Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and Acetaminophen

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Structure of Lecture

- Inflammation
- Examples of Inflammation
- COX-1 and COX-2

NSAIDs
- Mechanism of Action of NSAIDs: effects on COX-1 and COX-2
- Prostaglandin (Pg) and Thromboxane (Tx) synthesis
- Non-selective and Selective COX-2 inhibitors
- Adverse Effects
- Drug-drug interactions

Acetaminophen
- Mechanism of action
- Adverse Reactions

Individual variability in response to NSAIDs and acetaminophen
Research reports

Pain Management Market: an ever expanding market.... An ever expanding use

Pub Time: 2003/04
Growth spurred by 27 new drugs entering the pain management market by 2008.
A leader in strategic consulting and market analysis for the life sciences industries, today announced the completion of its new Strategic Market Report series, Pain Management Therapeutics. Front Line's report includes an in-depth analysis of current and emerging pain management therapeutics, key companies, and the future market. The worldwide pain management market is projected to experience a 10% overall compound annual growth rate (CAGR) through 2008. NSAIDs, estimated current 45.2% market share, account for the largest market segment.

US Pain Management Programs: A Market Analysis [Marketdata Enterprises Inc.]
This has grown into a $15.3 billion if one includes sales of painkilling drugs. Nearly 3,800 programs and sole practitioners (clinics and centers, anesthesiologists, chiropractors) treat an estimated 8 million Americans suffering from: chronic back pain, migraines, cancer, arthritis, migraines, carpal tunnel syndrome, etc..

Note that in 1990 NSAIDs worldwide market was ~$ 7 billion

9-10% of prescriptions worldwide are NSAIDs
1-2% of U.S. population uses prescriptions daily

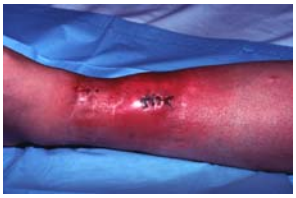
INFLAMMATION

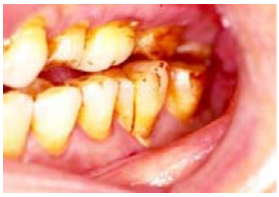
- Inflammation is a defense reaction caused by tissue damage or injury
- *Can be elicited by numerous stimuli including*:
- infectious agents
- antigen-antibody interaction
- ischemia
- thermal and physical injury

- Characterized by:
- Redness (*rubor*): *vasodilation* of capillaries to increase blood flow
- Heat (*calor*): *vasodilation*
- Pain (*dolor*): *Hyperalgesia*, sensitization of nociceptors
- Swelling (*tumor*): Increased vascular permeability (microvascular structural changes and escape of plasma proteins from the bloodstream)
- Loss of function (*functio laesa*)

• ***Inflammatory cell transmigration*** through endothelium and accumulation at the site of injury

Examples of INFLAMMATION





- Redness
- Heat
- Pain
- Swelling
- Loss of function

Inflammation

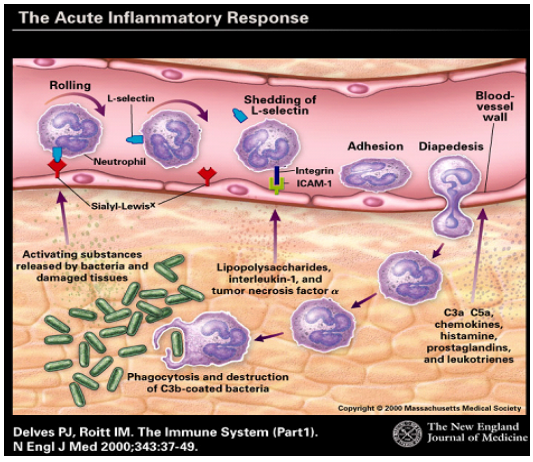
Mediators of Inflammation

- Vasoactive amines (mast cells and platelets)
  - Histamine – abundant in granules of mast cells (very abundant around blood vessels)
  - Serotonin – actions similar to histamine. Found in platelets. Released after platelet aggregation, or under the influence of platelet activating factor (PAF).
- Platelet activating factor (PAF)
- Complement system
- Kinin system
  - –Vasoactive peptides called kinins are generated by proteases called kallikrein
  - –Most important product is bradykinin
  - –Coagulation pathway
- Cytokines: Interleukin (IL)-1, -2, Tumor Necrosis Factor (TNF), granulocyte/macrophage colony stimulating factor (GM-CSF).
- Nitric oxide: made by NO synthase (NOS) both constitutive and Inducible; induced in macrophages by TNF-α or IFN-γ; Potent vasodilator; Involved in the pathogenesis of septic shock
- Adhesion Molecules
- Arachidonic acid metabolites: Prostaglandins (PGs), Thromboxane A2 (TXA2), HETE and Leukotrienes (LTs)----***mediated by cyclooxygenases (COX)***

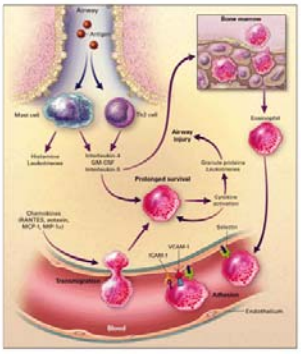
Inflammatory responses occur in three distinct phases:

- An acute *transient phase*, characterized by local vasodilation and increased cappilary permeability
- A delayed, *subacute phase*, most prominently characterized by infiltration of leukocytes and phagocytic cells
- A *chronic proliferative phase*, in which tissue degeneration and fibrosis occur

