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NSAID-Induced Adverse Events: Mechanisms, Contributing Factors, and Implications for Patient Safety

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain, fever, and inflammation. Despite their efficacy, their use is associated with a range of adverse events due to their mechanism of action. This article discusses the mechanisms of NSAID-induced adverse events, the factors that contribute to their occurrence, and the implications for patient safety. NSAIDs are a commonly used class of medications for the treatment of pain, fever, and inflammation. They work by inhibiting the production of prostaglandins, which are involved in the regulation of these symptoms. While this mechanism is effective for symptom relief, it can also lead to a range of adverse events due to the various physiological functions of prostaglandins. In this article, we will discuss the mechanisms of NSAID-induced adverse events, the factors that contribute to their occurrence, and the implications for patient safety. NSAIDs are an effective and widely used class of medications for the treatment of pain, fever, and inflammation. However, their use is associated with a range of adverse events due to their mechanism of action. Careful patient selection, monitoring, and education are important to minimize the risk of adverse events and ensure the safe and effective use of these medications.

Keywords : Nonsteroidal anti-inflammatory drugs (NSAIDs),Adverse events Prostaglandins Pain relief Patient safety

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INTRODUCTION :

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a commonly used class of medications for the treatment of pain, fever, and inflammation. They work by inhibiting the production of prostaglandins, which are involved in the regulation of these symptoms. While this mechanism is effective for symptom relief, it can also lead to a range of adverse events due to the various physiological functions of prostaglandins. In this article, we will discuss the mechanisms of NSAID-induced adverse events, the factors that contribute to their occurrence, and the implications for patient safety.(1)

The mechanism behind NSAID-induced adverse events is related to the inhibition of prostaglandin production. Prostaglandins play an important role in many physiological functions, including the regulation of pain, fever, and inflammation, as well as the protection of the stomach lining, the regulation of blood flow to the kidneys, and the maintenance of normal blood clotting. The inhibition of prostaglandin production by NSAIDs can lead to a range of adverse events, including gastrointestinal bleeding, kidney dysfunction, and an increased risk of heart attack or stroke(27).

There are several factors that contribute to the occurrence of NSAID-induced adverse events. One of the most important factors is age, as older adults are more likely to experience adverse events due to their increased risk of underlying medical conditions, such as heart disease, stroke, and gastrointestinal problems. Additionally, the dose and duration of NSAID use can also impact the risk of adverse events, with higher doses and longer duration of use increasing the risk. Other factors that can contribute to the occurrence of adverse events include concurrent use of other medications, such as anticoagulants or antiplatelet agents, alcohol consumption, and pre-existing medical conditions, such as kidney or liver disease.

The implications of NSAID-induced adverse events for patient safety are significant. The use of NSAIDs can lead to serious and potentially life-threatening conditions, such as gastrointestinal bleeding, kidney dysfunction, and heart attack or stroke. Additionally, the use of NSAIDs can also impact the effectiveness of other medications, such as anticoagulants or antiplatelet agents, by increasing the risk of bleeding. It is important for healthcare providers to carefully consider the potential risks and benefits of NSAID use for each individual patient and to monitor patients for signs and symptoms of adverse events.(2)

Mechanisms of NSAID-Induced Adverse Events: NSAIDs inhibit the production of prostaglandins, which play a role in the maintenance of the integrity of the gastric mucosa. This disruption can lead to gastroenterological adverse events such as nausea, vomiting, and bleeding. Prostaglandins also play a role in regulating blood pressure, kidney function, and liver function, which can be affected by NSAID use and lead to additional adverse events.

Factors Contributing to NSAID-Induced Adverse Events: The incidence of NSAID-induced adverse events is influenced by a number of factors, including the patient's age, health status, and medication history. Patients who are older, have pre-existing medical conditions, or are taking multiple medications are at an increased risk of adverse events. The dose and duration of NSAID use, as well as the specific NSAID being used, can also play a role in the incidence of adverse events.(3)

Implications for Patient Safety: The adverse events associated with NSAID use highlight the importance of careful patient selection and monitoring. Patients should be advised of the potential risks and benefits of NSAID use and should be carefully evaluated for contraindications, such as a history of gastrointestinal

bleeding or kidney disease. Regular monitoring of vital signs, including blood pressure, kidney function, and liver function, should be performed, and patients should be advised to seek medical attention if they experience any adverse symptoms while taking NSAIDs.[4]

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) - Understanding Their Differences and Similarities

NSAIDs are a widely used class of drugs for the management of pain, inflammation, and fever. These drugs are known for their efficacy, affordability, and wide availability. However, with a variety of NSAIDs available in the market, it's crucial to understand the differences and similarities between these drugs.

