Nonsteroidal Anti-Inflammatory Drugs

Zoe S. Gan | Christopher R. Page

Uses

- Incidence in USA: 100 million prescriptions are written per year; 17 million Americans use NSAIDs daily.
- Have analgesic, anti-inflammatory, and antipyretic properties.
- NSAIDs are the first step in the analgesic ladder of WHO; typically considered drugs of choice for mild to moderate pain.
- Can be obtained OTC or by prescription for chronic somatic pain states (e.g., arthritis) and rheumatologic disorders.
- Are given IV, IM, IN (intranasal ketorolac), and PO postop as part of a multimodal treatment regimen for acute pain.
- Should be considered in an enhanced recovery protocol.

Worry About

- Plt dysfunction
- Renal insufficiency
- Drug interactions
- Allergic reactions
- Effect on bone growth
- Gastric/GI bleeding
- Possible increased risk of thrombotic/CV events with long-term use.

Overview/Pharmacology

- Most NSAIDs are weak acids (pK_a 3–5) of diverse chemical structure and half-lives.
- Well absorbed from the stomach and intestinal mucosa.
- Highly protein-bound (>95%), usually to albumin.
- Work by inhibiting cyclooxygenase, which is a key enzyme in the synthesis pathway of prostaglandins.
  - Lead to decreased prostaglandin synthesis, thus decreasing the inflammatory response as well as the sensitizing effect of prostaglandins on nociceptors (both central and peripheral).
- Two isoforms of the COX enzyme have been identified.
  - COX-1: Expressed constitutively in most cell types; has an essential role in functions such as gastric protection, plt aggregation, and renal function.
  - COX-2: Traditionally considered to be induced by tissue injury/inflammation, now known to be constitutively expressed in some tissues (e.g., brain and/or kidney).
- Undergo liver metabolism to inactive metabolites, which are then excreted by the kidney.
- Have a low abuse potential but also a ceiling analgesic effect.

Drug Class

- Traditional or nonselective NSAIDs are both COX-1 and COX-2 inhibitors.
  - All NSAIDs inhibit both COX-1 and COX-2, although with varying ratios of COX-1/COX-2 inhibition.
- Several different subclasses
  - Salicylate (aspirin, salsalate, diflunisal, and choline magnesium trisalicylate)
  - Propionic (ibuprofen, ketoprofen, naproxen, fenoprofen)
  - Indole (indomethacin, sulindac, tolmetin)
  - Fenamate (mefenamic, meclofenamate)
  - Mixed (piroxicam, ketorolac, diclofenac)
- Coxibs are selective COX-2 inhibitors with a minimal degree of COX-1 inhibition at clinical doses.
  - Only celecoxib is commercially available in USA.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Htn, HF, thrombotic events	Worsening SOB	BP, edema, rales, chest pain	
RESP	Nasal polyps, rhinitis, dyspnea, bronchospasm, angioedema	In asthmatics	Wheezing	
HEPAT	Hepatitis	N/V, anorexia,	Jaundice	LFTs
GI	Gastropathy (can be asymptomatic), GI bleeding, esophageal disease, pancreatitis	Ulcers, heartburn		Stool heme, Hgb, upper endoscopy
HEME	Increased bleeding	Easy bruising/bleeding	Pallor	Bleeding time, Hgb
DERM	Urticaria, erythema multiforme, rash			
GU	Renal insufficiency, sodium/fluid retention, papillary necrosis, interstitial nephritis		BP, edema, weight changes	Increased K^+/BUN/Cr, decreased UO, biopsy,
CNS	Headache, aseptic meningitis, hearing disturbances	Cognitive dysfunction, somnolence, confusion		CSF

Key References: Patrignani P, Patrono C: Cyclooxygenase inhibitors: from pharmacology to clinical read-outs, *Biochim Biophys Acta* 1851(4):422–432, 2015; Pogatzki-Zahn E, Chandrasena C, Schug SA: Nonopioid analgesics for postoperative pain management, *Curr Opin Anaesthesiol* 27(5):513–519, 2014.

