INTRODUCTION

The term NSAID is an abbreviation of a class of drugs known as nonsteroidal anti-inflammatory drugs. This nomenclature was given to the class as a differentiation from steroids, the other major anti-inflammatory class of drugs. In addition to their anti-inflammatory effects, agents belonging to the NSAID class possess both analgesic and antipyretic activities. Hence, NSAIDs are sometimes referred to as non-narcotic analgesics or as aspirin-like drugs (aspirin was the first member of the class to be discovered). The class of NSAID drugs illustrates the close relationship between the chemical structure of drugs on one side and their biological effects and kinetic properties on the other side. The chemical features of NSAIDs explicitly explain different aspects of their behavior including kinetics (absorption, distribution, metabolism, and excretion, abbreviated “ADME”), mechanism of action and potential adverse effects.

General Statement of NSAID Chemistry and Actions

NSAID is an important therapeutic class of drugs used to suppress pain and inflammation in cases of rheumatoid arthritis and other inflammatory diseases. Recently, some NSAIDs have emerged as part of a new class of cancer chemotherapeutic and chemopreventive agents. Members of the NSAID class are characterized by having several common chemical and biological features. The following section outlines the major points to learn and observe about the NSAID group of drugs. Each general statement will be addressed in detail.

1. Disease state of inflammation and the role of prostaglandins as the pain-causing elements during inflammation.
2. Chemistry and structure activity relationships of NSAIDs.
3. NSAID kinetic properties (ADME: absorption, distribution, metabolism, excretion).
5. Ulcerogenic properties of NSAIDs as the primary adverse effect and its relationship to the mechanism of action and chemical nature of the class members.
6. Effects of NSAIDs on blood clotting and their relevance to both therapeutic use and adverse effects of class members.
7. NSAID as a new emerging class of drugs for cancer chemotherapy and prevention.

1. Disease State of Inflammation and Prostaglandins Biosynthesis

In a simplified term the inflammation process can be considered as an event of the immune response through which tissue damage occurs. The latter is accompanied by the release of several biochemical mediators such as histamine, bradykinin, platelet-activating factor, and a group of lipid material known as leukotrienes (LTs) and prostaglandins (PGs). These mediators are responsible...
Figure 1. Inflammation cascade and Formation of Prostaglandins and Leukotrienes from Arachidonic acid.

For the symptoms that accompany the inflammation process. While histamine, bradykinin, and leukotrienes cause the swelling and redness of the inflamed area (due to vasodilation and increased capillary permeability), prostaglandins, on the other hand, increase tissue sensitivity to pain and cause elevation of body temperature. Figure 1 depicts a simplified scheme for the inflammation cascade. Due to the pivotal role of prostaglandins in mediating pain during inflammation, a full understanding of their chemistry, biosynthesis, nomenclature, and pharmacological actions becomes essential. The section below and Figure 1 provide the needed information.
Prostaglandins

Prostaglandins are a group of autacoids (local hormones) that are endogenously synthesized from a 20-carbon polyunsaturated fatty acid common precursor called arachidonic acid (Figure 1, structure 1). Upon tissue exposure to any of the inflammation-precipitating factors (chemical, mechanical or hormonal), cell membranes release arachidonic acid by partial hydrolysis of lipids by the membrane-bound enzyme phospholipase. 

