

NSAIDS - non-salicylates

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Learning Objectives:



1. Learn the main **differentiating** property, use or side effect for the non-steroidal aspirin substitutes.
2. Understand concerns for toxicity of NSAIDs in those with compromised renal or liver function.

I. General Use



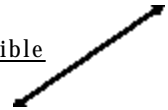
A. Similarities to aspirin

1. anti-inflammatory (inhibit PG synthesis)
2. analgesic,
3. antipyretic
4. antithrombotic

B. They differ from aspirin in that they **may**

1. produce fewer or more side effects,
2. have greater tissue distribution,
3. be more potent and
4. have a longer duration.

Unlike aspirin, they are reversible inhibitors of cyclooxygenase.



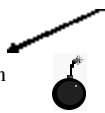
TOXICITY CONCERNS



Individuals who are allergic to aspirin will be allergic to other NSAIDs that inhibit cyclooxygenase.

Some NSAID aspirin substitutes produce fewer side effects compared to ASA (e.g. selective COX-2 inhibitors - less stomach upset).

NSAIDs should be used with caution in individuals with reduced renal or liver function.



NSAIDs can **decrease** GFR in those with renal failure, congestive heart disease or cirrhosis of the liver.



NSAIDs can produce idiosyncratic interstitial nephritis in a small population who are simply "allergic" to the NSAID.



Also NSAIDs can complicate anti-hypertensive therapy;



in some patients they can decrease renal function and excretion, which tends to increase blood pressure.

The elderly may quickly develop impaired renal function from NSAIDs.



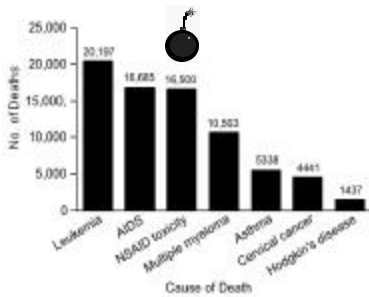
Older patients may also have fluid retention exacerbating heart failure and hypertension.

The elderly also have a significantly higher rate of NSAID-induced GI bleeding compared to age-matched controls not receiving NSAIDs, and often are asymptomatic.

Additionally, memory loss and other cognitive impairments occasionally occur in the elderly.



MORTALITY DATA FOR SEVEN SELECTED DISORDERS IN 1997. A TOTAL OF 16,500 PATIENTS WITH RHEUMATOID ARTHRITIS OR OSTEOARTHRITIS DIED FROM THE GASTRO INTESTINAL TOXIC AFFECTS OF NSAIDS. DATA ARE FROM THE NATIONAL CENTER FOR HEALTH STATISTICS AND THE ARTHRITIS, RHEUMATISM, AND AGING MEDICAL INFORMATION SYSTEM. (N. ENGL. J. MED 340: 1888-1899, 1999)



Ranking of NSAIDs on Basis of Adverse Reaction and Deaths per Million Prescriptions



Serious reactions/million prescriptions during the first years of marketing.

Azopropazone	87.9
Fenbufen	69.4
Piroxicam	68.1
Sulindac	54.3
Diflunisal	47.2
Fenoprofen	43.7
Naproxen	41.1
Diclofenac	39.4
Ketoprofen	38.6
Flurbiprofen	35.8
Ibuprofen	13.2

Ref:BMJ 292 May 1996

Learning Resources: Drugs to Remember:



1. Indomethacin
2. Sulindac
3. Diclofenac
4. Ibuprofen
5. Naproxen
6. Piroxicam
7. Oxaproxin
8. Ketorolac
9. Celecoxib
10. Rofecoxib



FYI

PHENYLBUTAZONE (BUTAZOLIDIN)

- An older effective anti-inflammatory agent (available since 1949)
- Was once widely used to treat inflammation associated with rheumatoid arthritis
- Long-term use is limited due to significant side effects such as: gastric distress, allergies, skin rashes, ulcer formation, liver and renal dysfunction, and severe abnormalities in various types of blood cells
- Half-life is quite long (~ 2 days)
- Rarely used in USA, more use in veterinary medicine (horses) and in Europe
- Use from theft from veterinary offices



Ibuprofen (Motrin) (OTC - Advil, Nuprin, Medipren, etc.)

