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BEYOND PAIN RELIEF: THE EXPANDING BOONS AND DETRIMENTS OF NSAIDS

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively used for their pain-relieving, anti-inflammatory, and fever-reducing effects. They work by blocking cyclooxygenase (COX) enzymes, which are essential for producing prostaglandins that contribute to inflammation and pain. Despite their wide application, NSAIDs raise several pharmacological concerns. Recent developments emphasize selective COX-2 inhibitors, which reduce gastrointestinal side effects but may increase cardiovascular risks, particularly in patients with existing heart conditions. Additionally, NSAIDs persist in the environment, causing ecological concerns by impacting aquatic organisms and entering the human food chain. Additionally, NSAIDs are linked to adverse effects such as gastrointestinal ulceration, kidney toxicity, and cardiovascular complications. Long-term use has been shown to reduce the incidence of Alzheimer's disease (AD) and Parkinson's disease (PD), suggesting a neuroprotective potential, though further clinical studies are required. The use of NSAIDs in combination with corticosteroids increases the risk of gastrointestinal toxicity, and their overuse can lead to asymptomatic overdoses, complicating risk management. The benefits of NSAIDs, including their role in pain relief for conditions like arthritis and cancer, are tempered by these potential harms. While NSAIDs are not banned in sports, their prophylactic use to prevent pain may raise concerns about long-term health impacts. Despite these risks, NSAIDs continue to play an essential role in pain management, with ongoing

research aimed at balancing their efficacy with safety. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used pharmaceutical agents globally due to their well-established anti-inflammatory, analgesic, and antipyretic properties. These drugs primarily exert their effects by inhibiting cyclooxygenase (COX) enzymes, which produce prostaglandins—key mediators in inflammation, pain, and fever. NSAIDs are classified into traditional non-selective inhibitors (NSAIDs), such as ibuprofen, naproxen, and diclofenac, and selective COX-2 inhibitors, such as celecoxib. While NSAIDs are highly effective in managing mild to moderate pain, particularly in conditions like arthritis and postoperative pain, their use is not without significant risks. Pharmacologically, NSAIDs are heterogeneous, differing in their pharmacokinetics and pharmacodynamics. While selective COX-2 inhibitors were developed to reduce gastrointestinal side effects associated with traditional NSAIDs, they are linked to an increased risk of cardiovascular events. Conversely, non-selective NSAIDs may cause gastrointestinal toxicity, renal complications, and hematologic toxicity, particularly with prolonged or high-dose use. These risks are compounded when NSAIDs are combined with other drugs, such as corticosteroids, which significantly increase the likelihood of gastrointestinal bleeding and ulceration. The environmental impact of NSAIDs has become a growing concern, as their widespread use contributes to contamination of water bodies and soil, with potential ecological repercussions. The discharge of pharmaceutical wastewater, improper disposal of unused drugs, and excretion of active substances by humans and animals all contribute to the persistence of NSAIDs in the environment. These substances can disrupt aquatic ecosystems, affect wildlife, and ultimately enter the human food chain, posing potential health hazards. On the therapeutic front, NSAIDs have demonstrated beneficial effects beyond their pain-relieving properties. Studies suggest that long-term NSAID use may reduce the risk of neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), although these findings are not consistently replicated in randomized controlled trials. In addition, NSAIDs have shown promise in mitigating the risk of conditions like amyotrophic lateral sclerosis (ALS), with certain NSAIDs conferring neuroprotective effects. The potential of NSAIDs to modify disease progression in neurodegenerative conditions highlights their broader therapeutic potential, though more research is needed to solidify these claims. However, the overuse or misuse of NSAIDs remains a significant concern. Many patients do not adhere to prescribed dosages, and excessive consumption of these drugs can result in adverse effects that may be asymptomatic, leading to delayed diagnosis of complications such as gastrointestinal bleeding or kidney damage. Furthermore, the use of NSAIDs in

sports medicine is prevalent, with athletes commonly using them prophylactically to prevent pain and inflammation before physical activity. While the World Anti-Doping Agency does not prohibit NSAIDs, their overuse for performance enhancement or injury prevention could lead to unintended long-term health consequences. In summary, NSAIDs represent a vital class of medications in the management of pain and inflammation, with proven efficacy in both acute and chronic conditions. However, their benefits come with significant risks, including gastrointestinal, renal, and cardiovascular complications, particularly with long-term or inappropriate use. The environmental impact of these drugs also raises serious concerns that need to be addressed. Ongoing research into the pharmacodynamics of NSAIDs, as well as their role in neurodegenerative diseases, offers hope for expanded therapeutic applications. Nonetheless, careful consideration of the risks and benefits is essential for optimizing their use in clinical practice and reducing adverse outcomes.

KEYWORDS: NSAIDs, Cyclooxygenase Inhibitors (COX-1 and COX-2), Gastrointestinal Toxicity, Cardiovascular Risk, Neuroprotection, Environmental Impact of Pharmaceuticals, Postoperative Pain Management, Over-the-Counter (OTC) Drugs, Renal Complications, Drug Safety and Efficacy.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) rank among the most frequently used medications worldwide owing to their analgesic, anti-inflammatory, and antipyretic properties. These drugs represent a diverse class with varying pharmacokinetic and pharmacodynamic profiles. Their mode of action primarily involves the inhibition of arachidonic acid metabolism through cyclooxygenase (COX) and lipoxygenase pathways. This diversity underscores the need for further research based on precise pharmacotherapy models of NSAIDs to uncover new mechanisms and optimize therapeutic potential.

