RATIONAL USE OF NSAIDS

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INTRODUCTION

- Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medicines for analgesia in primary care, after paracetamol.
- NSAID use can be associated with a range of serious adverse effects including: cardiovascular events, gastrointestinal complications, renal failure and hypersensitivity reactions.
- To maximize patient safety NSAID use requires careful consideration of individual patient risk factors.
- Prescribe all NSAIDs with caution, in all patient groups, even over short periods of time.
- Avoid prescribing long-acting formulations of NSAIDs, where possible, as these are associated with an increased risk of gastrointestinal adverse effects

RATIONAL USE OF ANALGESIC

- Osteoarthritis (NSAIDs > Acetaminophen)
- Acute migraine (NSAIDs = Acetaminophen)
- Tension headache (NSAIDs > Acetaminophen)
- Specific types of headaches (Indomethacin)
- Post ERCP pancreatitis (Diclofenac and Indomethacin suppository)
- Preterm labor (Indomethacin)
- Acute gout (Indomethacin, Naproxen > Celecoxib)
- Dysmenorrhea (NSAIDs > Acetaminophen)
- Pericarditis (Ibuprofen, Aspirin, Indomethacin)

CONTRAINDICATION OF NSAIDS

- Perioperative setting of coronary artery bypass graft surgery (CABG)
- Severe uncontrolled heart failure
- Active gastric, duodenal or peptic ulcers and inflammatory bowel disease
- Severe liver impairment
- Severe renal impairment
- Gestational age of 30 weeks
- History of life threatening allergic-type reactions after taking NSAIDs

DRUG INTERACTIONS WITH NSAIDS

- ASA (Ibuprofen and Naproxen)
- Antihypertensive medications (ACE Inh/ARBs, beta-blockers, diuretics, hydralazine)
- Hyperkalemia (spironolactone, ACE Inh and ARBs…)
- Increased risk of AKI (ACE inh/ARBs/ diuretics/ Cyclosporine/ Tacrolimus/Vancomycin, contrast media)
- Risk of bleeding (SSRIs/ Corticosteroids/antithrombotic agents)
- Lithium toxicity
- Methotrexate (chemotherapeutic dose)
- Sulfonamide cross sensitivity (Celecoxib and Meloxicam)

CASE 1

- A 60 year old female who is candidate for total knee arthroplasty (TKA) surgery because of severe osteoarthritis. The patient has been taking celecoxib 200 mg BID to control pain. Is it necessary to discontinue celecoxib prior to surgery?

NSAIDS PRIOR TO SURGERY

- On balance, we recommend discontinuing NSAIDs, including selective COX-2 inhibitors, prior to surgery.

- For most NSAIDs, platelet function normalizes within three days of discontinuation, suggesting that NSAIDs should generally be discontinued at least three days before surgery; ibuprofen can be stopped 24 hours prior to surgery.

- For patients whose pain is dramatically responsive to COX-2 inhibitors, consideration may be given to continuing these agents since they have minimal effects on platelet function.

CASE 1

- A 65 year old female who is candidate for total knee arthroplasty (TKA) surgery because of severe osteoarthritis. The patient has been taking celecoxib 200 mg BID to control pain. Is it necessary to discontinue celecoxib prior to surgery?
- Celecoxib could be continued if the risk of bleeding is not high.
- After the surgery diclofenac suppository 100 mg BID, oxycodone 5 mg BID was prescribed but her pain is not controlled. She asks if she could increase the frequency of diclofenac.
- Drugs: Enoxaparin 40 mg SC QD, Sertraline 50 mg QD
- What is the next step to control her pain?
- What should be done to lower the risk of GI blleding?

CEILING DOSE OF ANALGESICS VS. MAX DOSE OF ANTI-INFLAMMATORY

- The analgesic ceiling effect of a drug refers to the dose beyond which there is no additional analgesic effect.
- Virtually all NSAIDs relieve pain when used in doses substantially lower than those required to suppress inflammation.
- Higher doses do not provide any additional pain relief but may increase the likelihood of side effects as well as the cost of treatment.
- Although ibuprofen is commonly used in dosages as high as 800 mg for acute pain, the analgesic ceiling is only 400 mg/dose, to about 1200 mg/day. However, 2400 mg daily can relieve inflammation without providing additional pain relief.

NSAID	Analgesia ceiling dose	Inflammatory disorders max dose
Ibuprofen	1200-2000 mg	2400 (chronic)3200 mg (acute)
Naproxen	1000 mg	1500 mg
Diclofenac	100-150 mg	150-225 mg
Diclofenac XR	---	200 mg
Piroxicam	10-20 mg	20 mg
Indomethacin	---	150-225 mg
Indomethacin XR	---	150 mg
Mefenamic Acid	1000 mg	1000 mg
Ketorolac (oral)	40 mg (short-term)	---
Celecoxib	400 mg	400 mg
Meloxicam	---	15 mg
Sulindac	---	400 mg
Tolmetin	---	1800 mg

CASE 1

- After the surgery diclofenac suppository 100 mg BID, oxycodone 5 mg BID was prescribed but her pain is not controlled. She asks if she could increase the frequency of diclofenac.
- Multimodal analgesia provides superior pain relief, promotes recovery of the knee, and reduces opioid consumption and related adverse effects in patients undergoing TKA.
- Acetaminophen 1 gr TDS-QID could be added.
- The combination of paracetamol with NSAIDs may provide more effective analgesia for some patients, e.g. for post-surgical pain, than either medicine alone.

