NSAIDs: Friend or Foe in the Battle against Pain?

Presented by
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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
- 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 (PG) - lipids derived from acids: i.e. arachidonic (AA), linoleic, others
- PGs have Variety of functions
  - Constitutive
    - GI mucosal protection
    - Kidney function
  - Trauma response
    - Cell membrane trauma releases AA & COX enzyme converts to PGs → inflammation
    - PerIPHERAL & CENTRAL sensitization of nociceptors to mechanical & chemical stimuli
  - Pyretic response
    - PGs rise in CSF w/ pyrogen introduction
    - Although not an NSAID, acetaminophen blocks brain PG synthetase (COX3 inhibition)

Cyclo-oxygenase (COX): “The Convertors”

- Cyclo-oxygenase 1 & 2 = isoenzymes that convert AA to PGs (i.e. 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
    - Can be induced under stress

More Cyclo-oxygenase (COX) Specifics

- COX2
  - Regular expression in CNS (regulates brain injury/inflammation) & kidney
  - Also induced by trauma, endotoxins, neurotransmitters, cytokines, growth factors, hormones, etc
  - Promotes inflammation
    - Both peripheral inflammation & central actions
    - Increases electrical nerve activity (blunted w/ neural blockade & COX-2 inhibitors)
    - Humoral (biochemical) signal raises COX2 in CNS when inflammation occurs
      (blunted only by COX2 inhibition in CNS)
  - May help heal gastric ulcers
NSAID Class Characteristics

- Highly protein bound -
  - Hemodialysis does not remove them
  - Hypoalbuminemia will increase circulating level
- Effective analgesics - many studies
  - Opiate sparing (25-50% less opioid when NSAID used)
  - Multifocal 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 in NSAIDs is a continuum - not an absolute

### Relative COX Selectivity

<table>
<thead>
<tr>
<th>5-50 fold COX-2 preference</th>
<th>&lt; 5 fold COX-2 preference</th>
<th>COX-1 Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etodolac</td>
<td>Diclofenac</td>
<td>Fenoprofen</td>
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<tr>
<td>Meloxicam</td>
<td>Sulindac</td>
<td>Ibuprofen</td>
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<tr>
<td>Celecoxib</td>
<td>Meclofenamate</td>
<td>Tolmetin</td>
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<td>Naproxen</td>
<td>Diflunisal</td>
<td>Algin</td>
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<td>Piroxicam</td>
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<td>Ketoprofen</td>
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<td>Ketorolac</td>
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<td>Flurbiprofen</td>
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### Chemical Grouping of NSAIDs

<table>
<thead>
<tr>
<th>Acetylated salicylates</th>
<th>Non-acetylated salicylates</th>
<th>Propionic Acids</th>
<th>Acetic Acids</th>
<th>Oxicams (Eenic acids)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Diflunisal</td>
<td>Naproxen</td>
<td>Diclofenac</td>
<td>Meclofenamate</td>
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<tr>
<td>Choline-Mg Trisalicylate</td>
<td>Ibuprofen</td>
<td>Diclofenac</td>
<td>Proxocam</td>
<td>Mefenamic acid</td>
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<tr>
<td>Salicylate</td>
<td>Ketoprofen</td>
<td>Indomethacin</td>
<td>Mefenamic acid</td>
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<td>Flurbiprofen</td>
<td>Tolmetin</td>
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<td>Oxicam</td>
<td>Sulindac</td>
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<td>Ketorolac</td>
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**NSAID TOXICITIES**

- NSAIDs implicated in nearly 25% of all ADRs (mild to serious)
- Most common GI irritation: dyspepsia
- More serious: 5-7% of hospital admission due to adverse effects of drug
  - 11-12% of those admissions due to NSAIDs
  - 10% of those admissions due to NSAIDs
- Often cited > 100,000 hospitalizations and > 16,000 deaths/yr in US
- Based on 1999 obs study (ARAMIS) - found 19 NSAID bleeding deaths
- Inaccurate extrapolations to general population
- 2004 study = 3,200 deaths/yr NSAID GI bleeding (Garone et al., Am J Ther)
- 2010 study (Solomon et al, Arch Intern Med)
- Nonselective NSAID mortality 48/1000 person yrs
- Opioid mortality 75/1000 person yrs

**NSAID OVERDOSE & TOXICITY**

- Toxic incidence likely to increase per CDC
- Aging population w/ increases in degenerative & inflammatory conditions
- Potential increase as opioid alternatives
- Acute overdose (accidental or intentional) of single large dose
  - Typically well tolerated
  - May cause n/v, drowsiness, blurred vision, dizziness - rarely serious
- Chronic use ⇒ most toxicities