Less anti-inflammatory activity (AIA) than indomethacin, analgesic, antipyretic, well absorbed,

99% plasma protein bound, $t_{1/2}=2$ hrs.



dysmenorrhea, rheumatoid arthritis (RA), osteo-arthritis - for mild-moderate pain, well tolerated, few GI effects.

Indomethacin (Indocin)

Potent AIA, anti-pyretic, some analgesic effect.

Inhibits motility of PMNs, uncouples oxid. phos. in cartilage and hepatic mitochondria. Readily absorbed, 90% plasma protein bound, $t_{1/2}=4-12$ hrs.



For RA when ASA ineffect., ankylosing spon., acute gout, patent ductus art., Bartters Syndrome
frontal headache, GI and hematopoietic probs., antag. furosemide

Sulindac (Clinoril)

AIA, analgesic, anti-pyr. Deriv. of indo (1/2 as potent), well absorbed



Sulfoxide → Sulphone (no AIA) urine + bile
(Sulindac, Sulphide (active ($t_{1/2}=18$ hrs)

pro-drug

$t_{1/2}=7$ hrs, weak)

feces

RA, osteoarthritis

occasional GI effect, few headaches, compared to indomethacin

Diclofenac

(Voltaren)

Potent AIA, $t_{1/2} = 1 - 2$ hrs but effective longer because accumulates in synovial fluid



RA, osteoarthritis, ankylosing spondylitis

GI effects common

Naproxen (Naprosyn Anaprox, OTC - Aleve)

Slightly less AIA than indo., analgesic, anti-pyr., well absorbed, absorb. - by NaHCO_3 , - by Al(OH)_3 and antacids.



98% plas. prot. bound, $t_{1/2}=10-17$ hrs.

Excreted in urine unchanged, demethylated or as glucuronide conj.

RA

occasional GI effect

Piroxicam (Feldene)

Good AIA, long plasma $t_{1/2}=20-40$ hrs.



RA, osteoarthritis

better tolerated than ASA or indo. Some GI probs.

Oxaproxin
(Daypro)



Good AIA, long plasma t 1/2 = 50-60 hrs.

1/dayRA, osteoarthritis, ankylosing spondylitis

Ketorolac(Toradol)

Cyclooxygenase inhibitor with strong analgesic properties which are likely not due to CO inhibition but rather another mechanism, perhaps at opioid receptor



Can replace or reduce morphine and meperidine use which, unlike ketorolac, cause respiratory depression.

oral and injectable (IM) for acute pain, post-operative analgesia, adjunct use in surgery. Also good for those who cannot or should not be given opioids. Not used for chronic inflammation

relatively minor, same as other CO inhibitors, not for obstetrical use

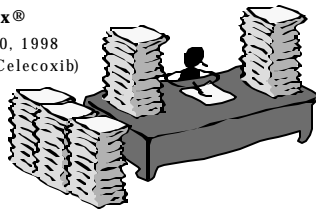
OTHER Side effects: excessive bleeding (due to platelet inhibition), and renal failure (minimized by limiting the use of the drug to 24-48 hrs after surgery)



Celecoxib (Celebrex) Rofecoxib (Vioxx)
Selective COX-2 inhibitor at normal therapeutic doses.

Celebrex®

December 30, 1998
NDA 20-998 (Celecoxib)



452 volumes x 400 pages/volume = 180,800 pages !!!

COX-2 is expressed constitutively in brain and kidney and induced in other tissues during inflammation.

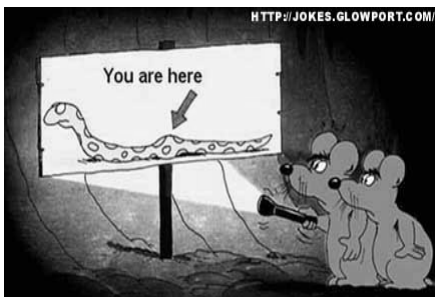
Minimal activity on COX-1, which forms cytoprotective GI PGs and forms the precursor to thromboxane A₂, which induces platelet aggregation.



Plasma t 1/2 = 11 hrs. Metabolized by cytochrome P2C9.

FDA approved for osteoarthritis and RA

Like other NSAIDs except less GI ulcers and little/no effect on bleeding time



Pain Control - Acetaminophen

Learning Objectives:

1. Understand the therapeutic uses for acetaminophen and how they differ from aspirin and aspirin substitutes.
2. Know the main toxic side-effects of acetaminophen overdose and the antidote for acetaminophen overdose

NSAIDs
To use or not to use?