Arachidonic acid is subjected to 1 of 2 biochemical transformation routes. One route involves hydroxylation of the fatty acid by the enzyme lipooxygenase, resulting in the formation of a group of autacoids called leukotrienes (these were first discovered in leukocytes). The second route involves oxygenation and a process of cyclization by an enzyme called cyclooxygenase (or COX) to produce a class of autacoids known as prostaglandins (see Figure 1). Several of these prostaglandins were isolated and identified and given abbreviated names such as PGE\textsubscript{2}, PGF\textsubscript{2}, PGI\textsubscript{2} (the letters are given to different intermediates of the biosynthesis process, and the subscript indicates the number of double bonds in the molecule; see Figure 1, structures 2, 3, and 4). The cyclooxygenase enzyme also converts arachidonic acid into another cyclization product called thromboxane (TXA), first isolated from thrombocytes, having a 6-membered ring instead of the 5-membered ring found in prostaglandin (see Figure 1, structure 5). The biological effects of various prostaglandins and thromboxanes indicate that both PGE and PGF are responsible for increasing tissue sensitivity to pain. The major effect of PGI\textsubscript{2} (also called prostacycline) is inhibition of the platelet aggregation process, while TXA\textsubscript{2} has the opposite effect on platelets. Both PGE and PGF induce the secretion of polysaccharide material in the stomach known as mucin. This polysaccharide substance acts as a natural protective agent against potential stomach ulceration from the effects of HCl and the enzyme pepsin. This explains the ulcerogenic effects of the NSAID class of drugs. Due to the apparent role of prostaglandins in the process of inflammation, inhibiting prostaglandin biosynthesis became an attractive approach to fighting inflammation. Prostaglandin biosynthesis inhibitors are the class of anti-inflammatory agents known today as NSAID.

2. Chemistry and Structure Activity Relationships of NSAID

The mechanism of action of NSAIDs involves reduction of prostaglandin synthesis by inhibition of COX enzyme through competitive antagonism for arachidonic acid binding to the cyclooxygenase enzyme (COX). For a drug to be an effective competitive inhibitor for arachidonic acid binding to COX, the drug must possess both high lipophilic and acidic properties to mimic the natural substrate chemistry. This is clearly apparent in the chemical structures of all NSAIDs (Figure 2) such as Ibuprofen\textsuperscript{3} (structure 6), flubiprofen\textsuperscript{4} (structure 7), ketoprofen\textsuperscript{5} (structure 8), naproxen\textsuperscript{6} (structure 9), indomethacin\textsuperscript{7} (structure 10), diclofenac\textsuperscript{8} (structure 11), and piroxicam\textsuperscript{5,6} (structure 12). The acidic functionality can be a propionic acid carboxylic group (see Figure 2, structures 6, 7, and 8), or an acetic acid carboxylic group (see Figure 2, structures 10 and 11), or as an enolic group (acidic proton of 1,3 diketo group; see structure 12). NSAIDs with a polar group in the lipophilic tail such as sulindac\textsuperscript{8} (structure 13) are not effective COX inhibitors before being metabolized into a more lipophilic substance (structure 14) as further explained under the metabolism section of NSAIDs kinetics. In a similar manner, lipophilic drugs lacking the acidic functionality, such as nabumetone\textsuperscript{9} (structure 15), are metabolized into products with acidic functional groups (structure 16) before becoming active. Therefore, both sulindac and nabumetone are classified as produgs. It is worth noting the correlations between drug generic names and their chemical structures, eg, all propionic acid NSAIDs include the letters “pro” in the name, while acetic acid derivatives include the letters “ac.” The names of both nabumetone and naproxen indicate that both are naphthalene derivatives.

3. Kinetics of NSAID (ADME)

Absorption: Since all NSAIDs are highly lipophilic substances, members of the class share similar, if not identical, absorption properties. Drug absorption after oral administration is generally rapid and complete. Most NSAIDs are given as oral tablets or capsules; others are given by injection to avoid gastric irritation (see section 5).

Distribution: The most significant aspect of NSAID distribution is plasma protein binding. The chemical nature of these agents suggests strong binding to plasma proteins. The major plasma protein component is albumin, which has several basic and lipophilic residues. NSAIDs with both acidic functionality and lipophilic tails bind to albumin through both ionic and hydrophobic forces of interactions. Plasma protein binding of NSAIDs may pose the potential for drug-drug interaction with other drugs that bind with albumin at the same sites. Plasma protein displacement is common when NSAIDs are concurrently administered with other drugs.
such as the oral anticoagulants, the anticancer agent methotrexate, the oral anti diabetic agents, and thyroid hormones. Displacement from albumin may increase the activity or toxicity of such drugs. The best example for such a drug-drug interaction is the observed increase of the anticoagulant effects by warfarin when concurrently administered with aspirin and aspirin-like drugs.