PPI PROPHYLAXIS

Table 1 GI risk factors with NSAID therapy

Patient inherent risk factors
History of GI event (ulcer, hemorrhage)
Advanced age (>65 y)
Higher disability level
Medicine-mediated risks
Glucocorticoids
Anticoagulants
SSRIs

CASE 2

- A.B. is a 54 year old male with prior history of chronic coronary syndrome and hypertension and knee osteoarthritis. He has been taking diclofenac 1% topical gel three times daily and acetaminophen 1 gr TDS hours. What is the preferred analgesic to control his pain?
- BP: 13/8
- Drug history:
- Amlodipine 5 mg QD
- Metoprolol tartrate 25 mg BID
- Aspirin 80 mg QD
- Atorvastatin 20 mg QD

NSAID IN CORONARY DISEASE

- Due to the relatively high baseline risk for cardiovascular events in patients with established disease, we try to avoid using NSAIDs, particularly long term.

- In addition, as most of these patients are taking at least one antithrombotic agent (aspirin), the potential for GI bleeding needs to be considered.

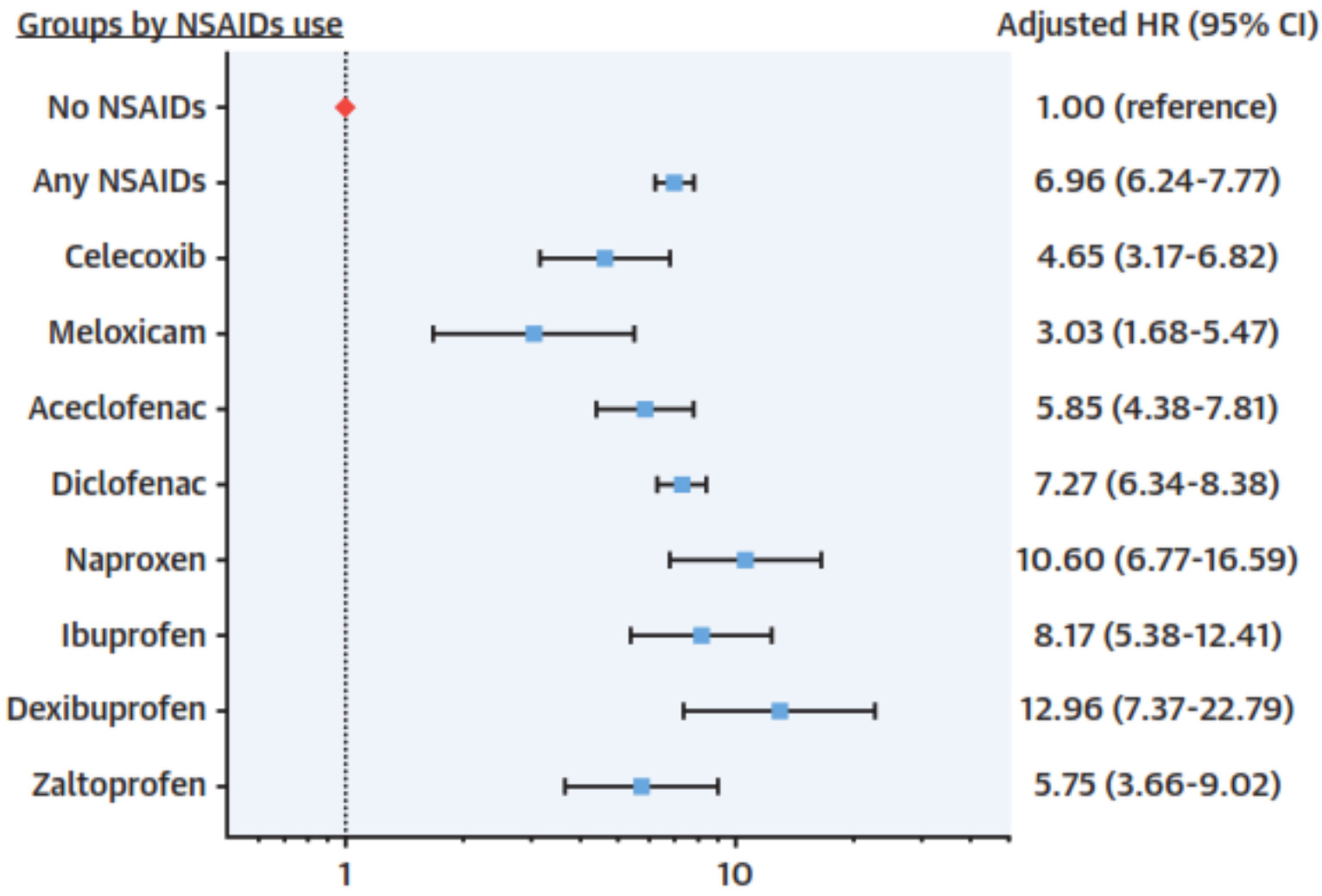
- In particular, we avoid NSAIDs in patients with recent acute MI, unstable angina, and during the perioperative period in patients undergoing coronary artery bypass surgery.