**Toxicity #1 - Hematologic**

- COX-1 converts AA to PGs
- PG in platelets = Thromboxane A2 (TXA2) - activates platelets & vasoconstricts
- PGs in vascular endothelium - inhibits platelets & vasodilates
- ASA irreversibly inhibits COX-1 action - inhibits platelet aggregation
- Platelets vulnerable to COX-1 inhibition as cannot regenerate PGs like other cells
- Effects last for life of platelet (7-10+ days)
- Non-selective NSAIDs reversibly inhibit COX-1 = transient effect
  - Single dose Ibuprofen 300-900mg inhibits platelet aggregation x 2 hr
  - Effect completely gone in 24hr
- Piroxicam - can last several days after discontinuation
Toxicity #1 - Hematologic

- Possible bleeding risk w/ platelet inhibition
  - NSAIDs w/ lower platelet effect
    - Non-acetylated (diflunisal, choline Mg trisalicylate, salsalate)
    - COX-2 (celecoxib)
  - No COX-2 activity found in platelets

- Neutropenia and aplastic anemia - rare (<1% of NSAID users)
  - Indomethacin associated w/ higher risk

NSAIDs & Peri-Op Bleeding Risks

- Studies showing higher postop bleeding risk
  - w/ nonautosed tissues - i.e. tonsillectomy, joint replacement
  - NSAIDs w/ 1/2 life > 6hr
  - NSAIDs given before surgical control of bleeding

- Many studies historically w/ low risk peri-operative bleeding
  - 1986-87: no difference in THA/TURP w/ diclofenac vs placebo (Lindgren, Acta Anaes Scan; Bricker et al, Eur J Anesth)
  - 2000: indomethacin w/ anorectal surgery - no increase in bleeding (Coloma et al., Anesth Analg)
  - 2009 meta-analysis variety surgeries show slight increased risk w/ NSAIDs (Meylan et al., J Anesth)

- Pre-Op Stoppage of NSAID
  - Gen rule—Hold NSAID 3 days to normalize Platelet function
  - Ibuprofen effect gone in 24 hr
  - ASA: stop at least 1 week

NSAIDs & Rx Combo Bleeding Risks

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

- Rx Combination Risks
  - Post MI study 2 groups; clopidogrel, ASA or warfarin with and without added NSAID
  - Bleeding risk doubled w/ NSAID addition
  - Bleeding risk seen as early as 1st three days of NSAID use
  - CAUTION w/ NSAID Rx w/ other anticoagulants (avoid, limit dose/duration)
Toxicity #2 -- GI Effects

- ADRs - range of dyspepsia, gastric/duodenal ulcers and GI bleeding
- Pathophysiology of Gastric damage
  - NSAID w/ 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
  - 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 ulcers/bleeding
  - Ulcers & bleeding due to systemic effect, small topical effect on mucosa

Gastro-duodenal Toxicity

- ASA - 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
- Other NSAIDS - even transient COX inhibition damages 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 (not due to COX inhibition)
  - H2 blockers may help (but not w/ gastric damage)
- H. pylori infection - independent AND synergistic risk of ulcers w/ NSAIDs

Risk & NSAID Gastro/duodenal Toxicity

Am College of Gastroenterology (ACG) 2009

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Stratification</th>
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<tbody>
<tr>
<td>Hx of Uncomplicated Ulcer</td>
<td>HIGH - Hx of complicated ulcer OR ≥ 3 risk factors</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>MOD+ - ≥ 2 risk factors</td>
</tr>
<tr>
<td>High dose NSAID (≥ 3x risk)</td>
<td>LOW+ - zero risk factors</td>
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<tr>
<td>Meds: Concurrent use of ASA (any dose) glucocorticoids, anticoagulants, (includes anti-platelet, warfarin, heparin, direct thrombin &amp; factor Xa inhibitors)</td>
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OTHER RISK FACTORS (beyond ACG table)

- Unrepaired H. pylori infection
- Chronic use (2004 meta-analysis = avg 84 days before s/s toxicity)
- Concurrent use SSRIs (platelet serotonin effect inhibits activation)
- Ketonazole: 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
- COX-2 plus PPI outcomes better than other NSAIDs plus PPI
- PRECISION Study (2016)- w/ ASA use – less upper GI events w/ PPI & COX-2 vs PPI & Non-selective NSAIDs
- CONCERN Study (2017)- on ASA– Hx healed ulcers after GI bleeding; PPI w/celecoxib or naproxen
  - Recurrent GI bleed 5.6 % celecoxib and 12% naproxen
  - Risk lower but still significant for 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 (Gastro-duodenal) Risk Reduction Actions

