NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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The topic of anti-inflammatory drugs (non-steroidal anti-inflammatory drugs-NSAIDs) is both a simple and a complex one. We call them simple for we all use them. The drugs all work to varying degrees and they all have similar, but not identical side effects. We call the drugs complex because we are only beginning to understand their effects, barely scratching the surface on how those "effects" actually work. We are baffled by the multiple internal organ and other drug interactions which which these drugs are associated.

This paper will touch on the actions and interactions of the group as a whole, attempting to classify or "pigeonhole" these by some sort of groupings, describing uses and side-effects in a relevant manner, and trying to give some idea as to a proper use or at least a rational approach to such use. It is not the attempt of this communication to describe each NSAID in its entirety (or even briefly) though points regarding specific drugs will be made when it appears appropriate.

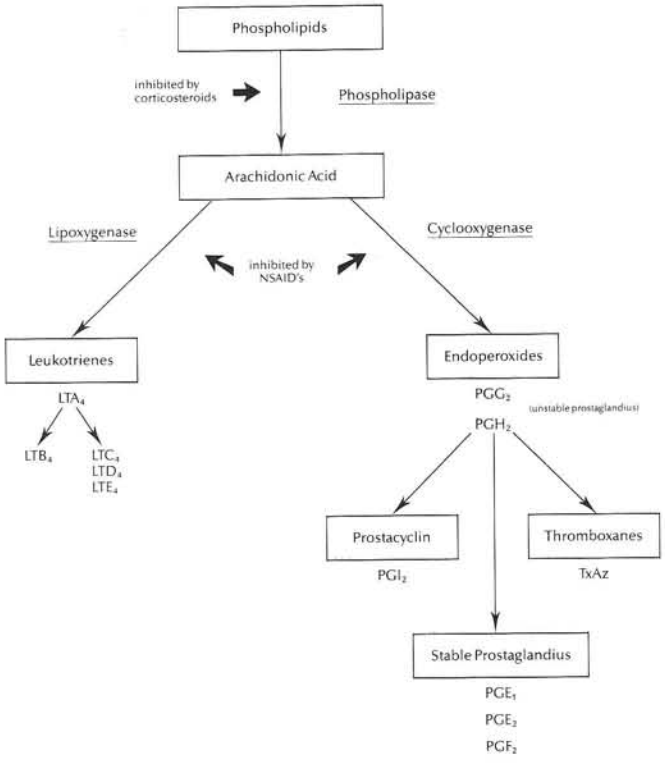
The NSAIDs will generally decrease the signs and symptoms of inflammation within several days of administration and are apparently effective so long as *blood levels are sustained.* Inflammation is not totally suppressed and joint damage does continue, but the inflammation does seem to be moderated and symptoms improved.

Mechanism of action of NSAIDs is felt to be through an inhibition of synthesis of some of the products of arachidonic acid metabolism (especially via cyclo-oxygenase and/or lipoxygenase suppression) (Fig. 1). However, NSAIDs also have effects on synovial cells, blood vessel walls, and infiltrating white blood cells (WBCs) as well as on WBC mobility, chemotactic responsiveness, phagocytic activity and the release of lysosomal enzymes. They also seem to have some effect on the generation of toxic oxygen radicals. In view of such diverse effects, it is unlikely that all the NSAIDs act through a single pathway (e.g., the prostaglandin [PG] or cyclo-oxygenase pathway).

Arachidonic acid is a constituent of cell membrane phospholipids and is produced in response to inflammatory stimuli. The NSAIDs block the conversion of arachidonic acid to endoperoxides PGG_2 and PGH_2 by inhibiting cyclo-oxygenase, a membrane-bound enzyme previously called prostaglandin synthetase. In flamed tissues, these endoperoxides are transformed to PGE_2 and in platelets to thromboxane A_2. Decreasing endoperoxide formation by NSAIDs therefore blocks the synthesis of both prostaglandins and thromboxanes, and it is postulated that the anti-pyretic, analgesic, and anti-inflammatory effects of these drugs are due to their effect on cyclo-oxygenase as various prostaglandins are known to mediate fever, inflammation, and pain.

