

### How Do NSAIDs Work?

NSAIDs have anti-inflammatory, antipyretic, analgesic and anti-platelet properties.

Goal is to inhibit the cox-mediated generation of pro-inflammatory eicosanoids and to limit extent of inflammation, pain and fever.

They do this by blocking the site in cyclooxygenase enzyme in which substrate arachidonic acid binds to

Most NSAIDs are metabolized in the liver by oxidation and conjugation to inactive metabolites which are typically excreted in urine

\*patient sensitive to one NSAID may be sensitive to any other NSAID. Studies show that meloxicam can be a good option for NSAID intolerant patients

### COX-1 Function

Contributes to homeostasis

Ongoing constitutive physiologic "house keeping", vascular homeostasis, maintenance of renal, myocardial and GI blood flow, platelet function, intestinal mucosal proliferation, antithrombogenesis

### COX-1 Inhibition

Decreases mucosal defense

Increase GI acid, and decreases GI mucus

Decreases HCO<sub>2</sub> secretion

Decreases mucosal blood flow

### Special Consideration for NSAIDs

1. Both ibuprofen and naproxen may reduce the effects of furosemide (diuretic) and may reduce the effectiveness of several antihypertensive agents

2. Indomethacin is the NSAID most likely to cause nephrotoxicity

### COX 2 Inhibitors

Due to sometimes severe GI adverse effects associated with long-term NSAID therapy, selective cox 2 inhibitors are used

Inhibition of the chemical mediators responsible for inflammation while maintaining the cytoprotective effects of the products of COX-1 activity

Meloxicam

Inhibition of COX-2 may generate some problems in wound healing, angiogenesis and the resolution of inflammation

Lower GI and renal problems

Cox 2 may induce hypertension, renal failure and cardiac failure

Naproxen has some cardioprotective properties

### Contraindication for NSAIDs (cont)

**Compromised Renal Function** NSAIDs reduce renal blood flow and therefore may further reduce renal function which may have an impact on the effects of concurrent meds and elimination of the NSAID and other meds and toxins

**Compromised Liver Function** Most NSAIDs are metabolised in liver

**Hypersensitivity** Happens more in asthmatics

### COX 2 Function

Works at the site of pain and inflammation

Source of prostacyclin- platelet stability/dilate blood vessels

### COX 2 Inhibition

Decrease pain and inflammation

Increases CV risk as it shifts the balance between platelet production TxA<sub>2</sub> and PGI<sub>2</sub>, predisposing to platelet aggregation, thrombus formation and vasoconstriction

### Salicylates

### Salicylates (cont)

A single administration of aspirin decreases for several days the amount of thromboxane that can be generated, shifting the vascular TxA<sub>2</sub>-PGI<sub>2</sub> balance toward PGI<sub>2</sub> mediated vasodilation, platelet inhibition, and antithrombogenesis

Long term use of aspirin can lead to GI ulceration and hemorrhage, nephrotoxicity and hepatic injury

Two unique toxicities of aspirin: induced airway hyperactivity in asthmatics and reye's syndrome

### NSAID Drug to Drug Interaction

### Contraindication for NSAIDs

<b>Reye's Syndrome</b>	For patients under 18 years old
<b>Pregnancy</b>	

Includes Aspirin which acts in an irreversible manner by acetylating the active site serine residue in both COX-1 and COX-2

Daily low dose aspirin is used as an anti-thrombogenic agent for prophylaxis and post event management of MI and stroke

Aspirin is antithrombogenic because of its irreversible inhibition of COX, which prevents platelets from biosynthesizing TXA<sub>2</sub>

Within an hour of aspirin, the effects of COX-1 activity on newly formed platelets is irreversibly destroyed (acetylated) therefore TXA<sub>2</sub> cannot be produced

**Wendy's LAMP** mnemonic for remembering drug interactions

**Warfarin** May increase risk of bleeding- Monitor PT and INR

**Lithium** May increase lithium plasma levels and decrease its clearance renally- need to monitor

**ACE Inhibitors** may decrease antihypertensive effects so need to monitor BP and CV function

NSAIDs increase BP and decrease effects of diuretics, ACE inhibitors and ARB which all relax blood vessels as NSAIDs inhibit COX-2 in kidneys which decreases sodium excretion due to a decrease in prostaglandins

NSAIDs may increase fluid retention and decrease blood flow to the kidneys as they block prostaglandins which dilate blood vessels and allow O<sub>2</sub> to reach kidneys

**Methotrexate** May lead to an increase in methotrexate toxicity- don't administer within 10 days of high dose methotrexate

**Probenecid** May lead to reversal or uricosuric effects



By happyfeet2020

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### Non-Selective COX 1 and COX 2 Inhibition

GI irritation due to decreased protection of gastric mucosa.- N&V, GI ulcer, diarrhea

Skin reactions - mild rash, hives, photosensitivity

Inhibition of platelet function- increase risk of bleeding

Decreased renal blood flow- decreases GFR can cause renal ischemia- look out for pts w/ renal disease

CVD risk

Respiratory- bronchospasm- look out for asthmatic pts

### Risk Factors for GI complications

Over 60 in age

history of peptic ulcer

use of anti coagulants or corticosteroids

History of pylori infection

High NSAID dose or use of two NSAIDs

Severe illness

### Reducing GI risks

**Misoprostol** Synthetic prostaglandin- Protects gastric mucosa from irritation

**Proton Pump Inhibitors** Long lasting reduction of gastric acid production

Drugs end in -"prazole"

**H2 Receptor Antagonists** Blocks the action of histamine on parietal cells in the stomach decreasing the production of acid by these cells

Drugs end in -"dine"

Not enough evidence that these alone will work in reducing GI issues

**COX-2 Inhibitor** Allow continued protective COX-1 function

### Acetaminophen

Not an NSAID

Has analgesic and antipyretic effects similar to aspirin

anti-inflammatory effects are insignificant because of its weak inhibition of COX

May be a third functional COX isoform (COX-3)

MOA believed to involve the prostaglandin pathways within the CNS with little influence on peripheral prostaglandin synthesis

Adverse effect= hepatotoxicity as it is metabolized by hepatic cytochrome p450 enzymes which produces a reactive molecule which is normally detoxified by conjugation with glutathione. An overdose of acetaminophen can overwhelm glutathione stores, leading to cellular and oxidative damage and in severe cases to acute hepatic necrosis

4000mg daily limit for adults. For those who are alcoholics or multiple medication patients and patients with liver disorders, even doses within the therapeutic range may be hepatotoxic



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