CHAPTER **28**

NSAID UPDATE 1995

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This article is intended to be a review and update on nonsteroidal anti-inflammatory drugs (NSAIDs). For a more complete review of the inflammatory process, prostaglandins synthesis, prostaglandin synthesis inhibition, and NSAIDs, the reader is referred to the 1988 and 1992 editions of *Reconstructive Surgery of the Foot and Leg*, and to the 1994 edition for a review of some of the newer anti-inflammatory drugs.[1-3] This article will provide a quick review of the arachidonic acid cascade, and how and at what point anti-inflammatory medications may exert their effects, in addition to a review of many of the drugs themselves.

ARACHIDONIC ACID "CASCADE"

As a class, these drugs are all believed to suppress inflammation by blocking production of prostaglandins (Fig. 1). Since prostaglandins serve many useful purposes, it is not surprising that their suppression is associated with relatively predictable side effects, the two most common being gastrointestinal (GI) disturbance and decreased renal function.

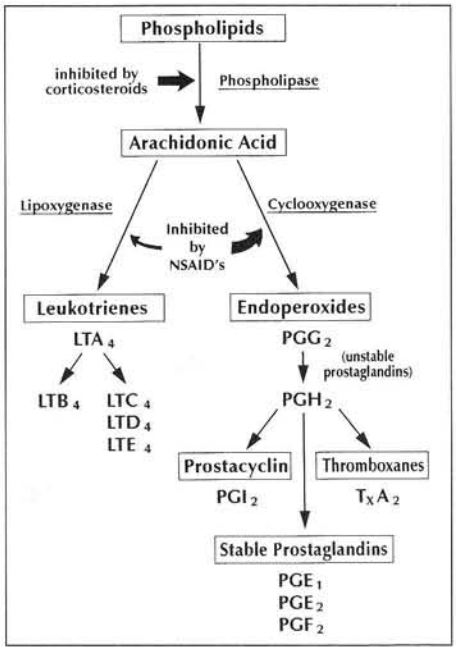

Figure 1. Arachidonic Acid Pathway

Certain prostaglandins are required to maintain gut integrity, and when their levels are decreased, erosion and ulcers may result. Other prostaglandins help maintain adequate renal blood flow, and decreasing their levels will decrease renal excretion of fluids, the end product being fluid retention.

GENERAL CONSIDERATIONS

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. 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 do not reach a steady state until almost a week.

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 pharmacokinetics 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 the 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.

2. NSAID-other drug interactions, such as:
   a. 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.
   b. Warfarin (Coumadin) anticoagulant, where displacement causes an increased free and active anticoagulant effect with a resulting possible greater-than-expected "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.

The plethora of effects of prostaglandins and related substances on various organs and organ systems include:

1. increased uterine contractions
2. dilation of the ductus arteriosus
3. platelet aggregation
4. various ocular effects
5. increased renal blood flow
6. gut wall integrity

As can readily be seen, the use of prostaglandin inhibitors such as the NSAIDs might be expected to produce the opposite effect.[1]

NSAIDS

The NSAIDs comprise many different "families" (Table 1) with rather different chemical structures, working at times through somewhat varied pathways, but all with the common end-point of suppression of inflammation. Some are more convenient to take (one a day vs. three or four times a day). Some are statistically associated with more, or more frequent, side effects, and some are much more expensive than others.

Table 1

NSAID FAMILIES

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	Lodine
Prazolones	
phenylbutazone	Butazolidin
oxyphenbutazone	Tandearil
azopropazone	
Phenlacetic acids	
diclofenac	Voltaren
fenclofenac	
Phenylpropionic acids	
ibuprofen	Motrin/Rufen/ Advil/Nuprin
naproxen	Naprosyn
fenoprofen	Nalfon
ketoprofen	Orudis/Oruvail
indoprofen	
carprofen	
flurbiprofen	Ansaid
fenbufen	Cincopal
benoxaprofen	Oraflex
suprofen	Suprol
oxaprozin	Daypro
Fenamates	
mefanamic acid	Ponstel
meclofenamate	Meclomen
flufenamic acid	
Oxicams	
piroxicam	Feldene
isoxicam	
Others	
nabumetone	Relafen

(This list is by no means complete, and not all are marketed in the United States. Several drugs have been withdrawn from the market. The right hand column is composed of patented trade names.)

A brief summary, emphasizing certain clinically important similarities and differences 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.

Salsalate (Disalcid)
1. Non-acetylated salicylate with extremely minimal GI toxicity.
2. Anti-inflammatory doses saturate biotransformation such that the half-life at those doses effectively increases from about five hours to as much as 16 hours, allowing for BID dosing.
3. Platelet aggregation is not inhibited.
4. Competitive binding will increase effect and potential toxicity of other protein-bound drugs, such as Coumadin.
5. Neurologic manifestations of salicylism may occur.