It is of some interest that the pKa (the pH at which the salt is one-half ionized) of most of these drugs is between 3.5 and 5.0. The lower the pKa, the lower the lipophilicity; the lower the lipophilicity, the slower the absorption; the slower the absorption, the slower the metabolism and clearance. The opposite is true for the higher the pKa. A steady state is achieved after about four or five half-lives, with short-acting drugs reaching steady state in one day. Drugs with a 12 hour half-life reach the steady state in about two days, and drugs with half-lives of 24-36 hours

Fig. 1. ARACHIDONIC ACID PATHWAY



do not reach a steady state until almost a week. Below a pKa of about 3.0, there is little if any anti-inflammatory effect but an increase in uricosuric effect.

The clinical value of this information can be seen when one realizes that at normal gastric acidity, NSAIDs are generally *un-ionized;* this causes an increase in their *solubility in lipids* which enhances their ability to enter gastric mucosal cells and *increases gastric toxicity.* However, neutralization of gastric acid increases the pH to greater than the pKa which increases *water solubility* and decreases lipid solubility and consequently decreases absorption (a process commonly called a "Catch-22"). Further, NSAIDs also enter the gastric mucosa from the plasma (kind of a "back door" arrangement) so there is the potential for systemic toxicity to gastric mucosa as well.

There are several effects related to the fact that these drugs are rather highly bound to protein—some good and some not so good. From a pharmacokinetic standpoint, inflammation is frequently associated with exudation which increases the concentration of protein in the inflamed area. Since these drugs are protein bound, it appears that their concentrations would consequently be greatest in exactly the areas where they are most needed. Further, there is an increase in acidity at sites of inflammation; acidity causes dissociation of drug from plasma proteins with a subsequent increase in cell membrane penetration of the drug—just where it is most needed. Some of the "good" and many of the "not so good" effects are related to competition for binding sites of these highly protein-bound drugs with other protein-bound substances. Examples of this include:

1. NSAID-NSAID interactions where one drug may displace or be displaced by another, and
2. NSAID-other drug interactions such as with oral sulfonylurea antidiabetic agents, where displacing the latter will increase its free-active level in plasma with a consequent decrease in blood glucose making control of the diabetes more difficult.

Another example is NSAID displacement of warfarin (Coumadin) with a subsequent increase in free/active anticoagulant and possibly too great a "blood thinning" effect. In general, "Competitive binding" may:

1. increase free drug levels,
2. decrease half-life clearance,
3. increase tissue penetrance, and/or
4. decrease *measurable* plasma drug levels since it is only albumin-bound drug levels that we generally are able to measure.

There are many variables that affect (and effect) metabolism of these drugs including the following:

1. The above-described competitive protein binding and its attendant drug-drug interactions.
2. NSAIDs are generally all altered/conjugated in the liver and then cleared by the kidney with very little renal clearance of unchanged drug; this makes both hepatic and renal function an integral part of these drugs' actions and interactions.
3. Renal impairment decreases protein-binding causing an increase in both effect and toxicity due to an increase in unbound drug.
4. Some of the drugs are actually "prodrugs" (the drug itself is inactive and only one or more of its metabolites have anti-inflammatory effect), making alterations in the liver (conjugation, oxidation, glucuronidation) all the more important for effectiveness; examples of these drugs include sulindac and fenbufen.
5. Aging is associated with a decrease in cardiac output where heart, brain, and muscle flow are preserved but liver and kidney flow diminish with time, thereby decreasing hepatic alteration of drug while also decreasing renal clearance. There is also a decrease in serum albumin with age and an associated decrease in available binding sites and a consequent increase in free drug and possible toxicity.
6. NSAIDs themselves may temporarily decrease creatinine clearance and increase serum creatinine (probably by impairing the vasodilatory function of renal prostaglandins) but the changes often disappear even though the drug is continued. There are, however, very rare cases of acute renal failure with marked proteinuria due to acute interstitial nephritis or papillary necrosis.
7. Genetics may also play a role in the variability of metabolism of some drugs (especially aspirin and phenylbutazone), and it is known that both steroids and male sex are associated with more rapid metabolism of salicylates.

The list of variables goes on.

