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SIDE EFFECTS OF ANTI-INFLAMMATORY DRUGS

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Abstract. Anti-inflammatory drugs are among the most widely prescribed pharmacological agents in modern medicine, used for the management of pain, fever, and inflammatory conditions ranging from arthritis to post-operative tissue injury. Despite their therapeutic efficacy, these drugs — both steroidal and nonsteroidal — are associated with a broad spectrum of adverse effects that can compromise patient safety, particularly with chronic use. The mechanisms underlying these side effects are complex, involving inhibition of prostaglandin synthesis, alterations in immune response, endocrine disruption, and gastrointestinal or renal toxicity. This article provides a comprehensive overview of the side effects of anti-inflammatory drugs, emphasizing their pathophysiological basis, clinical manifestations, and strategies for minimizing harm through rational pharmacotherapy and monitoring.

Keywords: anti-inflammatory drugs, NSAIDs, corticosteroids, gastrointestinal toxicity, nephrotoxicity, cardiovascular risk, pharmacology.

INTRODUCTION

Inflammation is a fundamental biological response to injury or infection, essential for tissue repair and host defense. Yet, when excessive or prolonged, it becomes pathogenic, leading to pain, swelling, and destruction of tissues, as seen in conditions such as rheumatoid arthritis, osteoarthritis, and autoimmune diseases. Anti-inflammatory drugs, which include nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, are pharmacological interventions designed to modulate these inflammatory processes.

NSAIDs achieve their effects primarily by inhibiting the cyclooxygenase (COX) enzymes responsible for prostaglandin synthesis, while corticosteroids suppress a wide range of inflammatory mediators by altering gene transcription. However, these same mechanisms interfere with physiological homeostasis, producing side effects that range from mild discomfort to life-threatening complications. Given the chronic nature of many inflammatory disorders, prolonged use of these agents amplifies the potential for toxicity. Therefore, a thorough understanding of their adverse effect profiles is critical to ensure safe, evidence-based clinical application [1].

MATERIALS AND METHODS

The pharmacological efficacy and toxicity of anti-inflammatory drugs are inextricably linked. NSAIDs inhibit the two main isoforms of cyclooxygenase: COX-1, which maintains normal physiological functions such as gastric mucosal protection, renal blood flow regulation, and platelet aggregation; and COX-2, which is induced during inflammation and mediates pain and fever. Non-selective NSAIDs block both isoforms, which explains their therapeutic and adverse effects. The inhibition of COX-1 is particularly responsible for gastrointestinal and renal toxicity.

Corticosteroids, by contrast, suppress the entire inflammatory cascade at multiple levels. They inhibit phospholipase A_2 activity, blocking the formation of both prostaglandins and leukotrienes, and downregulate cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interferon-gamma. These potent effects, while beneficial in controlling inflammation, also depress

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immune responses, alter carbohydrate and protein metabolism, and disrupt endocrine and bone homeostasis, leading to widespread systemic consequences [2].

RESULTS AND DISCUSSION

Gastrointestinal (GI) damage remains the most common and clinically significant adverse effect of NSAID therapy. Prostaglandins derived from COX-1 normally protect the gastric mucosa by stimulating mucus and bicarbonate secretion, maintaining mucosal blood flow, and promoting epithelial regeneration. When this protective mechanism is inhibited, the gastric and duodenal mucosa become susceptible to injury from acid and pepsin [3].

The result may range from asymptomatic gastritis and dyspepsia to peptic ulcers, bleeding, or perforation. Risk factors include advanced age, concomitant corticosteroid or anticoagulant use, alcohol consumption, and a prior history of peptic ulcer disease. Selective COX-2 inhibitors such as celecoxib reduce but do not eliminate the risk of ulceration, as they still affect mucosal healing pathways.

Corticosteroids also contribute to gastrointestinal injury, especially when combined with NSAIDs. They impair tissue repair, suppress prostaglandin synthesis, and increase gastric acid secretion. The combination of these two drug classes significantly increases the risk of upper GI bleeding, often necessitating concurrent gastroprotective therapy with proton pump inhibitors.

NSAIDs exert profound effects on renal physiology due to the critical role of prostaglandins in maintaining renal blood flow, particularly under conditions of dehydration or compromised perfusion. Inhibition of COX-mediated prostaglandin synthesis can precipitate acute kidney injury (AKI), sodium and water retention, and hyperkalemia. These effects are especially pronounced in elderly patients and those with pre-existing renal disease, heart failure, or cirrhosis. Chronic use may result in analgesic nephropathy, characterized by papillary necrosis and interstitial nephritis.

Corticosteroids, through their glucocorticoid and mineralocorticoid actions, also disrupt fluid and electrolyte balance. Sodium retention and potassium loss lead to edema, hypertension, and, in severe cases, congestive heart failure. Long-term therapy contributes to chronic kidney stress and metabolic alkalosis, exacerbating comorbid cardiovascular disease. The renal toxicity of anti-inflammatory drugs is often silent initially, underscoring the importance of regular monitoring of serum creatinine and electrolyte levels in long-term users.