Among all the most widely used drugs in the world, non-steroidal anti-inflammatory drugs are the cornerstone therapy for chronic and acute pain. In mild or moderate postoperative pain NSAIDs are often utilized alone, but in severe pain, they are associated with opioids, local analgesics, and or adjuvants.[5-9] Currently the guidelines of the American Society of Anesthesiologists, Task Force on Acute Pain Management, and Italian Group of Analgesia, advocate that NSAIDs have a significant role in postoperative pain control.[10,11] The use of NSAIDs is particularly interesting if the physiopathology of postoperative nociceptive inflammatory pain is considered: nociceptors are nerve endings of primary sensory neurons

Aδ and C fibers that are stimulated directly or sensitized by substances released by traumatized inflamed tissues.[3]

Nonsteroidal anti-inflammatory drugs (NSAIDs), widely used in human and veterinary medicine for pain relief and inflammation control, have increasingly emerged as notable environmental pollutants. Their pervasive use has led to their detection in various environmental compartments, including water bodies and soils. This environmental presence raises significant concerns due to potential ecological damage and risks to human health. Research has demonstrated that NSAIDs adversely affect aquatic organisms, disrupt ecological equilibrium, and may accumulate in the food chain, threatening both wildlife and humans.

Detriment

Selective inhibitors of COX-2 are linked to a heightened risk of cardiovascular events, whereas non-selective COX inhibitors carry a greater risk of gastrointestinal complications. NSAIDs that undergo lower renal excretion and primarily phase 2 metabolism tend to have fewer adverse effects and reduced potential for drug interactions. NSAIDs are the second leading cause of peptic ulcers in the upper gastrointestinal tract, following Helicobacter pylori infection. They induce mucosal damage by inhibiting COX-1, which decreases the production of protective prostaglandins and reduces secretion of the mucosal bicarbonate barrier in the stomach and small intestine. In 1971, Sir John Vane showed that aspirin and related NSAIDs inhibit prostaglandin synthesis associated with pain, inflammation, and fever, providing the physiological basis for their clinical use. Most NSAID overdoses remain symptomless, which presents a risk among those who overuse these drugs unknowingly.

Nonsteroidal anti-inflammatory drugs (NSAIDs) include traditional NSAIDs, such as ibuprofen, naproxen, and diclofenac, as well as selective cyclooxygenase-2 inhibitors (COXIBs), principally celecoxib. COXIBs were developed to decrease gastrointestinal side effects.[10] The Cyclooxygenase 2 and Non-Steroidal Anti-Inflammatory Drug Trialist collaboration conducted a comprehensive worldwide meta-analysis using individual patient data exploring the risks of various COXIBs and NSAIDs on cardiovascular disease (CVD).[11] NSAIDs, which nonselectively inhibit the cyclooxygenase enzymes (isoenzymes 1 and 2), pose a potentially serious risk of gastrointestinal toxicity with acute and chronic use, hematologic toxicity with acute use, and nephrotoxicity with chronic use.[12]

A limited nonclinical study indicates that the ulcer-causing potential of NSAIDs combined with corticosteroids appears to occur only with COX-1 inhibitors and not with COX-2 selective inhibitors. This may be due to corticosteroids reducing arachidonic acid levels, which decreases the substrate available for COX enzymes, potentially amplifying the gastrointestinal toxicity of NSAIDs. Although there are no specific studies clearly demonstrating increased gastrointestinal bleeding risk when over-the-counter NSAIDs are used together with oral corticosteroids, it is advisable for healthcare providers to consider prescribing COX-2 selective NSAIDs or to advise patients to avoid OTC NSAIDs to minimize the potential risk of GI bleeding.[13]

Boons

NSAIDs mainly work by inhibiting cyclooxygenase (COX), an enzyme necessary to convert arachidonic acid into important mediators like thromboxanes, prostaglandins, and prostacyclins. The absence of these eicosanoids accounts for the therapeutic effects of NSAIDs. Specifically, thromboxanes assist with platelet adhesion, prostaglandins facilitate vasodilation, increase the hypothalamic temperature set-point, and contribute to anti-nociception. This mechanism underlies their roles in controlling pain, inflammation, and fever. There are two COX isoforms: COX-1, which is constitutively active and maintains bodily functions like gastric mucosa protection and platelet aggregation, and COX-2, which is inducible during inflammation. Most NSAIDs block both COX-1 and COX-2, but selective COX-2 inhibitors target only COX-2, aiming to reduce side effects related to COX-1 inhibition.[14]