CHOICE OF NSAID IN PATIENTS WITH HISTORY OF CORONARY DISEASE

- 2015: Naproxen use (up to 1000 mg per day) does not appear to be associated with increased vascular risk, based on current evidence.
- 2016: In the PRECISION trial, no significant difference in cardiovascular safety among the three drugs evaluated (naproxen, celecoxib, and ibuprofen) was demonstrated.
- 2020: Among NSAID subtypes, the risk for cardiovascular and bleeding events was lowest with the use of celecoxib and meloxicam.

Cardiovascular Risk of Concomitant NSAIDs Treatment After MI

A Overall Population



CASE 2

- A.B. is a 54 year old male with prior history of chronic coronary syndrome and hypertension and knee osteoarthritis. He has been taking diclofenac 1% topical gel three times daily and acetaminophen 1 gr TDS hours. What is the preferred analgesic to control his pain?
- BP: 13/8
- Drug history: Amlodipine 5 mg QD, Metoprolol tartrate 25 mg BID, Aspirin 80 mg QD, Atorvastatin 20 mg QD
- Celecoxib could be an appropriate alternative.

CASE 3

- A 64 year old male with prior history of hepatitis B cirrhosis and chronic kidney disease is asking for a safe analgesic for osteoarthritis pain.
- Drug history:
- Propranolol 20 mg TDS, Furosemide 20 mg QD, Spironolactone 50 mg QD, Erythropoietin 10000 U SC weekly, Tenofovir disoproxil fumarate 300 mg q 48 hrs
- SrCr: 2 Clcr: 35 ml/min
- What is your recommendation?

NSAIDS IN LIVER DISEASE

- An increased risk of GI mucosal bleeding, variceal hemorrhage, impaired renal function, and development of diuretic-resistant ascites is seen with use of NSAIDs in patients with cirrhosis with portal hypertension.
- Most NSAIDs are metabolized by CYP and highly bound to serum albumin, increasing drug bioavailability and potential for toxicity in patients with advanced CLD or cirrhosis.
- Individual NSAIDs (eg, diclofenac) have been associated with hepatotoxicity and thrombocytopenia in general population.
- Experience with COX-2 inhibitors in patients with advanced chronic liver disease or cirrhosis is limited.

ACETAMINOPHEN IN LIVER DISEASE

- Acetaminophen is an effective and safe analgesic for most patients with chronic liver disease. Some studies suggest that up to 4 grams per day is safe.

- However, it is frequently recommended that patients with cirrhosis or advanced chronic liver disease limit acetaminophen intake to 2 grams per day.

- We typically limit acetaminophen intake to 2 grams per day for most patients, while avoiding it entirely in patients with severe alcoholic hepatitis or acute liver injury.

- In addition, we recommend that patients who drink alcohol, older adult, organ dysfunction or malnurished take no more than 2 grams per day.

CASE 4

- R.P is a 29 year old female who was referred to a rheumatologist because of moderated osteoarthritis in her hands. She works in a confectionary and she is in her 31 weeks of gestation. Before she gets pregnant she occasionally used naproxen for pain control. She asks if she could take naproxen to in pregnancy.
- What is your recommendation?

ANALGESICS IN PREGNANCY

- Chronic, severe pain that is ineffectively treated is associated with hypertension, anxiety, and depression none of which is conducive to a healthy pregnancy.
- **Acetaminophen:** has demonstrated efficacy and apparent safety at all stages of pregnancy in standard therapeutic doses.
- **Low-dose aspirin:** Overall, large trials demonstrate **low-dose aspirin's** relative safety and generally positive effects on reproductive outcomes.
- **High dose aspirin:** There are somewhat limited data regarding moderate- to high-dose aspirin, which should be avoided throughout pregnancy as well.

