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Interactions between NSAIDs and Alcohol in the Context of Clinical Practice – A Review of Studies

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ABSTRACT

Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used pharmacological agents with potent anti-inflammatory, analgesic, and antipyretic properties. Due to their broad application and availability, both prescription and over-the-counter, NSAIDs are highly popular across various age groups. Millions of people worldwide use these medications daily, making them one of the most commonly utilized drugs.

On the other hand, ethanol, one of the most widely consumed psychoactive substances, is widely ingested globally. Both alcohol and NSAIDs undergo complex pharmacokinetic processes, including absorption, distribution, metabolism, and elimination. The co-existence of these substances in the body can lead to significant interactions that affect the efficacy of therapy and increase the risk of adverse effects.

The objective of this study is to review the literature concerning interactions between NSAIDs and alcohol, with a particular emphasis on the impact of these interactions on usage practices and health outcomes. The study discusses the mechanisms of action of both substances, their effects on the gastrointestinal system, liver, and other organs, as well as the potential risks associated with their concurrent use.

Aim of study: The aim of this study is to summarize the available knowledge about how alcohol influence on metabolism of non-steroidal anti-inflammatory drugs in human. Particular emphasis has been placed on its impact on the gastrointestinal, renal, and cardiovascular systems, which have been thoroughly analyzed and summarized.

Material and methods: The literature available in PubMed, and the Google Scholar database was reviewed using the following keywords: „non-steroidal anti-inflammatory drugs", „alcohol", „COX-1", „COX-2"

Keywords: non-steroidal anti-inflammatory drugs, alcohol, COX-1, COX-2

Characteristics of NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit potent anti-inflammatory, antipyretic properties and analgesic, establishing them some of the most commonly utilized medications globally. [1,3]. They account for approximately 8% of all prescriptions globally, with many of these medications available over the counter, significantly contributing to their widespread use. In individuals over the age of 65, NSAIDs are considered among the most frequently utilized drugs [6]. It is estimated that between 30 and 50 million people worldwide use NSAIDs daily. [5]. NSAIDs are classified based on their chemical structure and selectivity into several groups: acetylated salicylates (e.g., aspirin), non-acetylated salicylates (e.g., diflunisal, salsalate), propionic acids (e.g., naproxen, ibuprofen), acetic acids (e.g., diclofenac, indomethacin), enolic acids (e.g., meloxicam, piroxicam), anthranilic acids (e.g., meclofenamate, mefenamic acid), naphthylalanine derivatives (e.g., nabumetone), and selective COX-2 inhibitors (e.g., celecoxib, etoricoxib) [1, 2, 24].

Mechanism of Action of Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their effects by inhibiting cyclooxygenase (COX) enzymes, which play a crucial role in the synthesis of prostaglandins, key mediators of inflammation and pain. Prostaglandins are lipid compounds involved in inflammatory processes, vascular tone regulation, and platelet aggregation [4,7].

The discovery of prostaglandins dates back to 1935 when Swedish physiologist Ulf von Euler and British pharmacologist M.W. Goldblatt independently isolated these compounds from seminal fluid. Initially, it was believed that prostaglandins were secreted by the prostate gland, which influenced their nomenclature [4].

Prostaglandin (PG) synthesis depends on the release of arachidonic acid, which undergoes a cascade of enzymatic reactions, including the cyclooxygenase (COX) and lipoxygenase (LOX) pathways. There are two known COX isoforms: COX-1, which maintains gastric mucosal integrity, and COX-2, which is induced in response to inflammation. NSAIDs act as competitive COX inhibitors by blocking the enzyme through acetylation, leading to a reduction in prostaglandin production, thereby alleviating pain, fever, and inflammation [7].

COX-1 is a constitutive enzyme with protective physiological functions, such as preserving gastric mucosal integrity and regulating renal blood flow. It is continuously present in the body and plays a role in homeostasis. In contrast, COX-2 is an inducible enzyme, meaning its

expression increases in response to inflammation, injury, or infection. It is primarily responsible for generating prostaglandins that mediate pain, fever, and inflammatory responses [2,7,8].
Selective COX-2 inhibitors, such as celecoxib, have been developed to mitigate inflammation and pain while reducing the risk of gastrointestinal adverse effects commonly associated with nonselective NSAIDs [8,9]. Most NSAIDs are nonselective and inhibit both COX-1 and COX-2. However, COX-2 selective NSAIDs, such as celecoxib, specifically target COX-2 and therefore have a different side effect profile. [1,24].