**Metabolism:** Knowledge of the mechanism of action of NSAIDs, as competitive inhibitors for arachidonic acid binding to COX, provides a good tool to predict whether NSAID metabolites are active or not. Generally, phase-I metabolism of NSAIDs produces more polar products. These polar metabolites are not
polar products. These polar metabolites are not efficient COX inhibitors because they lack the lipophilic properties to compete with arachidonic acid and prevent its binding to COX. Accordingly, it is easy to conclude that most of the NSAIDs are metabolized into inactive products, which is the case in reality. When the original drug is polar, like sulindac (due to the ionic sulfoxide group, structure 13), phase-I metabolism results in the conversion of the sulfoxide group into the very lipophilic sulfide group by a reduction mechanism to produce the nonpolar sulfide form of the drug (structure14). The latter (reduced form of sulindac) is the actual inhibitor for the enzyme COX. When the original drug lacks the acidic functional group, such as in nabumetone (structure 15), phase-I metabolism results in nabumetone conversion into the acetic acid derivative (structure 16) via an oxidative degradation process similar to that for fatty acids metabolism. Phase-I metabolism of NSAIDs can be affected if these drugs are co-administered with drugs that alter the metabolism of other drugs. Enzyme inhibitors such as cimetidine and valproic acid and enzyme inducers such as carbamazepine and phenobarbital may enhance or decrease the anti-inflammatory activity of NSAIDs depending on whether the drug is biologically activated or deactivated by metabolism.

Excretion: NSAIDs are mostly excreted as phase-II glucuronides and in a few cases as sulfate conjugates. In addition, small percentages of NSAIDs are excreted unchanged in urine. If the drug is excreted unchanged, its rate of excretion is expected to increase if the drug is coadministered with agents that render the urine pH alkaline such as the antacids aluminum hydroxide and milk of magnesia.

4. NSAID Mechanism of Action as Antipyretic, Analgesic, and Anti-Inflammatory Agents

As pointed out earlier, NSAIDs act as anti-inflammatory agents by inhibiting the biosynthesis of the prostaglandins that are classified as inflammation-inducing substances. For a given drug to act as an NSAID, the drug’s chemistry must fulfill 2 major criteria: it must have lipophilic properties and the presence of an acidic functional group. Drugs having either weak lipophilic or weak acidic properties are not expected to be good anti-inflammatory agents. Acetaminophen (structure 17), shows weak properties regarding both lipophilicity and acidity; therefore, it is void of any anti-inflammatory actions. On the other hand, acetylsalicylic acid (structure 18) has poor lipophilic properties but a strong acidic functional group produces anti-inflammatory effects only at much higher doses (10 g) than its analgesic dose of only 1g. Drugs with both strong lipophilic characteristics and strong acidic properties such as members of the acetic and propionic acid series show significant anti-inflammatory actions at much smaller doses (30 mg-100 mg).

5. Ulcerogenic Versus Nonulcerogenic NSAIDs

In general, NSAIDs exhibit a similar pattern of adverse effects on the gastrointestinal tract including nausea, vomiting, and diarrhea. However, the most serious and detrimental adverse effect attributed to the prolonged use of NSAIDs is the development of gastric ulceration. The ulcerogenic properties of NSAIDs stem from the fact that they are organic acids, which can irritate the gastric mucosa, and also from their inhibitory effects on prostaglandin biosynthesis. Prostaglandins are the natural stimulatory agents for mucin secretion. The latter is carbohydrate polymer, normally produced by the stomach, and acts as an endogenous cytoprotective substance against the digestive effects of trypsin and hydrochloric acid. Accordingly, by inhibiting prostaglandin synthesis, mucin secretion will be indirectly reduced and an increased risk of ulceration arises. The enzyme COX has 2 sub-types: COX-1 and COX-2. The former exists throughout the biological system including in the stomach, while the second (COX-2) is much less abundant in the stomach. This discovery prompted investigators and researchers to develop selective COX-2 inhibitors to minimize the ulcerogenic potential of NSAIDs. Two major drugs were produced by this approach: celecoxib\(^\text{10}\) (Figure 2, structure 19), and rofecoxib\(^\text{11}\) (Figure 2, structure 20). The medicinal chemistry of the 2 drugs indicates high lipophilic characteristics with an acidic functionality represented by the sulfonamido group in celecoxib, or the bio-isosteric group methylsulfone in rofecoxib. The subtype-COX-2 enzyme has a selective binding area for the sulfone group while the subtype-COX-1 lacks such an area.

