



International Foundation for
Functional Gastrointestinal Disorders

IFFGD
PO Box 170864
Milwaukee, WI 53217
www.iffgd.org

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NSAIDs: Good for the Joints, Bad for the Gut?

By: W. Grant Thompson, M.D., F.R.C.P.C., F.A.C.G.
University of Ottawa, Canada

In this article, we are concerned with how NSAIDs work, their problematic effects on the gut, and how the bad effects can be minimized.

NSAIDs: Good for the Joints, Bad for the Gut?

By: W. Grant Thompson, M.D., F.R.C.P.C., F.A.C.G., Professor Emeritus, Faculty of Medicine, University of Ottawa, Ontario, Canada

Non-steroidal anti-inflammatory drugs (NSAIDs) constitute one of the most widely used classes of drugs, with more than 70 million prescriptions annually in the United States. Although NSAIDs are generally well tolerated, adverse gastrointestinal events occur in a small but important percentage of patients. NSAIDs like aspirin, ibuprofen, naproxen, and others are known to have serious adverse effects, including severe gastrointestinal damage, that can be life threatening. These drugs, available both over the counter and by prescription, are widely used for relief of symptoms ranging from minor aches to inflammation and chronic pain.^[i]

Research supports the use of interventions to reduce and/or avoid NSAID-associated complications but these strategies are not always applied effectively. This reinforces the need for continued education to improve outcomes of care.^[ii]

Be sure to discuss the use of any drug with your doctor so that you understand how to use it as directed, are familiar with the risks as well as benefits, and know what to do if side effects occur or symptoms return.

References:

- i) Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med.* 1999 Jun 17;340(24):1888-99. Review.
- ii) Goldstein JL. Challenges in managing NSAID-associated gastrointestinal tract injury. *Digestion* 2004;69(suppl 1):25-33.

What are NSAIDs

NSAIDs is an acronym for “non-steroidal anti-inflammatory drugs.” The steroids referred to here are not those employed by wayward athletes, but rather those of the adrenalcortical steroid family such as hydrocortisone, prednisone, and betamethasone. Because they suppress inflammation they are employed in many chronic inflammatory diseases such as rheumatoid arthritis. Unfortunately, these drugs have important metabolic effects that limit their use. NSAIDs are a class of drugs that suppress inflammation through inhibition of the enzyme cyclooxygenase (COX). They have important analgesic (pain killing) effects as well. Examples are listed in Table 1.

Uses of NSAIDs

NSAIDs provide comfort to many people with chronic joint pains by promoting increased activity and general

health, but they may cause serious gastrointestinal disease. The most widely used NSAID is aspirin. This ancient painkiller is still a respected treatment for rheumatoid arthritis, headaches, and other inflammatory or painful conditions. Because it inhibits the platelet contribution to blood clotting, a small daily dose of aspirin (80mg) may prevent coronary artery occlusion and strokes in those at risk.

NSAIDs relieve pain and inhibit the inflammatory components of rheumatoid arthritis and other chronic joint diseases. These diseases are often chronic and incurable, and in many cases the drugs may be taken for life. Because of their pain killing effects, they are also used (perhaps unwisely) in a variety of painful conditions such as backache, headache, toothache, etc. In this article, we are concerned with how the drugs work, their problematic effects on the gut, and how the bad effects can be minimized.

Table 1

NSAIDs

ASPIRIN

Traditional NSAIDs

IBUPROFEN (Advil, Motrin)
DICLOFENAC (Voltaren)
NAPROXEN (Naproxen, Aleve)
SULINDAC (Clinoril)
FENOPROFEN (Nalfon)
KETOPROFEN (Orudis, Oruvail)

INDOMETHACIN (Indocin)
TOLMETIN (Tolectin)
MECLOFENAMATE (Meclomen)
PIROXICAM (Feldene)

Selective COX-2 Inhibitors

CELECOXIB (Celebrex)
VALDECOXIB (Bextra)

Note. This list is not comprehensive and only some trade names are given as examples. Many of the listed drugs are available as generic products.