Epidemiological studies have linked long-term NSAID use with a lower incidence of Alzheimer's disease (AD), but randomized controlled trials involving drugs such as indomethacin, naproxen, celecoxib, diclofenac, and nimesulide have failed to confirm these protective effects. Therefore, NSAIDs are not currently recommended for the prevention or treatment of AD. Nonetheless, evidence indicates that cognitively healthy individuals taking NSAIDs for other conditions over extended periods may experience a reduced risk of developing Alzheimer's, which is significant given the widespread use of these medications among the elderly. NSAIDs have also been explored in the treatment of Parkinson's disease, with drugs like indomethacin, ibuprofen, and celecoxib influencing several disease-related pathways, including nitrosative stress, neurotransmission, neuronal signaling, and activation of peroxisome proliferator-activated receptor-γ in experimental models. There is potential for

non-aspirin NSAIDs to offer neuroprotection, supporting the role of neuroinflammation in Parkinson's disease pathogenesis.[15]

Previous studies have established that diabetic wounds remain in a prolonged inflammatory state characterized by elevated levels of pro-inflammatory cytokines and proteases, alongside reduced expression of growth factors. Macrophages are recognized as the primary sources of these pro-inflammatory cytokines within the wound environment. Therefore, examining the impact of NSAIDs on wound healing could offer healthcare providers opportunities to tailor treatments that address both systemic diabetes and chronic wound healing in diabetic patients. Nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively used to manage arthritis and various acute and chronic pains, including those related to cancer. They are often prescribed as standalone agents for mild to moderate pain and combined with opioid or adjuvant analgesics for managing severe pain.[16]

Prostaglandins are crucial in maintaining the protective lining of the stomach, preventing ulcer formation, and ensuring proper blood flow in the kidneys and gastric mucosa. By reducing prostaglandin synthesis, NSAIDs can heighten the risk of gastric ulcers.[17]

The World Anti-Doping Agency does not ban NSAIDs since they are not performance-enhancing; rather, they are just pain and inflammation relievers, which often enables performance. Consequently, athletes generally have unrestricted, over-the-counter access to NSAIDs. However, concerns have been raised about athletes' prophylactic (preventative) use of these drugs. Studies across various sports disciplines show that many athletes self-administer NSAIDs before competing to prevent pain and inflammation, often without medical advice.[18]

Non-steroidal anti-inflammatory drugs (NSAIDs) appear to have a protective role against Alzheimer's disease (AD) and Parkinson's disease (PD), suggesting that inflammation worsens the pathologies of these conditions. NSAIDs show protective effects in transgenic animal models of AD, supporting the idea that inflammation contributes negatively to disease progression. An in vitro model based on neuronal cell death induced by activated microglia or microglia-like cells has been used to study NSAIDs' protective effects in AD. In this model, NSAIDs provide protection at therapeutically relevant concentrations in the low micromolar range. Some reports indicate that NSAIDs may exert effects independent of cyclooxygenase (COX) inhibition but only at higher doses. Despite the failure of certain

NSAIDs like naproxen, celecoxib, and rofecoxib in AD clinical trials, traditional NSAIDs remain the most plausible agents to slow disease progression or delay onset. Additionally, other categories of anti-inflammatory drugs have shown potential benefits in related assays, suggesting that combination therapies using drugs with varying mechanisms might offer improved therapeutic outcomes.[19]

NSAID administration reduces pain in the skin and cornea caused by acidic pH even when inflammation is absent. Tissue acidosis, common in inflammation, tumors, and ischemia, significantly contributes to pain and heightened sensitivity by directly activating nociceptive sensory neurons via proton-gated depolarizing currents. These neurons possess acid-sensing ion channels (ASICs), a key group of ion channels responsive to changes in extracellular pH. A moderate drop in extracellular pH can trigger action potentials through ASICs, which are regulated both transcriptionally and post-translationally during inflammation, contributing to pain hypersensitivity. One ASIC isoform is also implicated in mediating cardiac ischemic pain. Different NSAIDs have been shown to directly inhibit ASIC activity independently of cyclooxygenase (COX) at therapeutic doses, affecting native ASIC currents in sensory neurons and ASIC channels expressed in experimental systems. Furthermore, NSAIDs prevent the significant inflammation-driven increase in ASIC expression. These dual effects are believed to contribute significantly to NSAIDs' analgesic properties, alongside their classic COX inhibition, especially in inflammatory conditions.[20]

CONCLUSION

NSAIDs are particularly valuable in pain management, inflammation, and fever reduction with beneficial therapeutic applications in cases such as arthritis, pain related to cancer, and postoperative pain. Also, despite the effectiveness of NSAIDs, their side effects can be serious, especially in the gastrointestinal, renal, and cardiovascular systems, which can manifest after prolonged or irresponsible use. The introduction of selective COX-2 inhibitors was a major step forward to mitigate gastrointestinal toxicity, but those came with certain cardiovascular risks, showing once more how difficult it is to achieve a balance in treatment efficacy and safety.

Moreover, the emerging evidence NSAIDs pose a danger to the ecosystem is alarming. The potential bioaccumulation of these drugs threatens aquatic life as well as human beings in more ways than one. Even while posing some health risks, NSAIDs are certainly crucial in

treating patients. It is particularly worrisome in certain groups, such as athletes, where NSAIDs are often administered preventively, causing more hidden damage in the long term.

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