6. NSAIDs and Blood Clotting

The inhibitory effects of NSAIDs on the production of prostacyclin (PGI) and thromboxane (TXA) precipitate 2 opposing effects on the blood clotting process. Inhibition of PGI synthesis may promote blood clotting, while inhibition of TXA synthesis may inhibit blood clotting. However, the clinically observed effect accompanying NSAID use is primarily increased bleeding. If a peptic ulcer is also present, this constitutes a serious problem, even with COX-2 selective drugs. However, the effect of NSAIDs on blood clotting is a clinically useful approach with acetylsalicylic acid (aspirin), a prophylactic agent against stroke. Aspirin was found to...
decrease blood clotting by dual mechanisms; by inhibiting the thromboxane synthesis and through chemical acetylation of the blood platelets. The acetylated platelets have much slower rate of aggregation, a phenomenon that is needed for people with a high risk of developing internal blood clots after stroke.

7. NSAIDs and Cancer Chemotherapy and Prevention

COX-2 inhibitors have recently emerged as a promising new class of drugs that may be useful for cancer chemotherapy and prevention. Celecoxib was reported to be useful in decreasing the risk of developing colorectal cancer for patients with familial adenomatous polyposis (FAP). A recent indicated a possible role of COX-2 inhibitors in breast cancer chemoprevention. The interest in NSAIDs in cancer treatment and prevention is not limited to the selective COX-2 inhibitors. Piroxicam (a nonspecific COX inhibitor) was recently reported to potentiate the anticancer effects of cisplatin on human invasive bladder cancer. It must be indicated that the mechanisms through which NSAIDs suppress cancer growth is not yet fully understood. However, future research in such an exciting area may reveal and establish such mechanisms.

8. Summary and Conclusion

- The class of NSAID represents an important group of drugs indicated for treatment of inflammation. The drugs suppress inflammation through inhibiting prostaglandins synthesis.

- Chemistry and structure activity relationships of NSAID show that all members of the class have 2 basic chemical entities: an acidic functional group and a highly lipophilic tail.

- Most members of the class share similar kinetic properties of good absorption after oral administration and strong plasma protein binding. Phase-I metabolites are generally inactive as COX inhibitors except for the prodrugs: sulindac and nabumetone, where phase-I metabolism generates the active metabolites.

- All members of the class act by the same mechanism of action, reduction of prostaglandin synthesis through inhibition of the enzyme cyclooxygenase (COX). All members of the class possess antipyretic and analgesic properties; however, only those with strong inhibitory effects on PGs synthesis are useful as anti-inflammatory drugs.

- Most members of the class predispose for the development of peptic ulcer disease; hence, they are classified as ulcerogenic agents (ulcer-causing drugs). Gastric ulceration is attributed to the inhibitory effects of NSAIDs on prostaglandin synthesis and its subsequent inhibitory effects on mucus secretion.

- Due to the inhibitory effects on thromboxane (TXA2) biosynthesis, prolonged use of most of the class members results in decreased blood clotting, which can lead to serious bleeding problems if combined with the development of an ulcer.

- NSAIDs, especially selective COX-2 inhibitors, represent a new class of cancer chemotherapeutic and chemopreventive agents. Several members of the class were found to be promising in treatment and prevention of colon, breast, and bladder cancer.

Recommended Readings:


REFERENCES