How NSAIDs Work

NSAIDs decrease the production of prostaglandins [a group of compounds that transmit messages between

cells] from a component of cells called arachadonic acid by inhibiting the enzyme cyclooxygenase. Certain of these prostaglandins play a role in inflammation and the generation of pain in conditions such as rheumatoid arthritis. Therefore, by inhibiting cyclooxygenase, NSAIDs reduce inflammation and pain. However, cyclooxygenase also produces other prostaglandins that protect the lining of the stomach and duodenum against injury, notably peptic ulcer disease. At the same time most enzymes produce thromboxane, a chemical which assists in blood clotting (hemostasis). Thus, administration of NSAIDs has the undesirable side effect of causing erosions or ulcers in the upper gut, and interfering with blood clotting when they bleed.

While the anti-clotting effect of aspirin is put to good use preventing unwanted clotting in the vessels of the brain, heart, and legs, these effects are potentially dangerous. The disadvantages of traditional NSAIDs have stimulated research into measures to counteract them while maintaining their usefulness.

Bad for the Gut

As could be predicted from the gut and blood clotting effects cited above, NSAIDs cause gastric and duodenal ulcers and sometimes life-threatening intestinal bleeding. Such events require cessation of the drug, endoscopy to confirm the ulcer and, if necessary, control the bleeding, antiulcer therapy with proton pump inhibitors, and occasionally emergency surgery. The risk is greatest in older females, and other risk factors are listed in Table 2. Sometimes an ulcer develops without abdominal pain (dyspepsia) and bleeding may be the first manifestation. Paradoxically, NSAIDs may cause dyspepsia in many people without an ulcer.

Table 2

NSAID Adverse Effects Risk Factors

- Over age 60
- Female gender
- Duration of Treatment
- Dose
- Type of NSAID
- Multiple NSAID use
- Steroid Use
- Previous Ulcer
- Preexisting cardiovascular disease

Note: These risk factors are relative contraindications for NSAIDs. Depending upon the painful disorder being treated, these risks may be acceptable if the benefit is sufficiently satisfactory.

Other Side Effects

Because of the anti-platelet anti-clotting effects of most NSAIDs, they must be stopped one week before surgical or dental procedures, and bleeding from an injury may be more difficult to control. These drugs may worsen heart or kidney failure. Data exposed a risk of thromboembolic complications in those taking rofecoxib (Vioxx) and in 2004 the drug was withdrawn from the U.S. market. This discovery has cast doubt on the safety of all NSAIDs, particularly the remaining COX-2 inhibitors.^[1] [See Safety Alerts on page 4.]

How to Minimize the Risk to the Gut

Use Only When Necessary – Chronic painful conditions where inflammation plays a minor role such as headache or osteoarthritis may not require NSAID therapy. Acetaminophen (Tylenol) is a pain killer without the anti-inflammatory component, and is a better choice if pain relief is the only objective. In osteoarthritis, exercises developed with advice from your doctor, perhaps with the help of a physiotherapist, may help avoid the need for drugs. Despite this, many people with osteoarthritis and other chronic, painful conditions require NSAIDs.

Be Aware of an Individual's Risk of Bad Gut Effects – Statistically, older females are most at risk for the adverse gut effects of NSAIDs. Unfortunately, they are the group most likely to benefit from the drugs' good qualities. The risk also increases with the duration of treatment, the dose, concomitant use of other NSAIDs or steroids, and the presence of debilitating disease. A history of previous ulcer may also be a warning.

Use the Lowest Effective Dose – From the foregoing, it is obvious that one should employ the lowest dose of the drug that is effective, and only for as long as is necessary. Attempts have been made to identify those NSAIDs most likely to damage the gut. Ibuprofen, diclofenac, and naproxen are said to be among the safest. However, reports conflict, and it is difficult to know the risks in relation to efficacy. A safer drug could imply a weaker drug.

