INVITED ARTICLE

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS - USES AND COMPLICATIONS

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ABSTRACT

Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are important in the management of any inflammatory arthritis. However, all NSAIDs have side effects - NSAID related gastropathy (the most common serious side-effect), reversible NSAID nephropathy, dermal complications, hematologic complications, hepatic complications, central nervous system complications, pulmonary complications etc. Patients who have more severe forms of rheumatic disease, take higher doses of NSAIDs with steroids and suffer concomitant medical illness are at higher risk for these toxicities. In all cases, the benefits from the use of NSAIDs must outweigh the risk. When managing a high risk patient, consider alternate therapy and if an NSAID must be used, always monitor the patient carefully.

Keywords : Non-steroidal anti-inflammatory drugs, uses, complications

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) as the name suggests, are drugs which suppress inflammation. Patients often call them pain-killers, but they do more than stop the pain, they reduce the inflammation in arthritis. NSAIDs are used in all types of arthritis regardless of the etiology. Treatment with NSAIDs will quickly reduce the signs of inflammation which are pain, redness, swelling, heat and loss of function. However, they do nothing to treat the cause of the arthritis (unlike allopurinol for gout), or prevent initial tissue damage and modify the outcome of the chronic arthritis (unlike gold for rheumatoid arthritis). NSAIDs act quickly and the effect wears out quickly when the drug is discontinued. This is unlike Disease Modifying Anti-Rheumatic Drugs (DMARDs) like gold, which will continue to act for a while even after its administration has been discontinued.

CLASSIFICATION

There are many ways to classify NSAIDs and the simplest way is to follow the chemical structure. This is as given below:

Acidic Acid

Arylcarboxilic acid

Salicylic acid	-	acetyl salicylate, sodium salicylate, and salicylsalicylate
Anthranilic acid (fenamates)	-	mefenemic acid, flufenamate acid, meclofenamate acid

Arylalkanoic acid

Arylacetic acid	-	Diclofenac, fenclofenac
Arylpropionic acid	-	naproxen, ibuprofen, ketoprofen, fenbufen, fenoprofen
Heteroaryl acetic acid	-	tolmetin, zomepirac
Indole and indene acetic acid	-	indomethacin, sulindac

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Enolic acid

Pyrazolidinediones	-	phenylbutazone, oxyphenylbutazone
Oxicams	-	piroxicam, isoxicam

Nonacidic Acid

Proquazone, fluproquazone, azapropazone

Clinically, it is not very important to remember the chemical classification and often it is better to remember the half-lives of the different NSAIDs as this will determine the dosing interval. Drugs like piroxicam have a long half-life and are convenient as single day dose. However it may accumulate in the elderly. Naproxen with a slightly shorter half-life may be taken twice daily and is also convenient to use. A drug with a very short half-life is tolmetin and requires frequent dosing. It can sometimes be used for patients with arthritis requiring surgery up till 24 hours before the surgery. Some NSAIDs with shorter half-lives are now available in a sustained release formulation. However, sometimes the effect is not as long as desired and the patient may have morning stiffness the next day as the drug wears out.

NSAIDs are also available in injectable forms and are useful for rapid relief of acute rheumatic pains. Systemic side effects are the same as for oral formulations. Topical NSAIDs in the form of gels and creams are available for the treatment of local rheumatic pain. This is quite effective and fairly popular as some patients like to massage medication over a particularly painful joint. It can be used together with an oral NSAID. Side effects are mainly skin irritation or rash, and systemic side effects are minimal as the dose is small.