It is felt by most investigators that at least some if not all of the effects of NSAIDs are due to their suppression of prostaglandins (PGs) via inhibition of the cyclooxygenase pathway of arachidonic acid metabolism. Unfortunately (or fortunately), prostaglandins are responsible for much more than inflammation, and suppression is therefore associated with other systemic and/or local effects.

In the gastrointestinal (GI) tract prostaglandins are associated with decreased acid secretion (PGE_1, PGE_2, PGA), increased stomach cardiac sphincter tone (PGF_2), increased gastric mucin secretion, increased gastric blood flow and a tightening of the mucosal barrier; a suppression of prostaglandins would have the opposite effects. For comparison purposes, PGE_2 has 2000 times the potency of cimetidine (Tagamet) in decreasing gastric acid production. Additionally, some NSAIDs increase mucosal cell shedding and cause a local congestion and hemorrhage, further compounding their GI effects.

In the kidney, prostaglandins regulate renal blood flow (increase it), glomerular filtration rate, and sodium and water excretion—suppression having the opposite effects. NSAIDs also block the action of many diuretics, most notably furosemide (Lasiz). Discontinuing the NSAID will relatively rapidly reverse these renal effects.

Other effects of prostaglandins include:

1. Increased uterine contraction, hence the utilization of NSAIDs in both dysmenorrhea and premature labor uterine contractions.
2. Dilation of the ductus arteriosus, hence the utilization of NSAIDs (most notably indomethacin) in medically closing a patent ductus arteriosus. However, if used to slow premature uterine contractions, there is also the possibility of narrowing the ductus in utero.
3. Platelet aggregation is diminished by platelet cyclooxygenase via thromboxane production rather than via stable prostaglandin production, and NSAIDs decrease cyclooxygenase. Aspirin is itself acetylated and acetylates platelet cyclooxygenase. Because platelets lack mitochondria (they have no nuclei), they cannot synthesize additional cyclooxygenase, and aspirin therefore irreversibly diminishes the platelet aggregation of those platelets exposed to even small amounts. Other NSAIDs merely inhibit platelet cyclooxygenase in a manner directly proportional to the NSAIDs concentration [in the platelet, with aggregation inhibition decreasing as the NSAIDs concentration decreases (reversible platelet aggregation) and vice versa].
4. Prostaglandins also play a role in ocular disease. NSAIDs are variably of value in suppressing prostaglandin synthesis in uveal and conjunctival tissues. In this regard aspirin seems to have no effect while phenylbutazone, oxphenbutazone, and indomethacin do.

Most of this discussion has centered around NSAID suppression of cyclooxygenase and therefore also of prostaglandins. But, studies have shown that leukotrienes are also responsible for some components of the inflammatory response. Leukotriene B_4 [LTB_4] causes polymorphonuclear leukocyte aggregation, 0_2 [superoxide] generation, degranulation, and stimulation of guanylate and adenylate cyclase.

The enzyme responsible for transformation of arachidonic acid to leukotrienes is called lipoxygenase. The first NSAID to bring attention to this pathway was benoxaprofen which was a potent lipoxygenase inhibitor but only a weak cyclooxygenase inhibitor and yet which manifested potent anti-inflammatory effect. Since then, other NSAIDs have been shown to affect the lipoxygenase pathway to varying degrees.

Moving at this point to some of the NSAIDs themselves, it is noted that they comprise many different families with rather different chemical structures but all with the common end-point of suppression of inflammation. However, this is achieved, as was hinted at above, by varied pathways. This communication will only briefly touch on some of their differences and similarities.

The chemical groups into which these agents fall are the salicylates (aspirin, diflunisal), indole derivatives and related compounds (indomethacin, sulindac, tolmetin), pyrazolones (phenylbutazone, oxyphenbutazone), phenylacetic acids (diclofenac), phenylpropionic acids (ibuprofen, naproxen, fenoprofen), fenamates (meclofenamate), and oxicams (piroxicam) (Table 1).

