CHAPTER **34**

NSAID Update 1994

Sanford S. Hartman, M.D.

INTRODUCTION

This article is intended to be a review and update on nonsteroidal anti-inflammatory drugs (NSAIDs). For 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*.[1,2] 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. Some of the products used to counter the frequently-associated gastrointestinal side-effects will also be discussed.

One will recall that cell membrane phospholipids are acted upon by phospholipase to produce arachidonic acid. The latter is acted upon by at least two enzymes, cyclooxygenase to produce prostaglandins of various types, and lipoxygenase to produce leukotrienes (Fig. 1). While both pathways are involved in the inflammatory process, it is felt that the cyclooxygenase pathway is the major one involved in the inflammatory response, and that the NSAIDs exert their greatest effects through this pathway.

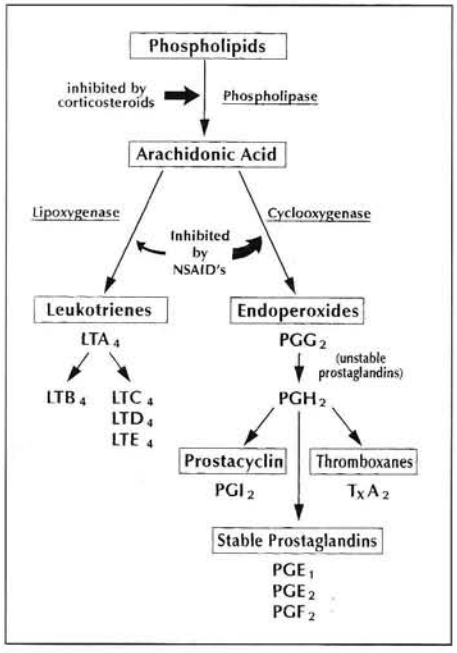

Figure 1. Arachidonic Acid Pathway

The "new" anti-inflammatory drugs have been chosen for this review so as to familiarize the reader with their similarities to and differences from other NSAIDs. However, as a class, these drugs are all believed to suppress inflammation by blocking production of prostaglandins. 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. 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.

RECENTLY INTRODUCED AND REFORMULATED NSAIDS

This review will include the following medications, which are either relatively new on the market, or a relatively new preparation of a previously available product: Disalcid, Ansaid, Daypro, Oruvail, Lodine, Voltaren, and Relafen. Disalcid may be considered to be an "old" product, but is included because of some of its unique features and relative obscurity.

Disalcid (salsalate)

Disalcid is a dimer of salicylic acid and is therefore in the same family as is aspirin (acetylsalicylic acid). The most distinguishing feature is its almost complete lack of gastrointestinal side effects. This drug is insoluble in gastric fluids and is hydrolyzed to two molecules of salicylic acid in the small intestine. As biotransformation is saturated at anti-inflammatory doses, this effectively increases its half-life to as much as 16 hours (from about five hours as occurs at lower doses). This allows for a 12 hour (BID) dosing

regimen. There is no greater fecal blood loss with Disalcid than with placebo, and also unlike its "cousin" aspirin, it does *not* inhibit platelet aggregation. Acidifying the urine can block excretion (effectively further increasing its half-life and potential toxicity), while increasing urinary pH will increase excretion. It is competitively bound to protein, so care must be taken with other drugs bound similarly (e.g. Coumadin and sulfonylureas), and it will antagonize the uricosuric effects of drugs such as probenecid (Benemid). While it has few if any of the GI side effects of acetylated salicylates, it can still cause the neurologic symptoms of salicylism (headache, dizziness, tinnitus, nausea, decrease in hearing, etc). The usual dose is two 750 milligram pills twice a day (3,000 milligrams), with downward adjustment appropriate in the elderly and in those with decreased renal function.