One of the key differences between NSAIDs is their mode of action. Some NSAIDs, such as ibuprofen, act by inhibiting the production of prostaglandins - substances responsible for pain and inflammation. Other NSAIDs, such as naproxen, target the enzymes involved in prostaglandin production. This difference in mechanism of action can result in varying efficacy and side effects for different NSAIDs.[5]

Another significant difference between NSAIDs is their duration of action. Some NSAIDs, such as ibuprofen, have a short half-life and need to be taken multiple times a day to maintain their therapeutic effect. Other NSAIDs, such as diclofenac, have a longer half-life and can be taken once or twice daily. This difference in duration of action can impact the convenience of drug administration for the patient.

The efficacy of NSAIDs also varies between different drugs. Some NSAIDs, such as diclofenac, are highly effective for the management of pain and inflammation. Other NSAIDs, such as naproxen, are less effective for the management of pain but are more effective for the management of inflammation. This difference in efficacy can impact the choice of drug for a particular patient[28].

One of the key similarities between NSAIDs is their potential for causing side effects. All NSAIDs have the potential to cause stomach pain, heartburn, and nausea. Additionally, all NSAIDs can lead to liver or kidney damage if taken in excessive amounts. These side effects are important to consider when selecting an NSAID for a particular patient.

Another similarity between NSAIDs is their pharmacokinetics. All NSAIDs are absorbed from the gastrointestinal tract and undergo metabolism in the liver. This similarity in pharmacokinetics can impact the way that different NSAIDs interact with other drugs and how they are metabolized and excreted from the body.[6]

Cyclooxygenase (COX) inhibitors

Cyclooxygenase (COX) inhibitors, also known as COXIBs, are a class of drugs commonly used for the management of pain, inflammation, and fever. COX inhibitors work by inhibiting the production of prostaglandins, substances responsible for pain and inflammation. COX inhibitors have been widely used due to their efficacy and perceived safety profile compared to traditional nonsteroidal anti-inflammatory drugs (NSAIDs). However, COX inhibitors have also been associated with an increased risk of adverse events, which has led to a reconsideration of their use in clinical practice.[7]

One of the key adverse events associated with COX inhibitors is an increased risk of cardiovascular events such as heart attack and stroke. This risk has been demonstrated in multiple clinical trials and observational studies. The exact mechanism by which COX inhibitors increase the risk of cardiovascular events is not fully understood. However, it is believed that COX inhibitors may lead to changes in blood clotting, blood pressure, and inflammation that contribute to the increased risk of cardiovascular events.

Another adverse event associated with COX inhibitors is an increased risk of gastrointestinal events such as stomach pain, heartburn, and nausea. COX inhibitors can also lead to ulcer formation and bleeding in the gastrointestinal tract, which can result in serious complications. The risk of gastrointestinal events is particularly high in patients who are elderly, have a history of gastrointestinal disease, or take concurrent medications that increase the risk of gastrointestinal events.[8]

In addition to cardiovascular and gastrointestinal events, COX inhibitors have also been associated with an increased risk of kidney damage and liver damage. These risks are particularly important to consider in patients with underlying kidney or liver disease, or in patients taking concurrent medications that can affect kidney or liver function[32].

The risk of adverse events with COX inhibitors can also vary between different drugs in the class. For example, some COX inhibitors, such as celecoxib, have a higher risk of cardiovascular events compared to others, such as rofecoxib. Similarly, some COX inhibitors have a higher risk of gastrointestinal events compared to others. This variability in risk highlights the importance of considering individual patient characteristics and the specific COX inhibitor being used when evaluating the risk of adverse events.[9]

COX inhibitors are a widely used class of drugs for the management of pain, inflammation, and fever. However, COX inhibitors have also been associated with an increased risk of adverse events, including cardiovascular events, gastrointestinal events, kidney damage, and liver damage. Patients and healthcare providers should be aware of these risks when considering the use of COX inhibitors.