As stated at the outset, they are all acidic compounds to differing degrees. Some are associated with more side effects (phenylbutazone, indomethacin), others with prolonged half-lives which therefore requires less frequent

TABLE I

GENERIC	BRAND NAME
Salicylates	
acetylsalicylic acid	aspirin
salicylsalicylic acid	Disalcid
diflunisal	Dolobid
choline magnesium trisalicylate	Trilisate
Indole derivatives and related compounds	
indomethacin	Indocin
sulindac	Clinoril
tolmetin	Tolectin
zomepirac	Zomax
etodolac	Ultradol
Pyrazolones	
phenylbutazone	Butazolidin
oxyphenbutazone	Tandearil
azopropazone	
Phenylacetic acids	
diclofenac	Voltarol/Voltaren
fenclofenac	
Phenylpropionic acids	
ibuprofen	Motrin/Rufen/Advil/Nuprin
naproxen	Naprosyn
fenoprofen	Nalfon
ketoprofen	Orudis
indoprofen	
carprofen	
flurbiprofen	Ansaid
fenbufen	Cincopal
benoxaprofen	Oraflex
suprofen	Suprol
Fenamates	
mefanamic acid	Ponstel
meclofenamate	Meclomen
flufenamic acid	
Oxicams	
piroxicam	Feldene
isoxicam	
Others	
nabumetone	Relafen

Notes: (a) not all these are marketed in the United States
(b) list is by no means complete
(c) several of these have been withdrawan from the market
(d) right hand column is composed of patented trade names

dosing (piroxicam, benoxaprofen), and others with greater efficacy in individual disease processes for uncertain reasons (indomethacin in crystal synovitis and juvenile rheumatoid, aspirin in juvenile rheumatoid and acute rheumatic fever, phenylbutazone in ankylosing spondylitis, possibly meclofenamate in psoriatic arthritis,and so on). Ingestion of food inhibits absorption of fenoprofen, slows absorption of ibuprofen, and increases absorption of isoxicam.

A brief summary, emphasizing clinical importance, of some of the agents follows.

Aspirin (ASA)

1. Albumin bound, peak within two hours, T 1/2 15 minutes
2. Once deacetylated, metabolized like other salicylates
3. Alkalinization of urine causes increased urinary salicylate excretion (same is true of uric acid)
4. Side effects include anaphylaxis (0.2%) with wheezing/asthma or urticaria/angioedema or both, hepatotoxicity, nephrotoxicity, GI toxicity, various "salicylism" syndromes.
5. Therapeutic blood levels are between 20-30 mg% and blood test measures salicylic acid.

Phenylbutazone

1. Oxyphenbutazone, its major metabolite, also marketed.
2. Albumin bound, T 1/2 40-90 hours, 2-3 weeks to peak and clear.
3. Especially helpful in ankylosing spondylitis and gout.
4. Side effects include GI toxicity, renal toxicity, severe hematological problems including asplastic anemia, agranulocytosis and thrombocytopenia (2-10 per million prescriptions).
5. Potentiates oral hypoglycemics and warfarin.

Indomethacin

1. Especially helpful in ankylosing spondylitis and gout.
2. Probenecid interferes with indomethacin elimination.
3. Peak in 1-3 hours, T 1/2 biphasic (2.2 and 11.2 hours)
4. Side effects especially include GI toxicity (increased since about 1/3 excreted in bile) and central nervous system effects (indole nucleus resembles serotonin), but does not change warfarin anticoagulant effect.
5. Many uses due to potent prostaglandin suppression.

Ibuprofen

1. Peak in 45-90 minutes (food delays absorption), T 1/2 2 hours.
2. Insignificant interaction with warfarin and only transient inhibition of platelet aggregation.
3. Especially helpful in juvenile rheumatoid, dysmenorrhea, premature labor and may limit size of infarct if given IV right after coronary occlusion.
4. Side effects include GI toxicity, edema, congestive failure, and an unusual aseptic meningitis in lupus patients.
5. Probenecid does not increase ibuprofen concentration as former blocks glucuro nidation and latter is metabolized by oxidation.

Sulindac

1. An inactive "prodrug" activated via liver metabolism.
2. Many (though infrequent) unusual side effects.
3. Less interference with renal mechanisms and diuretics than most NSAIDs.