REMEMBER: The ability to mount an inflammatory response is essential for survival in the face of environmental pathogens and injury, although in some situations and diseases the inflammatory response may be exaggerated and sustained for no apparent beneficial reason



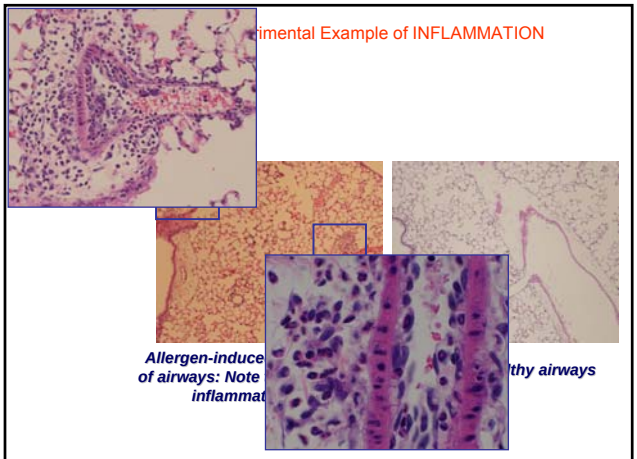
Cellular response to allergen (may be considered sub-acute)



Eosinophil recruitment during asthma:

1. *Priming of eosinophils in the circulation.*
2. *Rolling along the endothelial cells.*
3. *Firm adhesion to the endothelium.*
4. *Trans-endothelial diapedesis.*
5. *Chemotaxis into the inflammatory site.*

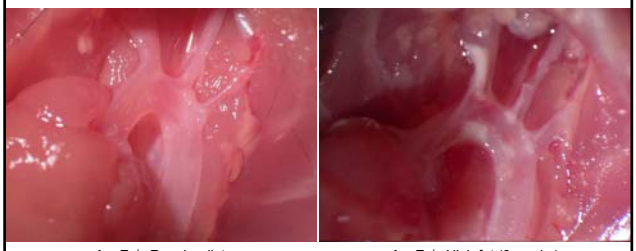
imental Example of INFLAMMATION



Allergen-induce
of airways: Note
inflammat

thy airways

Atherosclerosis, a chronic model of inflammation

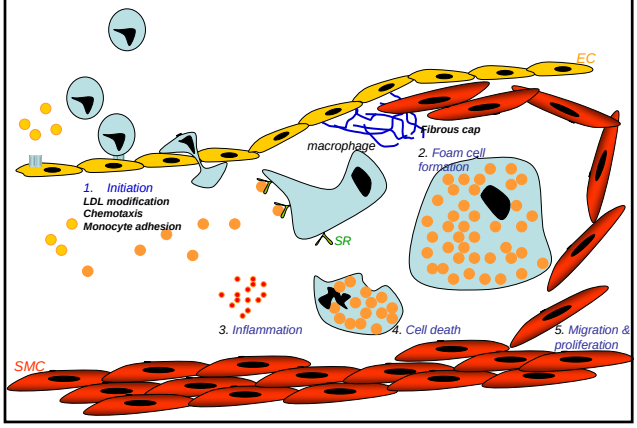


ApoE$^{-/-}$-Regular diet

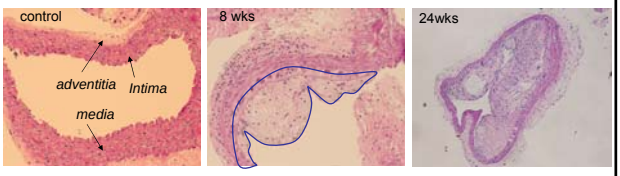
ApoE$^{-/-}$-High fat (8 weeks)

Six to eight weeks old ApoE$^{-/-}$mice receive regular chow or a high fat diet containing 21% fat by weight (0.15% cholesterol). Mice are sacrificed after 8, 12, 18, or 24 weeks

Atherosclerosis: How does it occur?



The animal Model: generation and progression of plaques



Cyclooxygenases (COX)

Two main forms of Cyclooxygenases (COX)

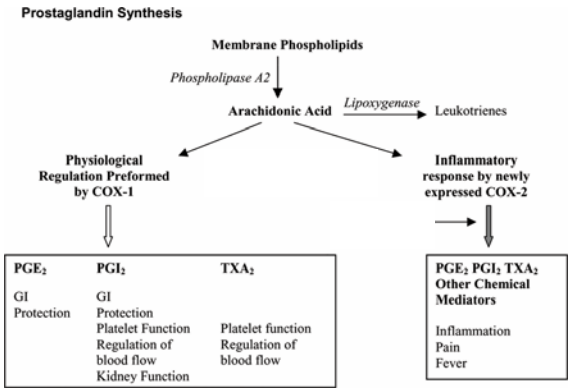
Cyclooxygenase-1 (COX-1)

•Produces prostaglandins that mediate homeostatic functions
• Constitutively expressed
• Plays an important role in Gastric mucosa; Kidney; Platelets; and Vascular endothelium

Cyclooxygenase-2 (COX-2)

• Produces prostaglandins that mediate inflammation, pain, and fever.
• Induced mainly in sites of inflammation by cytokines
• Constitutive expression in Brain and Kidney (Animal data)

COX-3???