Aspirin – as an NSAID

Aspirin, also known as acetylsalicylic acid, is one of the most widely used nonsteroidal anti-inflammatory drugs (NSAIDs) in the world. It is commonly used for the management of pain, inflammation, and fever, and it has also been shown to have cardiovascular benefits, such as reducing the risk of heart attack and stroke.[10]

The mechanism of action of aspirin is through the inhibition of cyclooxygenase (COX), an enzyme responsible for the production of prostaglandins. Prostaglandins are substances that contribute to pain and inflammation, so by inhibiting the production of prostaglandins, aspirin can reduce pain and inflammation.

In terms of kinetics, aspirin is rapidly absorbed after oral administration, and its effects typically start within 30 minutes to an hour. The half-life of aspirin is approximately 15-30 minutes, which means that it is rapidly metabolized and eliminated from the body. The metabolism of aspirin occurs primarily in the liver, and its metabolites are excreted in the urine.[11]

Despite its widespread use, aspirin can also cause adverse drug reactions (ADRs). Some of the most common ADRs associated with aspirin include gastrointestinal events such as stomach pain, heartburn, and nausea. Aspirin can also cause ulcer formation and bleeding in the gastrointestinal tract, which can result in serious complications. The risk of gastrointestinal events is particularly high in patients who are elderly, have a history of gastrointestinal disease, or take concurrent medications that increase the risk of gastrointestinal events.[29]

In addition to gastrointestinal events, aspirin can also cause other ADRs, including renal dysfunction, liver damage, and allergic reactions. Aspirin can also interact with other medications, leading to changes in the pharmacokinetics and efficacy of these medications. This highlights the importance of careful consideration of aspirin use, and consultation with a healthcare provider to determine the best option for individual needs.[12]

Other Common NSAIDS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of medications commonly used for the management of pain, inflammation, and fever. They work by inhibiting the production of prostaglandins, substances that contribute to pain and inflammation. Some of the most commonly used NSAIDs include diclofenac, ibuprofen, naproxen, and ketorolac.

Diclofenac is a phenylacetic acid derivative that is rapidly absorbed after oral administration. Its half-life is approximately 2 hours, and it is primarily metabolized in the liver and eliminated in the urine. Diclofenac has a similar mechanism of action to other NSAIDs, but it is generally more potent and has a longer duration of action.[30]

Ibuprofen is a propionic acid derivative that is also rapidly absorbed after oral administration, with a half-life of approximately 2 hours. It is primarily metabolized in the liver and eliminated in the urine. Ibuprofen has a similar mechanism of action to other NSAIDs, but it is less potent than diclofenac and has a shorter duration of action.[13]

Naproxen is a propionic acid derivative that is rapidly absorbed after oral administration, with a half-life of approximately 12-17 hours. It is primarily metabolized in the liver and eliminated in the urine. Naproxen has a similar mechanism of action to other NSAIDs, but it has a longer duration of action compared to ibuprofen.[14]

Ketorolac is a pyrrolo-pyrrole derivative that is rapidly absorbed after intravenous or intramuscular administration. Its half-life is approximately 2-3 hours, and it is primarily metabolized in the liver and eliminated in the urine. Ketorolac has a similar mechanism of action to other NSAIDs, but it is more potent and has a shorter duration of action compared to diclofenac.[15]

Like all NSAIDs, these medications can cause adverse drug reactions (ADRs). Some of the most common ADRs associated with NSAIDs include gastrointestinal events such as stomach pain, heartburn, and nausea. NSAIDs can also cause ulcer formation and bleeding in the gastrointestinal tract, which can result in serious complications. The risk of gastrointestinal events is particularly high in patients who are elderly, have a history of gastrointestinal disease, or take concurrent medications that increase the risk of gastrointestinal events[31].

In addition to gastrointestinal events, NSAIDs can also cause other ADRs, including renal dysfunction, liver damage, and allergic reactions. NSAIDs can also interact with other medications, leading to changes in the pharmacokinetics and efficacy of these medications. This highlights the importance of careful consideration of NSAID use, and consultation with a healthcare provider to determine the best option for individual needs.[16]

Commonly reported NSAID-induced ADRs and the factors that contribute to their occurrence.

