

Defining the Patient at Risk for NSAID Toxicity

Based on a presentation by G. James Morgan, MD

Presentation Summary

Being able to identify patients who may experience nonsteroidal anti-inflammatory drug (NSAID) toxicity before prescribing a drug for them is far more complex than simply identifying the adverse effects linked to NSAID use. There are some groups at risk for NSAID toxicity that can be easily identified by laboratory testing, such as patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Other patients may have a history of disease states or disorders that have been linked to increased NSAID side effects. However, there are many patients at risk who cannot be identified before NSAID therapy. Those who consume alcohol without the physician's knowledge, those who are combining certain over-the-counter products with NSAIDs, and those who misunderstand how to take their medica-

tion are of special concern. With other patients, it is impossible to predict whether they will have an idiosyncratic reaction to NSAIDs regardless of having a thorough patient history.

Distinct challenges are often presented when pregnant or breast-feeding women, children, and the elderly require NSAID therapy. Also, a significant number of literature reports have associated certain predisposing factors with an increased likelihood of developing renal dysfunction, blood coagulopathies, and gastropathy during NSAID use. Unfortunately, the exact causes of these relationships are not always well understood and it may not be feasible to anticipate which patients with a certain predisposing factor will, indeed, experience toxicity. Known interactions between NSAIDs and other medications should be studied and considered as well.

All patients are potentially at risk from taking nonsteroidal anti-inflammatory drugs (NSAIDs)," said G. James Morgan, MD, Associate Professor of Medicine, Department of

example, shows 29,293 suspected cases of NSAID overdose exposure including 76 severe poisonings and six deaths. "Patients are at risk, be it intentional or unintentional, of potential death from taking overdoses of NSAIDs," according to Dr. Morgan.

Overexposure to NSAIDs can be inadvertent, and toxicity can be complicated by pre-existing medical conditions or drug interactions. Regardless of the cause, it is clear that NSAIDs, including aspirin, can lead to a variety of toxicity symptoms ranging from mild nausea and vomiting to severe acidosis, hypokalemia, and hyperkalemia (Table 1).

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—Dr. G. James Morgan

Rheumatology, Dartmouth Hitchcock Medical Center, in Lebanon, New Hampshire. American Association of Poison Control Centers data for 1988, for

"There are patients who have NSAID reactions including hepatocellular damage with acute hepatitis and even liver failure, cutaneous reactions such as urticaria, and interstitial nephritis. These are adverse events but they are basically idiosyncratic. One cannot identify factors that predispose patients to these particular problems," according to Dr. Morgan.

However, a review of the literature helps physicians identify other patients and particular settings susceptible to NSAID side effects and efforts can be made to reduce the risk associated with prescribing decisions.

Inadvertent NSAID Exposure

Inadvertent NSAID exposure through breast feeding should be kept in mind when dealing with female patients. Precise statistics on the number of infant overexposures are difficult to gather and except for overexposure to aspirin, the number of cases is quite small, according to Dr. Morgan. Salicylates, indomethacin, nonaspirin NSAIDs, and mefenamic acid are linked to breast-feeding exposures while diclofenac and perhaps the oxicams are not, he said.

"There seems to be low milk-to-plasma ratios and very little glucuronide formation for some NSAIDs, both of which have to do with transport," Dr. Morgan said. Therefore, the best NSAID to select for breast-feeding patients is one with a short half-life, a low milk-to-plasma ratio and no glucuronide formation.

A more important source of inadvertent exposure is that which pushes patients already at risk for NSAID toxicity to the limit. This type of exposure can be divided into three areas: analgesic overuse, the use of ketorolac, and topical formulations. There are many over-the-counter NSAIDs being marketed for pain relief and several are available in a variety of dosages; some are combined with other agents. It is possible for patients to receive a prescription NSAID without being aware that their over-the-

counter analgesic contains an NSAID. Ketorolac presents a similar problem. "There are still a huge number of physicians who do not recognize the fact that ketorolac is an NSAID and they con-

Table 1. Clinical Features of Poisoning Due to Phenylpropionic Acid Derivatives

<ul style="list-style-type: none"> • Most overdose symptoms are mild and GI related • Nausea, vomiting, abdominal pain/tenderness, hematemesis • Headache, tinnitus, hyperventilation, sinus tachycardia, bradycardia • Hematuria, proteinuria, renal tenderness, acute renal failure • Hypotension, hypothermia, hypoprothrombinemia • Drowsiness, coma, respiratory depression, convulsions • Nystagmus, blurred vision, diplopia • Hepatocellular damage and cholestasis • Metabolic acidosis, hypokalemia, hyperkalemia, hypophosphatemia
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From Famaey and Paulus *Therapeutic Applications of NSAIDs*. 1992.

tinue to administer it with other NSAIDs," Dr. Morgan said.