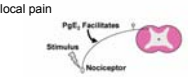


Roles of prostaglandins

PgE2

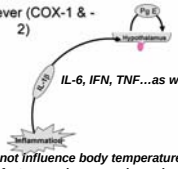
Pg & Pain (COX-1 & -2)

Intense local pain



FYI: In the past, PgE2 were used to induce labor at term (approved as a gel by FDA at 0.5 mg/g gel); they were also used as inducers of abortion (early or midterm)
Incomplete and Many side effects

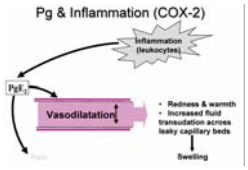
Pg & Fever (COX-1 & -2)



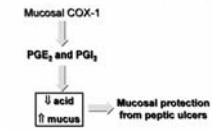
IL-6, IFN, TNF…as well as others

NSAIDs do not influence body temperature when it is elevated by factors such as exercise or in response to ambient temperature.

Pg & Inflammation (COX-2)

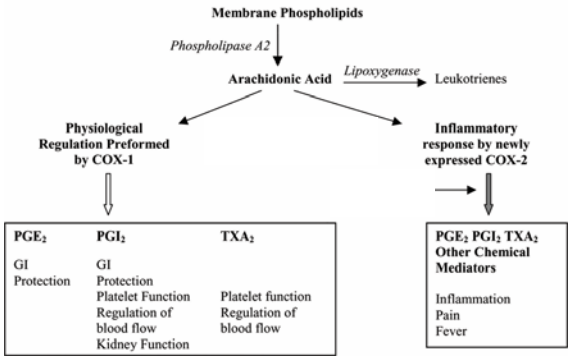


Pg & Gastric Mucosa (COX-1)



Where do COX inhibitors work?

Prostaglandin Synthesis



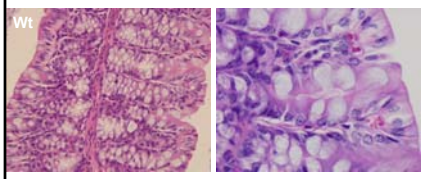
Mouse Model - APC^{min}

Multiple intestinal neoplasia (min). APC gene mutation. Truncated protein at codon 850.
Htz have increased propensity for tumors. Tumors acquire somatic mutation in wild type APC allele.
Tumors located in upper GI tract (not colorectal).
Genetic background of mouse influences tumor load (?modifiers).
MOM-1 - possibly secreted phospholipase A2
APC^{1638T} lacks C-terminal domain that binds tubulin, EB1-like proteins.
homozygous ES cells have high degree of chromosomal instability
but homozygous mice do NOT exhibit increased tumor susceptibility

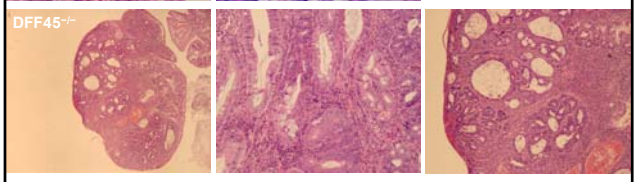
Cooperating Oncogenes.

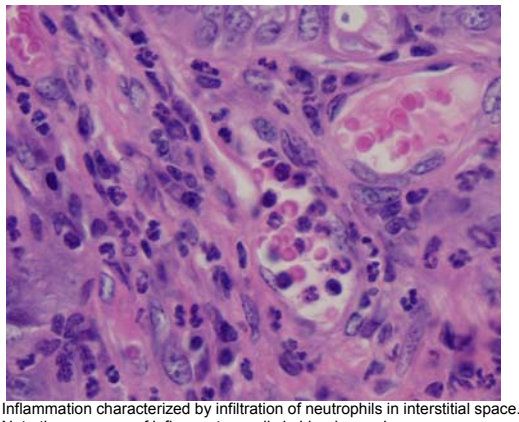
1. *Cyclooxygenase 2: deletion of COX-2 gene suppresses intestinal polyposis in APC$^{\Delta 716}$ mice. COX-2 levels are increased in premalignant polyps. But COX-2 is expressed in interstitial cells not intestinal epithelium.*
2. Smad4: deletion of Smad4 in APC$^{\Delta 716}$ mice resulted in more aggressive tumors (compound htz mice).
   Highlights the role of TGF signal in tumor progression.
3. DNA methyltransferase: compound htz have reduced polyp numbers (epigenetic events?).

Colon cancer



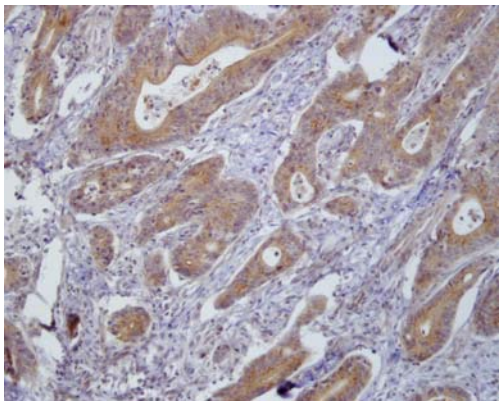
DMH treatment induces tumors in mice





Inflammation characterized by infiltration of neutrophils in interstitial space.
Note the presence of inflammatory cells in blood vessels

Expression of COX-2 in human colon carcinomas



Different types of NSAIDs

- Salicylates
- Propionic Acid Derivatives
- Enolic Acids (Oxicams)
- Arylacetic acid derivatives
- Selective COX-2 inhibitors

Therapeutics

- When used as analgesics, these drugs usually are effective only against pain of low-to-moderate intensity.
- Although their maximal effects are much lower, they lack the unwanted effects of the opioids on the CNS (dvpmt of physical dependence and respiratory depression).
- NSAIDs reduce body temperature (antipyretic effect)
- Anti-inflammatory: treatment of musculoskeletal disorders (Rheumatoid arthritis, osteoarthritis, ..).
- An important area where the use of NSAIDs is emerging is in the prevention of colon cancer (4-6 325 mg tablets/wk reduces risk to colon cancer by 50%).