NSAIDS IN FIRST TRIMESTER

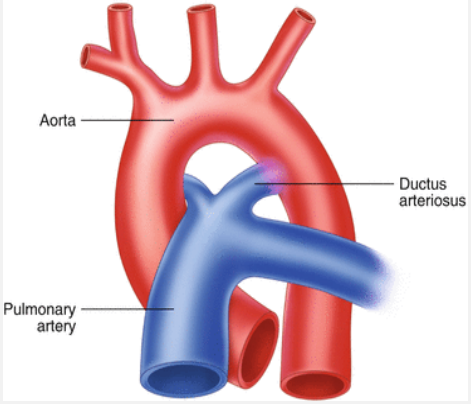
- In the first trimester, a possible modest increase in early pregnancy loss and some congenital defects has been suggested, but available evidence is limited and weak.
- To date, studies have failed to show consistent evidence of increased teratogenic effects in either humans or animals following therapeutic doses during the first trimester.
- Based on available information, NSAIDs can be continued during the first trimester of pregnancy in patients with rheumatic and musculoskeletal diseases. NSAIDs are not preferred for the acute management of migraine during pregnancy.
- The use of nonsteroidal anti-inflammatory drugs (NSAIDs) close to conception may be associated with an increased risk of miscarriage due to cyclooxygenase-2 inhibition interfering with implantation.

NSAIDS IN SECOND TRIMESTER

- **Oligohydramnios**
- Maternal administration NSAIDs after 20 weeks of gestation reduces fetal urine production and, in turn, amniotic fluid volume, potentially leading to oligohydramnios. The mechanism is enhanced vasopressin action and reduced renal blood flow. The greatest risk of oligohydramnios is with exposure >48 hours and particularly exposure for several days; amniotic fluid generally returns to normal within 24 to 48 hours of discontinuing the NSAID.

NSAIDS IN THIRD TRIMESTER

- **Constriction of the ductus arteriosus**
- Premature narrowing or closure of the ductus arteriosus can lead to pulmonary hypertension
- It has been described in gestations as early as 24 weeks but is most common after 31 to 32 weeks



- The use of NSAIDs in labor and delivery is contraindicated because it may adversely affect fetal circulation and inhibit uterine contractions. The risk of uterine hemorrhage may be increased.

NSAIDS IN LATE PREGNANCY

- The FDA has issued a drug safety communication alerting health care professionals that use of nonsteroidal anti-inflammatory drugs (NSAIDs) around 20 weeks' gestation or later in pregnancy.

- These effects are usually observed after days to weeks of NSAID use but may occur as soon as 48 hours after NSAID initiation. If NSAID use is necessary between 20 and 30 weeks of pregnancy, use should be limited to the lowest effective dose and shortest duration possible; consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours and discontinue the NSAID if oligohydramnios is found.

- NSAIDs should still be avoided after 30 weeks of pregnancy due to the risk of premature closure of the fetal ductus arteriosus.

ANSWER

- R.P is a 29 year old female who was referred to a rheumatologist because of moderated osteoarthritis in her hands. She works in a confectionary and she is in her 31 weeks of gestation. Before she gets pregnant she occasionally used naproxen for pain control. She asks if she could take naproxen to in pregnancy. What is your recommendation?
- Oral NSAIDs are not recommended.
- Six weeks later R.P gave birth to a healthy baby. She asks if she could take naproxen for pain control in breastfeeding. What is your recommendation?

NSAIDS IN BREASTFEEDING

- There is very limited information on the use of NSAIDs during breastfeeding; Limited information suggests that NSAIDs are excreted in breast milk in very small amounts.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered compatible for the treatment of rheumatic and musculoskeletal diseases in lactating patients; agents with a short half-life and established safety data in infants may be preferred.
- Maternal use of NSAIDs should be avoided if the breastfeeding infant has platelet dysfunction, thrombocytopenia, or a ductal-dependent cardiac lesion.
- Ibuprofen (extremely low levels in breastmilk, short half-life and safe)
- Celecoxib (Low levels in milk)
- Precautions should be taken, like feeding just before taking the drug.

