

REVIEW ARTICLES

NON STEROIDAL ANTI INFLAMMATORY DRUGS- AN OVERVIEW

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Epidemiology

More than 20 million Americans use various different nonsteroidal anti-inflammatory drugs (NSAIDs) on a regular basis, making this class of drugs one of the most commonly used. Approximately 1 to 2 percent of patients taking NSAIDs will develop serious gastrointestinal toxicity, which has resulted in 100,000 to 400,000 hospitalizations per year in the United States at a cost of over 2 billion dollars¹⁻³. In the United States, 10 to 20,000 peoples died every year of NSAID complications. There are at least 2600 excess deaths in the United States each year related to gastrointestinal toxic reactions in patients with Rheumatoid Arthritis (RA) who are treated with NSAIDs⁴⁻⁵. A variety of NSAIDs are readily available (at least 20 in the United States and more elsewhere) and widely used throughout the world⁶⁻⁷. Although, steroid and some other drugs (e.g. Tramadol) have value in reducing pain of RA, the content of this article will be limited to NSAIDs only.

History

The first effective analgesic documented in history was the powder of dried myrtle leaves used in Egypt in 1500 BC. Hippocrates recommended the use of the juice of the willow and poplar bark for this purpose. In 1763, Edward Stone established the efficacy of willow bark extract in relieving pain with the help of a clinical trial. Salicylic acid was first synthesized in 1860 and it was shown that all these myrtle leaves, willow and poplar barks contained salicylic acid. Aspirin, the magic drug of this age, was first synthesized in 1899. Several reports published almost simultaneously in 1971 established that aspirin acted by reducing the concentration of prostaglandins. More than 25 years ago, Sir John Vane showed that NSAIDs inhibited the biosynthesis of prostaglandins - mediators of inflammation, by inhibiting the key enzyme, prostaglandin endo peroxide synthase or cyclooxygenase (Cox) and proposed this as their mechanism of action. He proposed that the same mechanism was responsible for the various beneficial and toxic effects of NSAIDs. Prostaglandins are derived

from the cell membrane phospholipids by a cascade of enzymes. The sequence starts with release of arachidonic acid from the cell membrane by Phospholipase-A2. Arachidonic acid is then converted by cyclo oxygenase to prostaglandins, prostacyclin, and thromboxanes⁸. The Cox-1 gene was cloned and sequenced in 1988 and in 1991, a second cyclooxygenase gene was identified. Celecoxib, the first Cox-2 selective NSAID got the US FDA approval in 1998⁸⁻⁹.

Mechanism of action

Cyclooxygenase inhibition – The primary effect of NSAIDs is to inhibit cyclooxygenase (prostaglandin synthase), thereby impairing the ultimate transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. The extent of enzyme inhibition varies among the different NSAIDs, although there are no studies relating the degree of cyclooxygenase inhibition with antiinflammatory efficacy in individual patients¹⁰.

Two related isoforms of the cyclooxygenase (COX) enzyme have been described: COX-1 (PGHS-1); and COX-2 (PGHS-2). The most important differences between the two isoforms are the regulation and expression of the enzymes in various tissues:

- COX-1 is expressed in most tissues, but variably. It is described as a “housekeeping” enzyme, regulating normal cellular processes (such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function), and is stimulated by hormones or growth factors.
- COX-2 is usually undetectable in most tissues; its expression is increased during states of inflammation, or experimentally in response to mitogenic stimuli. COX-2 is constitutively expressed in the brain, kidney, bone, and probably in the female reproductive system. Another distinguishing characteristic of COX-2 is that its expression is inhibited by glucocorticoids. This observation may contribute to the significant anti-inflammatory effects of the glucocorticoids.

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Thus, differences in the effectiveness with which a particular NSAID inhibits an isoform of cyclooxygenase may affect both its activity and toxicity. It has been proposed that the perfect NSAID would inhibit the inducible COX-2 isoform (thereby decreasing inflammation) without having any effect on the constitutive COX-1 isoform (thereby minimizing toxicity). Three selective COX-2 inhibitors, celecoxib, rofecoxib, and valdecoxib have received approval from the Food and Drug Administration (FDA). These drugs have at least 200 to 300 fold selectivity for inhibition of COX-2 over COX-1. COX-2 inhibitors have not been approved for use in children¹⁰⁻¹³.

