A Review On Complications Of Non-Steroidal Anti-Inflammatory Drugs In Geriatric Patients At A Tertiary Care Hospital

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Abstract **- Non-steroidal anti-inflammatory medicines, or NSAIDs, are among the most commonly prescribed pain reliever medications. Although it is a very efficient class of medications for pain and inflammation, NSAIDs have numerous negative consequences, such as cardiovascular side effects, gastrointestinal hemorrhage, and NSAID-induced nephrotoxicity. It is important to have in-depth understanding of this class of medications prescribed in geriatric patients. So, we looked at the pharmacodynamics and pharmacokinetics profile, as well as the instructions for using NSAIDs, a list of their negative effects, and information on how they interact with other medications in geriatric patients.**

Keywords **– Non-steroidal anti-inflammatory drugs, geriatrics, liver injury, aseptic meningitis, cyclooxygenase 1 and 2, Aspirin-exacerbated respiratory disease, myocardial infarction, thrombocytopenia, acute kidney injury.**

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are medications with analgesic, anti-inflammatory, and antipyretic activity. Their impact is produced by a decrease in prostanoids production. Inhibition of prostanoids is responsible for a substantial risk of adverse effects.[1]

Non-steroidal anti-inflammatory medicines (NSAIDs) are frequently used to alleviate minor discomfort as well as edema and tissue damage brought on by inflammatory joint disease (arthritis).

In the clinical setting, NSAIDs are primarily used as anti-inflammatory drugs to treat musculoskeletal illnesses such rheumatoid arthritis and osteoarthritis.

In general, NSAIDs provide only symptomatic relief from pain and inflammation associated with the disease, do not arrest the progression of pathological injury to tissue, and are not considered to be "disease modifying" Several NSAIDs have received FDA approval for the treatment of gout and ankylosing spondylitis. In general, NSAIDs combined with rest and physical therapies are useful for treating minor arthropathies.

The peripheral inhibition of prostaglandin synthesis is linked to the analgesic action of NSAIDs, and the subcortical location may also experience it as a result of the reduction of pain impulses. Interleukin-1 and interleukin-6 suppression caused the hypothalamus to produce prostaglandin, which has an antipyretic effect and also resets the thermoregulatory system, which can cause vasodilation. NSAIDs are irrationally recommended in the outpatient department (OPDs). NSAIDs are linked to a variety of negative effects, some of which can be fatal.

The chance of any adverse effect varies from person to person, and serious side effects are less prevalent than mild ones. People who use medications often or in high dosages are more prone to have side effects.

CLASSIFICATION OF NSAIDS

A. Non-selective COX inhibitors

1. Salicylates:
   Aspirin
2. Propionic acid derivatives:
   Naproxen, Ibuprofen, Ketoprofen, Flurbiprofen
3. Anthranilic acid derivatives:
   Mephanamic acid
4. Aryl aceticacid derivatives:
   Diclofenac, Aeclofenac
5. Oxicam derivatives:
   Piroxicam,Tenoxicam
6. Pyrrolo – pyrrole derivatives:
   Ketorolac
7. Indole derivatives:
   Indomethacin
8. Pyrazolone derivatives:
   Phenylbutazone, Oxyphenbutazone

B. Preferential COX – 2 inhibitors: Nimesulide, Meloxicam, Nabumetone
C. Selective COX – 2 inhibitors: Celecoxib, Etoricoxib, ParecoxiB
D. Analgesic-antipyretic with less anti-inflammatory action
1. Paraaminophenol derivative:
   Paracetamol (Acetaminophen)
2. Pyrazolone derivative:
   Metamizol, Propiphenazone
3. Benzoxazocine derivative:
   Nefopam[2]

MECHANISM OF ACTION

The primary method by which NSAIDs work is by inhibiting the cyclooxygenase enzyme (COX). Arachidonic acid must be converted into cyclooxygenase in order to produce thromboxanes, prostaglandins, and prostacyclins. The absence of these eicosanoids is thought to be responsible for NSAIDs' therapeutic benefits. In particular, prostaglandins produce vasodilation, raise the temperature set-point in the hypothalamus, and contribute to anti-nociception. Thromboxanes are involved in platelet adhesion.

COX-1 and COX-2 are the two cyclooxygenase isoenzymes. In the body, COX-1 is constitutively produced and is involved in maintaining the lining of the gastrointestinal tract, renal function, and platelet aggregation. The body does not express COX-2 constitutively; rather, it expresses when there is an inflammatory reaction. The majority of NSAIDs inhibit both COX-1 and COX-2 and are nonselective. The side effect profile of COX-2 selective NSAIDs, such as celecoxib, is different since they solely target COX-2.

