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). However, note that Vioxx has been removed from the market- severe CV concerns! Celebrex also under scrutiny. 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 antihypertensive 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 6500 patients with rheumatoid arthritis or osteoarthritis die from gastrointestinal toxicity effects 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.

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Serious Reactions/million prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azopropazone</td>
<td>87.9</td>
</tr>
<tr>
<td>Fenbufen</td>
<td>69.4</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>68.1</td>
</tr>
<tr>
<td>Sulindac</td>
<td>54.3</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>47.2</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>43.7</td>
</tr>
<tr>
<td>Naproxen</td>
<td>41.1</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>39.4</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>38.6</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>35.8</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>13.2</td>
</tr>
</tbody>
</table>

(CSM Update)
Classes of Non-selective NSAIDs

**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
Indoles

Indoles (indoleacetic acid derivatives)
  a. indomethacin (Indocin®)
  b. sulindac (Clinoril®) less toxic than indomethacin, prodrug
  c. diclofenac

- similar antiinflammatory, analgesic, antipyretic properties as salicylates.
- potency is 10-20X greater than salicylates.
- potent inhibitor of the prostaglandin-forming cyclooxygenase.
- used as antipyretic for Hodgkin’s disease when other agents have failed.
- relieves pain, reduces swelling and tenderness of joints, increases grip strength
  and decreases morning stiffness.
- also relieves gout
- tocolytic agent (suppresses uterine contractions associated with preterm labor).

Indoles (continued)

Toxic Effects (indomethacin)
- biggest limitation of therapeutic use
- 35-50% patients experience untoward effect
- g.i. complaints and complication: anorexia, abdominal pain and nausea.
  ulcers
anemia, acute pancreatitis, diarrhea associated with ulcer lesions of the bowel.
- hepatic complications
  CNS effects = frontal headache (25-50% of long term patients),
  dizziness, vertigo, mental confusion.
Severe depression, psychosis hallucinations, and suicide have occurred.
- hypersensitivity: rashes, itching, urticaria, asthma
**Sulindac (Clinoril)**

AIA, analges, 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, osteoarthrosis

occasional GI effect, few headaches, compared to indomethacin

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**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
Propionic Acid Derivatives

Specific drugs
• Ibuprofen (Motrin) half-life 2 hours
• Naproxen (Naprosyn) half life 14 hours
• Naproxen sodium (Anaprox)
• Fenoprofen (Nalfon)
• Ketoprofen (Orudis)

- approved for long term symptomatic treatment
  rheumatoid arthritis
  Osteoarthritis
  **Less anti-inflammatory activity (AIA) than indomethacin**
- short term use:
  musculoskeletal injury
  post operative pain
  dysmenorrhea.

Propionic Acid Derivatives: Side Effects

- better tolerated than aspirin and indomethacin
- Side effects (20%) about 2% discontinue use.
- most common GI disruption
- CNS effects
- skin rashes
- allergic reactions
**Naproxen** (Naprosyn Anaprox, OTC - Aleve)

Slightly less AIA than indo., analges., anti-pyr., well absorbed, absorb. ↑ by NaHCO₃, ↓ 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

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**Oxicams:**

*Piroxicam* (Feldene)

Good AIA, long plasma t 1/2=20-40 hrs.

RA, osteoarthritis

better tolerated than ASA or indo. Some GI probs.
**Ketorolac (Toradol)**
Cyclooxygenase inhibitor with strong analgesic properties which are likely not due to COX inhibition but rather another mechanism, perhaps at opioid receptors? 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 AND NOT LONGER THAN 2 WEEKS GENERALLY. USUALLY NOT REC. FOR MORE THAN 2-5 DAYS)

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**Celecoxib (Celebrex)**
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

Learning Resources:
Drugs to Remember:

1. Indomethacin
2. Sulindac
3. Diclofenac
4. Ibuprofen
5. Naproxen
6. Piroxicam
7. Oxaprozin
8. Ketorolac
9. Celecoxib
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
3. Drugs to know: acetaminophen and N-acetylcysteine (Mucomyst®)

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.

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

- Acetanilid
- Aniline
- Conjugated Acetaminophen
- Methemoglobin-Forming and Other Toxic Metabolites
B. Acetaminophen Absorption, Distribution and Excretion

1. absorption - rapid and complete in $\frac{1}{2} - 1$ hr
2. plasma t $\frac{1}{2}$=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 prevention of vascular clotting or 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. Drugs to Remember:
Therapeutic use of
1. acetaminophen-
ASA substitute for analgesic and anti-pyretic effects only.
2. N-acetylcysteine (Mucomyst®) which
   is an oxygen free radical scavenger and
   promotes formation of glutathione.
QUESTIONS !!!!!