Therapeutics

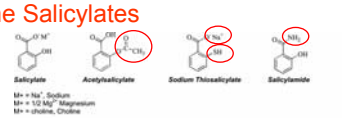
Niacin Tolerability: Large doses of niacin (nicotinic acid) lower serum cholesterol levels, reduce LDL, and raise HDL. *However*, niacin is tolerated poorly-induces intense flushing (mediated by a release of PG from the skin). Treatment with aspirin.

Systemic Mastocytosis: (excessive mast cells in the bone marrow, reticuloendothelial system, GI, bones, and skin)

In patients with *SM*, prostaglandin D2, released from mast cells in large amounts, has been found to be the major mediator of severe episodes of vasodilation and hypotension; *The addition of aspirin or ketoprofen would provide relief.*

The Salicylates

Despite the introduction of many new drugs, aspirin remains the most widely used and prescribed analgesic-antipyretic-anti-inflammatory drug (a lot of room for misuse)



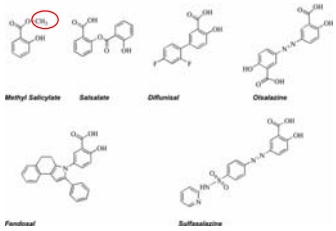
On Aug. 10, 1897 young Bayer researcher, Felix Hoffman, first synthesized acetylsalicylic acid.

Additional info:

• Salicymide HAS ANALGESIC action but LACKS INFLAMMATORY action.

• Diflunisal (Dolobid) is the result of extensive analog sysnthesis. Has prolonged analgesic effect (2x aspirin) and a more potent anti-inflammatory action (but equal GI toxicity)… used for rheumatoid and osteo-arthritis.

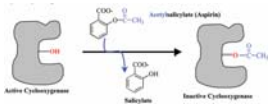
•Fendosal is believed to have greater analgesic and anti-inflammatory activity than aspirin but with less GI toxicity



Salicylates are highly bound to the plasma protein albumin. Thus, it will have a drug interactions with other medications leading to higher free drug levels.

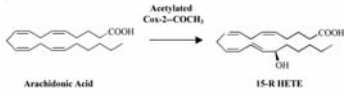
Mechanism of Action of Aspirin

Aspirin covalently and ***irreversibly*** modifies both Cox-1 and Cox-2 by acetylating Serine-530 in the active site



• Acetylation of Cox-1 creates a steric block that prevents the binding of arachidonic acid at the catalytic site.

•Acetylation of Cox-2 retains the cyclooxygenase activity although the reaction generates a different and novel product 15-R-HETE

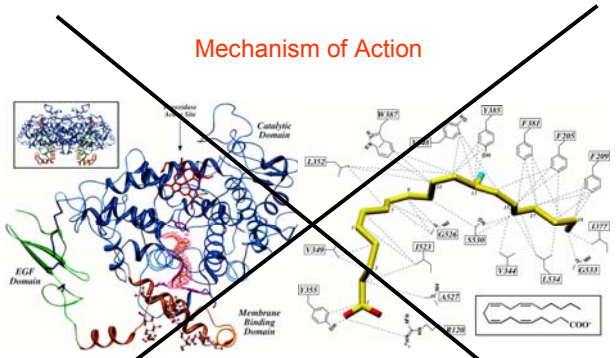


• In platelets (only the Cox-1 is detectable). Aspirin inactivates Cox-1 leading to a loss of Arachidonic acid-induced platelet aggregation by decreased production of Thromboxane A2 (TXA2). Since platelets do not form new enzyme, TXA2 synthesis is therefore irreversibly inhibited for the entire platelet lifetime (8 to 10 days) in circulation.

This is the basis and therapeutic aim of the "half an aspirin a day" prophylaxis against thromboembolic disease (importance in myocardial infarction); *remember the Bayer Ad*.

• Aspirin is metabolized by glucuronidation- an enzymatic reaction that can be saturated.

Mechanism of Action



Adverse Effects

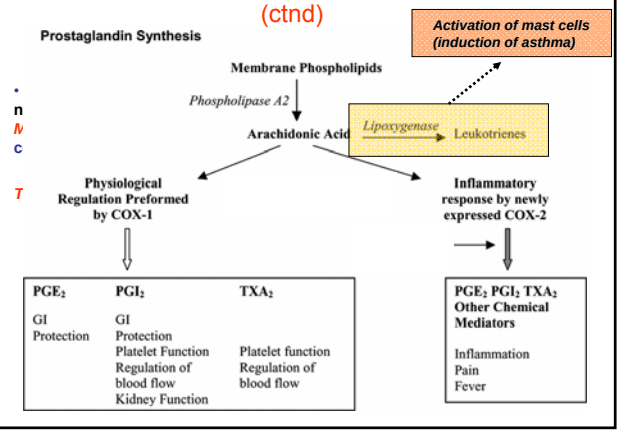
Salicylate Intoxication (from Salicylism to Death):

• Salicylism: Mild intoxication as a result of repeated high doses intake (headaches, dizziness, tinnitus, hearing impairment, mental confusion, etc…) to death as a result of seriously large doses intake (10-30 g).