Classification of NSAIDs

1. Drug with analgesic and weak anti inflammatory effect – Aniline derivative. Paracetamol.
2. Drugs with analgesic and mild to moderate anti-inflammatory effect.
 - a. Propionic acid derivatives : Ibuprofen, Fenbufen, Fenoprofen, Ketoprofen, Naproxen
 - b. Fenamic acid derivative : Mefenamic acid.
3. Drugs with analgesic and marked anti-inflammatory effect
 - a. Salicylic acid derivatives : Aspirin, Salsalate, Sodium salicylate
 - b. Pyrazolone derivatives : Azapropazone, Phenyl butazone
 - c. Acetic acid derivatives : Diclofenac, Etodolac, Fenclofenac
 - d. Indole derivatives : Indomethacin, Sulindac
 - e. Oxicam derivative : Piroxicam
4. Cox-2 Inhibitors : Celecoxib, Etoricoxib, Meloxicam

Adverse effects

The widespread use of these drugs has led to the recognition of numerous associated adverse effects. The most important complications are:

Gastroduodenal toxicity

NSAIDs can induce both unimportant and important effects in the gastroduodenum¹⁴⁻²². A variety of symptoms and signs are commonly associated with NSAID-induced gastrointestinal toxicity.

- Dyspepsia – Some believe that dyspepsia is the most common problem, affecting up to 50

percent of patients who take both over-the-counter (OTC) and prescription NSAIDs.

- Nausea and vomiting – These symptoms may or may not be directly related to a local mucosal irritation. The exact incidence with which they occur is unknown.
- Esophagitis – Esophagitis is a relatively common problem that can lead to stricture formation.
- Peptic ulcers – Gastric ulcers are far more common than duodenal ulcers in patients treated with NSAIDs. The point prevalence rate for gastric ulcers among NSAID users as determined by endoscopic trials is 15 to 30 percent, 10 times that for duodenal ulcers. Both types of ulcer are usually asymptomatic, and many do not become clinically significant.
- Gastrointestinal hemorrhage – The incidence of NSAID-induced gastrointestinal hemorrhage is difficult to define. The published NSAID-induced gastrointestinal complication rate varies from 0.1 to 4 percent per year¹⁴; many of these patients are bleeding because of NSAID use.
- Gastrointestinal perforation – Perforation is the rarest of the NSAID-induced gastrointestinal complications; the exact incidence is unknown.

Mechanism of gastroduodenal toxicity – An understanding of the mechanism by which NSAIDs induce gastrointestinal mucosal damage requires an understanding of normal gastric anatomy and physiology. The stomach is richly endowed with a multilayered protective barrier which includes^{17,20}

- A thick layer of hydrophobic mucous.
- Substantial glutathione to scavenge any superoxide radicals generated.
- Bicarbonate secreted by the superficial lining cells which serves to buffer acid that penetrates through the mucous barrier.
- Tight junctions between cells of the superficial lining.
- A significant blood supply, which maintains the highly metabolic activity of the superficial lining cells.

In addition, prostaglandins modulate the amount of gastric acid generated, regulate the integrity of the mucous barrier, the amount of bicarbonate and glutathione generated, and the amount of mucosal

blood flow. Thus, it is not surprising that prostaglandin inhibition by a NSAID might lead to gastrointestinal toxicity.