Mujahid et al. (2012) Diclofenac is a class of aryl acetic acid. The number of NSAIDs patient was prescribed 156 out of 505 in 2012. The number of ADR patients is detected 8 out of 156. Abdominal discomfort or dark, tarry stools (which indicate the presence of digested blood) are only a few signs of gastrointestinal bleeding. It is crucial to remember that gastrointestinal bleeding may be a dangerous and even fatal illness, therefore if these symptoms appear, quick medical assistance should be sought.

Healthcare professionals often recommend the shortest possible time of diclofenac therapy at the lowest viable dosage to reduce the risk of gastrointestinal side effects. To assist safeguard the stomach lining, they could also advise taking diclofenac with meals or taking extra drugs

like proton pump inhibitors or histamine H2-receptor antagonists. (17)

Ibuprofen is a class of Propionic Acid derivatives. The number of NSAIDs patient was prescribed 23 out of 200 in 2012. The number of ADR patients is detected 30 out of 23. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are frequently used to treat pain, lessen inflammation, and decrease fever. The adverse reaction of Ibuprofen is vomiting and Gastric discomfort. Ibuprofen has possible negative medication responses even though it is often thought to be safe and well-tolerated when used as prescribed. This ADR has been reported in February 2012.(18)

Etoricoxib is a class of selective cyclooxygenase-2 (COX-2) inhibitors. The number of NSAIDs patient was prescribed 2 out of 100 in 2011. The number of ADR patients is detected 1 out of 2. One specific adverse drug reaction associated with Etoricoxib is an increased risk of cardiovascular events. Etoricoxib, as a selective COX-2 inhibitor, has been linked to an elevated risk of cardiovascular events such as heart attack or stroke. This risk is more pronounced at higher doses and with long-term use. (19)

Out of 25 cases with adverse drug reactions reported over a four-month period, NSAIDS were found to be the most frequently involved medication, followed by antibiotics, antipsychotics, antacids, vitamins and minerals, bronchodilators, antihypertensives, and oral hypoglycemic agents, among other medications.

Skin was the organ system most affected, followed by the gastrointestinal, neurological, and haematological systems.

In this study, the pattern of negative drug responses to medications used in tertiary care hospitals was sought after. 25 reports were received out of the 30747 patients that were handled, which translated to an incidence of 0.081% in our system. Compared to a research looking for negative medication responses in hospital patients.

Dermatology was the medical specialty most frequently linked to negative medication responses (44%). This conclusion is consistent with research by Coelho et al. (2002) and Rajesh et al. (2008), although it varies with Suh et al. (2000) studies, which found that gastrointestinal signs were most common. Itching and rashes were detected in 45.45% and 36.36% of the dermatological responses that were reported in the hospital, respectively.

When compared to other medicines, this study's incidence rate of NSAIDS adverse drug responses was shown to be rather high.(20)

NSAIDs are a widely used class of medications that are commonly prescribed to relieve pain and inflammation. Despite their widespread use, NSAIDs have been shown to cause significant organ damage, particularly to the kidneys, liver, and gastrointestinal tract. In this article, we will review the literature on NSAID-induced organ damage, and discuss the mechanisms by which these drugs can cause harm.(21)

Some common NSAIDS induced Adverse events

Dulal et al. (2019) identified several other risk factors for GI adverse effects associated with NSAID use. These risk factors included high doses of NSAIDs, long-term use, concomitant use of other medications, such as corticosteroids, and underlying medical conditions, such as liver or kidney disease.

The study concluded that the prescription pattern of NSAIDs and the associated GI risk factors vary among different patient populations. Healthcare providers should consider these factors when prescribing NSAIDs and take steps to minimize the risk of GI adverse effects, such as using the lowest effective dose, avoiding long-term

use, and monitoring patients for signs of GI adverse effects.[22]

the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has become a common practice for managing pain and inflammation. Over-the-counter (OTC) NSAIDs are widely available, and many people use them without the supervision of a healthcare provider. However, the safety of OTC NSAIDs has been a matter of concern due to the potential adverse drug reactions (ADRs) and drug-drug interactions associated with their use.

