NASAIDS

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- **nonsteroidal antiinflammatory drugs** (NSAIDs) are available commercially, and these agents are used worldwide for their analgesic antipyretic and anti inflammatory effects for multiple medical conditions.
- NSAIDs all have the common property of inhibiting cyclooxygenase
- Different NSAIDs have varying inhibitory potentials of the two known isoforms of cyclooxygenase, ***COX-1 and COX-2***

- It is, therefore, **difficult to name** the “safest” NSAID.
- Many clinicians believe that ibuprofen is quite safe, which is true when the drug is used at the lowest possible dose. However, increasing the dose of any NSAID is associated with an increased risk of gastrointestinal toxicity.
- A potentially clinically relevant interaction between ibuprofen and aspirin referred to as “***aspirin resistance***” has been observed in **ex vivo platelet assays** when ibuprofen is administered to healthy controls before aspirin.

- risk factors have been identified for the development of **acute renal failure**, ***gastroduodenal toxicity***, and ***adverse cardiovascular effects***.
- ***The risk of acute renal failure*** is increased in patients with existing glomerular disease, renal insufficiency, hypercalcemia, in states of effective volume depletion (such as heart failure and cirrhosis), and in the presence of true volume depletion due to gastrointestinal or renal salt and water losses.
- ***The risk of gastrointestinal toxicity*** is increased by the presence of one or more of the following: a prior history of a gastrointestinal event (ulcer, hemorrhage), age >60, a high dose of a NSAID, the concurrent use of glucocorticoids, and the concurrent use of anticoagulants (eg, aspirin , warfarin , or clopidogrel).

- **Chronic** as opposed to short-term use, **untreated Helicobacter pylori** infection, and **use of selective serotonin reuptake inhibitors** (SSRI) may also ***increase the risk of bleeding or perforation.***
- Accidental or intentional ingestion of a larger than recommended dose of an NSAID is typically well-tolerated and usually does not cause serious adverse effects. However, **such ingestions may be accompanied by the taking of other analgesics**, which may have more **serious consequences**.
- Among these drugs, salicylates and acetaminophen are important ones to consider.
- Symptoms of acute overdose of NSAIDs are nonspecific

RENAL EFFECTS

- The development of acute renal failure due to renal vasoconstriction. Other forms of renal toxicity also can occur
- Modest worsening of underlying hypertension
- Electrolyte and fluid abnormalities including hyperkalemia, hyponatremia, and edema
- Increased risk of renal cell cancer

- **CARDIOVASCULAR EFFECTS** — NSAIDs have a variety of effects on the cardiovascular system. Some NSAIDs may interfere with the beneficial antiplatelet activity of aspirin , have an **uncertain effect on coronary risk, and can modestly exacerbate heart failure**
- **HEPATIC INJURY**
- **Elevations of serum aminotransferases** (transaminases) are commonly associated with NSAID use; however, liver failure is quite rare
- Diclofenac has been reported to cause clinical hepatitis, including ANA positivity and histologic evidence of chronic active hepatitis

- It has been suggested that liver function abnormalities due to NSAIDs may be disease-specific. There is, for example, evidence supporting ***an increased risk of hepatotoxic reactions in patients with systemic lupus erythematosus*** .
- In other studies, aspirin caused elevated serum aminotransferase concentrations in 40 percent of patients with active juvenile inflammatory arthritis .
- Some of these events had serious consequences.

- **ANAPHYLAXIS** — Anaphylaxis to NSAIDs has been reported and is assumed to be an **IgE-mediated immunologic reaction**.
- The symptoms of anaphylaxis include (but are not limited to) urticaria, angioedema, generalized pruritus, tachycardia or bradycardia, hypotension, cardiac arrhythmias, nausea and vomiting, headache, lightheadedness, and hypotension.
- **PULMONARY EFFECTS** — The NSAIDs rarely induce pulmonary problems, although the actual incidence of adverse events is unknown. The principal pulmonary reactions that can occur include **bronchospasm (which can be severe) and pulmonary infiltrates with eosinophilia.**

- **HEMATOLOGIC EFFECTS** — Some of the early NSAIDs (eg, ***phenylbutazone*** and, to a lesser degree, indomethacin) have been associated with an **increased risk for bone marrow failure** (ie, aplastic anemia).
- Although phenylbutazone is rarely used, neutropenia and antiplatelet effects can be induced by any of the NSAIDs.
- Neutropenia is an infrequent complication of NSAID therapy, probably occurring in less than 1 percent of users.