Ansaid (flurbiprofen)

Ansaid, a propionic acid derivative, is approved for use in osteoarthritis and rheumatoid arthritis, and really has no specific features that distinguish it from other NSAIDs. Ansaid is highly bound to plasma proteins (affecting levels of other drugs such as Coumadin), reversibly inhibits platelet aggregation, and may cause various GI problems, including ulcerogenesis and perforation. Care should be taken in patients with severe decreased renal or hepatic function. Ansaid has been associated with a decrease in renal blood flow and rarely with renal papillary necrosis, as is the case with almost all NSAIDs. Decreased renal blood flow is why this group of medications is commonly associated with fluid retention. Dosage is usually 200 to 300 milligrams per day.

Daypro (oxaprozin)

Daypro, another propionic acid derivative, has a fairly long half-life and therefore takes 4 to 7 days to achieve a steady state. Antacids have little to no affect on either the rate or extent of absorption, and the drug is primarily metabolized in the liver (liver conjugates are inactive); as there is insignificant enterohepatic circulation. Except for its effect on platelet adhesiveness, there is no interference with warfarin (Coumadin) despite being very highly protein bound. There is increased binding with decreased clearance at low concentrations, and the opposite occurs at high concentrations. Although probably insignificant, clearance does seem to also be decreased somewhat by H2 antagonists (such as cimetidine and ranitidine). The usual dose in osteoarthritis (OA) is 600 milligrams per day and 1200 milligrams in rheumatoid arthritis (RA), with no dosage adjustment necessary in the elderly. The dose can be taken all at once or divided, with a maximum dosage being 1800 milligrams per day.

Oruvail (ketoprofen)

Oruvail, another propionic acid derivative, is merely a new preparation of an old drug (Orudis, ketoprofen) with several distinguishing features. Probably the greatest difference between Orudis and Oruvail is the delivery/release system, the former being absorbed in an acid medium (i.e., the stomach) and the latter being absorbed in a more neutral environment (i.e., the small intestine). Oruvail consists of coated pellets of ketoprofen, dissolution of which is pH dependent. There is no dissolution at a pH of 1.0 as may be found in the stomach, with optimal dissolution occurring at a pH of 6.5 to 7.5 as may be found in the small intestine. The elimination half-life may be prolonged in the elderly and with a decrease in renal function; therefore, it is recommended to use Orudis rather than Oruvail in those instances so as to avoid potentially toxic accumulation. While Orudis is approved for RA, OA, primary dysmenorrhea, and pain, the longer half-life and slower absorption of Oruvail limits its effectiveness (and its approved uses) to OA and RA alone. The usual dose is 200 milligrams per day as one dose.

Lodine (etodolac)

Lodine is approved only in the treatment of pain and OA, but not in RA since studies in RA showed it to be better than placebo, but not as effective as any of the other NSAIDs against which it was compared. One does not need to decrease dosage with either renal or hepatic dysfunction (unless severe), and age does not seem to require a downward dosage adjustment. It is extensively metabolized in the liver and excreted through the kidneys, with very little enterohepatic circulation; hence, little if any is found in the stool. Ulcerogenesis and perforation have been noted with Lodine, as with almost all other NSAIDs. Renal blood flow may be decreased due to suppression of renal

prostaglandins, causing some fluid retention and a decrease in renal function. It does not interfere with Coumadin, there is no need to adjust the dose in the elderly, it may yield a false positive urine test for bilirubin, it may decrease uric acid, and it is not dialyzable. The usual starting dose is 800-1200 milligrams per day (divided), and the usual maintenance dose is 600 – 1200 milligrams per day (divided to BID or TID).

Voltaren (diclofenac)

Voltaren is approved in RA, OA and ankylosing spondylitis. Only about 50% of the systemically absorbed drug is available due to a significant "first pass" metabolism, and about 2/3 of the metabolized drug is found in the urine and 1/3 in stool, suggesting fairly extensive enteroheptic metabolism. Most of the side effects relate to the GI tract and dosing does not seem to need downward adjustment in renal or hepatic dysfunction. However, transaminitis does occur more frequently with Voltaren than with some of the other NSAIDs, and severe hepatic reactions do occur rarely. It is suggested that the first check for transaminase levels be done at about eight weeks, since most of the hepatic problems occur early in the course of treatment. Dosage does not usually need to be adjusted with concomitant use of Coumadin or oral hypoglycemics, although prudence dictates careful watchfulness. The usual dose in OA and ankylosing spondylitis is 100 to 150 milligrams per day (divided), and in RA is 150 to 200 milligrams per day.