NSAIDS IN BREASTFEEDING

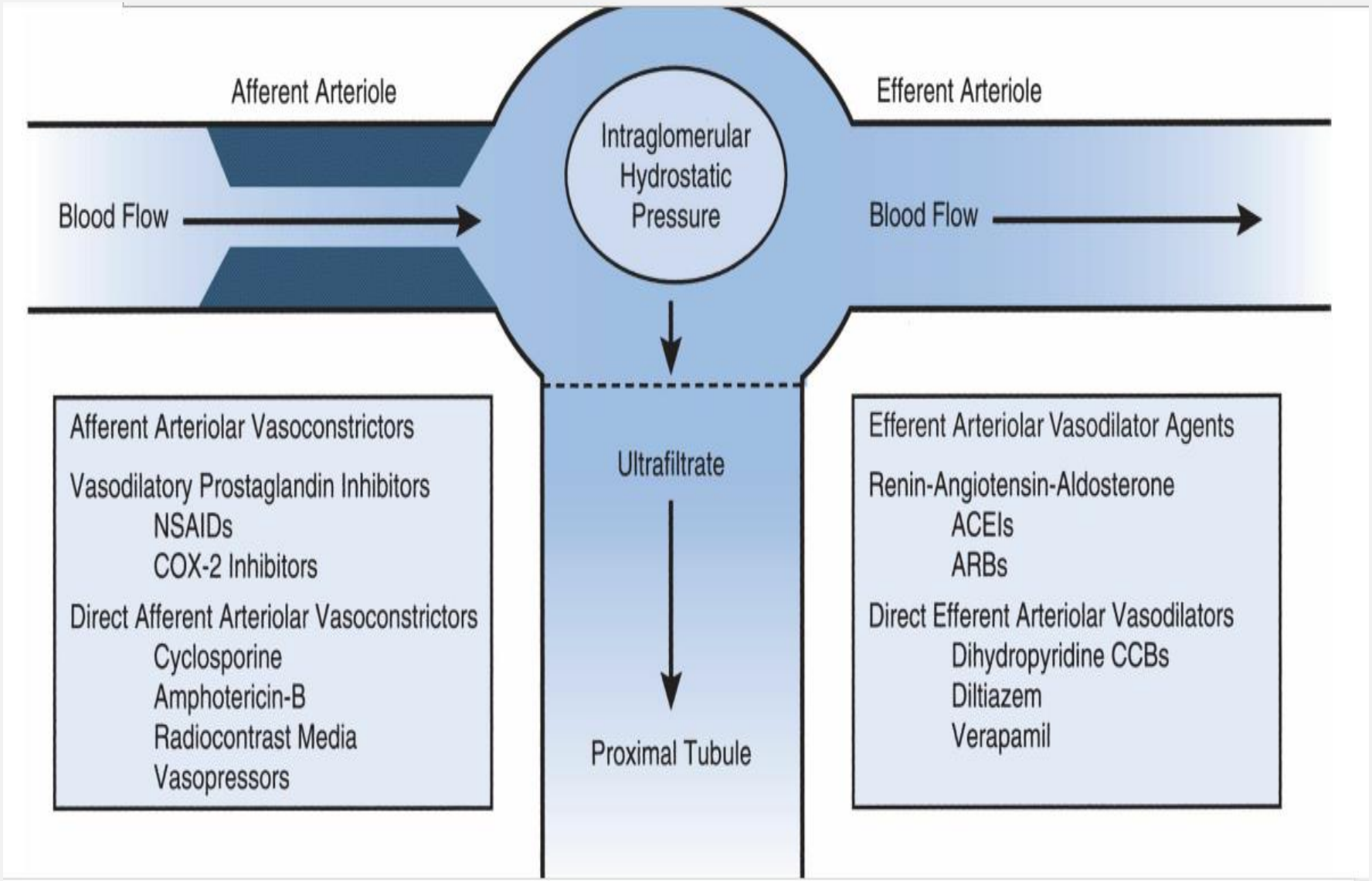
- Best to be avoided in preterm or newborn infants:
- Naproxen (low levels in milk, long half-life)
- Diclofenac (short half-life, limited data on extraction)
- Piroxicam (Limited data, long half-life)
- Mefenamic acid (Limited data, potential toxicity)
- Indomethacin (Limited data, low levels in milk, rare cases of hypertensive crisis, seizure and psychiatric problems)
- Better to use alternative agents because of limited data:
- Sulindac (Long half-life, limited data)
- Ketorolac (Long half-life, limited data)
- Meloxicam (Limited data)
- Low dose aspirin is compatible with breastfeeding
- Moderate- to high-dose aspirin should be avoided

ANSWER

- Six weeks later R.P had a baby. Now her baby is baby is 20 days old. She asks if she could take naproxen for pain control in breastfeeding. What is your recommendation?
- Limited information indicates that levels of naproxen in breastmilk are low and adverse effects in breastfed infants are apparently uncommon. However, because of naproxen's long half-life and reported serious adverse reaction in a breastfed neonate, other agents may be preferred while nursing a newborn or preterm infant.
- Ibuprofen would be a better choice.

CASE 5

- A 64 year old male with prior history of hypertension and osteoarthritis is referred for abdominal CT-scan because of suspected tumor mass. What is your recommendation to reduce the risk of acute kidney injury?
- Drug History:
- Captopril 12.5 mg TDS, Amlodipine 10 mg QD, Diclofenac XR 100 mg QD


Afferent Arteriole
Efferent Arteriole
Intraglomerular Hydrostatic Pressure
Blood Flow
Blood Flow
Afferent Arteriolar Vasoconstrictors
Vasodilatory Prostaglandin Inhibitors
NSAIDs
COX-2 Inhibitors
Direct Afferent Arteriolar Vasoconstrictors
Cyclosporine
Amphotericin-B
Radiocontrast Media
Vasopressors
Ultrafiltrate
Proximal Tubule
Efferent Arteriolar Vasodilator Agents
Renin-Angiotensin-Aldosterone
ACEIs
ARBs
Direct Efferent Arteriolar Vasodilators
Dihydropyridine CCBs
Diltiazem
Verapamil

DRUG INTERACTION AND RISK OF AKI

- Patients who are to receive intra-arterial contrast should avoid volume depletion and withhold nonsteroidal antiinflammatory agents (NSAIDs) for 24 to 48 hours prior to the procedure. Both volume depletion and NSAIDs can increase renal vasoconstriction, which increases the risk of contrast-induced acute kidney injury (CI-AKI).