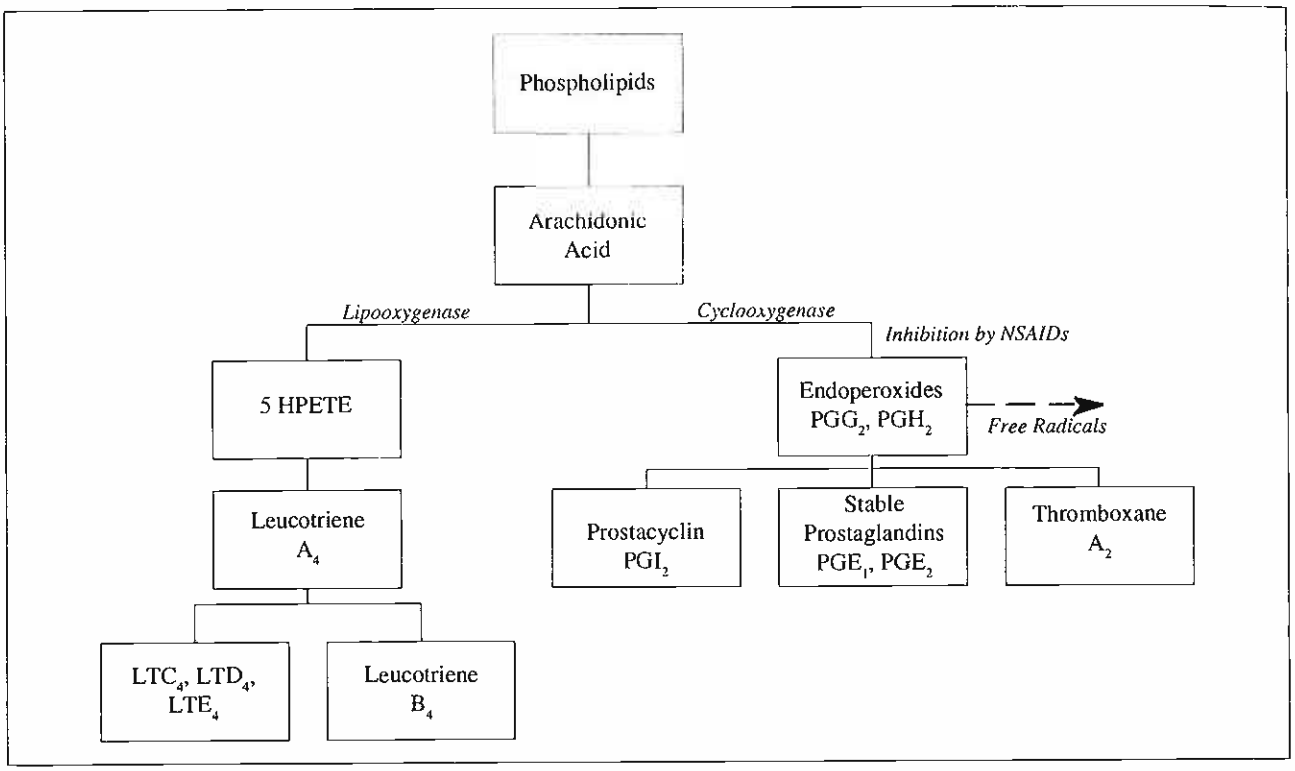
MECHANISMS OF ACTION

Since 1971, it has been known that most NSAIDs inhibit the synthesis of prostaglandins. The arachidonic acid metabolism to prostaglandins is shown in Fig 1. NSAIDs block the conversion of arachidonic acid to endoperoxidase by inhibiting the enzyme cyclooxygenase[2]. NSAIDs have also been shown to inhibit the lipooxygenase pathway in arachidonic metabolism[3]. Another mechanism postulated is the inhibition of free radicals[4]. It has also been shown that NSAIDs blunt neutrophil activation[5]. Another hypothesis is that NSAIDs act via the calcium channel pathway[6]. Clearly, there is still much to be studied about the actual mechanism of action of the different NSAIDs.

Adverse Effects

All NSAIDs have possible adverse effects on all the major organ system. Generally the toxicities are dose related though some are idiosyncratic.

Fig 1 - Arachidonic Acid Metabolism



Adapted from Ref 1

Gastrointestinal Complications

Gastrointestinal complications due to NSAIDs are the most prevalent serious drug toxicity in the United States. The yearly hospitalization incidence for NSAID gastropathy was 1.58% in rheumatoid arthritis patients and the risk of gastrointestinal related death was 0.19% per year[7]. The effect of NSAIDs on the gastrointestinal tract can be local or systemic[8]. The local effect of aspirin on the gastric mucosa is an endoscopically visible erosion. A prodrug like sulindac may have less local gastric toxicity because it has to be activated in the liver first. Likewise enteric coated aspirin may have less local effect on the gastric mucosa. The systemic effect is via the inhibition of gastric prostaglandins which have gastroprotective properties. All NSAIDs which inhibit cyclooxgenase may give this adverse effect. NSAIDs which do not inhibit cyclooxygenase, for example salicylsalicylate, may potentially be safer. The main risk factors for serious gastrointestinal events are higher age, concomitant use of prednisone, previous NSAID GI side effect, prior GI hospitalization, level of disability and high NSAID dose (more than 1.3 X recommended dose)[7]. Hence it is not just a question of which NSAID is safer to use but which patient is at higher risk of NSAID gastropathy. Misoprostal (a prostaglandin analogue) may be used to prevent NSAID induced gastric ulcers. Patients who develop gastric lesions may be treated with misoprostal while patients with duodenal lesions respond to H_2 Blockers. Those with difficult to treat lesions may respond to omeprazole. Patients who had previous ulcers or bleeding yet need to continue on NSAIDs have to be given concomitant long term ulcer treatment. Even then, there is no guarantee that there will not be any further problems. These patients have to be monitored carefully and if they do develop ulcers again, the NSAID has to be withdrawn. There is no need to routinely cover patients on NSAID with anti-ulcer drugs if they are elderly with disability and on concomitant low dose steroids but they must be monitored carefully and gastroscoped if they develop any symptoms or if the haemoglobin level drops. Such high risk patients should never be given supra-maximal doses of NSAIDs.