Importantly, COX-2 selective NSAIDs should offer anti-inflammatory treatment without harming the gastric mucosa because COX-1 is the key mediator for maintaining gastric mucosal integrity whereas COX-2 is primarily implicated in inflammation.[3]

SIDE EFFECTS OF NSAIDs
- Indigestion and other gut complaints
- Headaches
- Dizziness
- Drowsiness[2]

ADVERSE REACTION OF NSAIDs

Gastric adverse effects: The inhibition of COX-1, which prevents the production of prostaglandins that protect the gastric mucosa, is likely to cause detrimental consequences in the stomach. Patients with a history of peptic ulcers are more prone to suffer damage. The usage of COX-2 selective NSAIDs is a lower-risk option because it is COX-1 specific.

Renal adverse effects: COX-1 and COX-2 promote the formation of prostaglandins, which affect renal hemodynamics, there are detrimental consequences on the kidneys. In a patient with normal renal function, inhibiting prostaglandin synthesis does not present a significant issue; however, in a patient with renal dysfunction, these prostaglandins play a more important role and can be the cause of issues when lowered by NSAIDs. Acute renal dysfunction, fluid and electrolyte imbalances, renal papillary necrosis, and nephrotic syndrome/interstitial nephritis are some of the complications that can develop.

Cardiovascular adverse effects: The risk of cardiovascular side effects, such as MI, thromboembolic events, and atrial fibrillation, can also increase with NSAID use. Diclofenac was found to be the NSAID with the highest reported increase in adverse cardiovascular events.

Hepatic adverse effects: The risk of hepatotoxicity from NSAIDs (increased aminotransferase levels) is less common, and hospitalisation for liver-related conditions is quite uncommon**.** Among the various NSAIDs, Diclofenac has reported to have high risk of hepatotoxic effects.

Due to their antiplatelet activity, nonselective NSAIDs are more likely to have hematologic side effects. This antiplatelet action causes issues in patients with a history of GI ulcers, conditions that reduce platelet activity (such as von Willebrand disease, haemophilia, and thrombocytopenia), and in specific perioperative situations.

Other minor adverse effects include anaphylactoid reactions that involve the skin and pulmonary systems, like urticaria and aspirin-exacerbated respiratory disease.[3]

Rarely reported adverse effects of NSAIDs include:
- Fluid retention
- Kidneys
- Liver

NSAIDs may cause a rise in blood pressure. They make the kidneys work less hard by reducing blood flow to them. This leads to a build up of fluid in the body. Blood pressure increases when there is more fluid in the bloodstream. This could harm your kidneys over time.

Peptic ulcers, or stomach ulcers, can also form as a result of long-term or high-dose NSAID use. Prostaglandins aid the stomach lining to create mucus, which protects it from damage. NSAIDs inhibit prostaglandins' ability to reduce inflammation. NSAIDs expose the stomach to the effects of acid in this way.[2]

USE OF NSAIDs IN ELDERLY PATIENTS

The usage of NSAIDs among geriatric population was increasing nowadays, in that 96% of patients are above the age of 65. Roughly 7.3% of elderly patients over 60 years old filled atleast one NSAID prescription in one year period.

COMPLICATIONS OF NSAIDs IN GERIATRIC PATIENT

There are increasing number of complications associated with the use of NSAIDs in geriatric patients.[4]

EFFECT OF NSAIDs IN BLOOD PRESSURE

Hypertension is the most commonly affected disease in elderly patients which need pharmacological therapy. NSAIDs has an impact on kidneys function by decreasing renal blood flow, slowing glomerular filteration rate and increasing salt retention.[5] This sodium retention can cause increased blood pressure and also NSAIDs decreases the effect of antihypertensive medications such as ACE inhibitors, ARB blockers, Beta blockers, etc. The mechanism of NSAIDs promoting hypertension is related to the inhibition of prostaglandin synthesis and also interferes renal vasculature which regulates the blood pressure.[4]

EFFECT OF NSAIDs IN GASTROINTESTINAL TRACT

GI risks associated with the use of NSAIDs has widely increased. It ranges from dyspesis, gastric bleeding to life threatening conditions.[6] A significant GI problem during treatment was experienced by 1 to 2 percent of NSAID users. The existence of many risk variables, such as advanced age (>65 years), a history of a severe peptic ulcer, concurrent aspirin or anticoagulant use, as well as the kind and dose of NSAID, affects the relative risk of upper GI problems among NSAID users. NSAIDs damage gastric and duodenal mucosal injury, erosion, ulceration with clinical manifestation such as gastric discomfort, heart burn, epigastric discomfort, bloating and post prandial nausea.[7]

The most significant side effects of NSAIDs on platelets and a range of mucosal diseases are bleeding and perforation that develop in the oesophagus, stomach, and duodenum. Peptic ulcers that already exist, ulcers and erosions brought on by NSAID usage, and various lesions made bleeding due to NSAID-induced platelet dysfunction all result in complications.

