NON-STEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

I. Introduction

The non-steroidal antiinflammatory drugs (NSAIDs) are widely used for the treatment of minor pain and for the management of edema and tissue damage resulting from inflammatory joint disease (arthritis). A number of these drugs possess antipyretic activity in addition to having analgesic and antiinflammatory actions, and thus have utility in the treatment of fever. Most of these drugs express their therapeutic actions by inhibition of prostaglandin biosynthesis as described in the sections that follow. Some of the primary indications for NSAID therapy include:

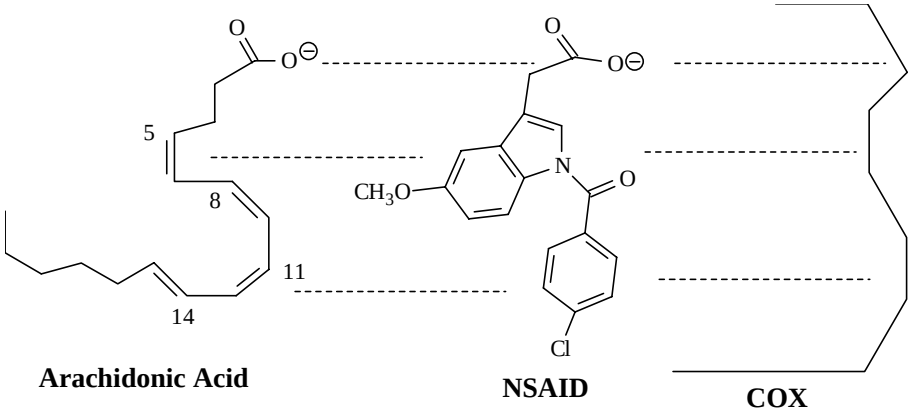
- Rheumatoid Arthritis (RA): No one NSAID has demonstrated a clear advantage for the treatment of RA. Individual patients have demonstrated variability in response to certain NSAIDs. Anti-inflammatory activity is shown by reduced joint swelling, reduced pain, reduced duration of morning stiffness and disease activity, increased mobility, and by enhanced functional capacity (demonstrated by an increase in grip strength, delay in time-to-onset of fatigue, and a decrease in time to walk 50 feet).
- Osteoarthritis (OA): Improvement is demonstrated by increased range of motion and a reduction in the following: Tenderness with pressure, pain in motion and at rest, night pain, stiffness and swelling, overall disease activity, and by increased range of motion. There are no data to suggest superiority of one NSAID over another as therapy for OA in terms of efficacy and toxicity. NSAIDs for OA are to be used intermittently if possible during painful episodes and prescribed at the minimum effective dose to reduce the potential of renal and GI toxicity. Indomethacin should not be used chronically because of its greater toxicity profile and its potential for accelerating progression of OA.
- Acute gouty arthritis, ankylosing spondylitis: Relief of pain; reduced fever, swelling, redness and tenderness; and increased range of motion have occurred with treatment of NSAIDs.
- Dysmenorrhea: Excess prostaglandins may produce uterine hyperactivity. These agents reduce elevated prostaglandin levels in menstrual fluid and reduce resting and active intrauterine pressure, as well as frequency of uterine contractions. Probable mechanism of action is to inhibit prostaglandin synthesis rather than provide analgesia.

II. NSAID Mechanism of Action

The major mechanism by which the NSAIDs elicit their therapeutic effects (antipyretic, analgesic, and anti-inflammatory activities) is inhibition of prostaglandin (PG) synthesis. Specifically NSAIDs competitively (for the most part) inhibit cyclooxygenases (COXs), the enzymes that catalyze the synthesis of cyclic endoperoxides from arachidonic acid to form prostaglandins (see Prostaglandin Chapter).