Renal toxicities

The most common renal toxicity is the so called reversible NSAID nephropathy. This is the result of inhibition of renal prostaglandins and is characterized by elevation in serum urea, creatinine, potassium and an increase in body weight due to fluid retention. If recognized early and the drug discontinued, the renal function returns to normal usually within 3 days. Renal prostaglandins are produced in the kidney in response to vasoconstriction caused by angiotensin II, norepinephrine and vasopressin. Vasodilatory renal prostaglandins especially prostaglandin E_2 and prostacyclin act to maintain renal blood flow and glomerular filtration rate. This action is not very important in normal circumstances but is vital in conditions causing decreased renal blood flow eg shock, congestive heart failure, cirrhosis with ascites, nephrotic syndrome and in patients with chronic renal disease. When such high risk patients are given NSAIDs, inhibition of the renal prostaglandins will result in decreased renal perfusion and NSAID nephropathy. Patients with advanced age, atherosclerotic cardiovascular diseases and who are taking concurrent diuretics are also at increased risk for the development of reversible NSAID nephropathy. Treatment of acute gouty arthritis was reported to be the most common clinical situation which precipitated NSAID nephropathy[9]. Such high risk patients should have their renal function carefully monitored if they really need to take NSAIDs. It has been suggested that sulindac may be a renal sparing NSAID as the active drug is deactivated in the kidney and hence sparing the renal prostaglandins. However, other investigators have reported patients who developed NSAID nephropathy with sulindac. Recent studies demonstrate that the active drug is indeed excreted in patients' urine in about 36% of the time[10]; hence these patients are indeed at risk of developing NSAID nephropathy just as with any other NSAID. Renal papillary necrosis is a more serious form of renal complication from NSAIDs. This is thought to be due to renal medullary ischaemia from inhibition of renal prostaglandins. Initially compound analgesics were blamed but subsequently, it is recognized that any NSAID can cause this

complication. Risk factors are dehydration, old age and pre-existing renal disease. NSAIDs have also been blamed for other renal problems including interstitial nephritis with nephrotic syndrome. Such patients often have associated hypersensitivity phenomenon like rash and eosinophilia. Fenoprofen is the drug most often implicated though other drugs have been reported.

Skin Complications

The adverse skin reactions to NSAIDs are numerous. They include urticaria, macular papular lesions, vesiculobullous lesions, fixed drug eruptions, photosensitivity reactions, erythema multiforme, exfoliative dermatitis, Stevens Johnson Syndrome and toxic epidermal necrolysis. Adverse skin reactions were most commonly reported with piroxicam, zomepirac, sulindac, meclofenamate and benoxaprofen[11]. However, the NSAIDs which are most often responsible for the serious even fatal skin toxicities are phenylbutazone and oxyphenylbutazone[12].

Haematologic Toxicities

Here again, phenylbutazone and oxyphenylbutazone are most often responsible for NSAID induced blood dyscrasias[13] like agranulocytosis and aplastic anaemia. The patients at high risk for this complication are elderly (age over 60 years) women. Mefenemic acid, a popular NSAID locally, has been reported to cause haemolytic anaemia. Thrombocytopenia has also been caused by NSAIDs. Another well known side-effect of NSAIDs on platelets is the inhibition of platelet aggregation. NSAIDs inhibit cyclooxygenase, blocking the synthesis of thromboxane A_2 which is important in platelet aggregation. This action is reversible in most NSAIDs except aspirin which irreversibly acetylates cyclooxygenase. Currently low dose aspirin is commonly used as an anti-platelet agent in the prevention of coronary and cerebral thrombosis. The NSAIDs which do not have significant anti-platelet effect are the nonacetylated salicylates eg salicylsalicylates[14]. They may be safer to use in patients with bleeding tendencies.

Liver Complications

Asymptomatic elevation of hepatic transaminases is not uncommon with the use of NSAIDs and hepatic toxicity is considered to be a class characteristic of NSAIDs[15]. If detected early and the NSAID discontinued, the transaminitis is reversible. Sometimes the patient is symptomatic and develops nausea, tender hepatomegaly and even jaundice and prolongation of prothrombin time. The more serious complications are toxic hepatitis, cholestatic jaundice and fulminant hepatic necrosis. Benoxaprofen is responsible for the most serious hepatic toxicities and has been withdrawn from the market. Phenylbutazone has also caused some fatalities from hepatic complications. The patients at increased risk to this are again the elderly.