The NSAIDs are all weak organic acids except for nabumetone. As a result, most of the NSAIDs that are not enteric coated are uncharged in the acid milieu of the stomach lumen. They are therefore able to rapidly penetrate the hydrophobic mucous barrier and enter the superficial lining cells^{17,20}. Inhibition of prostaglandin synthesis in the mucosa allows these drugs to degrade the integrity of the barrier that normally prevents gastric acid from reaching the cells, to reduce blood flow, and to decrease glutathione (a superoxide radical scavenger) and bicarbonate synthesis^{17, 20-21}. The concentration of drug builds up as blood flow decreases and the drug penetrates the lining cells, eventually leading to oxidative uncoupling of mitochondrial function at the cellular level and cell death. Another contributing factor to the rate of drug accumulation is whether or not it undergoes enterohepatic recirculation. The latter leads to repeated exposure of the intestine to the NSAID which, via bile reflux, can also lead to gastroduodenal injury. This cascade of events may culminate in superficial erosions, but also can lead to ulcer crater formation. The lack of local effect of some enteric products or drugs with a higher pKa (eg, nabumetone) may explain why some agents have a decreased incidence of gastrointestinal effects in population studies. However, any drug of any formulation (eg, enteric coated) that significantly inhibits systemic prostaglandin synthesis, regardless of how it is delivered (PO, PR, or IV), still retains a gastroduodenal risk which is proportional to its capacity to inhibit the synthesis of prostaglandins in the gastroduodenal mucosa¹⁵⁻¹⁷. Inhibition of prostaglandins may not be the only mechanisms involved in gastroduodenal injury from NSAIDs. NSAIDs impair angiogenesis by mechanisms that are only in part related to prostaglandin inhibition. This mechanism may impede healing in patients who develop ulcers while taking NSAIDs. The ulcer induced by NSAIDs often differs histologically from that caused by *Helicobacter pylori*. The latter is typically associated with chronic inflammation on biopsy of the surrounding gastric or duodenal tissues; in contrast, the tissue surrounding a NSAID-induced ulcer is usually not inflammatory²³. However, this distinction may be oversimplified from a clinical point of view since many patients with NSAID-induced

ulcer are also infected with *Helicobacter pylori*. There is little correlation between the majority of symptoms induced by NSAIDs and pathologic changes²⁴. However, local esophageal disease due to NSAIDs appears to be correlated with symptoms²⁵.

Risk of gastrointestinal toxicity – One important determinant is the duration of therapy. The administration of NSAIDs for a short period of time (less than one week) in healthy people is unlikely to result in any significant gastroduodenal toxicity²⁵⁻³⁰. In contrast, longer duration of therapy is associated with an increased risk of developing complications possibly because longer treatment increases the opportunity for patients to develop a toxic gastroduodenal event. Gastroduodenal toxicity may develop even in patients taking low doses of NSAIDs (such as for cardiovascular prophylaxis), which, despite the low dose, can be associated with a significant decrease in gastric mucosal prostaglandin concentrations³¹. Gastroduodenal complications are most common within the first three months after the initiation of therapy. A number of other factors are associated with increased risk of gastroduodenal toxicity and complications such as bleeding from NSAIDs^{25-28, 32}. Assessment of these risk factors is recommended (by American College of Gastroenterology) for identifying patients who should be considered for prophylaxis if it is felt that an NSAID must be given³³.

- Prior history of a gastrointestinal event (ulcer, hemorrhage).
- Age >60.
- High dosage of a NSAID.
- Concurrent use of glucocorticoids.
- Concurrent use of anticoagulants.

Patients with several risk factors are at high risk for NSAID toxicity (up to 9 percent at six months)³⁴⁻³⁵. The risk of toxicity may not be uniform among the NSAIDs. However, most of the studies that have attempted to stratify individual NSAID risks of gastrointestinal toxicity are difficult to interpret because they compared the effects of different NSAIDs used at varying doses^{25, 29}. The role of *Helicobacter pylori* (*H. pylori*) infection in NSAID-induced gastritis or ulcer formation is unsettled. It is not clear that eradication of *H. pylori* in patients with NSAID-induced peptic disease has the same benefit as in peptic disease not associated with

NSAIDs. Furthermore, whether or not eradication of *H. pylori* prior to treatment with NSAIDs reduces the risk of clinically significant PUD is also uncertain³⁶⁻³⁷.

Prevention and treatment of gastroduodenal toxicity- Misoprostol, H2-blockers, and proton pump inhibitors have been evaluated as prophylactic therapy for patients taking nonselective NSAIDs³⁸. The approval of the selective COX-2 inhibitors has permitted a new strategy for the prevention of NSAIDs related gastroduodenal toxicity in high-risk patients.

Misoprostol – The risk for NSAID-induced gastric or duodenal ulcer can be decreased with concomitant use of the prostaglandin analog misoprostol; complications of ulcers have also been reduced by this drug. The problem of misoprostol-induced diarrhea sometimes lead to discontinuation of this drug³⁸⁻⁴⁰.

