NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-.

Naproxen

Authors

Joseph C. Brutzkus[1]; Matthew Varacallo[2].

Affiliations

[1] Un of Illinois at Chicago College of Med
[2] Department of Orthopaedic Surgery, University of Kentucky School of Medicine

Last Update: October 27, 2018.

Indications

Naproxen was initially approved in 1976 for prescription use only and remained a prescription drug until it was approved as an over-the-counter (OTC) medication in 1994. Naproxen is FDA-approved for the treatment of acute gout, ankylosing spondylitis, bursitis, polyarticular juvenile idiopathic arthritis, osteoarthritis, tendonitis, rheumatoid arthritis, pain, and primary dysmenorrhea. It is the first-line treatment for acute gouty arthritis, osteoarthritis, musculoskeletal pain and inflammation and dysmenorrhea. While naproxen and other NSAIDs are approved for the treatment of inflammatory arthropathies such as rheumatoid arthritis and ankylosing spondylitis, they do not alter the course of the disease nor do they prevent joint and soft tissue destruction that are common sequelae of these diseases. Disease-modifying anti-rheumatic drugs (DMARDs) have become the first-line treatment for inflammatory arthropathies, and NSAIDs such as naproxen are used as adjunctive treatments.

Off-label uses of naproxen include the treatment of acute migraines and migraine prophylaxis. Naproxen is considered a first-line abortive medication for acute migraines. It can be used for chronic migraine prophylaxis as well, along with other medications such as beta blockers, anti-depressants, and anticonvulsants. [1]

Mechanism of Action

Naproxen blocks arachidonate binding to competitively inhibit both cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, resulting in analgesic and anti-inflammatory effects. COX-1 and COX-2 are catalysts of arachidonic acid conversion to prostaglandin G (PGG), the first step of the synthesis of prostaglandins and thromboxanes that are involved in rapid physiological responses. COX-1 is constitutively expressed in most tissues, while COX-2 appears to only be constitutively expressed in the brain, kidney, bones, reproductive organs, and select tumors such as in colon and prostate cancers. COX-1 is responsible for prostaglandin synthesis in response to stimulation by circulating hormones as well as maintenance of healthy renal function, gastric mucosal integrity, and hemostasis. COX-2 is inducible in many cells in response to certain mediators of inflammation (e.g., interleukin-1, tumor necrosis factor, lipopolysaccharide).

The anti-inflammatory mechanism of naproxen is due to decreased prostaglandin synthesis by inhibiting COX-1 and COX-2. The anti-inflammatory effects of Naproxen may be due primarily to inhibition of the COX-2 isoenzyme; however, COX-1 is expressed at some inflammation sites. COX-1 is expressed in the joints of patients with rheumatoid arthritis or osteoarthritis, especially the synovial lining. Naproxen targets both COX-1 and COX2, but is slightly more selective for the former. In addition, Naproxen is most effective in the setting of pain receptor sensitivity. It appears prostaglandins, specifically prostaglandins E and F, are responsible for sensitizing these pain receptors; therefore, naproxen has an additional, indirect analgesic effect by inhibiting further prostaglandin production.

Naproxen is extensively metabolized by the liver. About 95% of the drug is excreted in the urine. Naproxen's half-life is 12 to 17 hours.

Administration

Naproxen can be administered orally, in both immediate and extended-release tablets or suspension forms, or topically. Naproxen may be taken orally with food, milk, antacids (preferably aluminum and magnesium hydroxide-containing antacids), proton pump inhibitors (PPI) or misoprostol to decrease the incidence of GI adverse effects.[2] Naproxen sodium is the form that is most readily available, and it has been shown to have a faster absorption compared to naproxen.

As a rule, treatment with naproxen, as well as all NSAIDs, begins with the lowest effective dose for the shortest possible duration. Also consider starting with a lower dose in geriatric patients due to the likelihood that the patient has comorbidities such as cardiovascular disease, chronic kidney disease, or history of GI ulcer/bleeding that increase the risk of adverse effects from NSAID therapy.

Specific dosing recommendations and treatment durations:

Mild to moderate arthritis (osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis):

- 220—550 mg PO every 12 hours
- Take with food if GI upset occurs
- Max: 1650 mg daily for up to 6 months

Acute gouty arthritis:

- 825 mg PO once, followed by 275 mg PO every 8 hours until symptom resolution
- Take with food if GI upset occurs

Acute severe headache or migraine:

- Controversial with respect to isolated naproxen sodium use in patients suffering from acute migraines
- Naproxen sodium has a longer half-life compared to other NSAID options, but headache relief rates at 2 hours after initial treatment are lower compared to ibuprofen [3][4]
- Naproxen sodium dosing recommendations: 550 mg every 12 hours; can increase dosage to 825mg PO if needed; do not exceed max of 1375mg daily

Maximum recommended daily doses for children:

- 12 years and older - 20 mg/kg/day by mouth, not to exceed 1000 mg/day by mouth; for non-prescription use, 660 mg/day by mouth
- 2 to 12 years - 20 mg/kg/day by mouth not to exceed 1000 mg/day by mouth. Non-prescription use is not recommended
- Less than 2 years - Safety and efficacy have not been established

Patients with Hepatic Impairment Dosing

- Although specific guidelines are not available, caution is advised with respect to dosing; utilize the lowest recommended dosing regimen initially