Tolmetin

1. Approved for juvenile rheumatoid
2. Related to indomethacin but no indole nucleus.

Fenoprofen

1. Food inhibits absorption.
2. More frequent renal toxicity.

Naproxen

1. Probenecid increases blood levels.
2. No significant interaction with sulfonylureas and warfarin.

Diflunisal

1. Non-acetylated salicylate derivative.
2. Beware with renal impairment as cannot be hemodialyzed.
3. May increase amount of indomethacin reaching circulation.

Piroxicam

1. Very slow clearance, T 1/2 24 hours.
2. Little interference due to protein binding.

Many Others

1. Benoxaprofen - hepatotoxicity, hair and nail changes
2. Zomepirac—higher anaphylactic reactions
3. Fenbufen—a "prodrug"
4. Ketoprofen

5. Isoxicam
6. Diclofenac—does not interfere with hypoglycemics and anticoagulants
7. Azopropazone—related to phenylbutazone
8. Meclofenamate—loose stools; possibly better in psoriatic arthritis
9. Suprofen—flank pain
10. Salicylic acid—not acetylated
11. Fenclofenac—
12. Flurbiprofen—
13. Carprofen—
14. Nabumetone—non-acidic compound
15. Mefenamic acid—
16. Flufenamic acid—
17. Etodolac—
18. Indoprofen—

There is much debate as to how to use and monitor these drugs. Those that act more quickly are also lost from the circulation more quickly and those that act more slowly disappear more slowly. The practicality of that information is that the rapidly acting drugs may be metabolized so quickly that a bedtime dose may not be adequate to suppress symptoms through the night and so many need to be used at higher doses at that time of day—or even be replaced by a longer acting drug for nighttime use. The more slowly absorbed and metabolized drugs have a more prolonged effect and so may be dosed less frequently. But should there be a side-effect, it is more likely to last longer upon discontinuing the compound.

It is important to understand absorption, metabolism, and excretion of each drug so as to best be able to properly prescribe it. Is it best taken with or without food, during or after a meal, along with or separate from other drugs, and so on, and so on, and so on? How does one best monitor the drug (liver tests, blood counts, etc), and how often should the monitoring be done? Many feel that most NSAIDs should be monitored monthly for evidence of nephrotoxicity during the first year while others feel that is excessive, but most feel that appropriate monitoring for each drug should be carried out at regular intervals based on recommendations and experience. Unfortunately, package inserts and other information from the manufacturer are less than specific (as much to protect themselves, as it is that no one knows for certain) along these lines, so each practitioner has to make his or her own decision and adhere to it.

Finally, below is a list of well-described side effects that have been found with most of the compounds, though at relatively low incidences. While one cannot remember all of them, one should at least be attuned to the fact that rare and idiosyncratic reactions occur and should at least consider the NSAID in the differential diagnosis of signs and symptoms that are without obvious explanation in those taking the drugs.

1. GI symptoms of any type
2. Hepatitis, transaminitis and other evidence of liver dysfunction
3. Any and all types and degrees of renal dysfunction
4. Any and all hematological abberations
5. Pancreatitis
6. Allergic/hypersensitivity reactions
7. Pseudoallergic reactions (wheezing, nasal polyps and urticaria)
8. Any and all dermatological reactions (morbilliform rashes, urticaria, angioedema, Stevens-Johnson syndrome, erythema multiforme, erythema nodosum, toxic epidermal necrolysis, etc.)
9. Lesser or greater effects of concomitantly taken other drugs (especially oral hypoglycemics and anticoagulants)
10. Aseptic meningitis (ibuprofen and sulindac in lupus)
11. Anaphylactic reactions (especially tolmetin and zomepirac)

It should be apparent by now that these drugs have multiple and far-reaching effects and toxicities, multiple uses and various interactions. They are easy to prescribe and usually, but not always, relatively safe. As in other conditions, judicious choice of the proper agent for the proper condition in the proper individual is more likely to be associated with success than is a "shotgun" or more random approach. However, the shotgun is also often successful. Many of the chronic and acute conditions for which these agents are prescribed will not infrequently flare and/or remit spontaneously, an event that also makes wise choices more difficult. However, these drugs, as a class, are among the most frequently prescribed compounds in the world and have much to offer the quality of life to those who need and take them. One may increase the positive yield and decrease the odds of failure and toxicity by being knowledgeable about these drugs.

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