Another area of possible overexposure is in the use of topical NSAIDs. Cream and spray preparations are used for osteoarthritis in Europe but are not available in the United States. However, ophthalmic NSAIDs are used in this country and have been responsible for incidences of bronchospasm. Therefore, patients who are known to be sensitive to aspirin or NSAIDs should be warned against using these compounds. "These preparations generate NSAID plasma levels and therefore, carry all the risks of oral NSAIDs," according to Dr. Morgan.

NSAID Use in Special Patient Populations

The effects of NSAIDs on pregnancy and the fetus are one area of concern. There are data suggesting increased incidences of peripartur hemorrhage with aspirin use and this may also be true for drugs such as indomethacin, naproxen, and oxaprozin because they also have antiplatelet effects. Neonatal petechia formation has been reported and there is also some evidence that this antiplatelet function can cause a newborn to have

excessive bleeding, which may be observed during circumcision or in conjunctival hemorrhage.

Fetal malformations due to NSAID use have not been reported with any frequency but there have been reports of oligohydramnios associated with these drugs. Closure of the ductus, on the other hand, has been described with indomethacin and other NSAIDs taken within 2 to 4 weeks of delivery. "I cannot discern from the literature whether this is a prostaglandin effect and whether it is due to the cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2) enzyme. Since we know that the placenta produces COX-2, it would be interesting to find data on the differentiation of these enzymes in this particular phenomenon," Dr. Morgan said.

NSAID use among children is a second area deserving special attention. Renal dysfunction should be a concern in many of the same situations as it is in adults. Children with congestive heart failure from cardiomyopathy or chronic renal failure may be at increased risk of NSAID-induced renal side effects.

Acute and chronic renal failure has been fairly well described in children taking NSAIDs for fever and pain control during viral illnesses and these cases are attributed to dehydration. "The dehydrated child should be considered to be at significant risk of renal toxicity if

exposed to NSAIDs," according to Dr. Morgan.

The elderly population also requires special consideration with long-term NSAID therapy. Age appears to be a well-documented independent risk factor for NSAID-induced toxicity in the gastrointestinal (GI) tract. However, there is no evidence that age, in and of itself, in healthy patients without concurrent disease is a risk factor for NSAID-related renal toxicity, heart failure, or central nervous system effects.

Predicting Renal and Hematologic Effects

"We would like to try to predict which patients are at risk for the effects of NSAIDs on the kidney. Acute hemodynamic compromise could occur in any patient with vascular volume decrease, congestive heart failure, or cirrhosis with ascites and although this has been investigated, one cannot tell from the literature to what degree a particular patient must have these problems," Dr. Morgan said.

There is evidence that elderly men and diabetics are at particular risk for chronic problems with NSAID-related papillary necrosis and interstitial fibrosis. In addition, certain problems appear to predispose NSAIDs users to hyperkalemia. These mainly include a hyporeninemic state and concomitant use of potassium-sparing diuretics or angiotensin converting enzyme inhibitors. However, the elderly, those with renal failure, and diabetics may also be predisposed to this complication. Patients with edema-inducing states may be at risk of sodium and water retention when taking NSAIDs, but this relationship has not been extensively defined (Table 2).

There are certain situations in which the antiplatelet effects associated with some NSAIDs such as aspirin and oxaprozin may become more significant. "Certainly, hemophilia of either type predisposes a patient to problems as does Von Willebrand's disease because these patients have primary defective platelet function," Dr. Morgan said.

Table 2. Risk Factors Associated with NSAID-Related Renal Failure

<ul style="list-style-type: none"> · Acute (hemodynamic) <ul style="list-style-type: none"> - decreased vascular volume - CHF - cirrhosis with ascites · Chronic: papillary necrosis/interstitial fibrosis <ul style="list-style-type: none"> - elderly men · Hyperkalemia <ul style="list-style-type: none"> - hyporeninemic hypoaldosteronism - elderly/renal failure/diabetes · Sodium/water retention <ul style="list-style-type: none"> - patients with edema-inducing states

Chronic renal failure patients on dialysis also have poorly functioning platelets and may be at increased risk for NSAID toxicity.

Phenylbutazone has been well known to displace warfarin sodium from protein-binding sites. "Because any nonsteroidal, which is highly protein bound, could theoretically displace warfarin sodium, any patient on this drug challenged with an NSAID has to be considered at risk for coagulopathy," according to Dr. Morgan.