Patients with Renal Impairment Dosing

- If creatinine clearance (CrCl) is greater than or equal to 30 mL/min no dosage adjustment is needed

- Naproxen is not recommended for patients with CrCl less than 30 mL/min

Adverse Effects

Primary adverse effects for naproxen include dyspepsia, nausea, dizziness, elevated liver enzymes, increased blood pressure, diminished renal function, rash, increased bleeding risk, and GI ulcers. Serious but rare adverse effects include blood dyscrasias, Stevens-Johnson syndrome, myocardial infarction, stroke, heart failure, and anaphylaxis. The following are several mechanisms of the above adverse effects:

GI Effects*:* GI adverse effects of naproxen are primarily contributed to COX-1 inhibition. [5]

Renal Effects*:* Prostaglandins produced by both COX-1 and COX-2 are important regulators of renal function, hemodynamics, and sodium and water reabsorption in the kidneys. When renal blood flow is dependent upon prostaglandin synthesis, NSAID administration can result in significant decreases in renal blood flow, leading to acute kidney injury and renal failure. Also, alterations in sodium and water reabsorption may increase blood pressure, especially in patients with pre-existing hypertension.

Platelet Effects*:* Platelet aggregation inhibition with naproxen is due to the dose-dependent inhibition of COX-1 in platelets that leads to decreased levels of platelet thromboxane A2 and increased bleeding time. This inhibition is reversible upon discontinuation of naproxen. Despite the known inhibition of platelet function, the results of studies examining an increase in clinical bleeding time have been mixed. [6]

Contraindications

Absolute:

- Documented hypersensitivity to NSAID medications
- ASA or NSAID-induced asthma
- Pregnancy (caution against use in 1st trimester, absolute contraindication at 30 weeks gestation)
- Perioperative use for coronary artery bypass graft surgery (CABG)

Relative/Caution against use:

- Recent MI or history of heart disease
- Hypertension
- Congestive heart failure
- Fluid retention/edema
- Dehydration
- History of GI adverse events (peptic ulcer disease, GERD)
- Bleeding or coagulopathy conditions
- Hepatic disease
- Renal disease
- Asthma
- Sodium restrictions
- Chronic alcohol use

- Tobacco use
- Elderly/geriatric patients
- Females actively trying to conceive

Monitoring

Patients taking naproxen should be monitored for pain relief, significant changes in blood pressure, worsening kidney function, and GI symptoms such as gastroesophageal reflux disease (GERD), abdominal pain, or melena. For patients on chronic NSAID therapy, periodic monitoring with complete blood counts to assess for anemia and chemistry panels to assess kidney and liver function should be considered.

Toxicity

Naproxen overdose is common due to its OTC availability, but the overdose is usually mild in severity and serious adverse effects from overdose are rare. There is no available antidote for naproxen overdose. Monitoring of vital signs and supportive care is recommended. The role of activated charcoal is uncertain due to time constraints and unclear benefit, and there is no role for hemodialysis due to naproxen's high degree of protein binding.

Enhancing Healthcare Team Outcomes

Naproxen is readily available OTC and widely used for pain relief for many different types of patients. Some of these patients are taking medications or have medical comorbidities that place them at a significantly higher risk of serious adverse events, yet they are unaware of the risk and may think that naproxen's availability OTC means its use is safe for everyone. It is important for all health professionals who work in a primary care setting to routinely ask their patients whether they are taking OTC medications and educate them about the potential risks and benefits of NSAIDs, particularly as it relates to their specific medical histories and conditions. It is also important for specialist healthcare providers to communicate with primary care providers and pharmacists when starting medication or treating a patient for a condition in which NSAID therapy is not advised or contraindicated. Providers should also educate their patients about their medical condition and how it affects their ability to take a widely available OTC medication.

Questions

To access free multiple choice questions on this topic, click here.

References

1. Schafer AI. Effects of nonsteroidal anti-inflammatory therapy on platelets. Am. J. Med. 1999 May 31;106(5B):25S-36S. [PubMed: 10390125]
2. Gargallo CJ, Sostres C, Lanas A. Prevention and Treatment of NSAID Gastropathy. Curr Treat Options Gastroenterol. 2014 Dec;12(4):398-413. [PubMed: 25209136]
3. Pellicano R. Gastrointestinal damage by non-steroidal anti-inflammatory drugs: updated clinical considerations. Minerva Gastroenterol Dietol. 2014 Dec;60(4):255-61. [PubMed: 25384803]
4. Armstrong C., American Academy of Neurology. American Headache Society. AAN/AHS update recommendations for migraine prevention in adults. Am Fam Physician. 2013 Apr 15;87(8):584-5. [PubMed: 23668450]
5. Suthisisang CC, Poolsup N, Suksomboon N, Lertpipopmetha V, Tepwitukgid B. Meta-analysis of the efficacy and safety of naproxen sodium in the acute treatment of migraine. Headache. 2010 May;50(5):808-18. [PubMed: 20236345]
6. Law S, Derry S, Moore RA. Naproxen with or without an antiemetic for acute migraine headaches in adults. Cochrane Database Syst Rev. 2013 Oct 20;(10):CD009455. [PubMed: 24142263]

Bookshelf ID: NBK525965 PMID: 30247840