Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

ncbi.nlm.nih.gov/books/NBK547742

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Continuing Education Activity

NSAIDs are a class of medications used to treat pain, fever, and other inflammatory processes. This activity describes the indications, mechanism of action, administration, adverse effects, contraindications, monitoring, and important points for providers regarding NSAIDs.

Objectives:

- Identify the mechanism of action of NSAIDs.
- Describe the potential adverse effects of NSAIDs.
- Review the potential toxicity of NSAIDs.
- Summarize interprofessional team strategies for improving care and outcomes when using NSAID therapy.

Access free multiple choice questions on this topic.

Indications

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a drug class FDA-approved for use as antipyretic, anti-inflammatory, and analgesic agents. These effects make NSAIDs useful for treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, migraines, and used as opioid-sparing agents in certain acute trauma cases.

NSAIDs are typically divided into groups based on their chemical structure and selectivity: acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen, acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam) anthranilic acids (meclofenamate, mefenamic acid), naphthylalanine (nabumetone), and selective COX-2 inhibitors (celecoxib, etoricoxib).

Topical NSAIDs (diclofenac gel) are also available for use in acute tenosynovitis, ankle sprains, and soft tissue injuries.

Listed below are the FDA-approved NSAIDs (organized alphabetically):

Non-selective NSAIDs

- Diclofenac

- Diflunisal
- Etodolac
- Fenoprofen
- Flurbiprofen
- Ibuprofen
- Indomethacin
- Ketoprofen
- Ketorolac
- Mefenamic acid
- Meloxicam
- Nabumetone
- Naproxen
- Oxaprozin
- Piroxicam
- Sulindac
- Tolmetin

COX-2 Selective NSAIDs

- Celecoxib
- Rofecoxib
- Valdecoxib

(However, rofecoxib and valdecoxib were withdrawn from the market in 2004 and 2005, respectively)

Mechanism of Action

The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). Cyclooxygenase is required to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins. The therapeutic effects of NSAIDs are attributed to the lack of these eicosanoids.

Specifically, thromboxanes play a role in platelet adhesion, prostaglandins cause vasodilation, increase the temperature set-point in the hypothalamus, and play a role in anti-nociception.

There are two cyclooxygenase isoenzymes, COX-1 and COX-2. COX-1 gets constitutively expressed in the body, and it plays a role in maintaining gastrointestinal mucosa lining, kidney function, and platelet aggregation. COX-2 is not constitutively expressed in the body; and instead, it inducibly expresses during an inflammatory response. Most of the NSAIDs are nonselective and inhibit both COX-1 and COX-2. However, COX-2 selective NSAIDs (ex. celecoxib) only target COX-2 and therefore have a different side effect profile. Importantly, because COX-1 is the prime mediator for ensuring gastric mucosal integrity and COX-2 is mainly involved in inflammation, COX-2 selective NSAIDs should provide anti-inflammatory relief without compromising the gastric mucosa.

Administration

Most commonly, NSAIDs are available as oral tablets. According to the package insert, the dosage for the most common over-the-counter NSAIDs are as follows:

- Ibuprofen: for 200 mg tablets, 1 to 2 tablets every 4 to 6 hours while symptoms persist. The daily limit for ibuprofen is 1200 mg.
- Aspirin regular strength: 325 mg tablets, 1 to 2 tablets every 4 hours, or 3 tablets every 6 hours. The daily limit for aspirin is 4000 mg.
- Naproxen sodium: for 220 mg tablets, 1 to 2 tablets every 8 to 12 hours. The daily limit for naproxen sodium is 660 mg.

Topical NSAIDs are also available (diclofenac sodium 1.5% topical solution, diclofenac hydroxyethyl pyrrolidine 1.3% patch, and diclofenac sodium gel 1%). They are most useful for treating pain due to soft-tissue injuries and osteoarthritis.

Specific NSAIDs can also be administered parenterally; for example, intravenous ibuprofen is available, given as a 30-minute infusion; this can be used as a non-opioid analgesic to manage pain and can also reduce fever. Trials have shown that using intravenous ibuprofen and morphine in postoperative adult patients can lower the total use of morphine. For treating pyrexia, an initial 400mg dose then 400 or 100 to 200 mg every 4 to 6 hours as needed. For the treatment of pain, 400 to 800 mg, every 6 hours as needed, is the recommended dose regimen. Ketorolac is also available for parenteral administration.

Adverse Effects

NSAIDs have well-known adverse effects affecting the gastric mucosa, renal system, cardiovascular system, hepatic system, and hematologic system.

Gastric adverse effects are likely due to the inhibition of COX-1, preventing the creation of prostaglandins that protect the gastric mucosa. The damage is more likely in a patient who has a prior history of peptic ulcers. Since it is COX-1 specific, the use of COX-2 selective NSAIDs is a lower-risk alternative.

