NSAIDs: Friend or Foe in Battle against Pain?

Presented by June E. Oliver, RN-BC, MSN, CCNS, APN/CNS

NO Conflicts of Interest to Declare

Old & Natural!

- 1763 fever Rx: bark/leaves of willow/myrtle (salicylic acid)
- 1859: chemical structure discovered & synthesized in Germany
- 1914: Bayer Co. started manufacturing ASA
  - Current sales: 11 billion (2014)
- Early 20th Century: NSAIDs discovered
- 1971: discovered mechanism of action of NSAIDs by John R. Vane
- 1982: Nobel Prize in Physiology & Medicine
  - Vane, Bergström & Samuelsson for NSAIDs research
- 1990s-COX-2 isoenzyme successfully identified & cloned
- Current: script & OTC use = > 30 billion doses/yr of NSAIDs in US
  - Numbers increase every year
Prostaglandin (PG) Mechanism of Action

- Prostaglandins - lipids derived from acids such as arachidonic, linoleic, & others
- PGs have Variety of functions
  - Constitutive
    - GI mucosal protection
  - Trauma response
    - Cell membrane trauma releases AA; COX enzyme converts to PGs
    - Peripheral & central sensitization of nociceptors to mechanical & chemical stimuli
  - Pyretic response
    - PGs rise in CSF w/ pyrogen introduction
  - Acetaminophen blocks brain PG synthetase

Cyclo-oxygenase (COX) Specifics

- Cyclo-oxygenase 1 & 2 = isoenzymes that convert AA to PGs, prostacyclin, & thromboxanes
- COX-1
  - Expressed regularly: provides gastric & duodenal mucosal protection
  - Stimulates production mucin/bicarbonate/phospholipid that covers surface of stomach
  - Enhances GI mucosal blood flow w/ local vasodilation
  - Enhanced epithelial cell reproduction & migration towards lumen and
  - Can be induced under stress

- COX-2
  - CNS & kidneys expression regularly
  - Induced by trauma, endotoxins, neurotransmitters, cytokines, growth factors, hormones, etc
  - Promotes inflammation
  - Increased electrical nerve activity (blunted w/ neural blockade & COX-2 inhibitors)
  - Humoral signal that raises COX2 in CNS (blunted only by central COX2 inhibitors)
  - May help heal gastric ulcers
Relative COX Selectivity

<table>
<thead>
<tr>
<th>Relative COX Selectivity</th>
<th>COX-1 Preference</th>
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<tr>
<td>Etodolac</td>
<td>Diclofenac</td>
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<tr>
<td>Meloxicam</td>
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NSAID Characteristics

- Highly protein bound:
  - Hemodialysis does not remove them
  - Hypoalbuminemia will increase circulating level

- Effective analgesics: many studies
  - Opiate sparing (25-55%)
  - Multimodal use postop - less nausea, vomiting, sedation
  - Improved postop outcomes/recovery

- Different chemical subgroupings
  - If one ineffective at max dosing, try a different category

- COX-1 & COX-2
  - All NSAIDs inhibit BOTH to varying degrees
  - COX-2 selectivity is a continuum - not an absolute

Chemical Grouping of NSAIDs

<table>
<thead>
<tr>
<th>Acetylated Salicylate</th>
<th>Non-acetylated Salicylate</th>
<th>Propanic Acids</th>
<th>Acetic Acids</th>
<th>Oxicams (Enolic acids)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylate</td>
<td>Diflunisal</td>
<td>Ibuprofen</td>
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<td>Meclofenamate</td>
<td>Ibuprofen</td>
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<tr>
<td>Naproxen</td>
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<tr>
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<td>Flurbiprofen</td>
<td>Mefenamic acid</td>
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<tr>
<td>Diflunisal</td>
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<td>Flurbiprofen</td>
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<td>Oxaprozin</td>
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NSAID TOXICITIES

- 5.7% of hospital admission r/t adverse effects of drugs (UTD: overview AEs)
  - 11.2% of those admission r/t NSAIDs
- Implicated in nearly 25% of all ADRs (most common GI irritation)
- Other cited: 100,000 hospitalizations and > 16,000 deaths/yr in US r/t NSAID complications
- Costs > $2 billion (ARAMIS Medscape 2017)
- Based on 1999 observational study w/ inaccurate extrapolations
- 2010 study
  - Nonselective NSAID mortality 48/1000 person yrs
  - opioids 75/1000 person yrs