Alcohol Effect's on the Body

The primary metabolic pathway of ethanol occurs in the liver, where ethanol is oxidized by alcohol dehydrogenase (ADH) to the toxic intermediate acetaldehyde. Acetaldehyde is subsequently converted to acetate [10,11]. Alcohol dehydrogenase exists in multiple isoforms with varying substrate specificity and subcellular localization, facilitating efficient ethanol detoxification across different tissues [12].
Ethanol metabolism predominantly takes place in the liver, involving cytochrome P450 enzymes, with acetaldehyde being considered the most harmful byproduct of this process [11]. Acetaldehyde can induce neuronal damage, leading to neurotoxicity and impaired brain function. Furthermore, chronic alcohol consumption is associated with structural changes in the brain, negatively affecting cognitive abilities and behavior. Alcohol metabolites also contribute to oxidative stress and inflammation in various organs, resulting in tissue damage and the development of chronic diseases [12,13]. Moreover, prolonged alcohol intake leads to the accumulation of toxic metabolites that can damage cellular DNA, proteins, and lipids, further exacerbating cellular dysfunction and contributing to disease pathogenesis [12].
Alcohol that bypasses first-pass metabolism enters the bloodstream and spreads throughout the body's water compartments, including blood and intracellular and extracellular fluids. However, it does not dissolve in fat tissues. The distribution of alcohol in the body is influenced by variations in body water and fat content, which differ based on factors such as gender and age. Women and older individuals tend to have higher body fat and lower body water levels compared to men and younger individuals. Consequently, the way alcohol disperses in the body varies depending on a person's age and sex. [22]. Alcohol can interact with medications in different ways, depending on when both substances are consumed. For instance, interactions may occur when alcohol is taken with a meal before or after medication or when pain relievers are used after drinking to prevent a hangover. These interactions fall into two main types:

pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions involve alcohol interfering with the normal metabolism of medications. This can happen in two ways:

1) Delayed metabolism and excretion – Alcohol and medications compete for breakdown by cytochrome P450 enzymes, particularly CYP2E1, but also CYP3A4 and CYP1A2, slowing drug clearance.

2) Accelerated metabolism – Chronic alcohol use can enhance cytochrome activity, increasing the breakdown rate of medications when alcohol is absent, leading to faster drug elimination [22,23].

Mechanisms of Interaction Between NSAIDs and Alcohol

Similar to pharmaceuticals, alcohol undergoes four pharmacokinetic stages upon entering the body: absorption, distribution, metabolism, and elimination. The absorption phase, during which ethanol passes from the stomach and small intestine into the bloodstream, occurs rapidly. Peak blood alcohol concentration is typically observed approximately 20 minutes after ingestion, with 80–90% of ethanol being fully absorbed within 30–60 minutes. Ethanol metabolism follows different pathways, involving alcohol dehydrogenase (ADH) in the stomach, cytochrome P450 enzymes (primarily in the liver), and catalase [25].

Alcohol can influence the metabolism of nonsteroidal anti-inflammatory drugs (NSAIDs) through multiple mechanisms. Firstly, alcohol alters gastric emptying rates, which can affect NSAID absorption [14,15]. Additionally, alcohol impacts NSAID metabolism mainly by inducing cytochrome P450 2E1 (CYP2E1), an enzyme crucial for ethanol metabolism, particularly at higher blood alcohol concentrations. This enzymatic induction may lead to reduced drug efficacy or an increased risk of adverse effects [16].

Furthermore, alcohol interacts with alcohol dehydrogenase (ADH), a key enzyme in ethanol metabolism that converts ethanol into acetaldehyde, which is subsequently metabolized to acetic acid by aldehyde dehydrogenase (ALDH) [16,17]. Alcohol consumption may compete for metabolizing enzymes such as ADH, potentially reducing NSAID efficacy or prolonging their duration of action [17,20].

Additionally, alcohol intake can enhance the production of reactive oxygen species (ROS), contributing to oxidative stress within the body. Increased oxidative stress may result in hepatic cellular damage, which, when combined with NSAID use, could elevate the risk of hepatotoxicity [20].

Effects of Concurrent Use of NSAIDs and Alcohol

The most common risk factors for gastrointestinal adverse effects associated with nonsteroidal anti-inflammatory drugs (NSAIDs) include advanced age (over 70 years), renal and hepatic disorders, a history of peptic ulcer disease, smoking, alcohol abuse, dialysis therapy, *Helicobacter pylori* infection, predominant inhibition of COX-1 isoenzymes, high NSAID doses, concomitant use of multiple NSAIDs, and the administration of H2-receptor antagonists, which do not provide protection against NSAID-related complications [21].