Central Nervous System Complications

Indomethacin has been known to cause many symptoms like giddiness, confusion, drowsiness and even seizures[16]. Other NSAIDs also cause cognitive dysfunction, memory loss, paranoia in the elderly eg ibuprofen. Salicylates in high doses can also cause confusion, hallucinations and seizures. If not treated early, salicylate overdosage can be fatal. Aseptic meningitis has been reported with ibuprofen, sulindac and tolmetin. Ibuprofen has also been reported to cause amblyopia. It is well known that salicylates in high doses cause tinnitus.

Bronchopulmonary Complications

Some patients have the well known triad of aspirin sensitivity, bronchial asthma and nasal polyposis[17]. In these patients, inhibition of cyclooxygenase reduce bronchial prostaglandins and shunt arachidonic acid metabolism to the lipooxygenase pathway. The leucotrienes C4 and D4 may precipitate bronchial spasm. Generalized urticaria and angioedema can also occur. Other mechanisms have been postulated including the mast cell and mediator release theory, platelet activation theory, etc. These patients are often sensitive to many other NSAIDs. Drugs that do not inhibit cyclooxygenase like propoxyphene do not cross react with aspirin. Salicylates and phenylbutazone have been known to cause pulmonary edema. Ibuprofen has been reported to cause pleural effusion and naproxen has been reported to cause pulmonary infiltrates.

Rare Toxicities

Though NSAIDs are often used in all types of rheumatic conditions for arthritis, NSAIDs can themselves cause lupus-like syndrome (phenylbutazone and ibuprofen) and vasculitis (indomethacin, naproxen and fenbufen). Other rare toxicities include alopecia (ibuprofen) and reversible gynecomastia (sulindac).

A PRACTICAL GUIDE TO THE USE OF NSAIDs IN RHEUMATOLOGY

Doctors often choose an NSAID simply because they are familiar with it and because it is cheap and easily available. Indeed there is no strong evidence to suggest that any one NSAID is superior to the other. However, there are other factors to be taken into consideration - concurrent illness, concurrent drug therapy, past experience with NSAIDs and the underlying rheumatic disease. NSAIDs should not be prescribed casually to patients who have peptic ulcer disease, kidney disease, congestive cardiac failure and other high risk factors as described above. Patients who have aspirin sensitivity as described above should never be given any NSAIDs again.

Patients who have rheumatoid arthritis need long term NSAID therapy in anti-inflammatory doses. Such patients should be tried on an NSAID and the dose increased to the maximum recommended and kept at that dose for two weeks. If there is no good response, the first NSAID is discontinued and another NSAID is tried. Combining NSAIDs will only increase toxicity without increasing efficacy[18]. Concomitant use of Disease Modifying Anti-Rheumatic drug or drugs and steroids are decided on an individual basis.

NSAIDs are also used for osteoarthritis. There has been much interest in articular cartilage and anti-rheumatic drugs recently[19]. It has been demonstrated that proteoglycan synthesis in osteoarticular cartilage culture is inhibited by salicylates but not by ketotifen and that piroxicam downregulates the expression of interleukin-1 in organ culture of osteoarthritic synovial tissue. The clinical significance of these laboratory findings is unclear. A clinical study suggested that patients given indomethacin for osteoarthritis of the hips had faster loss of joint space and required hip surgery earlier than patients given azapropazone which is not an NSAID. More clinical studies to address the question of chondroprotection are required before new guidelines for the use NSAIDs in osteoarthritis can be made.

Patients with seronegative spondyloarthropathies require higher doses of NSAIDs to reduce pain and stiffness to enable them to do exercises to minimize flexion deformities. Fortunately these patients tend to be younger and do not suffer from complicating illness which put them at high risk for NSAID toxicities.

Patients with crystal arthritis like gout need supra maximal doses of NSAIDs during an acute attack. Unfortunately this group of patients are at increased risk of NSAID nephropathy and other complications. Alternate therapy with colchicine and steroids should be considered for those patients who are at increased risk of NSAID toxicity, for example those taking diuretics for congestive heart failure. Patients who have soft tissue rheumatism may be given short term NSAID, physiotherapy and advised rest or local steroid injections. Topical NSAIDs may also be used.

In all cases the benefits from the use of NSAIDs must outweigh the risk of toxicities. When managing a high risk patient, always consider alternate therapy and if an NSAID must be used, always monitor the patient very carefully looking out for the complications discussed above.

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