

The Toxicological Consequences of Naproxen

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ABSTRACT

Naproxen, a widely used nonsteroidal anti-inflammatory drug (NSAID), provides relief from various pain and inflammatory conditions, including arthritis, menstrual cramps, gout, and tendinitis. This article examines the mechanisms of action, diverse applications, and user experiences associated with naproxen. As a member of the propionic acid class, naproxen effectively inhibits the synthesis of prostaglandins, reducing inflammation and pain. The drug is available in various forms, including immediate-release, delayed-release, and extended-release tablets, as well as oral suspensions and capsules. Its over-the-counter availability has contributed to its popularity, particularly for those managing chronic pain. Despite its efficacy, naproxen may cause gastrointestinal disturbances and other side effects, particularly when used long-term. Safety concerns, such as the risk of gastrointestinal bleeding and cardiovascular issues, emphasize the importance of using the lowest effective dose for the shortest duration. This review highlights the importance of understanding naproxen's benefits, potential drawbacks, and safety precautions to guide informed decision-making in pain management.

Keywords: *Cardiovascular Risks, Drug, Gastrointestinal Toxicity, Naproxen, Toxicology*

Introduction

Millions of people rely on naproxen, a widely used nonsteroidal anti-inflammatory drug (NSAID), to relieve pain and inflammation. It is commonly used to manage conditions such as arthritis, menstrual cramps, gout, tendinitis, and bursitis (Nissen et al., 2016). Naproxen works by blocking the production of prostaglandins, which are hormone-like substances responsible for pain and inflammation (Davies & Anderson, 1997). By reducing these chemicals in the body, naproxen helps decrease swelling, stiffness, and overall discomfort.

This medication is available in different forms to meet various needs. Immediate-release tablets provide quick pain relief, while delayed-release and extended-release versions offer longer-lasting effects, making them ideal for chronic conditions like arthritis (Weisman & Brunton, 2020). Oral suspensions are available for individuals who have difficulty swallowing pills, and liquid-filled capsules provide another easy-to-ingest alternative. Over-the-counter naproxen, often sold under the brand name Aleve, is commonly used for mild to moderate pain, while prescription-strength versions such as Anaprox and Naprosyn are recommended for more severe conditions (Smith et al., 2017).

Naproxen's popularity is evident in its widespread use, with millions of prescriptions written annually in the United States. The accessibility of over-the-counter forms has further increased its usage, making it one of the most commonly purchased NSAIDs (Hui et al., 2017). Many users report significant relief from pain and inflammation, particularly those suffering from chronic conditions such as arthritis. Regular use often leads to improved mobility and reduced stiffness, allowing individuals to maintain a better quality of life.

However, like any medication, naproxen comes with potential side effects. Some individuals experience gastrointestinal issues such as nausea, heartburn, and stomach discomfort (Oliveira

et al., 2022). Others report headaches or dizziness as possible adverse effects. To minimize stomach-related issues, it is generally advised to take naproxen with food or milk. While many find the medication effective, responses can vary from person to person(Chaudhuri et al., 2013).

Safety should always be a priority when using naproxen. Those with pre-existing gastrointestinal or cardiovascular conditions should consult a healthcare professional before taking it. Long-term use of NSAIDs, including naproxen, may increase the risk of serious complications such as gastrointestinal bleeding, heart attacks, or strokes(Frost et al., 2014). To reduce these risks, medical professionals recommend using the lowest effective dose for the shortest possible duration(Moyer, 1986).

Overall, naproxen remains a highly effective and widely used option for managing pain and inflammation. Its versatility, availability, and effectiveness make it a staple in both over-the-counter and prescription medicine(Weisman & Brunton, 2020). While it provides significant relief for many individuals, understanding its uses, potential side effects, and safety precautions is essential for making informed healthcare decisions(Huntjens et al., 2006).

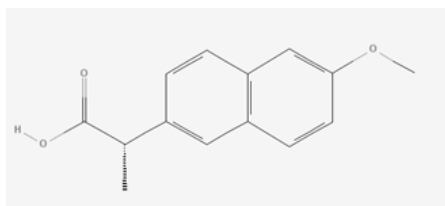


Fig 1: Structure of Naproxen (PubChem, <https://pubchem.ncbi.nlm.nih.gov>)

Naproxen Pharmacodynamics

Naproxen is a widely used non-steroidal anti-inflammatory drug (NSAID) known for its analgesic, anti-inflammatory, and antipyretic properties(Weisman & Brunton, 2020). Its primary mechanism of action involves inhibiting cyclooxygenase (COX) enzymes, specifically COX-1 and

COX-2. These enzymes play a crucial role in the production of prostaglandins, which are hormone-like substances responsible for triggering inflammation, pain, and fever by promoting vasodilation and increasing vascular permeability in affected tissues(Davies & Anderson, 1997).

When taken orally, naproxen is efficiently absorbed, reaching peak plasma concentrations within 2 to 4 hours in standard formulations and 1 to 2 hours in its more soluble form, naproxen sodium(Davies & Anderson, 1997). Due to its relatively long half-life of approximately 12 to 17 hours, it is often administered twice daily. The drug undergoes extensive hepatic metabolism, converting into inactive metabolites that are primarily excreted through the urine(Frost et al., 2014).

Naproxen is available in two formulations: free acid and sodium salt. Although both forms exhibit equivalent pharmacological and therapeutic effects, they differ slightly in absorption rates. At comparable doses—500 mg of naproxen being equivalent to 550 mg of naproxen sodium—the sodium salt formulation reaches peak plasma concentration about one hour after administration, whereas the free acid form takes approximately two hours(Moyer, 1986). This distinction is particularly important in acute pain management, where the faster absorption of naproxen sodium offers a quicker onset of relief(Davies & Anderson, 1997).