The term "NSAID gastropathy" which encompasses a number of pathogenetically unique mucosal diseases, has caused a lot of confusion.[8] Damage to the GI tract can occur when the production of prostaglandins is decreased by NSAID inhibition of COX-1. This results in a reduction in epithelial mucus, bicarbonate secretion, mucosal blood flow, epithelial proliferation, and mucosal injury resistance. As a result, the normally protective defence mechanisms of the GI mucosa are overwhelmed by such factors as gastric acid, pepsin, and bile salts. NSAIDs can potentially harm the gastric mucosa by directly toxicating the gastric mucosa. The acidic nature of these drugs may be one of the factors causing harm.

Non-selective NSAIDs are associated with GI damage that appears to be mainly because of their systemic, rather than local impacts. Therefore, the enteric coating on these prescription drugs or their distribution in another format (e.g., suppository) wouldn't be anticipated to lessen their risk of GI toxicity. The use of lower doses of NSAIDs cannot decrease GI adverse events. Prostaglandin production in the stomach mucosa has been found to be reduced by aspirin doses as low as 30 mg. Among older NSAIDs, ibuprofen seems to produce the lowest risk, but piroxicam and ketorolac produce the highest risk. Newer NSAIDs such as etodolac, meloxicam, and nabumetone are thought to cause less injury to the GI tract.[2]

NSAIDs INDUCED NEPHROTOXICITY

NSAIDs can cause renal failure in two different forms. These are acute interstitial nephritis and hemodynamically mediated failure (caused by NSAID-induced decrease in prostaglandin production from a direct toxicity of the drug on the renal parenchyma). In general, renal prostaglandins have vasodilatory property and has a little influence on renal blood flow and glomerular filtration rate. Thus in healthy patients, NSAIDs probably have minimal effect on renal function.[2]

The prevalence of nephrotoxicity in patients using NSAIDs is relatively low[9]. Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed pharmaceuticals linked to nephrotoxicity, particularly when used over an extended period of time. The risk of NSAID-related nephrotoxicity is increased by elements like advanced age and comorbidities, which by themselves already cause a decline in glomerular filtration rate. Acute Kidney Injury (AKI) has been linked to high NSAID dosages, particularly in the elderly. Hemodynamically mediated AKI is the most common type caused by NSAIDs. Acute interstitial nephritis, which may cause nephrotic proteinuria, is the second kind of NSAID-induced AKI. Chronic renal damage can result from long-term NSAID use.[10]

NSAIDs INDUCED CARDIOVASCULAR RISK

The NSAIDs have consistently higher cardiovascular risk where rofecoxib, diclofenac, etoricoxib as “high risk drugs”.[11] The most common underlying cause in patients is myocardial infarction, which is then followed by hypertension, valvular heart disease, and idiopathic cardiomyopathy. In numerous case reports and quantitative studies, nonsteroidal anti-inflammatory drugs (NSAIDs), which block the enzymes cyclo-oxygenase (COX) 1 and 2, have been linked to the occurrence of heart failure symptoms, mostly in patients with a history of cardiovascular disease or left ventricular dysfunction. By preventing the formation of prostaglandins, NSAIDs can compromise renal function in patients with a reduced effective circulation volume. As a result, these patients' unstable

cardiovascular homeostasis may be impacted, as may increases in renal blood flow and glomerular filtration rate, as well as sodium and water retention. This could result in cardiac decompensation in those who already have heart failure.[12]
NSAIDs can affect the CV system in many ways. They can aggravate heart failure (HF), raise blood pressure (BP), increase the risk of cardiovascular disease (CV), and interact with the antiplatelet efficacy of aspirin. Aspirin suppresses COX-1 and the duration of the platelet by acetylating a serine residue when it binds to COX-1. This decreases the level of COX-1– produced thromboxane A2, a proaggregatory vasoconstrictive substance. Some NSAIDs can compete with aspirin for the platelet COX-1 binding site when administered before aspirin. The presence of the NSAID prevents the aspirin from binding.[2]