H2 receptor antagonists – Standard doses of H2 receptor antagonists are not effective for the prevention of NSAID-induced gastric ulcers, although they may be useful for the long-term prevention of duodenal ulcers⁴¹. However, treatment with high-dose famotidine significantly reduced the incidence of both gastric and duodenal ulcers over the 24-week study period compared to placebo. High doses of famotidine (40 mg BID) also may decrease the rate of recurrence of NSAID-induced ulcer disease⁴²⁻⁴³. However, the use of H2 antagonists for prophylaxis may not be reliable, since tolerance to pH control occurs after long-term therapy with these drugs.

Proton pump inhibitors – Proton pump inhibitors may be useful for the prevention of NSAID-induced duodenal ulcers⁴⁴⁻⁴⁵. Clinical studies of lansoprazole and omeprazole find them to be less efficacious but better tolerated than misoprostol⁴⁴. Lansoprazole is approved by the United States Food and Drug Administration for use in treatment and/or prevention of NSAID-induced gastric or duodenal ulcers.

Recommendations for prevention of gastroduodenal toxicities

For patients who are at high risk for NSAID-related gastroduodenal toxicity, primary therapy with a COX-2 selective inhibitor is a reasonable option. It is uncertain whether adding a proton pump inhibitor or misoprostol to high-risk patients taking a COX-2

inhibitor would have added benefit. Testing and treatment for *H. pylori* should also be considered. Patients who have had a recent ulcer or whose ulcer has not completely healed may be an exception to this recommendation. Because of the possibility that selective COX-2 inhibitors could impair ulcer-healing, prophylaxis with a proton pump inhibitor may be preferred⁴⁶. The lack of antiplatelet effect of selective COX-2 inhibitors should also be considered in the context of patient need. For patients taking nonselective NSAIDs, misoprostol (at a dose of 200 µg QID) and lansoprazole (15 or 30 mg daily) have received FDA approval for prophylaxis against NSAID-induced ulcer disease and its complications. In comparison, omeprazole and high-dose H2 antagonists have not yet been approved for this purpose. Patients with several risk factors are at particularly high risk for NSAID toxicity (up to 9 percent at six months)³⁹⁻⁴⁰. It is also this population in which prophylactic therapy is most cost-effective⁴⁷.

Patients who suffer from NSAID-induced nonulcer dyspepsia may respond to H2 antagonists or proton pump inhibitors at standard doses, but of these choices only proton pump inhibitors also reduce the risk of NSAID-induced ulcer or its complications. Misoprostol does not alter symptoms, although it has been shown to improve outcomes.

Treatment of NSAID-induced ulcer disease

If a patient develops an ulcer while on NSAIDs, the drug should be stopped (if possible) and traditional ulcer therapy with an H2 antagonist or a proton pump inhibitor should be started. Although healing may occur more rapidly with a proton pump inhibitor than an H2 blocker, the long-term relapse rate after healing appears to be similar with the two drugs. A proton pump inhibitor is preferred in patients with large ulcers⁴⁸⁻⁵¹. The patient's status regarding infection with *H. pylori* also should be assessed (if not done previously); if positive, appropriate therapy should be instituted.

With continued NSAID therapy

There are many patients who must continue NSAID therapy despite the development of ulcers or erosions. Thus, patients with ulcers or erosions who must continue NSAIDs should be treated with a proton pump inhibitor, such as omeprazole (20 mg/day) or lansoprazole (15 or 30 mg/day) or with misoprostol⁴⁹⁻⁵¹. The length of therapy depends

upon the patient's response; four to eight weeks appears to be appropriate. Maintenance therapy is necessary for all patients who are continuing on NSAIDs due to the high rate of ulcer recurrence. Use of lansoprazole may be equivalent to misoprostol (200 µg BID) in this setting.

Adverse effects on the distal small bowel and colon

The distal small bowel and colon are not impervious to the deleterious effects of nonsteroidal anti-inflammatory agents (NSAIDs). The ileocecal region is a potential site for a variety of NSAID-induced injuries including erosions, ulcers, strictures, perforation, and the formation of diaphragms, which can lead to bowel obstruction. NSAIDs can also lead to colitis resembling inflammatory bowel disease (IBD), exacerbate preexisting IBD, or complicate diverticular disease (perforation or bleeding). The elderly and those on long-term NSAID therapy appeared to be at highest risk. There may also be an association between NSAID use and collagenous colitis. The lesion thought to be pathognomonic of NSAID injury is the diaphragm-like stricture, which is likely a scarring reaction secondary to ulcerative injury⁵²⁻⁵⁵.