Two COX isoenzymes have been identified: COX-1 and COX-2. COX-1, expressed constitutively, is synthesized continuously and is present in all tissues and cell types, most notably in platelets, endothelial cells, the GI tract, renal microvasculature, glomerulus, and

collecting ducts. Thus COX-1 is important for the production of prostaglandins of homeostatic maintenance, such as platelet aggregation, the regulation of blood flow in the kidney and stomach, and the regulation of gastric acid secretion. Inhibition of COX-1 activity is considered a major contributor to NSAID GI toxicity. COX-2 is considered an inducible isoenzyme, although there is some constitutive expression in the kidney, brain, bone, female reproductive system, neoplasias, and GI tract. **The COX-2 isoenzyme plays an important role in pain and inflammatory processes.**



Inhibition of COX by NSAIDs

Generally, the NSAIDs inhibit both COX-1 and COX-2. Most NSAIDs are mainly COX-1 selective (eg, aspirin, ketoprofen, indomethacin, piroxicam, sulindac). Others are considered slightly selective for COX-1 (eg, ibuprofen, naproxen, diclofenac) and others may be considered slightly selective for COX-2 (eg, etodolac, nabumetone, and meloxicam). The mechanism of action of celecoxib and rofecoxib is primarily selective inhibition of COX-2; at therapeutic concentrations, the COX-1 isoenzyme is not inhibited thus GI toxicity may be decreased.

Other mechanisms that may contribute to NSAID anti-inflammatory activity include the reduction of superoxide radicals, induction of apoptosis, inhibition of adhesion molecule expression, decrease of nitric oxide synthase, decrease of proinflammatory cytokine levels (tumor necrosis factor-a, interleukin-1), modification of lymphocyte activity, and alteration of cellular membrane functions.

Central analgesic activity has been demonstrated in animal pain models by some NSAIDs such as diclofenac, ibuprofen, indomethacin, and ketoprofen. This may be because of the interference of prostaglandin (PGE1, F2 and F2a) mediated pain formation or with transmitters or modulators in the nociceptive system. Other proposals include the central action mediated by opioid peptides, inhibition of serotonin release, or inhibition of excitatory amino acids or N-methyl-D-aspartate receptors. NSAIDs are mainly effective against the type of pain in which PGs sensitize pain receptors (inflammation and tissues) including the pain of arthritis, bursitis, pain of muscular and vascula origin and dysmenorrhea. The effectiveness of these agents against headache may result from their ability to inhibit PG-mediated cerebral vascular vasodilation.

Antipyretic activity of NSAIDs results from inhibition of prostaglandin E2 (PGE2) synthesis in

circumventricular organs in and near the preoptic hypothalamic area. Infections, tissue damage, inflammation, graft rejection, malignancies, and other disease states enhance the formation of cytokines that increase PGE2 production. PGE2 triggers the hypothalamus to promote increases in heat generation and decreases in heat loss.

III. Other Actions of the NSAIDs

The NSAIDs also express a variety of other actions in addition to their antiinflammatory, analgesic and antipyretic activities as outlined below:

- GI Tract (N/V, ulceration and hemorrhage). In the gastric mucosa, prostaglandins play a cytoprotective role inhibiting the proton pump and thereby decreasing gastric acid synthesis, stimulating the production of glutathione that scavenges superoxides, promoting the generation of a protective barrier of mucous and bicarbonate, and promoting adequate blood flow to the gastric muscosal cells. Since NSAIDs block PG biosynthesis in the GI tract, they block these cytoprotective processes. The primary toxicity seen with the NSAIDs is GI irritation which may lead to the production of ulcers when used in large doses over a long period of time. This occurs quite frequently in patients with RA and it may become so severe that the drug must be discontinued. There have been a number of attempts to eliminate this side effect and some success has been achieved but since most of the compounds suppress the production of PGs involved in limiting the secretion of gastric acid and since this a consequence of their mechanism of action it has been difficult to completely eliminate this side effect. In additional to inhibition of PG biosynthesis, NSAID gastric irritation may also be due to a direct irritation of the gut by these acidic compounds.