Toxicity #1 - Hematologic

- COX-1 converts AA to PGs in platelets (thromboxane A2) & vascular endothelium (PGI2)
- Platelets cannot regenerate PGs so vulnerable to COX-1 inhibition
- ASA irreversibly inhibits COX-1 action ---- inhibits platelet aggregation
  - Effects lasts for life of platelet (7-10 days)
- Non-selective NSAIDs reversibly inhibit COX-1 - transient effect
  - Single dose ibuprofen 300-900mg inhibits plat agg x 2 hr
  - effect completely gone in 24hr
  - Piroxicam - can last several days after discontinuation
Toxicity # 1- Hematologic

- Possible bleeding risk
  - Non-acetylated & COX-2 NSAIDs less platelet effect
  - No COX-2 activity found in platelets
  - Neutropenia and aplastic anemia- rare (<1% of NSAID users)
  - Indomethacin and phenylbutazone associated w/ higher risk

NSAIDs & Bleeding Risks

- Higher PPH post bleeding risk
  - w/ non-sutured tissues - i.e. tonsillectomy, joint replacement
  - NSAIDs w/ half-life > 6hr
  - NSAID given before surgical control of bleeding

- Many studies over many years w/ no or low increased risk peri-operative bleeding
  - i.e. 1995: no difference in bleeding during and after THA/TURP w/ diclofenac vs placebo
  - NSAID STUDY 2009 BENZON # 175: no increased risk any bleeding & severe bleeding

Combination Risks

- Post MI study: on clopidogrel, ASA or warfarin vs same regimen plus NSAID
  - Bleeding risk doubled w/ NSAID addition
  - Bleeding risk seen as early as 1st three days of NSAID use

NSAIDs & Bleeding Risks

- Most NSAIDs potentiate warfarin activity
  - Displace warfarin binding & inhibit hepatic metabolism — increased circulating levels
  - Pat w/ increased bleeding risk w/ combo NSAID and warfarin

- Discontinue NSAID 3 days to normalize PT function
  - Stop aspirin effect gone in 24 hr
  - ASA: stop at least 1 week
GI Effects
- AEs: dyspepsia, gastric/duodenal ulcers and GI bleeding
- Pathophysiology: Gastric damage
  - NSAID systemic effect decreasing COX (post-absorptive effect)
  - COX-1 enzymes produce mucosal protective PGs (cytoprotection)
  - Stimulates GI secretion – bicarbonate, mucin, phospholipids
  - Produces alkaline, unstirred water layer on gastric mucosa
  - Protects against acid & pepsin erosion
  - Enhances epithelial cell blood flow, migration to surface (repair), cell proliferation
  - COX block – increases risk of mucosal injury and decreased repair response
  - Gastric repair (restoration) associated w/ COX-2 activity
- Enteric coating
- Clinically no difference in preventing ulcer bleeding
- Bleeding due to systemic effect, not topical effect on mucosa

Gastro-duodenal Toxicity
- NSAID- irreversible COX inhibition
  - Doses 10mg/day inhibit gastric PG and can damage stomach
  - Damage increases as dose increases
  - After d/c of low dose ASA- 5-8 days for stomach to recover full COX-1 activity
  - Some COX-2 activity intact after ASA ingestion
- Other NSAIDS- even transient COX inhibition can damage gastric mucosa
  - 1 week Rx unlikely to cause major GI damage
  - Damage most common in first three months of Rx
- Duodenal damage r/t gastric acid
  - H2 blockers may help (but not w/ gastric damage)
- H. Pylori infection- independent AND synergistic risk of PUD w/ NSAIDs

Risk & NSAID Gastro/duodenal Toxicity
Am College of Gastroenterology 2009

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Risk Stratification</th>
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<tbody>
<tr>
<td>Hx of Uncomplicated U/C</td>
<td>HIGH= Hx of complicated U/C or &gt;3 risk factors</td>
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<tr>
<td>Age &gt;65 years</td>
<td>MOD= 1-2 risk factors</td>
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<tr>
<td>High dose NSAID (2x risk)</td>
<td>LOW= zero risk factors</td>
</tr>
<tr>
<td>Concurrent use ASA (daily)</td>
<td>INCLUDES anti-platelet, warfarin, heparin, direct thrombin &amp; Factor Xa inhibitors</td>
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</table>

