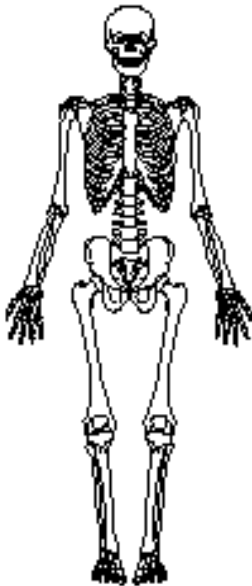


Preventing Complications of Non-Steroidal Anti-Inflammatory Drug Therapy

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NSAID SERIES, P2



In this article the risk factors associated with the development of complications from non-steroidal anti-inflammatory drug (NSAID) therapy, a description of the more clinically significant drug-drug interactions, and methods by which to manage and to prevent these adverse events are discussed. In addition, a blueprint for safe NSAID use is presented.

This information is the second part of a multiphasic intervention effort targeted at reducing the complications and decreasing the costs associated with the use of NSAIDs. Physicians, pharmacists, patients, other health professionals, and the Louisiana Department of Health and Hospitals will be working together in a coordinated effort to prevent predictable adverse drug reactions.

It is anticipated that through this coordinated effort we can decrease the morbidity and mortality associated with NSAID therapy, and thereby increase patients' quality of life, as well as reduce medical and pharmaceutical costs in the Medicaid Program. Through an awareness and educational campaign, directed at prevention and monitoring, we hope to accomplish these goals.

There are two primary foci of the NSAID therapy disease state management effort.

The first focus involves an awareness campaign targeted at providing information on at-risk patients; the etiology of NSAID-induced complications; presenting ways to prevent their occurrence; and minimizing the problems associated with these drugs. The second focus will involve assessing statewide and regional physician-specific prescribing information and outcomes in order to decrease the overall costs associated with this class of drugs.

INTRODUCTION

Every day in America, approximately 3 million people take a non-steroidal anti-inflammatory drug (NSAID) for a variety of reasons, making this category of products one of the most commonly used and prescribed.^{1,2} Although NSAIDs are effective in alleviating pain and inflammation, they do have the potential to cause serious adverse effects in certain patient populations. The gastrointestinal tract is the primary site of NSAID-induced adverse reactions and these events are insidious in that patients may remain asymptomatic until the untoward effect has reached a critical stage. The risk of GI hemorrhage or perforation resulting in hospitalization or death is 3 times higher in NSAID users than in non-users. The incidence rate of NSAID-induced gastropathy is estimated at 1% in patients taking NSAIDs for three to six months and 4% in patients on NSAID therapy for longer than one year. The annual health care costs for NSAID-induced gastropathy and its sequelae are estimated at \$4 billion. Thus, effective efforts aimed at preventing these complications would have a major impact on health care costs.¹

RISK FACTORS

It is difficult to predict which patients will experience serious adverse reactions. Yet, there are patients who are at an increased risk for developing serious NSAID-induced GI complications. The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), a database for arthritis patients in the U.S. and Canada, has established a number of risk factors for gastrointestinal complications with NSAIDs (see Table 1). Additionally, there appears to be a direct relationship between the length of time a patient is on NSAID therapy and the development of GI complications.³ On the other hand, studies have also shown that there may be an increased risk of gastric corrosions and ulcers within the first 30 days of NSAID exposure with the risk decreasing thereafter.⁴

Table 1

Patients at Risk for Developing NSAID Complications

Age greater than 60
History of peptic ulcer disease
Previous intolerance to NSAIDs
History of GI hemorrhage
High-dose NSAID therapy
Long-term NSAID therapy
Cigarette smoking
History of alcoholism
Multiple NSAID use
On anticoagulant therapy
On corticosteriod therapy
Concomitant serious illness

Some of the risk factors involve concomitant drug therapy or the presence of other disease states. The listing found in Table 1 is not ranked by order of prevalence or stratified by clinical significance. Two of the listed risk factors, however, stand out as being primary indicators of patients most at risk for developing a NSAID-induced gastropathy. These factors are increased age or having a history of gastric or duodenal ulcers.¹ The elderly are especially vulnerable to developing GI complications secondary to an age-related decrease in endogenous prostaglandin production.