- CNS: High NSAID doses cause CNS stimulation (confusion, dizziness, etc), tinnitus, etc. PGE2 may also cause fever via interactions within the hypothalamus

- Respiratory: Direct and indirect (increased CO_2 production) stimulation of respiratory centers, stimulation of O_2 consumption in muscle (increased CO_2); respiratory alkalosis. Also PGI2 and the PGEs cause bonchodilation while PGF2a, PGGs, PGH2, PGD2 and TxA2 are bronchoconstrictors (asthma)

- Acid-Base: Initial respiratory alkalosis. This is generally somewhat unique to the salicylates and is only seen with large doses.
- Cardiovascular: PGH2 and PGH2 cause transient vasoconstriction, but these intermediates are converted to PGI2 and other PGS (PGD2 PGF2a) which are vasconstrictors. At high doses NSAIDs cause vasodilation and depression of the vasomotor center.
- Uterus: PGF2a and PGE2 (in low concentrations) promoate uteral contraction while PGI2 and PGE2 in high concentrations promote uteral relaxation. NSAIDs decrease contractility and prolong gestation
- Blood clotting: PGS I2 (vascular endothelium), E2 and D2 inhibit platelet aggregation while TXA2 (platelets) promotes aggregation. NSAIDs may significantly increase clotting times and can be used for prophylaxis of thromboembolism and MI. However, patients with liver damage, vitamin K deficiency, hypoprothrombinemia or hemophilia should avoid aspirin

therapy.

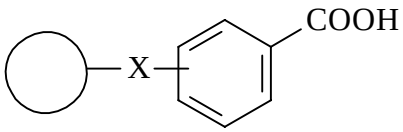
- Renal: The inhibition of PGE_2 and PGI_2 both of which produce vasodilation in the kidney results in a decrease blood flow to the kidneys due to constriction of afferent arterioles which is mediated by norepinephrine and Angiotensin II. NSAIDs may decrease sodium and fluid elimination resulting in edema
- Reye's syndrome: This is seen in children who take an NSAID such as aspirin while recovering from mild viral infection. Although it occurs rarely there is a 20-30% mortality seen with this type of side effect.

IV. General Structure and Properties of the NSAIDs

The NSAIDs can be sub-classified on the basis of chemical structure as follows:

- Salicylates
- Propionic Acids (Profens)
- Aryl and Heteroarylacetic Acids
- Anthranilates (Fenamates)
- Oxicams ("Enol Acids")
- Phenylpyrazolones
- Anilides

In general, NSAIDs structurally consist of an acidic moiety (carboxylic acid, enols) attached to a planar, aromatic functionality. Some analgesics also contain a polar linking group, which attaches the planar moiety to an additional lipophilic group. This can be represented as follows:



NSAID General Structure

As a result, the NSAIDs are characterized by the following chemical/ pharmacologic properties:

- All are relatively strong organic acids with pKas in the 3-5 range. Most, but not all, are carboxylic acids (see drug classes). Thus, salts forms can be generated upon treatment with base and all of these compounds are extensively ionized at physiologic pH. The acidic group is essential for COX inhibitory activity!

- The NSAIDs differ in their lipophilicities based on the lipophilic character of their aryl groups and additional lipophilic moieties and substituents.

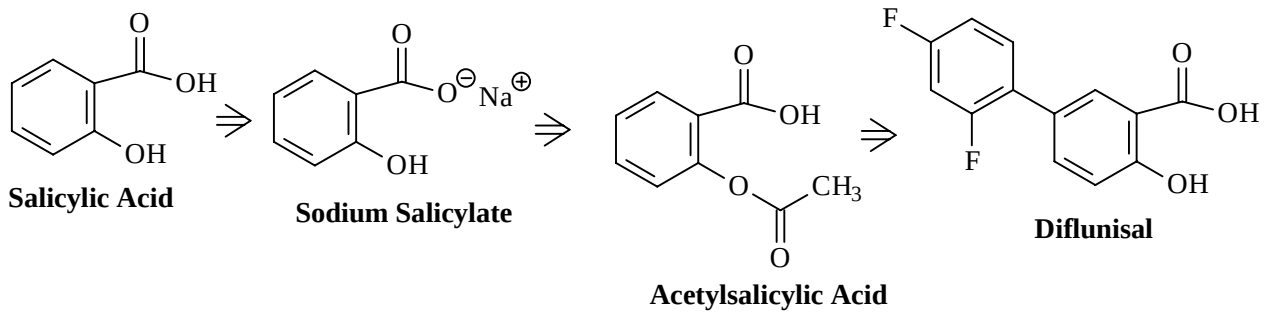
- The acidic group in these compounds serves a major binding group (ionic binding) with plasma proteins. Thus all NSAIDs are highly bound by plasma proteins (drug interactions!).