NSAIDs INDUCED HEPATOTOXICITY

Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to induce liver injury is most commonly seen in a mixed pattern characterised by cholestasis and hepatitis which causes mild elevation of liver enzymes which may leads to severe hepatic failure. Among NSAIDs, Naproxen is the propionic acid derivative NSAID which has been reported to cause liver injury.[13] Pro-inflammatory prostaglandins, are important mediators in inflammatory and pain pathways, are decreased as a result of naproxen's suppression of tissue cyclo-oxygenases (Cox-1 and -2). Naproxen is indicated for mild-to-moderate pain from various causes including trauma, tendonitis, headache, dysmenorrhea, and various forms of arthritis including osteoarthritis, rheumatoid arthritis, gout and ankylosing spondylitis.[14]
Mechanism of nsaids induced hepatic injury:
As most of the NSAIDs produce hepatic injury occurs as a result of unusual susceptibility of the individual patients (i.e, host idiosyncrasy) rather than direct cytotoxic effect of the drug. Idiosyncrasy injury can be mediated by immunological factors and accompanied by clinical features such as fever, rashes, etc.[15]

NSAIDs EFFECT ON CENTRAL NERVOUS SYSTEM

Ibuprofen overdose noted that 30% of patients experienced CNS effects ranging from drowsiness to coma and various neurological problems like vertigo, dizziness, headache, disorientation, ataxia. One of the most important side effects attributed by the use of NSAIDs is aseptic meningitis. Some of the clinical signs includes fever, headache, photophobia, stiff neck, etc.[16]

1. ***ASEPTIC MENINGITIS***
   Aseptic meningitis is defined as meningeal inflammation. It can be categorized into 3 groups,
   - Systemic disease with meningeal involvement
   - Drug induced aseptic meningitis
   - Neoplastic meningitis

   Drug induced aseptic meningitis caused due to overuse of NSAIDs like ibuprofen, naproxen, etc.[17]
2. ***DIMENTIA AND COGNITIVE DECLINE***
   Alzheimer's disease is a most common form of dementia. Long term use of NSAIDs causes impaired cognitive function. A study revealed that long term use of ibuprofen leads to cognitive decline.
3. ***STROKE***
   NSAIDs can increase the risk of stroke and the risk varies with different type of NSAIDs. Compared with naproxen, the least harmful NSAID for cardiovascular outcomes, valdecoxib was associated with the high risk of stroke.[4]
4. ***DEPRESSION***
   Some findings revealed that NSAIDs can induce or exacerbate reproducible symptoms (depression) in patients with affective disorder or schizophrenia.[18]

NSAIDs INDUCED RESPIRATORY TRACT INFLAMMATION AND INFECTION

Aspirin or other NSAIDs that inhibit prostaglandin-H-synthase (PGHS-1) were reported to cause potentially deadly bronchospasms in roughly 7% of asthma patients. Aspirin-exacerbated respiratory disease (AERD), which is characterised by asthma, persistent rhinitis, nasal polyps, and an acute respiratory tract reaction in response to aspirin and NSAIDs.[19]

DRUG INTERACTION OF NSAIDS AND COMMONLY USED MEDICATIONS[4]

MEDICATION	INTERACTIONS
• Antiplatelets (aspirin, clopidogrel)	Increases risk of GI bleeding
• Angiotensin converting enzyme inhibitor (ACEI) and Angiotensin Receptor Blockers (ARB)	Increases in blood pressure by attenuating antihypertensive effects
• Beta blockers	Increases in blood pressure by attenuating antihypertensive effects
• Calcium antagonists	Increases in blood pressure by attenuating antihypertensive effects
• Corticosteroids	Increases risk of GI bleeding

• Digitalis glycosides	Increase serum digoxin level
• Diuretics	Increases in blood pressure by attenuating antihypertensive effects
• Methotrexate	NSAIDs reduce renal excretion of methotrexate, causing methotrexate toxicity.
• Selective serotonin reuptake inhibitors (SSRIs)	Increases risk of GI bleeding
• Warfarin and other anticoagulants	Increases risk of GI bleeding

CONCLUSION

Elderly care must be comprehensively provided in order to understanding the mechanism of action, current recommendations, the pleiotropic effects of drugs and adverse drug reactions. NSAIDs are one of the most commonly prescribed drugs in geriatrics. In order to prevent GI, renal, and cardiovascular damage, these drugs should be taken for the shortest duration possible at the lowest effective dose. Elderly patients, in particular, are more susceptible to and are most sensitive to the NSAIDs' negative effect characteristics. The use of NSAIDs is supported by some evidence in improving muscular performance, preventing dementia, lessen the risk of and/or improve urine incontinence and a few distinct malignancies. To maximise overall results, particularly in the elderly, these risks and benefits should be considered in each patient.

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