Both NSAIDs and corticosteroids have been implicated in cardiovascular complications, although through different mechanisms. NSAIDs can elevate blood pressure, cause fluid retention, and interfere with antihypertensive drug efficacy. Selective COX-2 inhibitors, initially developed to minimize gastrointestinal toxicity, paradoxically increase the risk of myocardial infarction and stroke. This occurs because COX-2 inhibition suppresses endothelial prostacyclin (a vasodilator and inhibitor of platelet aggregation) without affecting thromboxane A_2 (a platelet activator), thus creating a prothrombotic environment [4].

Corticosteroids, meanwhile, induce dyslipidemia, enhance vascular sensitivity to catecholamines, and accelerate atherosclerosis. Chronic systemic steroid use also contributes to left ventricular hypertrophy and endothelial dysfunction. Therefore, patients with pre-existing hypertension, ischemic heart disease, or cerebrovascular disorders require cautious dosing, short treatment duration, and, whenever possible, the use of alternative anti-inflammatory strategies.

Hepatotoxicity is an infrequent but serious complication of anti-inflammatory therapy. Certain NSAIDs, including diclofenac and nimesulide, are known to cause hepatic enzyme elevation,

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cholestatic hepatitis, or fulminant liver failure in susceptible individuals. The mechanism may involve reactive metabolite formation and immune-mediated injury.

Corticosteroids profoundly influence metabolism. They stimulate gluconeogenesis, leading to hyperglycemia, exacerbate insulin resistance, and promote lipid redistribution, resulting in centripetal obesity, moon face, and buffalo hump. Long-term therapy leads to muscle wasting, skin thinning, and impaired wound healing due to protein catabolism. Corticosteroid-induced osteoporosis arises from decreased calcium absorption, increased urinary calcium loss, and suppression of osteoblast activity. This adverse effect significantly increases fracture risk in postmenopausal women and elderly patients.

Neuropsychiatric complications of corticosteroids are well-documented. Short-term therapy can cause euphoria and insomnia, while chronic use may provoke depression, mania, or steroid-induced psychosis. Cognitive impairment and delirium are also seen in elderly patients.

NSAIDs occasionally cause central nervous system disturbances such as headache, dizziness, and tinnitus, particularly at high doses or with prolonged use. Rarely, aseptic meningitis may occur, especially in patients with autoimmune diseases like systemic lupus erythematosus [5].

Both drug classes can exacerbate pre-existing psychiatric or neurological disorders, emphasizing the need for individualized risk assessment and patient education.

Corticosteroids are potent immunosuppressants. While beneficial in autoimmune conditions, they also increase susceptibility to bacterial, viral, and fungal infections by impairing macrophage function and lymphocyte proliferation. Opportunistic infections such as candidiasis and tuberculosis reactivation are major concerns in long-term therapy.

NSAIDs, particularly non-selective agents, may inhibit platelet aggregation by reducing thromboxane A_2 synthesis, prolonging bleeding time. Hypersensitivity reactions, including urticaria, angioedema, and anaphylaxis, can occur, especially in individuals with aspirin-exacerbated respiratory disease. Hematologic complications such as agranulocytosis, aplastic anemia, or hemolytic anemia are rare but serious idiosyncratic events associated with some NSAIDs like metamizole.

Chronic corticosteroid administration leads to suppression of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in secondary adrenal insufficiency upon abrupt withdrawal. This condition manifests as fatigue, hypotension, and potential adrenal crisis during stress. Gradual tapering of steroid dosage is therefore mandatory.

Reproductive effects include menstrual irregularities, delayed wound healing in pregnant women, and fetal growth restriction with high-dose corticosteroid exposure. NSAIDs, on the other hand, can delay ovulation and increase miscarriage risk due to prostaglandin inhibition, which affects follicular rupture and uterine contractility.

CONCLUSION

Anti-inflammatory drugs stand among the most powerful and widely used pharmacological tools in clinical medicine. Yet their therapeutic benefits are inevitably intertwined with significant potential for harm. The side effects of these agents, encompassing gastrointestinal bleeding, renal impairment, cardiovascular complications, hepatic injury, and systemic metabolic changes, reflect the delicate balance between efficacy and safety inherent to all pharmacological interventions.

In the evolving landscape of modern pharmacology, newer selective COX-2 inhibitors, transdermal formulations, and steroid-sparing agents offer hope for safer anti-inflammatory treatment. However, no drug can be entirely devoid of risk. The responsibility lies with the clinician to apply

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pharmacological knowledge judiciously — to relieve suffering without causing new harm, balancing benefit and danger with clinical wisdom and compassion.

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