Use COX-2; mod reduction GI bleeding compared to non-selective NSAID
- Risk still increased c/w placebo
- Low risk benefit lessened w/ concurrent low dose ASA or warfarin
- Test & treat H. Pylori—BEFORE starting NSAIDs if hx of ulcers OR long-term NSAID anticipated
- PPIs- Best Practice Advice expert opinion (Freedberg et al.,Gastroenterology, 2017)
  - If High risk for GI ulcer/bleeding — PPI as long as on 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
- Side effects- Low quality data; i.e. Vit B12 deficiency, possible Osteoporosis

PPI Potential Side Effects (low quality data)

- Bone Fracture +10-30%
- GI perforations +5%
- Malabsorption in 5%
- Myocardial infarction +1-4%
- SAEs +10-30%
- Infusions 1-30%
- Mild diarrhea 10-30%

PPI: Consult the use of PPI and side effects data.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5817415/figure/f4-jpr-11-361/?report=objectonly
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
    - i.e. Acetaminophen
  - Suspect ulceration if:
    - Unexplained blood loss/ anemia
    - Iron deficiency
    - Significant dyspepsia
    - Any i/s 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 sm bowel
- Erosions, ulcers, scars, strictures
- High Incidence
  - 53-76% in healthy short-term NSAID users; 50-71% in long-term use (>3 months)
  - While on acid suppression
  - Can occur as early as 2 weeks of use
- SBI manifestations
  - Iron deficiency anemia / occult bleeding
  - Protein-losing enteropathy/malnutrition ( permeability)
  - Recurrent abdominal pain assoc w/ strictures
  - Sm bowel diaphragm disease
  - Circular mucosal membranes divide & narrow bowel lumen– potential strictures & obstruction

Small Bowel Injury

- Lit review - Increased risk w/Oxicams & diclofenac
- NSAIDs w/ ASA more damaging than ASA alone
- Not associated w/ duration of NSAIDs OR lowered w/PPI use
- Lesions can persist > 18 months after stopping NSAID
- Prophylaxis
  - PPIs & H2- blockers shown effective w/ gastro-duodenal dz
  - PPI may worsen NSAID SBI - GI altered bacteria (Gwee et al. J Pain Res. 2018)
  - Celecoxib w/o PPI = lowered risk in some studies
  - Rebamipide (not available in US) & misoprostol co-prescription
  - Studies show prevention & enhanced healing of SBI
  - Rx for inflammatory Bowel Dz (IBD) reduces SBI
  - Novel agent- nitric oxide donors ( mucosal blood flow, bicarb secretion, mucous production)
Risk & NSAIDs; Upper & distal GI

<table>
<thead>
<tr>
<th>Risk Factors Gastro/duodenal</th>
<th>Risk Factors G2E</th>
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<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>Age &gt; 30 years</td>
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<tr>
<td>&gt; 7 days of therapy</td>
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<tr>
<td>High dose NSAID</td>
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<tr>
<td>Prior Peptic Ulcer Di/Prior NSAID toxicity</td>
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<tr>
<td>H/Pylori infection</td>
<td>Comorbidity/arthritis</td>
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<tr>
<td>Genetic polymorphisms</td>
<td>Genetic polymorphisms</td>
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<tr>
<td>Concurrent use anti-platelets, glucocorticoids, anticoagulants, SSRIs</td>
<td>Concurrent anti-platelet Rx</td>
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<tr>
<td>Use of dietietenac and celecoxib (i.e. meloxicam)</td>
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Toxicity #3 --Cardiovascular

- 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 inhibitors block PG1 only
  - Contributes to 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- Included high risk pts w/ RA but no ASA used
    - Uncertain risk w/ ASA use in high risk pts
    - Voluntarily withdrawn from market 2004

Cardiovascular Risk-Celecoxib

- Gastricoma Prevention w/ Celecoxib) APC study (2004)= 200-400mg bid x 33 mo
  - 2.3-3.4 Increase in CV events after 12 month
- PreSAP study (2002)= 380mg qod vs placebo x 32 months
  - Smaller increase in CV events
- (Alzheimer's Disease Anti-Infm Prev Trial) ADAPT study (2004)= 200mg od vs placebo
  - No increase in pg celecoxib ; but increase risk w/ naproxen
- Valdecoxib studies -- 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

(Wee et al, J Pain Research 2018)
Figure 2. Combined analysis showing 3 separate dosing regimens in the PreSAP and APC studies.