OTHER RISK FACTORS (beyond ACG table)
- Untreated H. Pylori infection
- Chronic use (2004 meta-analysis = avg 84 days before s/s toxicity)
- Higher Doses
- Concurrent use SSRI (r/t effects on platelet serotonin)
- Ketorolac- 5.5 x more likely than other NSAIDs to cause GI toxicity (limit 5 day use)
Risk Reduction with Medications

- **PPI**
  - Once daily dosing, well tolerated; probably all w/ equal effect
  - Unclear if COX-2 plus PPI outcomes better than other NSAIDs plus PPI
  - PRECISION Study (2016): w/ ASA use – lower GI events w/ PPI & COX-2 vs PPI & Non-selective NSAIDs
  - CONCERN Study (2017): healed ulcers after GI bleeding; on ASA; PPI w/celecoxib or naproxen
  - Recurrent GI bleed 6.6% celecoxib and 12% naproxen
  - Risk lower but significant – Celecoxib & PPI; 1 in 20 patients w/ recurrent GI bleeding
  - Misoprostol (prostaglandin analogue) 200 mcg qid
    - Less well tolerated than PPI (dyspepsia, diarrhea, abd pain)
    - Less than qid ineffective risk reduction

GI Risk Reduction

- COX-2 mod reduction GI bleeding risk compared to non-selective NSAIDs
  - Risk of increased CV placebo
  - Reduced risk eliminated w/ concurrent low dose ASA or warfarin
  - Test for H Pylori and treat – BEFORE starting NSAIDs if hx of ulcers OR long-term NSAID anticipated
    - Based on expert opinion
    - High Risk for GI/ulcer/bleeding
      - W/long-term NSAID
    - Use lowest dose PPI review periodically
    - Long term PPI use
      - Do NOT routinely raise intake Ca, Vit B12, Mg
      - Do NOT routinely take probiotics to prevent infection
      - Do NOT routinely monitor bone density, creatinine, Mg, B12
    - PPI side effects - Vit B12 deficiency, possible Osteoporosis

Monitoring Gastro-duodenal toxicity

- GI toxicity often asymptomatic until shortly before clinical event
  - Little correlation between dyspepsia & presence of ulcers/erosions
  - Drugs w/o COX inhibition can cause dyspepsia w/o known ulcer risk
    - Acetaminophen, salicyclic acid (salsalate)
  - Suspect ulceration if:
    - Unexplained blood loss anemia
    - Iron deficiency
    - Significant dyspepsia
    - Any w/ GI bleeding
  - Endoscopy indicated w/ suspicion
  - CT abd if perforation suspected
Small Bowel Injury (SBI) - Beyond duodenum

- Under-reported, affected area beyond reach of routine endoscopy
- Video Capsule Endoscopy (VCE) increased findings in distal small bowel
- Incidence:
  - 5% in healthy short-term users
  - On acid suppression
  - 10% in acute, 2 weeks of use
  - 10% in long-term use (>3 months)
- SBI manifestations:
  - Iron deficiency anemia due to occult bleeding
  - Protein-losing enteropathy with malnutrition
  - Recurrent abdominal pain associated with strictures
  - Small bowel diaphragm disease
    - Circular membranes of mucosa divide and narrow bowel lumen – potential strictures & obstruction.
- Incidence:
  - 53-75% in healthy short-term users on acid suppression
  - Can occur as early as 2 weeks of use
  - 50-71% in long-term use (>3 months)

SBI manifestations:

- Iron deficiency anemia due to occult bleeding
- Protein-losing enteropathy with malnutrition
- Recurrent abdominal pain associated with strictures
- Small bowel diaphragm disease
- Circular membranes of mucosa divide and narrow bowel lumen – potential strictures & obstruction.