Treat or Prevent Ulcers – There have been attempts to use a variety of anti-ulcer drugs along with the NSAIDs to prevent gut damage, especially in high-risk patients. H2 blocking drugs (e.g., ranitidine), prostaglandins (e.g., misoprostol) and proton pump inhibitors (e.g., omeprazole) have all been tried. Misoprostol has been combined with diclofenac (Arthrotec) and shown to reduce the gut complications. More recently, omeprazole has been shown to be superior to misoprostol for this purpose. If an ulcer is present, it should be treated, but elimination of *H. pylori* [the bacteria that causes most peptic ulcers] may not itself prevent NSAID ulcers. This is a difficult subject, and if a person is at high risk, he or she should discuss these preventative measures with a doctor.

The Specific COX-2 inhibitors

As discussed above, ordinary NSAIDs owe both their good and bad effects on their ability to inhibit the enzyme cyclooxygenase and reduce prostaglandin production. However, it turns out that this enzyme has two forms; cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 inhibitors reduce good prostaglandins, the ones that protect the lining of the stomach and duodenum from damage, while COX-2 inhibitors were developed to reduce “bad” prostaglandins and thereby permit beneficial anti-inflammatory and analgesic effects.

The result of this discovery was the development of specific COX-2 inhibiting NSAIDs. In the United States and Canada, the COX-2 NSAIDs are celecoxib (Celebrex) and valdecoxib (Bextra). In chronic inflammatory conditions such as rheumatoid arthritis, these drugs were developed because they appear to be as effective as the original NSAIDs, but have less adverse effects on the gut. However, the increased cardiovascular risk for those taking rofecoxib and its removal from pharmacists’ shelves indicates cautious use for the remaining COX-2 drugs. [Note: Concerns about the safety of the COX-2 inhibiting NSAIDs has resulted in either the removal or limited usefulness of this class of drugs.]

Conclusions

NSAIDs have become a very important weapon in the control of inflammation and pain in joint disease, and in other chronic, painful conditions. Their use has been limited by their propensity to cause gut symptoms or actually damage the gut. These drugs exert their anti-inflammatory, anti-clotting, and gut damaging effects through inhibition of cyclooxygenase and decreased prostaglandin production. Anti-clotting and untoward

effects on the gut are due to the COX-1 form of cyclooxygenase. Employing a few precautions (especially in older females requiring multiple drugs for long periods) can minimize adverse effects. Those COX-2 drugs that remain available should be used only when you and your doctor agree that an NSAID is the best drug for your painful condition, a high risk of gastrointestinal bleeding is present and the overall risk of untoward or problematic events are acceptable given the degree of your disability and pain.

Reference:

1) Maxwell SR, Webb DJ. COX-2 selective inhibitors - important lessons learned. *Lancet* 2005; 365:449-451.

About IFFGD

The International Foundation for Functional Gastrointestinal Disorders (IFFGD) is a 501(c)(3) nonprofit education and research organization. We work to promote awareness, scientific advancement, and improved care for people affected by chronic digestive conditions. Our mission is to inform, assist, and support people affected by gastrointestinal disorders. Founded in 1991, we rely on donors to carry out our mission. Visit our websites at: www.iffgd.org or www.aboutGERD.org.

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Safety Alerts

On July 18, 2005 the FDA issued supplemental request letters to sponsors of all non-steroidal anti-inflammatory drugs (NSAIDs) requesting that they make labeling changes to their products. These letters included recommended proposed labeling for both the prescription and over-the-counter (OTC) NSAIDs and a medication guide for the entire class of prescription products.

All sponsors of marketed prescription non-steroidal anti-inflammatory drugs (NSAIDs), including Celebrex (celecoxib), a COX-2 selective NSAID, were being asked to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. The Celebrex labeling will, in addition to the general labeling that will apply to all NSAIDs, also contain safety data from long-term treatment trials with celecoxib.

Manufacturers of non-prescription (over-the-counter) NSAIDs were being asked to revise their labeling to provide more specific information about the potential CV and GI risks of their individual products and remind patients of the limited dose and duration of treatment of these products in accordance with the package instructions.

On April 7, 2005 the FDA asked Pfizer to voluntarily remove Bextra (valdecoxib) from the market.

On September 30, 2004 Merck & Co., Inc. announced a voluntary withdrawal of Vioxx (rofecoxib) from the U.S. and worldwide market due to safety concerns of an increased risk of cardiovascular events (including heart attack and stroke) in patients on Vioxx.