Cardiovascular Risk Updates

- All NSAIDs can contribute to HTN
  - Celecoxib w/ possible lower effect
  - Rated CV thrombotic risk of various NSAIDs in 31 million patients
  - Rofecoxib - 45% increase
  - Diclofenac - 40% 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
- 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 Study (Solomon et al, Rheum 2018)
  - COX2 has superior safety profile to NSAIDs—but ASA eliminates that advantage likely (if GI effects ?) and equalizes overall safety compared to non-selective NSAIDs

NSAID Competition w/ ASA

- 400mg Ibuprofen & ASA together may lower antiplatelet effect of ASA
- ASA irreversible effect on COX-1 in platelets
- ASA has short half-life of 0.25-0.3hr- so short window for irreversible action to occur
- Nonselective NSAIDs compete w/ ASA for binding sites on platelets
- Studies show ibuprofen, naproxen interfere w/ ASA platelet effect
- Cox-2 NSAIDs – no competition w/ ASA ( meloxicam, diclofenac, celecoxib)
- 2006 & 2016 FDA recommendations
  - Ingest Ibuprofen 8 hr before or 30min after ASA dose
  - Ingest Naprosyn 30 min after ASA
- COX-2 selective has NO interference (ASA acts on COX-1)
- Other non-selective NSAIDs w/ same potential- although studies lacking
- Unclear timing w/ enteric ASA as absorption/action delayed
- 2018 FDA added warning w/ naproxen and concomitant ASA

Aspirin Action Film
- Eats (receptor binding), Shoots (inhibits platelets), Leaves (short half-life)
Toxicity #4- Renal

Incidence= 1-5% of NSAID users (> 2.5 million patients/year)
- NSAID- induced renal disorders include:
  - Hemodynamically mediated acute injury (AKI)
  - Electrolyte and acid-base disorders
  - Acute interstitial nephritis (AIN)
  - Papillary necrosis (PN)
- 2 main mechanisms of injury
  - Functional & inflammatory
  - COXs locally produced at multiple sites in kidney
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Functional Mechanism- hemodynamics

- COX (more COX1) = renal vasodilator -- controls hemodynamics & GFR
- Block COX1 = decrease renal synthesis of PGs affecting autoregulation & renal blood flow
- Decreases GFR (glomerular filtration rate)
- Renal ischemia
- GFR NOT PG dependent in normal renal function, & normal hemodynamics
- Renal poor perfusion -- PG mechanisms necessary to maintain renal blood flow and normal GFR
- i.e dehydration, AKI, CHF, cirrhosis

NSAID & Renal Electrolyte Effects

- COX (More COX2) - promotes excretion salt & H2O
- Na+ & Fluid retention / COX2 blockade = edema/HTN
- Chronic NSAID Rx = 0.5-1Kg weight gain in healthy pts
- Fluid retention usually resolves w/ongoing NSAID in 1-8 weeks
- NSAIDS can alter/block diuretic binding or diuretic effect

Hyperkalemia

- NSAIDs impair renin & aldosterone secretion
- Mild effect in healthy pts w/o additional risk factors
- Increased effect in AKI
- Increased effect w/ ACE inhibitors/ARB drugs, K-sparing diuretics

Hyponatremia (Uncommon)

- NSAIDs enhance ADH -- increased water reabsorption -- dilutional low Na
- Clinical effect if underlying ADH conditions (SIADH, volume depletion)
**NSAID & Renal Toxicity**

**Inflammatory Mechanism**
- Interstitial nephritis & glomerulopathy = Hypersensitivity reaction
- Non-dose dependent, allergic type response
- Proteinuria and leukocytes in urine (may lead to nephrotic syndrome)

**Summary of Risk Factors for renal toxicities**
- Chronic NSAID use
- Multiple NSAIDs used
- Dehydration
- Age > 60 yr
- Comorbid renal dz, CHF, Lupus, liver dz, hypercalcemia affects renal perfusion
- Concurrent Medications -- diuretics, ACE inhibitors, ARBs (inhibit \( vasoconstriction \) w/ low volume states = renal ischemia risk)
- Nephrotoxic drugs/contrast- heightened response w/ NSAID

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**NSAID Renal Toxicity - Clinical Monitoring**

- Asymptomatic till advanced injury
- Monitor for 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
- Monitor UA
  - 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(116,00 pts) suggests heterogeneity among NSAIDs w/ renal effect
  - Celecoxib lower risk than other NSAIDs ( RR 0.83)

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**Renal Toxicity INTERVENTIONS**