- We do not withhold angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). There are insufficient data to support a benefit of withholding ACE inhibitors and ARBs, and there are risks associated with resulting hypertension.

CASE 6

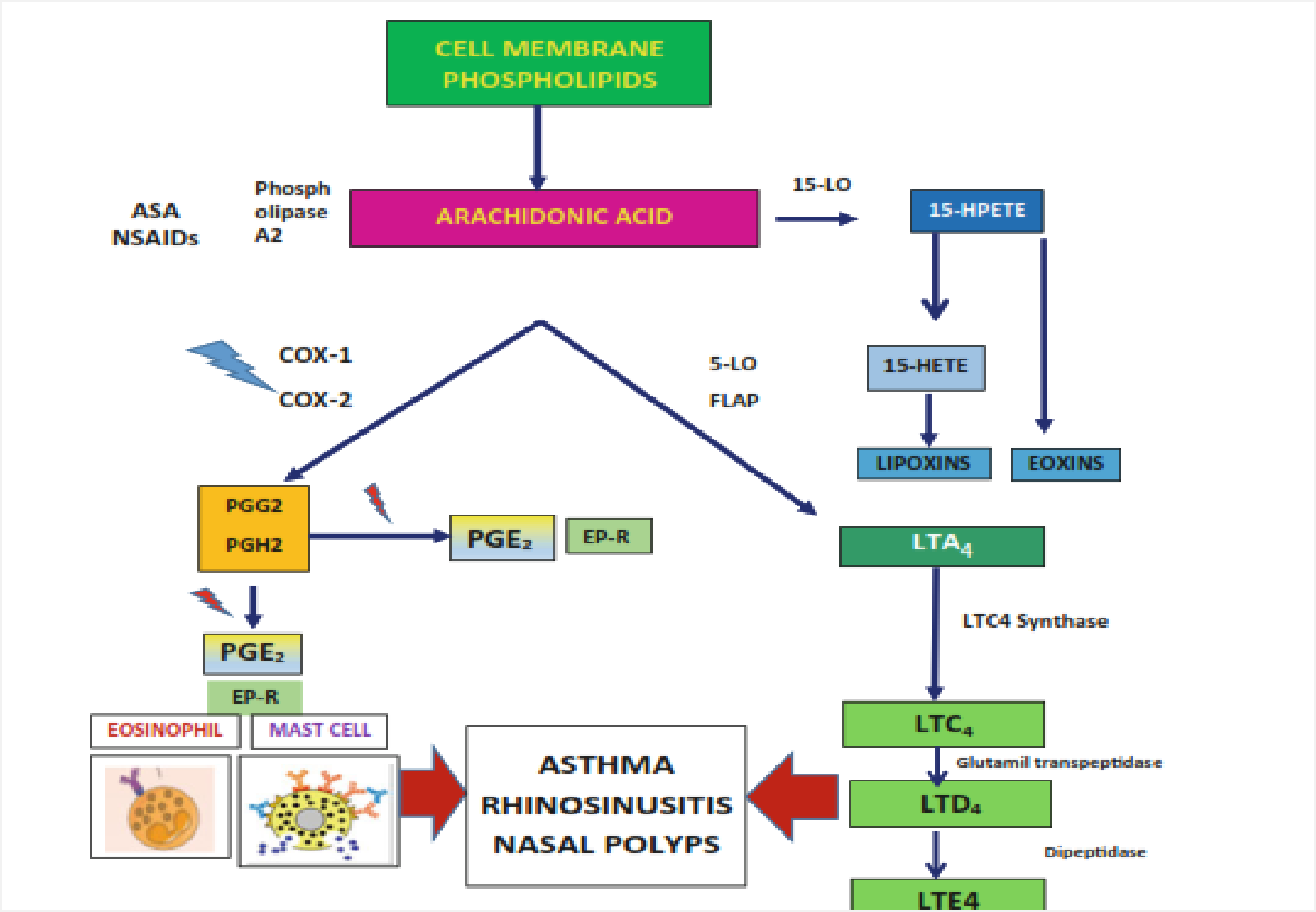
- A 34 year female with prior history of immune thrombocytopenia (ITP) and cervical osteoarthritis asks if she could NSAIDs for pain control.
- Platelet count: 110,000 (150,000-400,000)
- Is it safe to administer NSAIDs in this patient?
- What is the preferred NSAID?

NSAIDS IN THROMBOCYTOPENIA

- NSAIDs exert antiplatelet effects through inhibition of the cyclooxygenase (COX)-1 isoform, 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.
- NSAIDs should be avoided in patients with preexisting qualitative or quantitative platelet defects (eg, due to uremia or von Willebrand disease) and in those with thrombocytopenia (platelet count <50,000/microL).
- Selective COX-2-inhibiting agents are safer therapeutic alternatives in these patients.