It is important to note that NSAIDs exert their effects by inhibiting cyclooxygenase (COX), leading to reduced prostaglandin synthesis. Prostaglandins play a crucial role in maintaining gastric mucosal integrity; therefore, their decreased production can result in mucosal injury [14,15]. Additionally, alcohol consumption in combination with NSAIDs can further increase the risk of adverse effects such as gastric mucosal damage, gastrointestinal bleeding, and hepatic injury. Alcohol can potentiate the gastrointestinal toxicity of NSAIDs, leading to an elevated risk of ulcers and bleeding [14].

Moreover, the concomitant use of alcohol and NSAIDs can have serious renal consequences. Alcohol may enhance the nephrotoxic effects of NSAIDs, leading to kidney damage. Specifically, alcohol consumption increases the risk of acute kidney injury (AKI), particularly in individuals who are dehydrated or have preexisting renal impairment [14,17]. Chronic alcohol use in combination with NSAIDs may also contribute to the development of chronic kidney disease (CKD), characterized by progressive renal injury and renal papillary necrosis [15].

Furthermore, combining alcohol with NSAIDs may be associated with an increased risk of colorectal cancer. Alcohol can exacerbate the gastrointestinal effects of NSAIDs, potentially leading to intestinal mucosal damage and increased inflammatory responses. Long-term use of these substances may contribute to chronic inflammation, a recognized risk factor for colorectal cancer. Additionally, interactions between alcohol and NSAIDs may be influenced by genetic polymorphisms involved in inflammatory pathways, affecting individual susceptibility to colorectal cancer. Studies have indicated that individuals with specific genetic polymorphisms may be more vulnerable to the adverse effects of alcohol-NSAID interactions, thereby increasing their risk of developing colorectal cancer [17].

Referring to the cited mechanism of action of NSAIDs, scientists believe that the creation of selective COX-2 inhibitors (coxibs) may provide analgesia, simultaneously avoiding well-known gastrointestinal side effects. Even though the physiological roles for COX-2 inhibitors

and their rising possibility of cardiovascular side effects had been discovered before the first launch of these medicines to the market, they were advertised as "safer NSAIDs". Afterwards, numerous trials confirmed that COX-2 inhibitors increase cardiovascular adverse events, including heart attacks. Finally, most selective COX-2 inhibitors were either removed from the market or had their usage limited, leading to a halt in the development new compounds. Estimates indicate that in the first five years after their introduction, prescribing COX-2 selective NSAIDs to millions of patients in the United States alone resulted in around 70,000 extra heart attacks and 26,000 deaths. [26] Other researchers claim that except for naproxen (which has no evidence of atherothrombotic risk), there is no clear difference between coxibs and nsNSAIDs about the incidence of vascular events.[27] Variety of mechanisms may also lead to increased blood pressure caused by coxibs and other nsNSAIDs. The data additionally suggests that not only coxibs, but also nsNSAIDs in general increase the risk of thrombotic events. [27,28] The cardiovascular safety profiles of coxibs and certain traditional NSAIDs seem similar because both fail to prevent platelet activation, regardless of their selectivity for COX-2. [27]

Conclusions

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their anti-inflammatory, antipyretic properties and analgesic However, their mechanism of action—primarily the inhibition of cyclooxygenase (COX) enzymes—contributes not only to their therapeutic benefits but also to adverse effects, particularly gastrointestinal, renal, and cardiovascular complications. While selective COX-2 inhibitors were designed to reduce gastrointestinal toxicity, their association with increased cardiovascular risk has led to restrictions in their use.
The concomitant use of NSAIDs and alcohol poses significant health risks. Alcohol alters NSAID metabolism by inducing cytochrome P450 2E1 (CYP2E1) and competing for metabolic pathways involving alcohol dehydrogenase (ADH). These interactions can exacerbate gastrointestinal mucosal damage, increase the risk of ulcers and bleeding, and contribute to hepatotoxicity. Additionally, alcohol enhances NSAID-induced nephrotoxicity, increasing the likelihood of acute kidney injury (AKI) and chronic kidney disease (CKD). Emerging evidence also suggests that chronic NSAID and alcohol use may promote inflammation-mediated carcinogenesis, potentially increasing the risk of colorectal cancer.
Given the prevalence of NSAID use and alcohol consumption, awareness of these interactions is crucial in clinical practice. Healthcare providers should carefully assess patient risk factors,

particularly in individuals with a history of gastrointestinal disorders, renal impairment, or cardiovascular disease. Patient education on the risks associated with NSAID and alcohol co-administration remains essential in minimizing adverse health outcomes. Future research should focus on developing safer analgesic alternatives with improved therapeutic profiles and reduced systemic toxicity.

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