Perioperative Implications

Preoperative Concerns

- Preop nonselective NSAID use has been associated with increased intraop blood loss due to plt inhibition.
  - Unlike aspirin, NSAID plt inhibition is reversible; common practice is to hold the NSAID for a period of 5 half-lives before surgery (e.g., ibuprofen 1 d, naproxen 5 d).
  - Coxibs do not affect plt function and therefore do not need to be held.
- For pts on aspirin for a primary or secondary ACC/AHA guideline indication, it may be safe to continue aspirin in the case of a non–closed space procedure or nonprostate surgery.
- NSAIDs displace albumin-bound drugs (e.g., warfarin) and can potentiate their effects.

Regional Anesthesia

- According to the consensus guidelines of ASRA, NSAIDs do not significantly increase the risk for spinal hematoma in pts undergoing neuraxial anesthesia.
  - May increase risk if combined with other anticoagulant/antiplatelet medications or if there is coexisting coagulopathy.
- Use of NSAIDs alone should not interfere with the performance of neuraxial blocks or the timing of neuraxial catheter removal.

Intraoperative Concerns

- Intraop administration of NSAIDs has been shown to cause a slight increase in the need for reoperation in surgeries at high risk for postop bleeding (e.g., tonsillectomy/CABG surgery).
  - In deciding to administer an NSAID, consider the need for improved analgesia, pt's ability to achieve hemostasis, and the risk of postop bleeding inherent to the surgery.
- May exacerbate asthma, especially in pts with a Hx of NSAID-induced bronchospasm, angioedema, urticaria, or rhinitis.

Postoperative Period

- NSAIDs may not consistently reduce pain intensity but do reduce opioid requirements and subsequent side effects (e.g., N/V, sedation).
- NSAIDs can be resumed with cautious monitoring for GI bleeding/renal dysfunction; avoid resumption in seriously ill pts.
- Risk of adverse effect on renal function is the same for both nonselective NSAIDs and COX-2 inhibitors.
  - For pts with baseline normal renal function, transient reduction in renal function with acute postop NSAID administration is usually clinically insignificant (normal function restored 2–7 d after stopping NSAID treatment).
  - Use caution when initiating therapy in pts with preexisting heart/kidney disease, use of loop diuretics, or loss of blood volume >10%.
- May increase risk of anastomotic leakage following GI surgery
- Both nonselective NSAIDs and coxibs have been implicated in potentially inhibiting bone healing.
  - May be prudent to avoid in cases where bone formation is especially crucial (e.g., spinal fusion).
  - Especially short treatment may be safe; decision to use postop should be done in consultation with surgeon.

Anticipated Problems/Concerns

- Generally associated with chronic rather than acute use.
- All NSAIDs pose a risk of gastropathy; ulcers are typically asymptomatic before an episode of GI bleeding.

- Risk with coxibs is approximately 50–60% less than with nonselective NSAIDs but still present.
- Concurrent treatment with a PPI or misoprostol may further decrease risk.

- All NSAIDs may carry an increased risk of CV events, especially if used with aspirin (one NSAID may antagonize benefit of another) and with chronic use.
  - Significantly increased risk with COX-2s led to withdrawal from market of most coxibs; increased CV risk was later determined to be a class effect.
  - Periop use is generally safe in pts with low CV risk, but contraindicated in cardiac surgery pts.
  - For most pts, increased risk is small; a risk/benefit analysis should be undertaken before continuing long-term use.
- Can exacerbate and/or induce CHF in susceptible pts.
  - Risk is nearly equivalent to that of NSAID-induced gastropathy.
- Can lead to increases in BP, especially in pts with preexisting Htn.
- Use in pregnancy considered safe for short courses of therapy (<72 hr) and up to 32 wk of gestation.
  - Chronic use and use of aspirin generally contraindicated
  - Some concern for increased risk of miscarriage early in first trimester and premature closure of ductus arteriosus after 32 wk.

Nutritional Support

Alan David Kaye | Mark R. Jones | Rachel J. Kaye

Risk

- Up to 40% of pts may be undernourished on admission to hospital, and two-thirds of all pts lose weight during hospital stay. 60% of elderly pts are malnourished at discharge. More than 376,000 people depend on TPN per year in USA.