CASE 7

- A 52 year old female with history of asthma is diagnosed with osteoarthritis of knee. Naproxen 500 mg BID is prescribed for pain control. Three hours after ingestion of naproxen she feels shortness of breath. She also has a history of aspirin-induced asthma exacerbation.
- What alternatives could be prescribed for the patient?


CELL MEMBRANE PHOSPHOLIPIDS
ASA NSAIDs
Phosph olipase A2
ARACHIDONIC ACID
15-LO
15-HPETE
15-HETE
LIPOXINS
EOXINS
COX-1
COX-2
5-LO
FLAP
PGG2
PGH2
PGE2
EP-R
LTA4
LTC4 Synthase
PGE2
EP-R
EOSINOPHIL
MAST CELL
LTC4
Glutamil transpeptidase
LTD4
Dipeptidase
LTE4
ASTHMA
RHINOSINUSITIS
NASAL POLYPS

PSEUDOALLERGIC REACTIONS

- NSAID reactions can be categorized as either pseudoallergic or allergic. Pseudoallergic reactions are nonimmunologic reactions that are related to the cyclooxygenase 1 (COX-1)-inhibiting properties of the drug.
- In susceptible individuals, these reactions may be elicited by any NSAID that inhibits COX-1, including aspirins. Pseudoallergic reactions are induced by multiple different NSAIDs.

- Type 1: NSAID-induced asthma and rhinosinusitis
- Type 2: NSAID-induced urticaria/angioedema in patients with chronic urticaria
- Type 3: NSAID-induced urticaria/angioedema in asymptomatic individuals
- Type 4: Mixed respiratory andcutaneous reactions in asymptomatic individuals

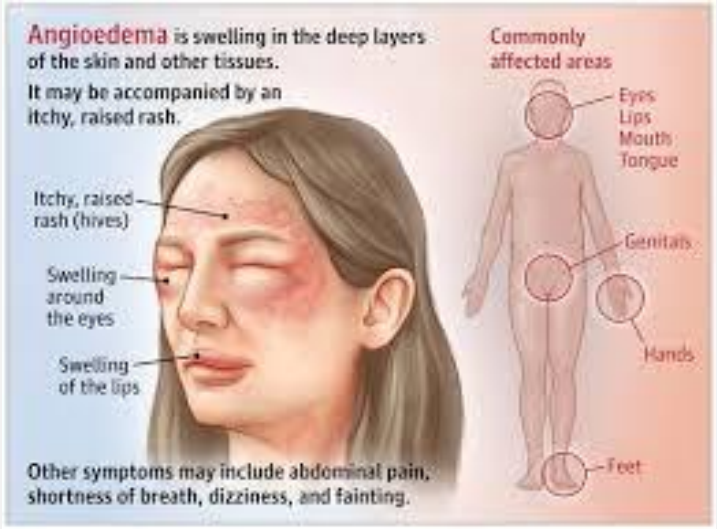
PSEUDOALLERGIC REACTIONS

- For treatment of minor pain, most patients can safely receive doses of acetaminophen up to 650 mg per dose.

- Highly selective COX-2 inhibitors (e.g. Celecoxib) are tolerated by most patients with pseudoallergic reactions to NSAIDs.

CASE 8

- A 20 year old female with no past medical history presented with swelling (edema) of face, and tongue, pruritis and hives 30 minutes after ingestion of ibuprofen.
- What is your recommendation?
- What other alternative analgesics could be used in this patient?



ALLERGIC REACTIONS

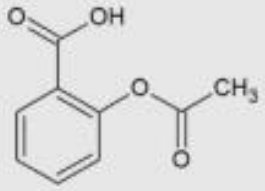
- Allergic reactions to NSAIDs range from urticaria/angioedema to life-threatening anaphylaxis.
- In contrast to pseudoallergic reactions, these reactions are elicited by a single NSAID or rarely by more than one agent with similar molecular structures.
- Patients with allergic reactions to an NSAID have had at least one prior exposure to the culprit drug, which presumedly sensitizes them and results in symptoms upon repeat exposure to the same drug
- Type 5: Urticaria/angioedema to a single NSAID
- Type 6: Anaphylaxis to a single NSAID (not ASA)

ALLERGIC REACTIONS

- Is the reaction elicited by one NSAID or multiple NSAIDs?
- It is important to discern if the patient took any other cyclooxygenase 1 (COX-1)-inhibiting NSAIDs subsequent to the first recognized reaction. If so, did this drug also cause a reaction?
- Is there underlying asthma/rhinosinusitis/nasal polyposis (ie, aspirin-exacerbated respiratory disease [AERD]) or chronic idiopathic urticaria?
- Referral to an allergist/immunologist with expertise in drug allergy
- Once a definitive diagnosis has been made, patients may safely take NSAIDS that are structurally dissimilar to the drug that caused the initial reaction