Lit Review - Increased risk w/Oxicams & diclofenac

- NSAIDs w/ASA more damaging than ASA alone
- Not associated w/duration of NSAIDs or PPI use
- Lesions persisted >16 months after stopping NSAID
- COX-2 (Celebrex) lowered risk in some studies

Prophylaxis:

- PPIs & H2RA shown effective w/gastro-duodenal dz
- No clear Rx for prophylaxis of SBI
- Rebamipide (not available in US) & misoprostol co-prescription
  - Studies show prevention & enhanced healing of SBI
- Rx for inflammatory bowel dz (IBD) reduce SBI
  - i.e. sulfasalazine, mesalamine
- Novel agent - nitric oxide donors (mucosal blood flow, bicarb secretion, mucous production)

Risk & NSAIDs; Upper & distal GI


Risk Factors Gastro/duodenal

- Age > 65 years
- > 7 days of therapy
- High dose NSAID
- Prior Peptic Ulcer dz or prior NSAID toxicity
- H. Pylori infection
- Comorbid arthropathy
- Genetic polymorphisms
- Concurrent use of anti-platelets, glucocorticoids, anticoagulants, SSRIs

Risk Factors SBI

- Age > 70 years
- Concurrent use anti-platelets, glucocorticoids, anticoagulants, SSRIs
- Use of diclofenac and oxicams (i.e. meloxicam)
Cardiovascular Toxicity

- CV thrombotic events, MI, stroke
- Increased risk w/ COX-2 inhibitors (more studied: initial view)
  - Unbalanced synthesis PG1 (vessel endothelium) & thromboxane (platelets)
  - Normal platelet action is a balance between PG1 and TXA2
  - PG1 = platelet inhibitor & vasodilator
  - TXA2 = platelet activator & vasoconstrictor
- COX-2 Inhibits PG1 only
  - Atherosclerosis & exaggerated thrombotic response to plaque rupture
  - MI/CVA risk = 1.7 - 5x risk w/ rofecoxib in VIGOR & APPROVe studies in 9-18 mo
  - VIGOR: high-risk pts w/ SA but no ASA used
  - Voluntarily withdrawn from market 2004

Cardiovascular Risk-Celecoxib

- (Adenoma Prevention w/ Celecoxib) APC study (2004)= 200-400mg bid x 33 mo
  - 2.3-5.4 increase in CV events after 12 month
  - PreSAP study (2002)= 400mg qd vs placebo x 32 months
    - Smaller increase in CV events
  - Alzheimer’s Dz Anti-inflamm Piv trial ADAPT study (2004)= 200mg qd vs placebo
    - No increase in risk celecoxib; but increase risk w/ naproxen
- Valdecoxib increase risk w/ supramaximal doses x 14 days (40mg bid)
  - But not w/ therapeutic dosing
- 2005 FDA
  - Affirmed risk of celecoxib similar to non-selective NSAIDs
  - Deemed risk high w/ valdecoxib and requested withdrawal from market
  - Black box warning for NSAID category: script & OTC

Figure 3. Combined analysis showing 3 separate dosing regimens in the PreSAP and APC studies.

[Graph showing hazard ratios for different dosing regimens with celecoxib and naproxen]
Cardiovascular Risk Updates

- All NSAIDs can contribute to HTN
  - Rated CV risk of various NSAIDs in 31 million patients
  - Rofecoxib- 45% increase
  - Celecoxib- 30% increase
  - Rofecoxib- 45% increase (increases w/ higher doses)
  - Indomethacin- 30% increase
  - Meloxicam- 20% increase
  - Ibuprofen- no increase at lower doses; increase w/ higher doses
  - Naproxen- slight increase at any dose
  - Celecoxib- similar to ibuprofen

2016 PRECISION Study:

CV Safety of Celecoxib, naproxen or ibuprofen

- 24,081 patients w/ RA/OA w/ increased CV risk; ASA 80mg /day allowed
- Avg /day = Celecoxib 200 mg, naproxen 875mg, ibuprofen 2045 mg
- Rx for 20 months & follow up 34 months
- Esomeprazole 20-40mg qd for all patients
- Intention to treat analysis of CV related death, nonfatal MI/CVA
- Celecoxib 2.3% vs Naproxen 2.5% vs Ibuprofen 2.7%

CONCLUSION:

- CV RISK W/ CELECOXIB AT MODERATE DOSES IS NOT GREATER THAN RISK WITH NON-SELECTIVE NSAIDS.