The mainstay of treatment for NSAID-induced injury is discontinuation of the NSAID. For nonstrictured ileocecal lesions, this is usually followed by prompt improvement. A repeat colonoscopy six to eight weeks later should confirm partial or complete resolution of ulcerations and/or colitis. Obstructive symptoms due to strictures are unlikely to resolve without some form of intervention⁵⁴⁻⁵⁵.

Acute renal failure and nephrotic syndrome

Nonsteroidal antiinflammatory drugs (NSAID) can induce two different forms of acute renal failure: hemodynamically-mediated and acute interstitial nephritis (which is often accompanied by the nephrotic syndrome). The former and perhaps the latter are directly related to the reduction in prostaglandin synthesis induced by the NSAID.

Hemodynamically-mediated acute renal failure

Inhibition of prostaglandin synthesis with an NSAID can lead to reversible renal ischemia, a decline in glomerular hydraulic pressure (the major driving force for glomerular filtration), and acute renal failure. The rise in the plasma creatinine concentration is seen within the first 3 to 7 days of therapy, the time required for attainment of steady state drug levels and therefore maximum inhibition

of prostaglandin synthesis. Acute renal failure can occur with any NSAID, including the parenteral analgesic, ketorolac. The selective COX-2 inhibitors also may precipitate acute renal failure in certain patients. The relative frequency with which this occurs compared to the nonselective NSAIDs is not known.

There is suggestive evidence that some nonselective NSAIDs have a lower nephrotoxic potential than others. Low-dose aspirin (studied at approximately 40 mg per day, although somewhat higher doses may have a similar effect), low-dose over-the-counter ibuprofen, and perhaps sulindac appear to be safer because of their relative sparing of renal prostaglandin synthesis. With aspirin, for example, the inhibition of glomerular cyclooxygenase may only be partial and transient, in contrast to the irreversible acetylation in platelets. Over-the-counter ibuprofen is also safe in most subjects, although hypovolemic patients may be at some risk. The mechanism by which sulindac might spare renal prostaglandin synthesis is not well understood⁵⁶⁻⁶⁰.

Acute interstitial nephritis and nephrotic syndrome

The second form of NSAID-induced acute renal failure has two components, one or both of which may be present in a given patient: an acute interstitial nephritis, with an interstitial infiltrate composed primarily of T lymphocytes; and the nephrotic syndrome due to minimal change disease. The latter may be due to release of a toxic lymphokine from the activated T cells. This disorder is most likely to occur with fenoprofen, but probably can be induced by any NSAID. How it occurs is not known; it is possible that cyclooxygenase inhibition by the NSAID results in the preferential conversion of arachidonic acid to leukotrienes, which can then activate helper T cells. Spontaneous recovery generally occurs within weeks to a few months after therapy is discontinued⁶¹⁻⁶².

Membranous nephropathy

Although initial reports found that virtually all cases of NSAID-induced nephrotic syndrome that were biopsied had minimal change disease, it is now evident that membranous nephropathy can also occur. Many of the patients who developed membranous nephropathy were treated with a specific NSAID, diclofenac, but probably any NSAID can be involved⁶³.

Chronic renal disease

In addition to the above acute effects, it has been proposed that daily NSAID use for more than one year may be associated with an increased risk of chronic renal disease, perhaps due to papillary necrosis similar to that seen with other analgesics.

Hepatic injury

Elevations of serum aminotransferases (transaminases) are commonly associated with NSAID use; however, liver failure is quite rare. Sulindac was the only NSAID with a substantially greater risk than that of the overall NSAID group. However, the liver injury associated with sulindac and the other NSAIDs was generally mild and reversible. Users of NSAIDs who had rheumatoid arthritis had a tenfold increased risk of acute liver injury compared with NSAID-treated patients with osteoarthritis. Concomitant exposure to other hepatotoxic medications probably increased the risk of hepatic injury in patients with rheumatoid arthritis. Transient minor increases in liver enzymes were not a useful predictor of diagnosed NSAID-associated acute liver injury⁶⁴⁻⁶⁵. Diclofenac has been reported to cause clinical hepatitis with features including ANA positivity and histologic evidence of chronic active hepatitis that often caused misdiagnosis and inappropriate treatment. Introduction of another class of NSAID in many of these patients appeared to be safe. It is recommended that liver enzymes and function tests be measured within eight weeks after the initiation of chronic NSAID therapy; monitoring symptoms is not sufficient, since symptomatic hepatitis is rare. NSAIDs should be discontinued if the aminotransferases rise to greater than three times the upper limit of normal, if there is a fall in serum albumin (suggestive of a synthetic defect induced by the drug), or if the prothrombin time is prolonged⁶⁵⁻⁶⁷.