- The **antiplatelet** effects of NSAIDs are due to **inhibition of COX-1**, an isoform of cyclooxygenase, leading to **decreased production of thromboxane A2 (TxA2)** .
- **TxA2** is released by platelets in response to a number of agonists, amplifying the platelet response and ***leading to aggregation***.
- These effects have therapeutic applications, such as the use of aspirin in ***patients with coronary heart disease***.
- ***NSAIDs should be avoided*** in patients with preexisting platelet defects (eg, due to ***uremia*** or ***von Willebrand disease***) and in those with ***thrombocytopenia*** (platelet count <50,000/microL).
- ***Nonacetylated salicylates or selective COX-2 inhibiting*** agents are ***safer*** therapeutic alternatives in these patients.

- In addition, **when NSAIDs and oral anticoagulants are taken concurrently**, a clinically significant **increase in INR may occur.**
- Nonselective NSAIDs have been associated with an increased risk of **renal cell cancer.**
- although **decreased risk for several other malignancies**, including **colorectal, prostate, and breast cancer**, has also been described with NSAID use .
- The reported central nervous system (CNS) side effects of NSAIDs include ***aseptic meningitis, psychosis, and cognitive dysfunction***

- ***Psychosis and cognitive impairment*** are more prevalent in older patients, particularly with the use of indomethacin
- **Aseptic meningitis** seems to be more prevalent in patients with **SLE** who are treated with NSAIDs of the phenylpropionic acid class (eg, ibuprofen , naproxen);
- however, this diagnosis should be considered in any patient with aseptic meningitis who has been using NSAIDs.
- Various skin reactions may develop in association with the use of NSAIDs. Severe, potentially life-threatening reactions such as toxic epidermal necrolysis (TEN) and the Stevens-Johnson syndrome (SJS) are uncommon.

- **Pseudoporphyria** — **Blistering can also occur in sun-exposed areas** as a result of **NSAID use.**
- A small increased risk of **nonunion** in patients with bone fractures has been reported with the use of ***nonselective NSAIDs or COX-2 selective agents.***
- However, a causal relationship has not been proven, and the effect of these drugs on fracture healing in humans is uncertain.

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Aspirin*

- Standard for comparison but now **used infrequently for treatment of chronic pain and inflammation** due to its ***association with severe gastropathy***.
- Unlike other NSAIDs, irreversibly **inhibits platelet function for platelet life (7 to 10 days)**
- **Usual analgesic dose and interval**
- 325 to 650 mg every 4 to 6 hours
- maximum dose
- 4000mg/day

Ibuprofen*

- Initial dose * 1600* 400 mg every 4 to 6 hours
- ***Max dose per day3200mg acute, 2400mg chronic***
- Treatment of **mild to moderate pain, minor fever and acute or chronic inflammatory conditions**.
- ***A 200 to 400 mg dose is comparable in analgesic effect to 650 mg acetaminophen or aspirin***.
- Reversibly inhibits platelet function and **increases bleeding time.**
- **Can alter cardioprotective effect of low dose aspirin** .
- Minimal risk of severe gastropathy with daily dose ≤2400 mg.

Diclofenac

- 75 or 100 mg once Δ
- ***50 mg every 8 hours***
- ***Maximum dose per day 150 mg***
- For treatment of mild to moderate pain and acute or chronic inflammation.
- Also available as a topical patch for pain due to trauma and as a gel for treatment of painful joints.

Ketorolac (intravenous and intramuscular)	Initial dose <65 yrs 60 mg IV or IM once	Usual dose 15 to 30 mg every 6 hours	Maximum dose 120	Short term treatment of moderate acute pain when oral administration of an NSAID is not available and as an adjunct to other analgesics for the treatment of moderate to severe postoperative pain. ***Not indicated for treatment of chronic cancer pain.*** Risk of gastropathy is increased when use **exceeds five days.** An oral preparation of ketorolac is available but offers no advantage over other oral NSAIDs.
	≥65 yrs 30 mg IV or IM once	15 mg every 6 hours	60	

Celecoxib

- An option for patients requiring chronic NSAID treatment who may be **at risk for gastropathy**. Demonstrated efficacy and relative reduction in GI toxicity compared to non-selective NSAIDs. **No effect on platelet function**. **Dosage above 200 mg daily associated with increased cardiovascular risk.**
- **400 once Δ initial dose**
- **Usual dose 200 mg daily or 100 mg every 12 hours**
- ***Maximum dose 400mg***

Mefenamic acid

- For acute pain and **dysmenorrhea**.
- Anti-inflammatory efficacy is comparatively low. ***Not indicated for treatment of chronic cancer pain.***
- Initial dose 500 once Δ
- ***Usual dose 250 mg every 6 hours***
- **Maximm dose per day 1000mg**