Relafen (nabumetone)

Relafen is unique in that it is non-acidic and practically insoluble in water. This pro-drug is not found in plasma as it is well absorbed from the GI tract, and then rapidly undergoes hepatic biotransformation to the active substance 6-methoxy-2-naphthylacetic acid (6 MNA), which is strongly protein bound. There is no evidence of enterohepatic recirculation, so the active, acidic drug essentially never comes into contact with the GI tract. The elimination half-life is about 24 hours and steady state plasma levels of the active product are higher in the elderly. Furthermore, it is not dialyzable. Dosing need not be decreased with renal insufficiency, since it is primarily metabolized by the liver, but care must be taken when using Relafen in association with other protein bound drugs such as Coumadin. Probably because of the parent drug's lack of acidity and the lack of enterohepatic recirculation, the incidence of endoscopically noted GI lesions is lower than with most NSAIDs, although the overall incidence of all GI symptoms is about the same. Relafen is approved in RA and OA, and starting doses are about 1,000 mg per day (single dose), with or without food. Maintenance doses are usually 1,000 to 2,000 mg per day (either single dose or divided BID).

It is clear that while the previously-described medications have several new and unique facets, most of them share the majority of the features found in the group of NSAIDs as a whole. They all have the potential for GI toxicity, they may affect renal or hepatic function to varying degrees, and they are all fairly strongly bound to plasma proteins. These drugs differ somewhat in their potential for displacement of other protein-bound drugs. It is felt that much of their "good" effect is secondary to prostaglandin suppression, while many of the "bad" effects are secondary to prostaglandin suppression.

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.

ADJUNCTIVE THERAPY — GI PROTECTION

Although many drugs are used to counteract the gastrointestinal side effects of NSAIDs, only Cytotec (misoprostil) has been extensively studied and is approved for the prevention of NSAID-induced gastric ulcers. Cytotec has both anti-gastric acid secretory and mucosal protective effects, but has not been shown to either prevent duodenal ulcers or to give symptomatic relief of NSAID-induced GI pain or discomfort. Its side effects include an often use-limiting diarrhea and possibly abdominal pain. If the originally recommended dose of 200 micrograms four times a day with food can not be tolerated, 100 micrograms four times a day with food should be tried. The drug should be taken the entire time that NSAIDs are being used. Cytotec is contraindicated in pregnancy due to its know abortion-inducing potential.

Other drugs used (but with only anecdotal data to support their use) include the H_2 antagonists Tagamet (cimetidine), Zantac (ranitidine), Pepcid (famotidine), and Axid (nizatidine). The poorly absorbed, and therefore locally acting Carafate (sucralfate) does not seem to have any effect on NSAID-induced GI symptoms. Reglan (metoclopramide) stimulates upper GI motility without concomitantly stimulating gastric, biliary, or pancreatic secretions. It is approved only for gastroesophageal reflux, nausea, and vomiting.

SUMMARY

It is evident from the foregoing review that while we continue to provide new products for the treatment of arthritis, many of them are "me too" drugs with properties not much different from their ancestors. Some drugs, such as Ansaid (flurbiprofen) and Oruvail (ketopforen), seemed to appear on the market just as their predecessors from the same company were losing patent exclusivity. However, since the response to a particular medication by a particular patient is relatively individual, each drug has found its "circle" of responders and is therefore a welcome addition to the arthritis treatment armamentarium. Despite occasional serious toxicity, when taken and monitored properly, NSAIDs have provided relief to millions with relative safety and ease of administration.

REFERENCES

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2. Hartman SS: Medications Used in the Rheumatic Diseases. In Ruch JA, Vickers NS (eds) *Reconstructive Surgery of the Foot and Leg, Update '92* Tucker, Ga, Podiatry Institute Publishing, pp. 48-52, 1992.