- The acidic group also serves as a major site of metabolism by conjugation. Thus a major

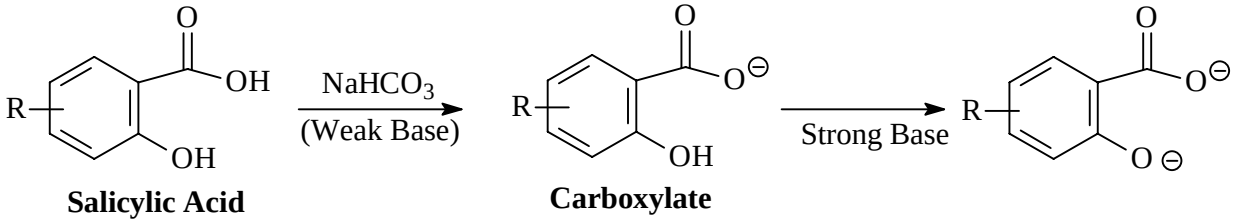
pathway of clearance for many NSAIDs is glucuronidation (and inactivation) followed by renal elimination.

V. Salicylates

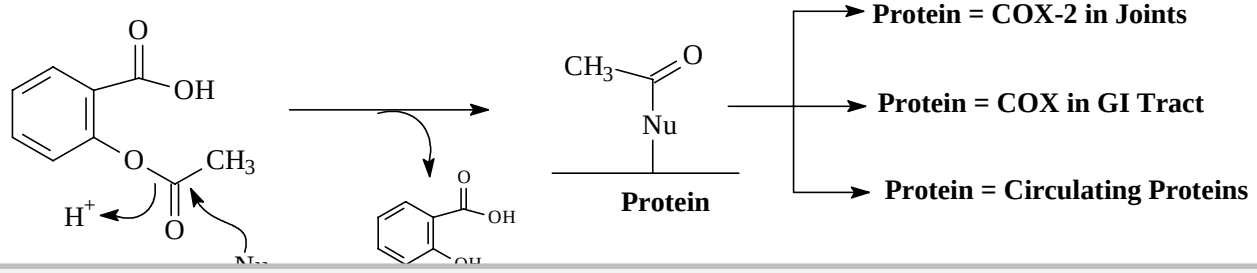
- Structure and Chemistry: The salicylates are derivatives of 2-hydroxybenzoic acid (salicylic acid). The salicylates were discovered in 1838 following the extraction of salicylic acid from willow bark. Salicylic acid was used medicinally as the sodium salt but replaced therapeutically in the late 1800s by the acetylated derivative, acetylsalicylic acid (ASA) or aspirin. Therapeutic utility is enhanced by esterification of the phenolic hydroxyl group as in aspirin, and by substitution of a hydrophobic/lipophilic group at C-5 as in diflunisal:



The salicylates are strong organic acids and readily form salts with alkaline materials. Note that the carboxyl group is substantially more acidic (and ionizes readily at physiologic pH) than the phenolic hydroxyl:



- Actions: The salicylates have potent antiinflammatory activity with mild analgesic and antipyretic activities. These compounds are mainly "COX-1 selective" – they are bound with higher affinity by COX-1. Toxicities include GI irritation, hypersensitivity reactions, inhibition of platelet aggregation, and ototoxicity (tinnitus). The therapeutic and certain of the toxic actions (i.e. gut) of aspirin can be related to its ability to inhibit COX in various tissues and participate in transacetylation reactions *in vitro*. For example, acetylation of COX results in irreversible inhibition of this enzyme and antiinflammatory effects in joints, and adverse effects in the GI tract. Also acetylation of circulating proteins may result in a hypersensitivity response.



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