Pulmonary effects

The NSAIDs rarely induce pulmonary problems, although the actual incidence of adverse events is unknown. The principal pulmonary reactions that can occur include bronchospasm (which can be quite severe) and pulmonary infiltrates with eosinophilia.

Bronchospasm

Aspirin-induced asthma is a well recognized entity that presents in the third to fourth decade in

individuals not previously sensitive to aspirin or NSAIDs. Reactions are usually slow in onset, thirty minutes to two hours after ingestion, and may be slow to resolve. In addition to wheezing, reactions are usually accompanied by profound nasal symptoms; facial flushing, angioedema, and gastrointestinal symptoms can also occur. Hives are uncommon, being primarily seen in a distinct syndrome characterized by aspirin sensitivity without asthma, called aspirin-induced urticaria/angioedema. Despite its name, aspirin-induced asthma also occurs after the use of many classes of NSAIDs in addition to aspirin. The mechanism by which aspirin-induced asthma occurs is unclear, but probably involves inhibition of prostaglandin synthesis via the cyclooxygenase pathway, shunting of arachidonic acid into leukotriene production, or both. There appears to be an association between the development of this disorder and the occurrence of nasal polyps and sinusitis. Treatment of aspirin-induced asthma includes NSAID avoidance, desensitization, and possibly the use of leukotriene inhibitors. Acetaminophen and the nonacetylated salicylates (choline magnesium trisalicylate and salicylsalicylic acid) may be considered since they are relatively weak cyclooxygenase inhibitors. However, bronchospasm can still be precipitated by these drugs, suggesting the need for careful monitoring, perhaps with an air flow meter after a single dose of the chosen drug to determine if bronchospasm develops⁶⁸⁻⁶⁹.

Hematologic effects

Some of the early NSAIDs (eg, phenylbutazone and to a lesser degree indomethacin) have been associated with an increased risk for bone marrow failure (ie, aplastic anemia). Although phenylbutazone is now rarely used, neutropenia and antiplatelet effects can be induced by any of the NSAIDs⁷⁰.

Antiplatelet effects

The antiplatelet effects of NSAIDs are due to inhibition of COX-1, an isoform of cyclooxygenase, leading to decreased production of thromboxane A₂ (TxA₂). TxA₂ is released by platelets in response to a number of agonists, amplifying the platelet response and leading to aggregation. These effects have therapeutic applications, such as the use of aspirin in patients with coronary heart disease. However, this same activity has potentially negative consequences in other groups of patients:

- NSAIDs should be avoided in patients with preexisting platelet defects (eg, due to uremia or von Willebrand disease) and in those with thrombocytopenia (platelet count < 50,000/ μ L). Nonacetylated salicylates are a safer therapeutic alternative in these patients. Doses of nonacetylated salicylates should remain within recommended dosage ranges (eg, 1.5 to 3.0 g/day for salsalate and choline magnesium trisalicylate) to avoid inhibition of platelet cyclooxygenase which can occur at high doses⁷¹⁻⁷².
- NSAIDs should be withheld preoperatively for at least four to five times the drug half-life. Aspirin irreversibly inhibits platelet cyclooxygenase and platelets lack the machinery to produce new cyclooxygenase; thus, patients should stop aspirin for at least one week prior to a planned surgical procedure to allow the body to repopulate the platelet pool with platelets that have not been exposed to the drug⁷¹⁻⁷².
- Concomitant use of anticoagulants and NSAIDs is not strictly prohibited; however, anticoagulants may predispose to an increased risk of hemorrhage once a mucosal break has been precipitated by an NSAID⁷¹⁻⁷².