- Stop NSAID
- Fluid balance- replace, treat underlying disease
- Correct electrolytes if needed
- Expect AKI recovery w/ norm creatinine in 3-7 days
- If delayed recovery, further w/ ultrasound or biopsy
- NSAID choice
  - ALL carry risk
  - Indomethacin MAY be more toxic
  - Lower risk w/ sulindac & ASA & possibly celecoxib
  - ASA partial/temp effect on renal COX
- Restarting NSAID after AKI resolved
  - Cautiously if NO underlying dz, low risk factors & reversible/corrected cause
    (i.e. dehydration)
Toxicity #5 --Liver

- 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)
  - 30 cases assoc w/ 8 different NSAIDs (2.45% of all cases)
  - Mean onset 67 days post NSAID start
  - Hepatocellular injury most common pattern (70%) vs autoantibodies (30%)
  - Diclofenac most frequently implicated
  - Caution/avoid w/ advanced liver disease
  - Increases variceal bleeding risk
  - Contributes to diuretic resistant ascites

Toxicity #6 --BONE HEALING

- Literature in early 2000s stated risk of non-union of spinal fusion/fx
  - Animal studies often used
  - No level 1 evidence from human studies
- Study of 9995 pts w/ humeral fx (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 fx may be cause of NSAID & opioid use

NSAIDs & BONE HEALING

- Systematic review of 138 studies (Sivaganesan, Eur Spine J, 2017)
  - Studies after 2005 show use < 2weeks 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
A Word on Topical NSAIDs

- **Comparable efficacy** to oral NSAIDs w/OA/musculoskeletal pain in RCTs and meta-analysis (Rannou et al, Sem Arth Rheum 2016)
  - 50% pain relief in OA w/diclofenac over 8-12 weeks
  - Number needed to treat (NNT) 6 for solution & 11 for gel formulation
  - Ketoprofen recent studies failed to show benefit over placebo
  - Topical salicylates separated out in some studies - Slightly less effective

- **Variable topical absorption rates through skin**
  - Etodolac (21%), diclofenac (6%), ibuprofen (5%), ketoprofen (1%), salicylic acid (1-2%)
  - Evidence for accumulation in target tissues - synovium, fascia, muscle, ligament
  - Diclofenac 10-20x higher in synovial tissue than plasma w/topical use

- **TOPICAL NSAIDs**
  - Use may lower po NSAID use
  - Study 3500 pts w/40% reduction in po NSAID w/top etofenamate
  - Lower toxicity profile
    - Blood level w/topica/3.4-2.2% of blood level w/po diclofenac
    - No GI harm or renal failure noted
  - Improved tolerability
    - Mild skin rash most common side effect
  - American College of Rheumatology
    - Strongly recommended over po NSAID for patients > 75 yrs

### NSAID vs Opioids: which is better?

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<tr>
<th></th>
<th>NSAIDs</th>
<th>OPIOIDS</th>
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</thead>
<tbody>
<tr>
<td><strong>Side Effects</strong></td>
<td>Y (increase w/use)</td>
<td>Y (decrease w/use)</td>
</tr>
<tr>
<td><strong>Major Organ toxicity</strong></td>
<td>Y (GI, kidney, liver, CV)</td>
<td>N</td>
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<tr>
<td><strong>Obscurable early S/S of toxicity</strong></td>
<td>Off/na</td>
<td>Y (sedation)</td>
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<tr>
<td><strong>Fluid/Electrolyte imbalance effect</strong></td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td><strong>Use-threatening toxicities</strong></td>
<td>Y (bleeding, MI, CV, renal failure)</td>
<td>Y (respiratory arrest/sedation)</td>
</tr>
<tr>
<td><strong>Substance Use Disorder Risk</strong></td>
<td>N</td>
<td>Y</td>
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NSAID AS FRENEMY!
KNOW HOW TO USE IT & WHEN NOT TO!

- Effective Analgesic
- Anti-Inflammatory
- Opioid sparing
- Non-serious & serious side effects
- Helpful in acute & chronic nociceptive pain
- Unlikely to replace opioids for mod/severe pain
- Adjunctive use helpful
- Limited effect on neuropathic pain
- Best use - time limited, dose limited, appropriate patient selection, monitored side effects

References
- Available on request

PCSS Mentoring Program
- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.
- PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medication-assisted treatment
- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.
- No cost.

For more information visit: pcssnow.org/mentoring
PCSS Discussion Forum

Have a clinical question?

Ask a Colleague

Educate. Train. Mentor

PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

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Educate. Train. Mentor

www.pcssNOW.org
pcss@aaap.org
@PCSSProjects

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