DRUG-DRUG INTERACTIONS

Taking certain medications with NSAIDs is a potential risk factor for developing GI complications. There are also drug-drug interactions associated with NSAID therapy; the more clinically significant ones are listed in Table 2. Most of these potential problems involve the NSAID's anti-platelet activity or their effect on the GI mucosa.

Table 2 NSAID Drug-Drug Interaction

Drug	Effect
Corticosteroid	Increased incidence and severity of GI ulceration
Methotrexate	Increased serum methotrexate concentrations secondary to decreased excretion and/or displacement from plasma proteins (especially with salicylates and ketoprofen)
Warlin-Type Anticoagulants	USE CAUTION due to NSAID anti-platelet activity and induction of GI injury (especially with aspirin and phenylbutazone)
Lithium	Increased lithium plasma concentration (EXCEPT aspirin and sulindac)
Antihypertensive Agents	Antihypertensive effects may be attenuated by concurrent use of NSAIDs

Corticosteroid therapy can increase the potential for NSAID-induced toxicities. Although some patients may need to be given both types of agents concomitantly, which can be done successfully for short periods of time without sequelae, prolonged concomitant administration of these two classes of drugs should be avoided. Another problem area involves multiple NSAID therapy. When ibuprofen is given concomitantly with other NSAIDs, the risk of GI toxicity is increased.³

High-dose methotrexate therapy and concomitant administration of NSAIDs can cause a severe, possibly fatal methotrexate toxicity. Methotrexate is primarily eliminated by renal secretion and since NSAIDs have a propensity to impair renal perfusion in some individuals, there is a potential for drug levels to build up, especially in those patients taking either salicylates or probenecid. Salicylates, phenylbutazone, and other NSAIDs can displace methotrexate from protein binding sites thereby, increasing the amount of free drug in the circulation and increasing its activity. Even though these events are associated with high-dose therapy, it is recommended that NSAIDs be used cautiously with any dose of methotrexate; even when it is used in low-dose rheumatoid arthritis treatment.⁷

Most NSAIDs can cause pharmacokinetic and/or pharmacodynamic interactions with warfarin. The problem is due to NSAIDs effects on platelet aggregation and their

potential for causing GI bleeding. The inhibitory action on platelets is most pronounced with aspirin. Salicylates also interact with warfarin by displacing it from protein binding sites. All NSAIDs, especially piroxicam and sulfinpyrazone, should be used cautiously in patients receiving warfarin.

NSAIDs reduce the excretion of lithium which leads to elevated levels. Whenever a NSAID is either added or discontinued during lithium therapy, serum lithium concentrations should be monitored closely and the patient observed for signs of lithium intoxication for four to seven days after. Aspirin and sulindac do not appear to exhibit this effect.⁷

Nephrotoxicity can occur during concomitant treatment with certain diuretics and NSAIDs. This interaction is well described for the combination of indomethacin and triamterene. In these patients, reversible renal insufficiency occurs after several days of combination therapy. Manifestations include azotemia, hyperkalemia, and hyperuricemia. Patients experiencing this problem most often were elderly and/or receiving NSAID therapy for treating acute gouty arthritis. NSAIDs should be used cautiously in patients receiving diuretics because of the contribution of renal vasodilatory prostaglandins to renal perfusion, especially if the patient is in a dehydrated state.⁷

CLASSIFICATION OF NSAID RISKS

Many attempts have been made at ranking NSAIDs with respect to their gastrointestinal toxicity; yet many have been somewhat inconsistent. However, a new ranking presented at the American College of Rheumatology meeting in November 1997 provided the best information thus far. The data for this analysis came from 9000 courses of NSAID therapy in almost 4000 patients followed for two years. The results are as follows:

Low Risk	Moderate Risk	High Risk
Nabumetone(Relafen)	Ibuprofen(various)	Fluibiprofen(Ansaid)
Etodolac(Lodine)	Ketoprofen(various)	Piroxicam(Feldane)
Salsalate(Disalcid)	Naproxen(various)	Fenoprofen(Nalfon)
Sulindac(Clinoril)	Aspirin(various)	Indomethacin(Indocin)
	Tolmentin(Tolectin)	Meclofenamate(Meclomen)
	Diclofenac(Voltaren)	Oxaprozin(Daypro)

PREVENTING ADVERSE EFFECTS

The identification of at-risk patients should help physicians and other healthcare professionals decide whether to use a less toxic NSAID, add protective agents such as misoprostol, or avoid an NSAID altogether.