New highly selective inhibitors of the COX-2 isoform of cyclooxygenase may have no effect on the platelet, since COX-2 activity has not been found in platelets. Another issue that may arise is concurrent therapy with aspirin and a nonsalicylate NSAID. The dose of aspirin used to protect against cardiovascular disease is often quite low (eg, 81 to 325 mg/day of aspirin). Such patients may have an indication for NSAID use. None of the nonsalicylate NSAIDs has been evaluated for cardioprotective effects in large studies; they are therefore not a substitute for aspirin therapy. The desirable antiplatelet effects of aspirin may be attenuated by prior or ongoing administration of a nonselective NSAID. This interference with the antiplatelet effects of aspirin has been demonstrated to affect in-vitro platelet aggregation, but it is unclear whether there are any clinical consequences. Nevertheless, until the issue is better understood, it may be prudent to avoid the combined use of nonselective NSAIDs and aspirin if possible. Selective COX-2 inhibitors may be preferred when an NSAID and aspirin must be used together. However, as discussed above, this combination may

largely eliminate the gastroduodenal safety advantage of the COX-2 inhibitor, and thus require, for the patient at high risk of gastrointestinal ulceration or bleeding, additional antiulcer therapy⁷¹⁻⁷³.

Blood pressure – Patients with treated hypertension may have elevated levels of angiotensin II and norepinephrine. These vasoconstrictors increase the release of vasodilator prostaglandins from the kidney, which act locally to minimize the degree of renal ischemia. When this compensatory response is inhibited by an NSAID, the increase in renal and systemic vascular resistance can cause an elevation in blood pressure. This effect can generally be induced by any NSAID (including over-the-counter ibuprofen), but may be less likely to occur with sulindac or low-dose aspirin, or with other types of analgesics such as acetaminophen. NSAID-induced blood pressure changes are small; in one meta-analysis the mean rise in supine blood pressure was 5.0 mmHg. NSAIDs antagonized the antihypertensive effect of beta blockers (blood pressure elevation 6.2 mmHg) more than vasodilators and diuretics in this report. Piroxicam produced the most marked elevation in blood pressure (6.2 mmHg), while sulindac and aspirin had the least hypertensive effect. The consequences of these modest increases in blood pressure in patients taking NSAIDs have not been specifically studied. However, a 5 to 6 mmHg elevation in diastolic blood pressure over several years may be associated with a 67 percent increase in total stroke occurrence and a 15 percent increase in coronary heart disease⁷⁴⁻⁷⁵.

Central nervous system

The reported central nervous system (CNS) side effects of NSAIDs include aseptic meningitis, psychosis, and cognitive dysfunction. Psychosis and cognitive impairment are more prevalent in elderly patients, particularly with the use of indomethacin. Aseptic meningitis seems to be more prevalent in patients with SLE who are treated with NSAIDs of the phenylpropionic acid class (eg, ibuprofen, naproxen); however, this diagnosis should be considered in any patient with aseptic meningitis who has been using NSAIDs. Tinnitus is a common problem, particularly in patients prescribed high doses of salicylates, although it can occur with all of the available NSAIDs. Tinnitus is typically reversible upon cessation of drug therapy, and is a good warning

sign to identify those patients who are developing high blood levels of the drug. However, it may not be as evident in patients at the extremes of age ⁷⁶.

Pregnancy and lactation

Studies in rhesus monkeys have not found aspirin to be a teratogen. However, it is best to avoid NSAIDs if possible during pregnancy. The safety of these drugs has not been extensively evaluated in controlled studies in pregnant women; in animal models, NSAIDs have been shown to increase the incidence of dystocia and postimplantation loss, and to delay parturition. In addition, the inhibition of prostaglandin synthesis by NSAIDs, particular by aspirin, may result in premature closure of the ductus arteriosus, and other harmful effects including smaller babies and neonatal bruising. Despite these concerns, aspirin has been used for years in patients requiring NSAID therapy during pregnancy. It was concluded from a prospective study that aspirin can be used if absolutely necessary in pregnant women with inflammatory disease. It should be stopped in the last two months of pregnancy to avoid potential bleeding complications and premature closure of the ductus arteriosus; the shorter acting NSAIDs can be substituted with very close monitoring.

NSAIDs are excreted in breast milk in very small amounts. It is generally agreed that salicylates in normally recommended doses are not harmful to nursing infants. In contrast, misoprostol causes increased uterine contractility; it is considered an abortifacient agent. Thus, contraception is essential in women of childbearing potential who take misoprostol ⁷⁷⁻⁷⁸.