There are significant risks of anemia in some patients taking NSAIDs, which cause hemoglobin oxidation and secondary methemoglobin formation. Patients with G6PD deficiency are unable to reduce oxidized hemoglobin and may develop a brisk, hemolytic anemia upon NSAID exposure. Patients with pyruvate kinase deficiency, glutathione peroxidase deficiency, NADH reductase deficiency, and certain other hemoglobin abnormalities are similarly predisposed. "Screening for G6PD is not something we do on a regular basis but it is obviously a problem, not only with NSAIDs but also with hydroxychloroquine," Dr. Morgan said (Table 3).

Other Specific Risk Factors

Other groups of patients who may have difficulty with NSAIDs have been identified. Aspirin-induced asthma is well documented and this risk is present with many other NSAIDs. It has been suggested that only the nonacylated salicylates are not associated with this crossover phenomenon. Overall, 15% of normal patients are at risk for bronchospasm with NSAID treatment and there are no identifiable patient characteristics that seem to have predictive value beyond nasal polyps and asthma.

Neurological complications have also been reported in conjunction with NSAID use. Piroxicam and diclofenac, for example, can exacerbate underlying porphyria and lead to ascending neuropathy so porphyria patients should be considered at increased risk of NSAID complications. There have

been some cases of aseptic meningitis in systemic lupus erythematosus and mixed connective tissue disease patients taking ibuprofen, and to a lesser extent, tolmetin. Again, there do not seem to be any particular features that

Table 3. Risk Factors Linked to NSAID-Associated Blood Coagulopathies

<ul style="list-style-type: none"> • Platelet effects of specific NSAIDs (hemophilia/von Willebrand's patients at higher risk) • Coumadin-specific drugs • Exacerbation of G6PD deficiency

Table 4. Specific NSAID Side Effects and Related Risk Factors

<ul style="list-style-type: none"> • Bronchospasm <ul style="list-style-type: none"> - aspirin-induced asthma - 15% of "normals" • Neurologic <ul style="list-style-type: none"> - piroxicam/diclofenac – exacerbate porphyria neuropathy - meningitis – SLE/MCTD • Esophageal stricture <ul style="list-style-type: none"> - old age with motility disorder/reflux
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would help identify which patients will have problems, according to Dr. Morgan.

Esophageal stricture is described in many patients taking NSAIDs, especially in those over the age of 60. "However, the literature suggests that age is not the predisposing factor; it is a history of significant motility disorders or reflux associated with strictures," he said (Table 4).

Many factors have been associated with a tendency to develop gastropathy with NSAID use. An age of more than 60 years, female gender, and various co-existing diseases including bleeding disorders, rheumatoid arthritis, renal dysfunction, hepatic disease, and cardiovascular diseases have all been implicated. Recent or past ulcer disease has a definite effect on GI tract NSAID tox-

icity. Stress, alcohol and smoking may increase GI side effects as well.

Long-term, high dose NSAID treatment is associated with an increase in gastropathy as is the use of multiple NSAIDs simultaneously. Anticoagulants, corticosteroids, and immunosuppressive agents have also been reported to cause GI difficulty when taken with nonsteroidals.

Finally, there is the issue of drug interaction. NSAIDs, specifically diclofenac and ibuprofen, appear to increase serum digitalis levels by decreasing renal clearance of the drug and these patients may develop digitalis toxicity or irregular rhythm.

Lithium toxicity manifests as confusion and tremors, and has been described in relation to NSAID use. "Patients taking lithium should be advised to have their lithium levels checked when they are exposed to NSAIDs. The mechanism of this interaction is probably related to a decrease in lithium clearance caused by NSAIDs," Dr. Morgan said.

Aminoglycoside serum levels have been shown to increase with NSAID exposure which is most likely due to decreased renal clearance and may lead to aminoglycoside toxicity. This would be an important consideration in patients who already have decreased renal function. Antiseizure medications, primarily valproic acid, may have increased toxicity potential due to decreased protein binding and decreased oxidative metabolism when combined with NSAIDS.

The effects of combining alcohol with NSAID use must not be overlooked. "In fact, the use of alcohol with NSAIDs produced greater, more serious GI effects than the use of either substance alone. Only the combination of aspirin and alcohol was associated with greater adverse effects. Chronic alcohol users may be at higher risk for NSAID toxicity," Dr. Morgan said (Table 5).

Table 5. Risks for Serious Upper GI Complications with Aspirin, Other NSAIDs, and Alcohol Alone and in Combination

Drug(s)	Odds Ratio (95% CI)
Aspirin alone	3.0 (2.2-4.0)
Alcohol alone (≥5 drinks/session)	2.8 (1.9-4.0)
Aspirin and alcohol	8.1 (4.1-16.1)
NSAIDs alone	3.8 (2.8-5.2)
NSAIDs and alcohol	6.0 (3.3-11.0)

CI = confidence interval.
From Henry et al. *Gastroenterology* 1993;105:1078.