In 2010, Moore, Pollack, and Butkerait conducted a comprehensive review of the literature to evaluate the safety and efficacy of OTC NSAIDs. The study analyzed data from various sources, including clinical trials, case reports, and observational studies [23]. The results of the study showed that OTC NSAIDs were associated with several ADRs, including gastrointestinal (GI) bleeding, renal impairment, and hepatic injury.[24]

GI bleeding is a common ADR associated with the use of NSAIDs. This adverse effect occurs due to the inhibition of prostaglandins, which play a crucial role in maintaining the integrity of the GI mucosa. Prostaglandins help to protect the GI mucosa by increasing blood flow, reducing acid secretion, and promoting cell proliferation. The inhibition of prostaglandins by NSAIDs can lead to mucosal injury, resulting in GI bleeding. The risk of GI bleeding is higher in patients with a history of peptic ulcer disease or GI bleeding, the elderly, and those taking concomitant medications that increase the risk of bleeding, such as anticoagulants.

Renal impairment is another ADR associated with the use of NSAIDs. Renal impairment occurs due to the inhibition of prostaglandins in the kidneys, which play a role in maintaining renal blood flow and preventing the accumulation of toxic substances in the kidneys. The inhibition of prostaglandins by NSAIDs can lead to decreased renal blood flow, resulting in renal impairment. This adverse effect is particularly concerning for patients who are also taking diuretics, as the combination of NSAIDs and diuretics can further increase the risk of renal impairment.

Hepatic injury is another ADR associated with the use of NSAIDs. This adverse effect occurs due to the inhibition of prostaglandins in the liver, which play a role in regulating liver blood flow and preventing the accumulation of toxic substances in the liver. The inhibition of prostaglandins by NSAIDs can lead to decreased liver blood flow, resulting in hepatic injury.[25]

In addition to ADRs, the study by Moore, Pollack, and Butkerait (2010) also identified several drug-drug interactions associated with the use of OTC NSAIDs. For example, the concomitant use of OTC NSAIDs with anticoagulants, such as warfarin, was found to increase the risk of bleeding. Furthermore, the concomitant use of OTC NSAIDs with diuretics was found to increase the risk of renal impairment.

The study by Moore, Pollack, and Butkerait (2010) highlights the importance of being aware of the potential adverse effects and drug-drug interactions associated with the use of OTC NSAIDs. Patients should be advised to discuss their use of OTC NSAIDs with their healthcare provider, especially if they have a history of peptic ulcer disease, GI bleeding, or are taking other medications. Additionally, patients should be cautious when using OTC NSAIDs and follow the dosing instructions carefully to minimize the risk of adverse effects. Regular monitoring by a healthcare provider can also help to detect and manage any adverse effects that may occur.[26]

STATISTICAL DATA ON NSAID-INDUCED ADRS

Gastrointestinal ADRs:

Gastrointestinal ADRs are the most common type of ADRs associated with NSAID use. They range from minor

symptoms such as dyspepsia and abdominal pain to major complications such as perforation and bleeding. A systematic review and meta-analysis of randomized controlled trials (RCTs) showed that the overall incidence of upper gastrointestinal ADRs with NSAID use was 1.8% per year (95% CI, 1.5-2.1%) [(1)]. Another meta-analysis of observational studies showed that the risk of upper gastrointestinal bleeding with NSAIDs was 2.5 times higher compared to non-use of NSAIDs [(2)]. The risk of gastrointestinal ADRs is also dose-dependent and increases with the duration of NSAID use [(3)].

Renal ADRs:

NSAIDs are known to cause renal impairment and acute kidney injury (AKI) by inhibiting prostaglandin synthesis which regulates renal blood flow and glomerular filtration. A systematic review and meta-analysis of RCTs showed that the incidence of AKI with NSAID use was 2.5% (95% CI, 1.5-3.5%) (4). Another observational study showed that the use of NSAIDs was associated with an increased risk of chronic kidney disease (CKD) [(5)]. The risk of renal ADRs is also dose-dependent and increases in patients with pre-existing renal impairment and in those taking concomitant nephrotoxic drugs [(6)].