Advantages and disadvantages of COX-2 inhibitors

Rofecoxib got USFDA approval in 1999 for treating osteoarthritis, acute pain in adults, menstrual pain and for treating rheumatoid arthritis. In September 2004 Merck (manufacturer of rofecoxib, Vioxx) announced voluntary worldwide withdrawal of rofecoxib following a prospective randomized clinical trial (APPROVE) which found confirmed cardiovascular events. In 2004 an ongoing clinical trial on celecoxib to prevent colonic polyps was stopped due to increased risk of cardiovascular events in patients taking celecoxib versus those taking placebo. USFDA then advised the use of lowest effective dose of celecoxib. In 2005 USFDA asked Pfizer to withdraw valdecoxib (Bextra) from

the market because of its overall risk versus benefit profile for the drug was unfavorable. These drugs have at least a 200 to 300-fold selectivity for inhibition of COX-2 over COX-1. COX-2 inhibitors have not been approved for use in children. Meloxicam, another drug, relatively less selective COX-2 inhibitor is also available.

The principal benefit with the selective COX-2 inhibitors is the production of comparable analgesia and antiinflammatory effects to the nonselective NSAIDs, but with fewer symptomatic gastric and duodenal ulcers and a decrease in gastrointestinal symptoms. An additional benefit is possible protection against the development of colon cancer. Lack of effect upon platelets is also an important advantage. Celecoxib, approved by FDA was based upon the results of five clinical trials (some of which have been published only preliminary form) involving more than 5200 patients with osteoarthritis or rheumatoid arthritis in which its efficacy and toxicity were compared to nonselective NSAIDs and placebo. These data demonstrate that celecoxib produced comparable analgesia and antiinflammatory effects to nonselective NSAIDs, but with fewer gastric and duodenal ulcers detected by serial endoscopy⁷⁹⁻⁸².

The precipitation of hemodynamically-mediated acute renal failure is limited to selected patients in whom the secretion of vasodilator prostaglandins is increased in an attempt to counteract the effect of increased renal vasoconstrictors such as angiotensin II. Patients at risk include those with volume depletion, heart failure, cirrhosis, intrinsic renal disease, and hypercalcemia. There is evidence that selective COX-2 inhibitors adversely affect renal function in such at risk patients. These observations suggest that selective COX-2 inhibitors should be avoided in patients with chronic renal insufficiency, severe heart disease, volume depletion, and/or hepatic failure⁸³⁻⁸⁵.

The molecular structure of celecoxib includes a sulfonamide moiety, as a result, celecoxib is contraindicated in patients who are allergic to sulfonamides. Patients who have had anaphylactoid reactions to aspirin or nonselective NSAIDs may be at risk for similar effects when challenged with COX-2 selective agents ⁸⁶.

NSAID selection and clinical use

It is therefore difficult to name the "safest" NSAID. The nonacetylated salicylates are probably safer than

the other NSAIDs, since they are weak inhibitors of cyclooxygenase activity. Many clinicians believe that ibuprofen is also quite safe, which is true when the drug is used at the lowest possible dose. However, increasing the dose of any NSAID is associated with an increased risk of a toxic event.

The choice of an NSAID for a particular patient is based upon a number of factors, including relative efficacy, toxicity, concomitant drugs, concurrent disease states, the patient's age, renal function, cost and, to a certain extent, on the prescriber's preference.

Differences in anti-inflammatory activity between NSAIDs in different groups are small but there is a wide variation in the incidence of side effects and in individual patient response. In considering patient response it is important to give each NSAID an appropriate therapeutic trial before an alternative is tried. An analgesic effect should normally be obtained within one week of starting therapy whereas a full anti-inflammatory effect may not be achieved (or may not be clinically assessable) for up to three weeks. Ibuprofen has the lowest risk of developing GI toxicities among nonselective NSAIDs,

For patients who are at high risk for NSAID-related gastroduodenal toxicity, primary therapy with a COX-2 selective inhibitor is a reasonable option. Although the cost-effectiveness of this approach has not been established, the increased expense may be justified when considering the costs associated with ulcer complications, the convenience of minimizing the number of medications patients have to consume, the potential to reduce other types of NSAID-related toxicity such as dyspepsia, and the cost associated with other prophylactic therapies.

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