Phenylbutazone (Butazolidin)
1. Oxyphenbutazone, its major metabolite, has also been 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 (Indocin)
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.
6. Side effects seem to be more common with the generic preparations.

Ibuprofen (Motrin, Rufen, Nuprin, Advil, etc.)
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 glucuronidation and latter is metabolized by oxidation.
6. Side effects have been more frequently reported in the years that it has been available over-the-counter.

Sulindac (Clinoril)
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 (Tolectin)
1. Approved for juvenile rheumatoid.
2. Related to indomethacin but no indole nucleus.

Fenoprofen (Nalfon)
1. Food inhibits absorption.
2. More frequent renal toxicity.

Naproxen (Naprosyn, Aleve, etc.)
1. Probenecid increases blood levels.
2. No significant interaction with sulfonylureas and warfarin.

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

Piroxicam (Feldene)
1. Very slow clearance, T 1/2 > 24 hours.
2. Little interference due to protein binding.

Ketoprofen (Orudis/Oruvail)
1. Orudis is absorbed in an acid medium (stomach) and Oruvail in a more neutral one (small intestine).
2. Oruvail pellet coating is not dissolved in an acid medium.

Etodolac (Lodine)
1. Approved in osteoarthritis and pain but not in rheumatoid arthritis.
2. Dosage does not usually need to be adjusted for renal or hepatic dysfunction.
3. Does not interfere with Coumadin.
4. May cause a false-positive urine bilirubin test.

Flurbiprofen (Ansaid)
1. Highly bound to plasma proteins and so may need to adjust Coumadin dose downward.
2. No particular distinguishing features relative to other NSAIDs.

Oxaprozin (Daypro)
1. Fairly long half-life (four to seven days for steady state achievement).
2. No interference with Coumadin despite being highly protein bound.
3. Clearance seems to be decreased by H2 antagonists (e.g., cimetidine, rantidine, etc.).
4. Dosage can be QD or split to BID.

Diclofenac (Voltaren)
1. Only about 50% of absorbed drug is available due to large "first pass" metabolism.
2. 2/3 of metabolized drug found in urine and 1/3 in stool, suggesting fairly extensive enterohepatic recirculation.
3. Transaminitis is fairly common though severe hepatic reactions occur only rarely; should probably first check transaminase levels at about eight weeks or so.
4. Coumadin doses probably do not need adjusting with concomitant diclofenac.

Nabumetone (Relafen)
1. Only non-acidic NSAID.
2. Practically insoluble in water.
3. Pro-drug (6-methoxy-2-naphthylacetic acid is the active agent, 6-MNA).
4. 6-MNA is not enterohepatically recirculated so the acidic "drug" essentially does not come into contact with the GI tract.
5. Endoscopically noted GI lesion incidence is lower than with other NSAIDs, but overall incidence of GI symptoms is about the same.

Many Others
1. Benoxaprofen (Oraflex) – hepatotoxicity, hair and nail changes.
2. Zomepirac (Zomax) – higher anaphylactic reactions.
3. Fenbufen (Cincopal) – a "prodrug".
4. Meclofenamate (Meclomen) – loose stools; possibly better in psoriatic arthritis.
5. Suprofen (Suprol) – flank pain, highly uricosuric.

As is evident from the description of some of the similarities and differences outlined above, the intended effects of the agents are similar, while some notable differences exist between many of them. It is these differences that should lead to a rational approach to NSAID use in individual patients and circumstances.

NSAID MONITORING

There is considerable debate on how to monitor these drugs for potential toxicity. The most obvious and best way is to provide the patient with the information necessary for self monitoring. Patient reported side effects should be followed up, especially gastrointestinal symptoms of any type, fluid retention, skin rashes, etc. In view of the real possibility of GI bleeding, blood counts should be monitored regularly, stool samples examined for occult blood, and/or GI studies (endoscopy, barium studies, etc.) should be obtained as dictated by symptoms or a drop in blood counts. Hepatic and renal function should be assessed regularly as well, both because of possible toxicity to these organs, and because decreased function of either the kidney or the liver will predispose the patient to other toxic effects of the drug. There is no rule of thumb as to the frequency of such monitoring, but prudence dictates it be done at least twice a year for those taking the medications regularly.

SUMMARY

It is the hope of this review to familiarize the user/prescriber with the physiology and rationale behind the use of nonsteroidal anti-inflammatory drugs, some unique features of many of the drugs, and the best way to prevent or minimize their various toxicities. Since the response to a particular medication by a particular patient is relatively individual, each agent may well find its circle of responders. It is not inappropriate to change from one to another after adequate time to achieve efficacy if the efficacy (or lack thereof) is not acceptable in light of associated toxicity. Despite occasional serious toxicity, when taken and monitored properly, NSAIDs have provided relief to millions with relative safety and ease of administration.

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