Pain Control - Acetaminophen

I. Acetaminophen

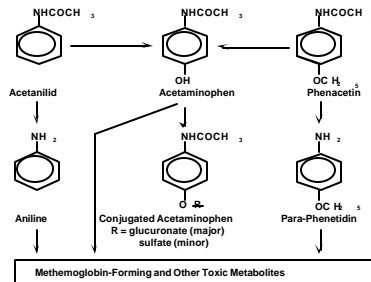
Acetaminophen is not an anti-inflammatory or anti-thrombotic agent, because it does not inhibit systemic cyclooxygenase. It is however equal to aspirin in analgesic and antipyretic properties.

Acetaminophen (Tylenol®, Tempra®)
Phenacetin - chemically related to acetaminophen and once prevalent in many OTC agents. Its use is no longer advised since phenacetin is believed to cause analgesic nephropathy.



Pain Control - Acetaminophen

Table 29-2. STRUCTURAL FORMULAS OF MAJOR PARA-AMINOPHENOL DERIVATIVES, AND THEIR INTERRELATIONS



B. Acetaminophen Absorption, Distribution and Excretion

1. absorption - rapid and complete in $1/2 - 1$ hr
2. plasma $t_{1/2} = 1-3$ hrs
3. metabolized by liver microsomal enzymes
4. 80% excreted in urine after liver conjugation predominantly with glucuronic acid

C. Pharmacological Effects

Analgesic and antipyretic, equals aspirin,

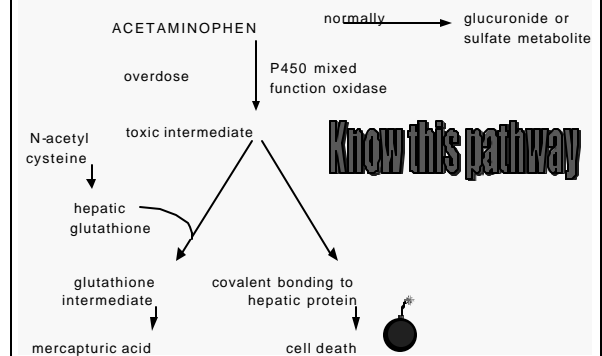
MOA - unknown

Doesn't inhibit platelet aggregation, therefore is not useful for prophylaxis against heart attacks or stroke



D. Toxicity - Very well tolerated in recommended doses, although elderly people may experience toxicity at lower doses than younger adults. However, overdose effects serious, including hepatic necrosis and death due to formation of toxic metabolite by liver P450 metabolism of acetaminophen.

Antidote - N-acetylcysteine (Mucomyst®) which is an oxygen free radical scavenger and promotes formation of glutathione. Glutathione promotes detoxification and elimination of P450 metabolite.



There has been some concern about the simultaneous use of acetaminophen and alcohol.



Regular use of alcohol may lower the threshold for acetaminophen-induced liver damage because it induces the enzymes that catalyze oxidative metabolism of acetaminophen and

thus may more readily form the toxic P450 metabolite N-acetyl-benzoquinoneimine.

In addition, alcoholics may have depleted stores of glutathione and an already damaged liver. However the risk of regular or sporadic use of acetaminophen in patients who regularly drink moderate amounts of alcohol is not clear.

E. Therapeutic use -

ASA substitute for analgesic and anti-pyretic effects only.

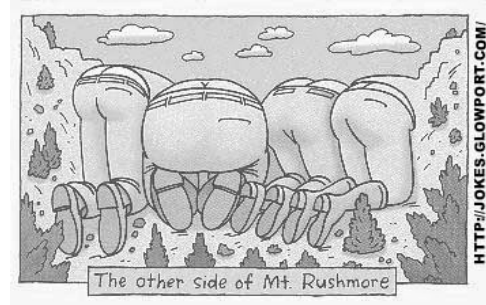
LEARNING RESOURCES :

Drugs to Remember:

1. Acetaminophen
2. N-acetylcysteine

Recommended Reading:

1. Basic and Clinical Pharmacology, B.G Katzung(ed.), 8th ed., 2001
2. Goodman and Gilman's The Pharmacological Basis of Therapeutics, Hardman and Limbird (eds), 10th ed., 2001.



THE END !!