Perioperative Risks of Malnutrition

- Decreased respiratory, cardiac, and skeletal muscle mass and strength.
- Up to 50% of heart failure pts are malnourished.
- Decreased visceral protein mass, altered GI mucosal barrier.
- Altered humoral, cell-mediated immunity.
- Altered neutrophil function.
- Increased pulm, thromboembolic complications.
- Pts with protein-calorie malnutrition have increased risk for postop cardiac, noncardiac complications.
- Increased risk for nosocomial infections and decreased wound healing.
- Increased risk for multiple organ failure.
- Increased length of hospital stay.

Worry About

- Hypoglycemia or hyperglycemia, depending on additives to TPN.
- Decreased ability to secrete insulin in malnourished pts.
- Kidney dysfunction and failure prevalent in cases of severe malnutrition.
- Increased free fraction of certain protein-bound drugs with low albumin levels.
- Vitamin B_{12} and/or folate deficiency, leading to anemia.
- Higher rates of infection with TPN.
- Excess carbohydrate administration via TPN may lead to increased CO_2 production and increased difficulty in weaning from ventilatory support and hepatic steatosis.
- Excess fat administration via TPN may lead to hyperlipidemia, decreased immune function, and reduced reticuloendothelial function.

Overview

- NRI = 1.519 × serum albumin (g/L) + [0.417 × (current weight/usual weight) × 100]. (Malnutrition defined as NRI <100; severe malnutrition defined as NRI <83.5.)
- Preop nutritional support for 5–7 d may result in decrease in infectious complications in severely malnourished pts.
- TPN composition:
  - Fluid: 30 mL/kg/d, additional losses
  - Calories: 25–30 kcal/kg/d
  - Glucose: 3.0–5.0 g/kg/d
  - Fat: 1.0–1.5 g/kg/d
  - Protein: 1.5–2.0 g/kg/d
  - Additives:
    - Multivitamins in the form of balanced formula should be provided daily.
    - IV formula requires addition of vitamin K, 2 mg/d.
    - Trace elements should be given daily to pts with GFR >20 mL/d; magnesium: 15–20 mg/d; zinc: 15–40 mg/d. (Requirement for replacement is based on serum level.)
- Special formulas: Modified amino acid formula is more efficient in restoring positive nitrogen balance, decreasing ureagenesis, and increasing support of protein synthesis.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
MS	>10% loss of body weight over 6 mo	Renal Hx of renal, hepatic dysfunction Short gut	Muscle wasting Decreased triceps and skinfold thickness, decreased mid-arm circumference	Alb <2.5 g/dL Total lymphocyte count <1500 cells/mm^3

Key References: Fernández López MT, Fidalgo Baamil O, López Doldán C, et al.: Prevalence of malnutrition in not critically ill older inpatients, *Nutr Hosp* 31(6):2676–2684, 2015; Fessler TA: Trace elements in parenteral nutrition: a practical guide for dosage and monitoring for adult patients, *Nutr Clin Pract* 28(6):722–729, 2013.

Perioperative Implications

Monitoring

- Daily monitoring of wt, electrolytes, magnesium
- Weekly monitoring of zinc, liver function tests, PT/PTT
- Nutritional variable: Prealbumin and transferrin are better indicators of nutritional status due to their shorter half-life compared to albumin. Failure to improve or maintain adequate levels usually represents inadequate nutritional support, intercurrent systemic inflammatory response, or advanced organ failure.

Induction/Maintenance

- TPN is usually continued intraop.
- Monitor glucose.
- Malnutrition may predispose a pt to having a higher risk for pseudocholinesterase deficiency; use succinylcholine with caution.

Adjuvants

- For morbidly obese pts, use ideal weight for calculation of TPN requirement.
- For severely underweight pts, use half the difference between pt's ideal weight and actual weight.

Anticipated Problems/Concerns

- Caloric and glucose overload can result in hyperglycemia and hepatic dysfunction.
- Moderate and severe hypoglycemia occur frequently in critically ill pts assigned to intensive glucose control, and are both strongly associated with an increased risk of death.
- Fat overload can result in WBC dysfunction, infectious complication, and increased CO_2 production.