities that may increase their susceptibility to NSAID toxicity, such as congestive heart failure [30].

Sodium bicarbonate is not a designated antidote for NSAID poisoning. Nevertheless, it is recommended to be used as part of the supportive treatment provided to acidic patients, with other appropriate interventions. Transient acidosis in cases of mild to severe NSAID poisoning is often self-limiting and exhibits quick improvement. Lactic acidosis, occurring in the context of reduced blood flow to tissues and failure of several organ systems, may exhibit resistance to the administration of bicarbonate and need the implementation of intensive supportive measures focused on restoring adequate tissue oxygenation and perfusion. The use of hemodialysis with an alkaline bath has the potential to aid in the correction of acid-base and electrolyte imbalances, as well as assist in the regulation of volume status in patients who are critically sick [22]. The use of extracorporeal membrane oxygenation (ECMO) has shown efficacy in the management of resistant hypotension resulting from a severe ibuprofen overdose [31].

In cases of severe NSAID toxicity with gastrointestinal bleeding, it may be necessary to involve a gastroenterologist for further evaluation and intervention. Endoscopic procedures, such as an upper gastrointestinal endoscopy, can help identify the source of bleeding and facilitate appropriate treatment measures, such as cauterization or the application of hemostatic agents [32].

**NSAID Toxicity Prevention in Emergency Care Settings:**

Prevention and public awareness play a crucial role in mitigating the risks associated with NSAID toxicity. Healthcare professionals should educate patients about the potential side effects of NSAIDs and the importance of proper usage.

It is advisable for healthcare professionals to refrain from providing NSAIDs at excessive dosages to patients who are at a heightened risk of experiencing problems. Risk factors include the following elements:

- Elderly individuals
- Alcoholism
- Diabetes and other chronic medical disorders.
- The presence of an actively occurring stomach ulcer condition.
- The use of drugs that have the potential to hinder the flow of blood to the kidneys, such as ACE inhibitors and cotrimoxazole.

In order to mitigate the potential harmful effects of NSAIDs, practitioners have the option to explore alternate pharmaceuticals for pain and inflammation management or provide alternative approaches to pain reduction, such as acupuncture or other physical and rehabilitation therapies. According to the guidelines set out by the American College of Rheumatology, acetaminophen is recommended as a suitable therapeutic option for managing pain associated with mild to moderate osteoarthritis. Additional options for hand arthritis management include the use of topical capsaicin or topical NSAIDs, as well as the administration of tramadol [33].

It is suggested that patients be instructed to refer to product labels while using over-the-counter analgesics, so as to prevent surpassing the authorized dosages. This situation may arise when employing two medicines that contain identical chemicals or belong to the same class of medication concurrently. Similar to the regulations imposed on paracetamol in the United Kingdom, restrictions on the quantity of NSAIDs that may be obtained in a single transaction, as well as variations in packaging, have the potential to mitigate the risk of acute NSAID poisoning [22].
Conclusion:
In conclusion, NSAID toxicity is a common occurrence in emergency rooms, and it can lead to severe health complications if not treated promptly. It is essential to understand the risk factors and symptoms associated with NSAID toxicity and to seek medical attention immediately if any adverse effects are experienced. The use of NSAIDs should be closely monitored, and patients should be advised to follow the prescribed dosages and avoid long-term use. Healthcare providers should also be vigilant in identifying and managing NSAID toxicity cases to prevent further complications and ensure optimal patient outcomes. Overall, increased awareness and education on NSAID toxicity can help reduce the incidence and severity of this potentially life-threatening condition.

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