Salicylates

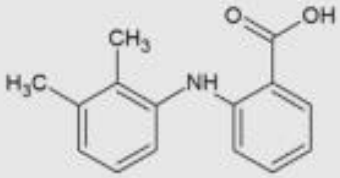
Aspirin
Diflunisal



Aspirin

Fenamates

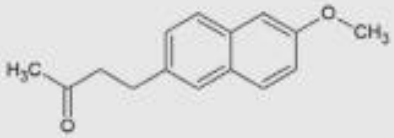
Mefenamic acid
Meclofenamate
Flufenamic acid



Mefenamic acid

Alkanones

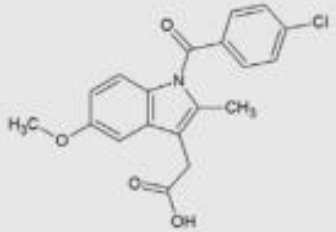
Nabumetone



Nabumetone

Acetic acid derivatives

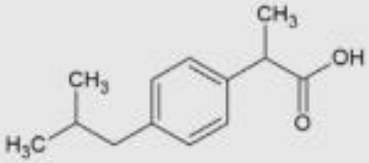
Indomethacin
Etodolac*
Diclofenac



Indomethacin

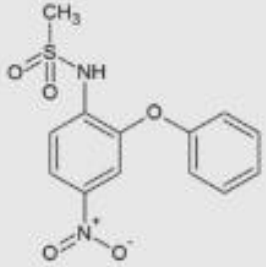
Propionic acid derivatives

Ibuprofen
Naproxen
Oxaprozin



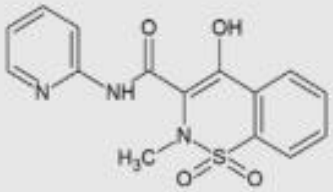
Sulfonanilides

Nimesulide*



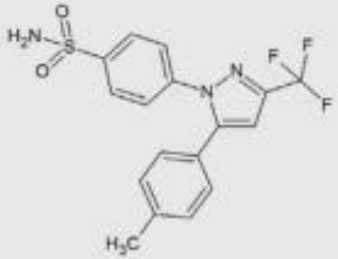
Enolic acid derivatives

Piroxicam
Meloxicam*
Tenoxicam



Diaryl heterocyclic

Celecoxib*
Etoricoxib*



CASE 9

- A 44 year old female, with no past medical history is referred to take urine drug test. Her employer wants to check if she has recently used illegal drugs. Today she experienced back pain and she wants to take ibuprofen to control the pain. She is concerned if the urine drug test could be affected by taking her medications.
- What is your recommendation?

TABLE 3

Common Medications That Can Cause False-Positive Results on Urine Drug Testing

Drug	Cross-reactive medications/substances
Amphetamines	Amantadine, benzphetamine (Regimex), bupropion (Wellbutrin), chlorpromazine, clobenzorex (not available in the United States), desipramine, dextroamphetamine, ephedrine (Akovaz), fenproporex (not available in the United States), isometheptene (component of Prodrin), labetalol, levomethamphetamine (active ingredient in some over-the-counter nasal decongestant inhalers), methamphetamine, 3,4-methylene-dioxymethamphetamine (MDMA), methylphenidate (Ritalin), phentermine (Adipex-P), phenylephrine, promethazine, pseudoephedrine, ranitidine (Zantac), selegiline (Elde-pryl), thioridazine, trazodone, trimethobenzamide (Tigan), trimipramine (Surmontil)
Benzodiazepines	Oxaprozin (Daypro), sertraline (Zoloft)
Cannabinoids	Dronabinol (Marinol), efavirenz (Sustiva), hemp-containing foods, proton pump inhibitors, tolmetin and other nonsteroidal anti-inflammatory drugs
Cocaine	Coca leaf tea, topical anesthetics containing cocaine
Opioids	Dextromethorphan, heroin, quinine, quinolones, rifampin, verapamil
Phencyclidine	Dextromethorphan, diphenhydramine (Benadryl), doxylamine, ibuprofen, ketamine (Ketalar), meperidine (Demerol), thioridazine, tramadol, venlafaxine

Adapted with permission from Smith MP, Bluth MH. Common interferences in drug testing. Clin Lab Med. *2016;36(4): 665-666.*

KEY POINTS

- For patients with severe organ failure (kidney failure, liver failure) acetaminophen (max dose: 2 gr/day) is recommended.
- Maximum analgesic effect of ibuprofen appears at 1200 mg/day
- Maximum anti-inflammatory effect of ibuprofen appears at 2400 mg/day.
- Avoid NSAIDs 24-48 hours before Contrast CT-scan because of the risk of acute kidney injury.
- NSAIDs are not recommended after 20 weeks of gestation.
- Clinically significant interactions with NSAIDs (Lithium, MTX, anticoagulants and anti-platelet agents)
- Ibuprofen is considered safe in breastfeeding.


THANK YOU
FOR YOUR ATTENTION