OTHER PRECISION OUTCOMES

- Pain control similar w/ all 3 drugs w/ small benefit w/ naproxen
- Does NOT support naproxen as safer CV side effect profile
- Serious GI events lower in celecoxib group
- Serious renal events lower in celecoxib group vs ibuprofen but not naproxen
- Hospitalization for HTN lower in celecoxib group than ibuprofen but not naproxen
- Secondary Analysis
  - COX2 superior safety profile to NSAIDs— but ASA eliminates advantage and equal safety to non-selective NSAIDs
ASA Competition w/ NSAIDS

- 600mg ibuprofen and ASA concomitantly may decrease antiplatelet effect of ASA
- NSAID irreversible effect on COX-1 in platelets
- ASA irreversible effect on COX-1 in platelets
- ASA has short half-life of 0.25-0.5hr- so short window for irreversible action on platelets
- Studies showing ibuprofen, naproxen interfere w/ ASA platelet effect
- COX-2 NSAIDs – no competition w/ ASA ( meloxicam, diclofenac, celecoxib)
- 2006 FDA recommendations
  - Ingest ibuprofen 8hr before or 30min after ASA dose
  - Naprosyn 500mg 2hr before or after ASA—WARNING?
  - COX-2 selective w/ interference as ASA acts on COX-1 ( diclofenac, celecoxib)??? reference
  - Other non-selective NSAIDs w/ same potential although studies lacking
  - Unclear w/ enteric ASA as absorption/action delayed
  - 2018 FDA added warning w/ naproxen and concomitant ASA

Renal Toxicity & NSAIDs

- Incidence of 1-5% of NSAID users (> 2.5 million patients/year)
- NSAID- induced renal disorders
  - Hemodynamically mediated AKI
  - Electrolyte and acid-base disorders
  - Acute interstitial nephritis ( AIN)
  - Papillary necrosis ( PN)
- Main mechanisms
  - Functional & inflammatory
  - COXs locally produced at multiple sites in kidney
  - Vasodilation pre-glomerulus and peritubular capillaries
  - Increase renin, enhance sodium excretion, antagonize ADH
Renal Toxicity from NSAIDs

- **Functional Mechanism:** hemodynamic changes
  - COX1 - renal vasodilator—controls hemodynamics & GFR
  - Block COX1 - decrease renal synthesis of PGs effecting autoregulation of renal blood flow
  - Decrease GFR (glomerular filtration rate)—renal ischemia
- **GFR NOT PG dependent in normal renal function and hemodynamics.**
- Renal stress or poor perfusion—PG mechanisms necessary to maintain renal blood flow and normal GFR

NSAID Renal Toxicity- Electrolyte Disorders

- **COX2:** promotes excretion salt & H2O (macula densa, Loop of Henle)
- Na+ retention—fluid retention/edema/HTN
  - Chronic Rx: 0.5-1Kg weight gain in healthy pts
  - Most cases resolve w/ continued therapy in 1-8 weeks (Benzon)
- NSAIDs can alter/block diuretic binding or diuretic effect
- Hyperkalemia—
  - Impair renin & aldosterone
  - Increased effect w/ ACE inhibitors/ARB drugs, K-sparing diuretics
  - Mild effect in healthy pts w/o additional risk factors
- Hyponatremia
  - Blocks ADH—increased water reabsorption—dilutional low Na

NSAID & Renal Toxicity

- **Inflammatory Mechanism:**
  - Hypersensitivity reaction — interstitial nephritis & glomerulopathy
  - Non-dose dependent, allergic type response
  - Proteinuria and leukocytes in urine (may lead to nephrotic syndrome)
- **Risk factors for renal toxicities:**
  - Chronic NSAID use
  - Multiple NSAIDs used
  - Dehydration
  - Age > 60 yr
  - Comorbid renal dz, CHF, SLE, liver dz, hypercalcemia (affects renal perfusion/ function)
  - Concurrent Medications — diuretics, ACE inhibitors, ARBs
  - Nephrotoxic drugs/contrast—heightened response w/ NSAID
NSAIDs & BONE HEALING

- Literature in early 2000s stated risk of non-union of spinal fusion/fix
- Animal studies often used
- No level 1 evidence from human studies
- Study of 9995 pts w/ humeral fix (Arthritis Rheum 2005)
- NSAID use in first 90 days significantly assoc w/ nonunion
- BUT only days 61-90 showed relationship between NSAID & nonunion
- Same relationship demonstrated w/ opioid use in days 61-90
- Suggest painful non-union fix may be cause of NSAID & opioid use