• Severe effects:
- Hyperventilation
- Hyperthermia (due to inhibition of oxidative phosphorylation)
- Alteration of acid-base and electrolyte balance (Effects on renal elimination)
- Gastric irritation, microbleeding (additive with alcohol).
- Impairment of platelet function
- Edema and acute renal failure (Individuals with preexisting renal dysfunction or Chronic Heart Failure (CHF).
- Convulsion, Coma,

• Death usually occurs as a result of cardiovascular collapse and respiratory failure

Adverse Effects (ctnd)



An alternative for babies/infants to avoid the Reyes syndrome:

the use of a "safer for children" drug: acetaminophen

•Reyes Syndrome: the small orange tasting little pill (*Children Aspirin*) that dissolved in the mouth. In the early 1970's a rare condition called Ryes Syndrome sometimes developed in children when they were given aspirin for high fevers associated with viral illnesses.

FYI: *Reye's syndrome is characterized by the acute onset of encephalopathy, liver dysfunction, and fatty infiltration of the liver and other viscera (**can be lethal**)*

Doctors Rethinking Aspirin-Plavix Combination

March 13/2006 (HealthDay News) -- A startling new study has doctors rethinking the practice of prescribing the blood thinner Plavix in combination with low-dose aspirin to patients at risk of a first heart attack or stroke. (study included more than *15,000 patients* with heart disease or risk factors for heart disease)

The conclusion: The tandem therapy was of some benefit to those with diagnosed heart disease, but it nearly doubled the risk of death, heart attack or stroke in patients with heart-threatening conditions such as high cholesterol and high blood pressure.

Aspirin and Diabetes (FYI)

1. Aspirin should be used in any diabetic patient who has evidence of:
• a prior heart attack
• a previous bypass procedures
• a stroke, angina, claudication, or blood vessel disease.

2. Aspirin therapy should be considered in high-risk men and women with type 1 or type 2 diabetes. This includes diabetic patients with the following:
• a family history of heart disease
• Cigarette smoking
• Hypertension
• Positive protein in the urine (albuminuria)
• High cholesterol
• Over age 30

Propionic Acid Derivatives

May represent better alternatives to some patients over aspirin and other NSAIDs

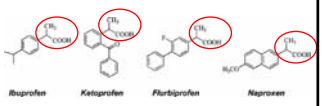
- Ibuprofen (200-800 mg) [Advil, Nuprin, etc…); Only the 200 mg tablets are available over the counter
  - Prescribed for Rheumatoid arthritis and osteoarthritis.
  - Peak concentrations in plasma within 15-30 min; half-life: 2 h
  - 99% bound to plasma proteins

Side effects: GI effects are experienced in 5-15% of patients (pain, nausea, heartburn, and sensation of "fullness".

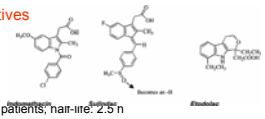
- Naproxen [Aleve, Naprosyn, etc…]: (20 times more potent than Aspirin)
  - Peak concentrations in plasma within 2-4
  - 99% bound to plasma proteins

Side effects: GI discomfort, heartburn, nausea, vomiting, and gastric bleeding. In CNS: drowsiness, headache.

- Ketoprofen (Orudis, generic, OTC)
- Oxaprozin (Daypro): Once daily (long half-life)



Arylacetic Acid Derivatives



- Indomethacin [Indocin]: ~25 mg 2-3 times daily
  - Prescribed for Rheumatoid arthritis and other arthritis.
  - Peak concentrations in plasma peak after 1-2h in fasting patients; half-life: 2.5 h

Side effects: Although indomethacin is used widely and is effective, toxicity often limits its use. 35-50% of patients experience GI effects. 20% of patients discontinue its use. CNS side effects as well.

- Sulindac [Clinoril]: was developed in an effort to limit the toxicity of indomethacin (or aspirin).
  -8 times more effective than aspirin but less potent than Indomethacin
  -~200 mg twice a day.
  - Peak concentrations in plasma within 1-2 h
  - Half-life: 7 h

Side effects: Lower than Indomethacin.

- ***Ketorolac (Toradol): a potent analgesic but a moderate anti-inflam***
  -It has a greater analgesic activity when used i.m. it has therapeutic effectiveness similar to the opioids without CNS side effects (only i.m.)---***Used routinely used in emergency rooms***
- Diclofenac (Voltaren)
- Bromfenac (Duract)
- Etodolac: Has been shown to be selective to COX-2, a single dose of 200-400mg provides 6-8 h of postoperative analgesia
- Nabumetone (Relafen): typical dose of 1000 mg. ***Pro-drug*** (converted by the liver into 6-methoxy-2-naphthylacetic acid, a potent COX inhibitor) hence its low Gastric effect.