A variety of medications have been used to prevent the GI complications associated with NSAID therapy. H₂ receptor antagonists have been shown to prevent duodenal ulcers in NSAID users, but their utility in averting gastric ulcer formation has not been proven. Mucosal barrier agents, such as sucralfate (Carafate), have not been proven to prevent NSAID-induced gastric ulcerations. Proton-pump inhibitors have shown some promise in preventing NSAID-induced gastric ulcers. Hawkey, et al., in a 1998 NEJM article entitled “Omeprazole compared with misoprostol for ulcers associated with NSAIDs” revealed that omeprazole 20 mg is better tolerated and more effective than misoprostol 200 mg BID as maintenance therapy against recurrent gastrointestinal lesions.

A prostaglandin analogue, misoprostol (Cytotec) is effective as a prophylactic agent in the prevention of NSAID-induced gastric disease and is FDA approved for this indication. This product, however, is only as effective as the aforementioned agents in preventing NSAID-induced duodenal disease. It is controversial as to the extent to which prostaglandin analogue prophylaxis is cost effective. This, in part, is due to the fact that more than half of the NSAID-induced bleeding is from non-ulcer sources and prophylaxis against ulcer development might not prevent bleeding in over half the patients. Due to the rarity and unpredictability of GI bleeds, universal ulcer prophylaxis is not practical or cost effective. For those patients most at risk, however, some consideration should be given to instituting prophylactic therapy with prostaglandin analogues.⁸ Additionally, these agents are not without their side effects. Diarrhea has been reported in up to 40% of patients, thus leading to compliance problems.⁷

MANAGING GI-INDUCED ADVERSE EFFECTS

When treating NSAID-induced gastric ulcers, the causative agent should be discontinued if at all possible. Then, the ulcer should be treated with H₂ - receptor antagonists (H₂RAs), proton pump inhibitors (PPIs), or appropriate antibiotic therapy to eradicate *Helicobacter pylori*, if indicated.

If a patient must continue to take the NSAID when a GI complication is present, they

should also be prescribed maintenance doses of H₂RAs or PPIs in order to minimize the potential for developing further problems. Finding an alternative treatment for the patient's condition and discontinuing the NSAID product is usually the best path to follow due to the fact that ulcer relapse rates are so high after discontinuation of the ulcer treatment.⁸

There will be a new class of NSAID on the market very soon. The much awaited class of drug is the COX-2 inhibitor. These drugs will apparently have little, if any, side effect on the stomach while providing similar anti-inflammatory and analgesic activity to currently marketed NSAIDs. The first product to market will be celecoxib, marketed by Searle, a division of Monsanto, and Pfizer Pharmaceuticals. The second product will be Vioxx, marketed by Merck and Company. Within the next several months, as more post-marketing surveillance data is available, we will provide you with additional information regarding COX-2 technology.

CONCLUSION

Because NSAIDs are one of the most widely used medications in the U.S., promoting their safe and effective use is important and represents a logical approach to practicing cost-effective medicine. There are several important factors to consider when choosing a NSAID. They are:

- The patient's age;
- Concomitant medications;
- Individual risk factors;
- Medical history, especially prior GI problems

Some individuals are more at-risk for developing complications while on NSAID therapy. These problems can be minimized by pursuing a conscientious prevention effort. The blueprint for safe NSAID use includes:

- Identifying at risk patients, counseling them more thoroughly, and monitoring their therapy more closely;
- Evaluating the patient's drug therapy on a continual basis for appropriateness and duration;
- Using Therapeutic Drug Monitoring principles to screen for both efficacy and toxicity;
- Finding alternative agents for the patient to use to alleviate pain and inflammation, whenever possible;
- Checking regularly for supplemental over-the-counter NSAID use;
- Maintaining an open communications link between yourself and the patient;
- Using frequent follow-up visits and periodic diagnostic testing for GI problems as a surveillance technique;
- Prescribing or recommending other treatments, in some cases, in order to reduce the severity of the adverse effects when cessation of NSAID therapy is not a viable option.

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