INTERVENTIONS

- Stop NSAID
- Fluid balance: replace, treat underlying disease
- Correct electrolytes if needed
- Expect recovery w/ norm creatinine in 3-7 days
  - If delayed recovery, further w/u w/ ultrasound or biopsy
- NSAID choice
  - ALL carry risk
  - Indomethacin MAY be more toxic
  - Lower risk w/ sulindac & ASA
  - ASA partial/temp effect on renal COX
- Restarting after AKI resolved
  - Cautiously if NO underlying dz, low risk factors & reversible/corrected cause

NSAID Renal Toxicity - Clinical Monitoring

- Asymptomatic till advanced injury
- Increased plasma creatinine
  - Can occur in first 3-7 days of therapy (time to reach max PG blockage)
  - Can occur at any time in therapy
- AKI: UA w/ low proteinuria (< 500 mg/day), no hematuria, maybe hyaline casts
- ATN: UA w/ epithelial cell casts, granular casts, WBCs, WBC cell casts
- Meta-analysis of 114 trials (116,000 pts) suggests heterogeneity among NSAIDs w/ renal effect
  - Celecoxib lower risk than other NSAIDs (RR 0.83)

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NSAIDs & BONE HEALING

- Systematic review of 138 studies (Sivaganesan, Eur Spine J, 2017)
  - Studies after 2005 show use < 2 weeks postop w/o effect on non-union
  - Particularly low risk x 48 hr use postop
- Systematic review of 38 yr literature & 12,895 pts (J Clin Anesth, 2018)
  - Overall study quality low w/ conflicting data; RCTs needed
  - Human trials w/ NO strong evidence of NSAIDs increasing non-union after fx or fusion
  - Animal & human tissue studies
  - Short perioperative use not deleterious

Liver Toxicity

- Drug induced liver injury (DILI)
  - Less common than other toxicities but less studied
- U.S. Registry of drug induced liver injury 2016 report
  - 1221 cases reviewed
  - 30 cases assoc w/ 8 different NSAIDs (2.45%)
  - Mean onset 67 days post NSAID start
  - Hepatocellular injury most common pattern (70%) vs autoantibodies (30%)
  - Diclofenac most frequently implicated
  - Caution/avoid w/ liver disease
  - Increase variceal bleeding risk
  - Contribute to diuretic resistant ascites

Topical NSAIDs

- Comparable efficacy to oral NSAIDs w/ OA, musculoskeletal pain in RCTs and meta-analysis
  - For 50% pain relief w/ diclofenac over 8-12 weeks
  - Faster onset w/ enteric coated
  - Topical NSAIDs separated out in some studies - Slightly less effective
- Topical absorption varies
  - Ethyl salicylate 21% - diclofenac 6% - ibuprofen 6% - ketoprofen 1% - salicylic acid 1-23%
- Evidence for accumulation in target tissues: synovium, fascia, muscles, ligaments
  - Diclofenac 10-20 x higher in synovial tissue than plasma
  - Lower toxicity profile
  - Blood level w/ topical 0.4-2.2% of blood level w/ po diclofenac
  - No GI harm or renal failure noted
  - Improved tolerability
  - Mild skin rash - most common side effect
NSAID vs Opioids; which is better?

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>OPIOIDS</th>
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<tbody>
<tr>
<td>Side Effects</td>
<td>Y; increase w/ use</td>
</tr>
<tr>
<td>Major Organ toxicity</td>
<td>N</td>
</tr>
<tr>
<td>Observable early S/S of toxicity</td>
<td>Often NO</td>
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<tr>
<td>Fluid/Electrolyte imbalance effect</td>
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<td>Life-threatening toxicities</td>
<td>Y; (bleeding, MI, CVA, renal failure)</td>
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<tr>
<td>Substance Use Disorder Risk</td>
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NSAID AS FRENEMY!

KNOW HOW TO USE IT & WHEN NOT TO USE IT!

- Effective Analgesic
- Anti-inflammatory
- Non-narcotic
- Non-serious & serious side effects
- Helpful in acute nociceptive pain
- Unlikely to replace opioids for chronic pain
- Adjunctive use helpful
- Limited effect on neuropathic pain
- Best use: time limited, dose limited, patient selection, monitored side effects

References

Available on request