Enolic Acids (Oxicams)

This class has been fairly recently discovered (some members are still under study)

- Piroxicam [Feldene]: Can be better tolerated than aspirin or indomethacin
  Advantage: Long half-life as well as it has additional effects as an anti-inflammatory drug: inhibits the activation of neutrophils

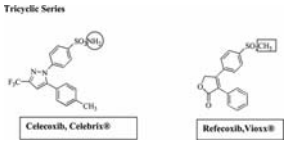
- Meloxicam [Mobic] recommended dose: 7.5 mg once a day for osteoarthritis; 15 mg once a day for rheumatoid arthritis.
- More selective COX-2 inhibitor than the other NSAIDs.
- Less potent than Piroxicam

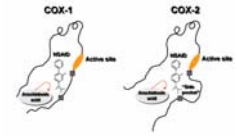
Drug Interactions

- Most (if not all) NSAIDs can increase the anticoagulant effect of WARFARIN: displacement of warfarin from plasma albumin and the subsequent inhibition of warfarin metabolism and elimination
- Potentially all NSAIDs can blunt the diuretic actions of THIAZOLE by competing for the active secretion proximal tubule.
- May enhance the toxicity of METHOTREXATE (a cancer drug) by blocking its tubular secretion.
- May reduce the renal elimination of Li^+ ions (Manic depression disorders) and cause a significant elevations of the plasma [Li^+]
- May interfere with the anti-hypertensive actions of beta-blockers, diuretics, and ACE-inhibitors.
- NOV2004 study: In high risk patients with recent ischemic stroke or transient ischemic attacks, adding aspirin to clopidogrel (PLAVIX; an antiplatelet agent) increased the risk of life-threatening or major bleeding events (Diener et al. 2004 *Lancet)*

Specific COX-2 inhibitors (NSAIDs of the Future??)

- Celecoxib (Celebrex)
- Refecoxib (Vioxx)
- Valdecoxib (Bextra)





Inhibition of COX-1 and COX-2 by NSAIDs

Specific COX-2 inhibitors such as Celecoxib do not inhibit COX-1

Concept of the Cox-2 IC50 to Cox-1 IC50 Selectivity Ratio

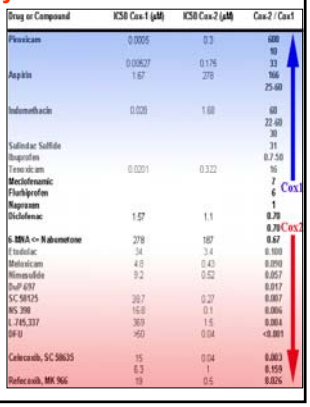
The Cox-2 Hypothesis is that Cox-2 specific (i.e reduces pain, fever and inflam w/out gastrointestinal/renal injury).

In order to achieve this goal, it is necessary to design compounds that have:

1. ***low IC50 values for Cox-2 (i.e. tight binders)***
2. ***high IC50 values for Cox-1 (i.e. weak binders).***

- ***Cox-1 selective drugs will have Cox-2/Cox-1IC50 ratios much greater than 1***

- ***Cox-2 selective drugs will have values much less than 1.***



BMC Anesthesiology

Research article

Single-dose rofecoxib for acute postoperative pain in adults: a quantitative systematic review

Jodie Barden, Jayne E Edwards, Henry J McQuay and R Andrew Moore*

Abstract

Background: Rofecoxib is a cyclo-oxygenase 2 selective inhibitor. This systematic review of rofecoxib in acute pain examined studies in adults of analgesic efficacy over six hours, the amount and quality of the evidence on extended duration of analgesia, and the quality and quantity of evidence on adverse events.

Methods: Cochrane Library (issue 4, 2001), Biological Abstracts (March 2002), MEDLINE (March 2002) and PubMed (March 2002) were searched using rofecoxib as a free text term. The area under the pain relief versus time curve was dichotomized using validated equations to derive the proportion of patients on rofecoxib 50 mg or placebo with at least 50% pain relief over six hours. This was used to calculate the number needed to treat for at least 50% pain relief over six hours for rofecoxib compared with placebo. Information on duration of analgesia and adverse events was also collected.

Results: Five included trials investigated 1,118 patients, of whom 211 received placebo and 464 received rofecoxib 50 mg. The NNT for rofecoxib 50 mg was 2.3 (95% confidence interval 2.0 to 2.6). The weighted mean remedication time was 1.9 hours for placebo (124 patients), 7.4 hours for ibuprofen 400 mg (97 patients) and 13.6 hours for rofecoxib 50 mg (322 patients).

Conclusions: Rofecoxib at 2–4 times the standard daily dose for chronic pain is an effective single dose oral analgesic in acute pain. Limitations in trial reporting constrain conclusions about longer duration of analgesia and adverse event profiles.

From:

Spine-health.com **Vioxx recall**

In late September 2004, Vioxx—a brand of COX-2 inhibitor commonly prescribed for arthritis, acute pain and several types of back pain—was withdrawn from the market. The Vioxx recall occurred after Merck, the drug's manufacturer, reported findings of increased risk of heart attack and stroke among participants in an ongoing clinical trial. The U.S. Food and Drug Administration (FDA) did not require a Vioxx recall; Merck voluntarily pulled Vioxx from the market on September 30, 2004. All patients who were prescribed Vioxx stopped using the drug and consult their physician. Since the Vioxx recall, the potential risks of other COX-2 inhibitors (e.g. Celebrex, Bextra) and other types of NSAIDs such as naproxen (e.g. Aleve, Naprosyn) have also been called into question. Many patients have been left with concerns about certain NSAIDs and questions about treatment options.

From *Drug Facts and Comparisons News* (May 2004): Vioxx received FDA approval for acute treatment of migraine attacks. *What??*

American Association for Cancer Research

BREAKING NEWS

March 1, 2005

Celecoxib Provides Two-Pronged Attack on Prostate Cancer Cell Proliferation
Celecoxib, a selective COX-2 inhibitor with promising anti-cancer properties, has been found to attack prostate cancer cells in a second way that differs from Vioxx (rofecoxib). In studies published in the March 1 issue of the journal *Clinical Cancer Research,* scientists at the Weill Medical College of Cornell University revealed that celecoxib, marketed under the name Celebrex, not only targets COX-2, but also reduces levels of a key protein, cyclin D1, that is critical for cell replication. For the complete article, visit http://www.aacr.org/pdf_files/journals/CCR_Celecoxib_Dannenberg_3-01-05.pdf

What?? Again: a moment for reflection!