Renal adverse effects are because COX-1 and COX-2 facilitate the production of prostaglandins that play a role in renal hemodynamics. In a patient with normal renal function, inhibition of prostaglandin synthesis does not pose a large problem; however, in a patient with renal dysfunction, these prostaglandins play a greater role and can be the source of problems when reduced via NSAIDs. Complications that can occur include elevated blood pressure, acute renal dysfunction, fluid and electrolyte disorders, renal papillary necrosis, and nephrotic syndrome/ interstitial nephritis.

Cardiovascular adverse effects can also be increased with NSAID use; these include MI, thromboembolic events, and atrial fibrillation. Diclofenac seems to be the NSAID with the highest reported increase in adverse cardiovascular events.

Hepatic adverse effects are less common; NSAID-associated risk of hepatotoxicity (raised aminotransferase levels) is not very common, and liver-related hospitalization is very rare. Among the various NSAIDs, diclofenac has a higher rate of hepatotoxic effects. NSAIDs should be avoided in patients with liver dysfunction. Severe reactions, including jaundice, fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Hematologic adverse effects are possible, particularly with nonselective NSAIDs due to their antiplatelet activity. This antiplatelet effect typically only poses a problem if the patient has a history of GI ulcers, diseases that impair platelet activity (hemophilia, thrombocytopenia, von Willebrand, etc.), and in some perioperative cases.

Other minor adverse effects include anaphylactoid reactions that involve the skin and pulmonary systems, like urticaria and aspirin-exacerbated respiratory disease.

For a complete list of adverse effects for an individual NSAID, please see the StatPearls article for that particular drug.

Contraindications

According to the package insert, NSAIDs are contraindicated in patients:

- With NSAID hypersensitivity or salicylate hypersensitivity, as well as in patients who have experienced an allergic reaction (urticaria, asthma, etc.) after taking NSAIDs
- Who have undergone coronary artery bypass graft surgery
- During the third trimester of pregnancy

- Renal failure

Monitoring

Recommended monitoring includes a CBC, renal tests, and hepatic panel. These recommendations are from the American College of Rheumatology for use in rheumatoid arthritis patients who use NSAIDs chronically and who have no comorbidities nor history of complications. Monitoring is less common in patients not considered high risk for NSAID toxicity. However, NSAIDs are either contraindicated, or their use requires monitoring in patients with liver or renal problems.

Toxicity

NSAID toxicity can manifest as GI bleeding, hypertension, hepatotoxicity, and renal damage. Typically, acute NSAID overdose is asymptomatic or has negligible gastrointestinal symptoms. However, other symptoms of toxicity complications may include anion gap metabolic acidosis, coma, convulsions, and acute renal failure. Also, NSAIDs can confer gastrointestinal damage by inhibiting COX-1, which causes decrease gastric mucosa production. Nephrotoxicity can also occur with NSAID use because these medications reduce prostaglandin levels, which are essential for the vasodilation of the renal arterioles. Lastly, neurologic toxicity can present with drowsiness, confusion, nystagmus, blurred vision, diplopia, headache, and tinnitus.

Enhancing Healthcare Team Outcomes

The general public widely uses NSAIDs because of their wide range of commonly encountered indications. Patient education on the use of NSAIDs is an important piece of care that providers need to pay attention to because of the many possible adverse effects on multiple different organ systems. Because these adverse effects occur at a much higher rate in patients with specific comorbidities, it is crucial for physicians, nurses, and pharmacists to pay close attention to a patient's history and to educate the patient accordingly on risks and dosing. The treating clinician will initiate therapy, whether for a short or long-term regimen. The pharmacist will need to verify the dosing and administration and check for potential drug-drug interactions. Pharmacists should also offer patient counseling on how to best use their NSAID and minimize adverse events; this is particularly the case when the patient uses NSAIDs as an OTC agent. Nursing must also take a careful medication history and include OTC NSAID use, so the clinician can make an informed choice for prescribing NSAID therapy. MUrses, pharmacists, and clinicians all need to be cognizant of the signs and symptoms of NSAID toxicity or adverse effects to make changes to the patient's regimen as needed.

The healthcare team should communicate and work together to ensure that each patient receives the proper dose for their specific condition and comorbidities, high enough for efficacy but as low as possible to reduce the incidence of adverse effects. Through collaborative interprofessional

teamwork, NSAID therapy can confer maximum benefit with minimal downside. [Level 5]

Review Questions

- Access free multiple choice questions on this topic.
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Disclosure: Ida Ghlichloo declares no relevant financial relationships with ineligible companies.

Disclosure: Valerie Gerriets declares no relevant financial relationships with ineligible companies.