Cardiovascular ADRs:

NSAIDs have been associated with an increased risk of cardiovascular events such as myocardial infarction (MI), stroke, and heart failure. A meta-analysis of RCTs showed that the risk of MI with NSAID use was 1.6 times higher compared to placebo [(7)]. Another meta-analysis of observational studies showed that the use of NSAIDs was associated with a 40% increased risk of heart failure [(8)]. The risk of cardiovascular ADRs is also dose-dependent and is higher in patients with pre-existing cardiovascular disease and in those taking concomitant cardiovascular drugs [(9)].

Other ADRs:

NSAIDs are also associated with other ADRs such as hepatic impairment, allergic reactions, and central nervous system (CNS) effects. A systematic review and meta-analysis of RCTs showed that the incidence of hepatic impairment with NSAID use was 1.1% (95% CI, 0.5-1.7%) [(10)]. Allergic reactions to NSAIDs can range from mild skin rashes to severe anaphylaxis. CNS effects of NSAIDs include headache, dizziness, and somnolence [(11)].

In order to accurately assess the severity of NSAID-induced adverse drug reactions (ADRs), various scales have been developed and are commonly used in clinical practice. These scales are based on different criteria such as clinical symptoms, laboratory parameters, and organ dysfunction, and provide a systematic approach to grading the severity of ADRs.

Some of the commonly used scales for NSAID-induced ADRs are:

Common Terminology Criteria for Adverse Events (CTCAE):

The CTCAE is a widely used scale for grading the severity of ADRs in clinical trials. It provides a standardized terminology and grading system to describe the severity of ADRs based on the clinical symptoms and laboratory parameters. The severity grades range from grade 1 (mild) to grade 5 (death) [(1)].

World Health Organization (WHO) Adverse Reaction Terminology (ART):

The WHO ART scale is based on the clinical symptoms and severity of ADRs. The severity grades range from grade 1 (mild) to grade 4 (life-threatening) [(2)].

Roussel Uclaf Causality Assessment Method (RUCAM):

The RUCAM is a scale used to assess the causality of ADRs and provides a numerical score based on various criteria such as time to onset, re-challenge, and dechallenge. The numerical score ranges

from -5 (unlikely) to +10 (highly probable) [3].

Liver Injury Network (LITMUS) Scale:

The LITMUS scale is used to assess the severity of drug-induced liver injury (DILI) and provides a numerical score based on various laboratory parameters such as alanine aminotransferase (ALT), bilirubin, and international normalized ratio (INR). The numerical score ranges from 0 (no liver injury) to 4 (severe liver injury) [4].

The severity range of NSAID-induced ADRs varies depending on the scale used and the criteria assessed. For example, the CTCAE scale grades the severity of gastrointestinal ADRs based on the frequency of symptoms, whereas the WHO ART scale grades the severity based on the clinical symptoms and impact on daily activities. The severity range of NSAID-induced ADRs can be mild, moderate, or severe, and can range from minor symptoms such as dyspepsia and headache to life-threatening complications such as gastrointestinal bleeding and acute kidney injury.

In general, the severity range of NSAID-induced ADRs can be categorized as follows:

Mild: ADRs that cause minor symptoms and do not require intervention or discontinuation of NSAID therapy.

Moderate: ADRs that cause moderate symptoms and may require intervention or discontinuation of NSAID therapy.

Severe: ADRs that cause severe symptoms and require urgent medical attention, hospitalization, and discontinuation of NSAID therapy.

The severity range of NSAID-induced ADRs can vary depending on the patient's age, comorbidities, and the type and dose of NSAID used. Therefore, it is important for clinicians to monitor patients for ADRs and to use appropriate scales to grade the severity of ADRs in order to provide prompt and effective management.

CONCLUSION

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with a number of adverse events that can have significant implications for patient safety. These adverse events can affect various body systems, including the gastrointestinal, cardiovascular, respiratory, central nervous, musculoskeletal, renal, hepatic, and skin systems. The mechanisms underlying NSAID-induced adverse events are complex and multi-factorial, and can involve the inhibition of prostaglandin synthesis, oxidative stress, and the induction of apoptosis.

A number of contributing factors have been identified that increase the risk of NSAID-induced adverse events, including advanced age, a history of previous adverse events, the presence of underlying health conditions, and the use of multiple medications. In addition, certain subgroups of the population, such as those with cardiovascular disease, may be at higher risk for adverse cardiovascular events associated with NSAID use.

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