FYI

Ann Clin Lab Sci. 2005 Autumn;35(4):347-85.

Cardiovascular complications of non-steroidal anti-inflammatory drugs.

Fosslien E.

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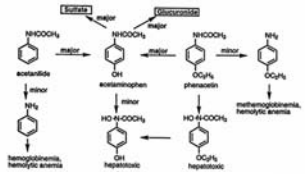
Coxibs, such as rofecoxib, celecoxib, and valdecoxib, selectively inhibit cyclooxygenase (COX)-2, the mainly inducible, pro-inflammatory COX isoform. Unlike traditional non-steroidal anti-inflammatory drugs (NSAIDs) most coxibs do not significantly inhibit COX-1 and are therefore less toxic to the gastrointestinal tract. Hence, coxibs widely replaced traditional NSAIDs for treatment of arthritis and other painful inflammatory conditions. In many, but not all, clinical studies, coxibs became associated with higher risks of myocardial infarction (MI) and stroke. Several mechanisms may be involved in the pathogenesis of such complications. First, selective inhibition of COX-1 lowers platelet synthesis of thromboxane (TXA(2)), a thrombogenic and atherogenic eicosanoid. Selective inhibition of COX-2 limits endothelial cell synthesis of prostacyclin (PGI(2)), an arachidonic acid product that opposes the effects of thromboxane. **In apoE-/- mice, interruption of TXA(2) signaling by deletion of its receptor (TP) limits atherogenesis, whereas interruption of PGI2 signaling by deletion of its receptor (IP) accelerates atherogenesis. This suggests that selective inhibition of COX-2 can disrupt the physiological balance between thromboxane and prostacyclin and thus increase atherosclerosis,** thrombogenesis, and the risk of cardiovascular complications. Second, COX inhibition can raise levels of arachidonic acid, which can inhibit mitochondrial oxidative phosphorylation (OXPHOS) and increase OXPHOS generation of reactive oxygen species. Several NSAIDs, including coxibs and meloxicam, directly uncouple or inhibit OXPHOS. Studies of apoE-/- mice indicate that mitochondrial dysfunction plays an early role in atherogenesis. Third, many NSAIDs exhibit COX-independent properties. For example, in animal models, short-term treatment with celecoxib reduces monocyte chemotaxis by reducing expression of monocyte chemoattractant protein (MCP)-1. However, long-term treatment results in the opposite effect and accelerates atherogenesis. In conclusion, to reduce the risk of cardiovascular complications during long-term coxib therapy, low-dose aspirin supplementation should be considered. An alternative is to use a less COX-2-selective inhibitor such as meloxicam. Genotyping of -765 alleles of the COX-2 gene promoter and examining the polymorphism of other genes involved in eicosanoid metabolism or NSAID degradation may become helpful in predicting patients who are at higher risk of cardiovascular complications during selective COX-2 inhibitor therapy.

Acetaminophen

[Acetyl-para-Aminophenol (APAP), paracetamol, Tylenol]

- APAP is effective as an anlgesic and an antipyretic
- It has little to no anti-inflammatory action (weak inhibition of COX enzymes…weak inhibition of prostaglandin synthesis).
- Well tolerated and lacks many of the side-effects of aspirin and other NSAIDs.
- No gastric irritation or ulceration
- No platelet function interference
- Does not inhibit neutrophil activation
- No effect on cardiovascular or respiratory systems
- Peak concentrations in plasma within 30-60 min; half-life: 2 h
- 20-50% bound to plasma proteins
- After therapeutic doses, 90-100% recovered in the urine within the first day as hepatic conjugates: glucoronide(60%)
- The conventional oral dose: 325-1000mg; should not exceed 4000 mg.

Acetaminophen Metabolism



Mechanism of Action

- A COX-3 connection??

Toxic Effects

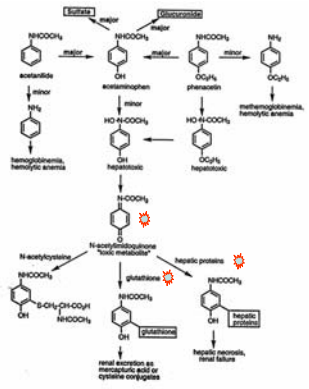
• Skin rash and other allergic reactions (occasional)

• Hepatic and renal necrosis upon overdose, leading to failure of both organs with possible subsequent death;

• Due to glutathione (GSH) depletion (generation of NAPQI)
- GSH: glu-cys-gly
- Cysteine is an essential amino acid
- Cysteine availability is rate limiting for GSH synthesis.

• TREATMENT: N-acetyl-cysteine (Mucomyst, Mucosil) is the antidote for APAP overdose… Replenishing of GSH
-Exhibits low toxicity

Acetaminophen Metabolism



New non-hepatotoxic Acetaminophen?

- Scp-1

Recent Data on NSAIDs relevant to Dentistry

- J Orofac Pain. 2003 Summer;17(3):237-44. Related Articles, Links

Analgesic efficacy of low-dose diclofenac versus paracetamol and placebo in postoperative dental pain.