Pharmacokinetic Characteristics

Naproxen is characterized by rapid and complete absorption when administered orally or rectally. Different formulations, including immediate-release, enteric-coated, and controlled-release types, yield comparable peak plasma concentrations (C_{max}), which typically range between 94 mcg/mL and 97.4 mcg/mL(Davies & Anderson, 1997).

A pharmacokinetic study revealed that 500 mg of immediate-release naproxen reaches peak concentration (T_{max}) in approximately 3 hours, whereas the controlled-release formulation Naprelan (1000 mg) takes around 5 hours. Despite this variation in T_{max}, the total drug exposure over 24 hours, measured by the area under the curve (AUC), remained nearly identical at 1446 mcg•hr/mL for the immediate-

release form and 1448 mcg•hr/mL for the controlled-release version(Moyer et al., 1986).

Another study comparing standard tablets to enteric-coated tablets found that the T_{max} for Naprosyn was 1.9 hours, while for EC-Naprosyn, it was 4 hours. Corresponding AUC values were 767 mcg•hr/mL and 845 mcg•hr/mL, respectively. These findings highlight the importance of formulation selection in achieving optimal therapeutic outcomes (Davies & Anderson, 1997).

Factors Affecting Absorption

Food intake can slightly delay the absorption of naproxen when taken orally, but it does not significantly alter the overall amount of the drug absorbed. This means that naproxen can be taken with or without food without compromising its overall effectiveness.

Metabolism

Naproxen undergoes extensive liver metabolism through Phase I and Phase II processes. In Phase I, cytochrome P450 enzymes (CYP1A2, CYP2C8, CYP2C9) facilitate demethylation, converting naproxen into its active metabolite, 6-desmethylnaproxen [12]. Phase II metabolism involves glucuronidation by UGT enzymes (UGT1A1, UGT1A3, UGT1A6, UGT1A7, UGT1A9, UGT1A10, UGT2B7) and sulfation by sulfotransferases (SULT1A1, SULT1B1, SULT1E1), forming conjugated metabolites for excretion. (Oliveira et al., 2022)

Mechanism of Action

Naproxen works by inhibiting cyclooxygenase (COX) enzymes, reducing prostaglandin synthesis, which plays a key role in pain, fever, and inflammation. COX-1 supports essential functions like stomach lining protection and platelet aggregation, so its inhibition may cause gastrointestinal side effects(Nissen et al., 2016). COX-2, primarily involved in inflammation, is responsible for pain and swelling(Weisman & Brunton, 2020) . By non-selectively blocking both COX-1 and COX-2, naproxen effectively reduces pain and inflammation but carries a risk of gastrointestinal issues. It is well-absorbed,

with high bioavailability (~95%) and peak plasma levels occurring within 1–4 hours(Frost et al., 2014).

Excretion

Around 95% of naproxen and its metabolites are excreted in urine, mostly as conjugates, with minimal unchanged drug elimination. It is highly protein-bound (>99%), but at higher doses, saturation can lead to increased free drug levels(Moyer, 1986). The half-life of naproxen is 12–17 hours, with metabolite clearance affected in renal impairment(Oliveira et al., 2022).

In Vitro Toxicology Assay

- **Cytotoxicity Assessment:** The MTT assay evaluated naproxen's impact on cell viability at concentrations of 0.3–100 μM over 24, 48, and 72 hours. Results showed a time- and dose-dependent reduction in cell viability, with significant chondrotoxic effects observed in human chondrocytes (1–1,000 μM) ($p < 0.01$). (Smith et al., 2017)
- **Enzyme Inhibition (COX-2 & 5-LOX):** Studies assessed how naproxen derivatives inhibit COX-2 and 5-LOX by determining IC₅₀ values. MTT assays demonstrated a decline in optical density (OD), reflecting reduced cell viability (24-hour control OD: 0.369; 72-hour naproxen OD: 0.325). (Nedeljković et al., 2023)
- **Apoptosis Induction:** Annexin V-FITC tests indicated that prolonged exposure to higher naproxen concentrations triggered apoptosis. Naproxen-HBTA reduced melanoma cell proliferation (10–100 μM), inhibited migration and invasion, and suppressed colony formation. It also activated caspase-3, a key protein in programmed cell death, suggesting potential anticancer effects. (Ercolano et al., 2019)
- **Mutagenicity Potential:** Experiments on mammalian cells suggested naproxen may pose a genetic risk under specific conditions, emphasizing the need for caution with long-term exposure. (Huntjens et al., 2006) (Correia et al., 2014)

- **Toxicological Impact:** The primary adverse effects of naproxen stem from its role in prostaglandin suppression, leading to potential gastrointestinal issues and kidney damage, underscoring the importance of careful use. (Huntjens et al.,2006)

Conclusion

Naproxen is a commonly used NSAID known for its anti-inflammatory, pain-relieving, and fever-reducing effects. By inhibiting COX-1 and COX-2 enzymes, it effectively manages inflammation and pain but may also cause gastrointestinal and kidney-related side effects. It is well-absorbed, undergoes liver metabolism, and is mainly excreted through urine. In vitro studies indicate its cytotoxic effects, potential for genetic alterations, and ability to trigger apoptosis in specific cell types, suggesting possible anticancer applications. However, its long-term use should be approached with caution due to associated health risks. A thorough understanding of its pharmacological effects and safety considerations is essential for optimizing its therapeutic use while minimizing adverse outcomes.

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