Kubitzek F, Ziegler G, Gold MS, Liu JM, Ionescu E.

Clinical Research and Development of Pharmaceuticals, Morge, Switzerland.

AIMS: To compare the efficacy and safety of diclofenac-K (12.5 mg) vs paracetamol (500 mg) and placebo given in a flexible dosage regimen to treat pain resulting from extraction of impacted third molar teeth. METHODS: This was a 2-day, double-blind, double-dummy, randomized, parallel-group, placebo-controlled study of diclofenac-K (12.5 mg) tablets vs paracetamol (500 mg) tablets and placebo in patients with moderate or severe pain within 8 hours of extraction of impacted third molars. RESULTS: After the first 2-tablet dose, patients took on average 2.5 additional tablets of diclofenac-K or 2.4 tablets of paracetamol, almost all as 1-tablet doses. Most placebo patients discontinued by taking rescue medication (ibuprofen 200 mg) on the first day. Pain relief after the initial dose of diclofenac-K (2 x 12.5 mg) was superior to placebo (P < .01 for all efficacy outcomes) and comparable to paracetamol (2 x 500 mg). About 30% of patients in each active treatment group took rescue medication during the study, compared to 78% on placebo. About 70% in each active treatment group considered the overall pain relief to be "some," "a lot," or "complete" compared to only 15% on placebo. The incidence of adverse events in each active treatment group was low and comparable between the treatments. CONCLUSION: An initial double-dose of diclofenac-K (2 x 12.5 mg) or paracetamol (2 x 500 mg) adequately relieved the most intense postoperative pain, and the flexible multiple dose regimen (1 or 2 tablets) maintained adequate pain relief thereafter. Most patients needed only 1-tablet doses following the initial 2-tablet dose.

FYI

1: Anaesth Intensive Care.
2004 Dec;32(6):770-4.

A randomized crossover trial of tenoxicam compared with rofecoxib for postoperative dental pain control.

Zacharias M, De Silva RK, Herbison P, Templer P.

Dunedin School of Medicine and School of Dentistry, University of Otago, Dunedin, New Zealand.

Two non-steroidal anti-inflammatory drugs, tenoxicam and rofecoxib, were compared for the control of postoperative pain following surgical extraction of bilaterally and symmetrically impacted wisdom teeth performed under intravenous sedation and local anaesthesia. Thirty-five young fit adult patients received each analgesic treatment for four days in a randomized, crossover design. *The results suggest statistically better pain relief for the selective COX-2 inhibitor rofecoxib compared to tenoxicam, a traditional NSAID*. There were side-effects with both treatments. Abdominal discomfort was significantly more common following rofecoxib compared to tenoxicam. Both analgesics were acceptable to most participants in the trial.

Individual variability in response to NSAIDs and acetaminophen

Br J Pharmacol advance online publication, January 5, 2004; doi:10.1038/sj.bjp.0705623

British Journal of Pharmacology (2004) 1–4 www.nature.com/bjp

SPECIAL REPORT

Genetic predisposition to acute gastrointestinal bleeding after NSAIDs use

[1]Carmen Martínez, [2]Gerardo Blanco, [3]José M. Ladero, [4]Elena García-Martín, [3]Carlos Taxonera, [2]Francisco G. Gamito, [3]Manuel Díaz-Rubio & *,[1]José A.G. Agúndez

[1]Department of Pharmacology, Medical School, University of Extremadura, Badajoz, Spain; [2]Service of Surgery, University Hospital Infanta Cristina, Badajoz, Spain; [3]Service of Gastroenterology, Hospital Clínico San Carlos, School of Medicine, Complutense University, Madrid, Spain and [4]Department of Biochemistry, School of Biological Sciences, University of Extremadura, Badajoz, Spain

Impaired drug metabolism is a major cause of adverse drug reactions, and it is often caused by mutations at genes coding for drug-metabolising enzymes. Two amino-acid polymorphisms of cytochrome *P*4502C9 (CYP2C9), an enzyme involved in the metabolism of several nonsteroidal anti-inflammatory drugs (NSAIDs), were studied in 94 individuals with acute bleeding after NSAIDs use and 124 individuals receiving NSAIDs with no adverse effects. The frequency of *CYP2C9* variant alleles was increased in overall bleeding patients, with a significant trend to higher risk with increasing number of variant alleles ($P = 0.02$). The odds ratio for bleeding patients receiving CYP2C9 substrates ($n = 33$) was 2.5 for heterozygous and 3.7 for homozygous carriers of mutations ($P < 0.015$), suggesting that the inherited impairment of CYP2C9 activity increases the risk for severe adverse drug reactions after NSAIDs use.

British Journal of Pharmacology (2004); doi:10.1038/sj.bjp.0705623

Keywords: Nonsteroidal anti-inflammatory drugs; adverse drug effects; acute gastrointestinal bleeding; cytochrome *P*4502C9; pharmacogenomics

Abbreviations: CYP2C9, Cytochrome *P*4502C9; NSAIDs, nonsteroidal anti-inflammatory drugs

Safety Issue

- January 2004: The FDA notified health care professionals of a national education campaign designed to optimize the safe and rational use of over-the-counter (OTC) pain and fever reducers that contain APAP and NSAIDs. The campaign is intended to raise consumer awareness of these safety issues and to inform health care providers about the role they can play in preventing APAP-induced hepatotoxicity, NSAIDs-related GI bleeding, and renal toxicity in patients using these medicines. Visit: www.fda.gov/cder/drug/analgesics/default.htm