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A Comprehensive Review on Clinical Pharmacology of Non-Steroidal Anti-Inflammatory Drugs

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ABSTRACT

An increasing number of non-steroidal anti-inflammatory drugs (NSAIDs) is available for clinical use each year. This article reviews significant differences between NSAIDs currently available in worldwide, and helps the clinician to evaluate new NSAIDs. While their mechanism of action and efficacy are similar, side effects and cost vary considerably from one agent to another. Because all NSAIDs can produce adverse effects, patients, especially if they are elderly, should be selected carefully for treatment with a particular agent.

KEYWORDS: *Non-steroidal anti-inflammatory drugs, COX, NSAIDs, inflammation*

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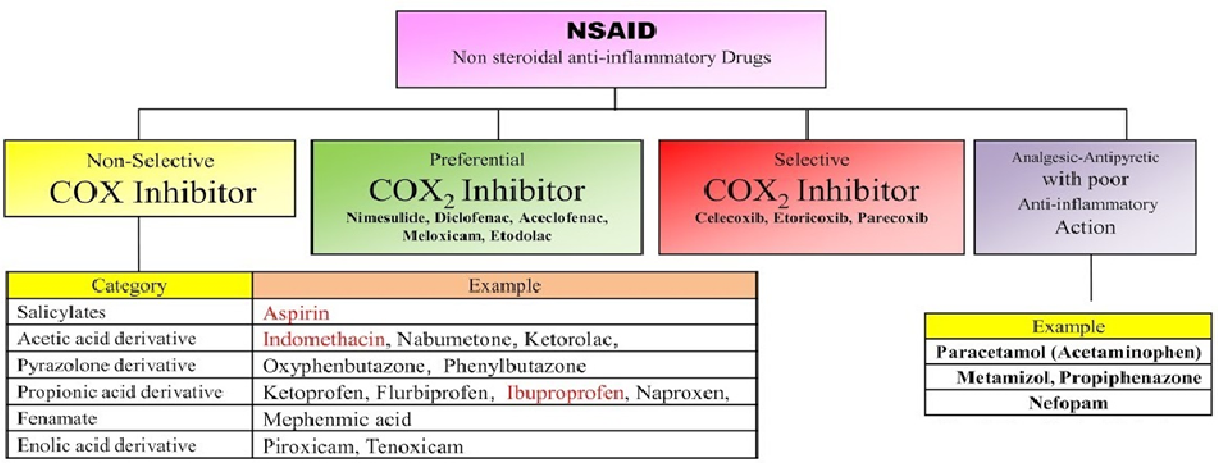
INRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a diverse group of compounds with similar biological capabilities: all NSAIDs reduce or eliminate the erythema, swelling, elevated temperature and pain caused by a variety of inflammatory stimuli. The mechanisms of action of NSAIDs have not yet been fully elucidated, but evidence suggests that their anti-inflammatory effects are primarily achieved through inhibiting prostaglandin production. This mode of action is common to all NSAIDs. The prototype for NSAIDs is ASA, a drug which has been used successfully for almost 100 years and which continues to be the 'gold standard' against which new compounds are judged. At present, at least NSAIDs are available for clinical use in Canada and more appear on the market every year. This article will review significant differences between currently available compounds and will give the clinician a basis on which to evaluate new NSAIDs.

CLASSIFICATION

On the basis of their chemical and pharmacological properties and COX selectivity NSAIDs can be classified as follows

Fig1: Classification of NSAIDs



POTENCY

The reader may be familiar with television commercials advertising 'extra-strength' analgesics and analgesics containing an extra 325 mg of pain reliever. Common sense dictates that three 325 mg tablets will deliver as much active ingredient as one 'extra strength' 975 mg tablet. The same is true of NSAIDs. Moreover, side effects are seldom related to the number of milligrams of NSAID when a therapeutic dose is administered; that is, 50 mg of diclofenac will not necessarily produce fewer side effects than 1,000 mg of ASA. In short, potency is an irrelevant issue which should not be confused with efficacy, a measure of how well the drug works.

EFFICACY

The efficacy of a drug can be assessed only through well-designed randomized clinical trials. Unfortunately, very few clinical trials of NSAIDs have been rigorous enough to truly differentiate agents; the result is considerable difficulty in interpreting and evaluating their conclusions. Nevertheless, a review of the literature indicates that there are no large differences in efficacy between NSAIDs used in the treatment of rheumatoid arthritis, osteoarthritis and (for those NSAIDs studied) the seronegative arthropathies and gout. The initial choice of drug must therefore be based on side effects and cost.

PHARMACOKINETIC

Absorption

Almost all currently available NSAIDs are rapidly, and virtually completely absorbed after oral ingestion. It takes longer for enteric-coated ASA to be completely absorbed than non-enteric-coated ASA, but the minor disadvantage of a slight delay in achieving therapeutic serum concentrations is offset by a significant decrease in the incidence of gastric erosions. Moreover, speed of absorption does not equal speed of onset of therapeutic effect. Maximum therapeutic effect may take considerably longer to achieve than maximum serum concentration. Thus, the clinical significance of manufacturers claims about rapid absorption should be interpreted critically.

Distribution

All NSAIDs which have been investigated have been found in joint fluid in concentrations high enough to inhibit prostaglandin production. How ever, there is no good evidence that synovial fluid concentrations correlate with clinical response, so at present no one drug is preferable to another in this respect.

Biotransformation and excretion

Aspirin, phenylbutazone and sulindac are the only NSAIDs which have therapeutically active metabolites. When both parent compound and metabolite have anti-inflammatory actions, the drug's benefits and adverse effects are prolonged. In theory, this may lengthen the dosage interval for such drugs. In practice, the presence of active metabolites becomes important only in cases of serious overdose. The exception to this is sulindac, which is in itself virtually inactive; its sulfide metabolite is the therapeutically active compound. One might expect that the parent compound's inactivity would result in a lower incidence of gastrointestinal side effects-a finding that is not borne out in practice (see 'Side Effects', below)."

Salicylates demand special consideration because of their peculiar elimination kinetics." ASA is metabolized to salicylic acid by esterases in the gut lumen. Salicylate is then metabolized through four simultaneous pathways. The two major pathways have limited capacity to convert salicylic acid to its metabolites, and when this capacity is overwhelmed by a moderately large amount of ingested salicylate, the result is a metabolic 'backlog' and an increase in the serum half-life of the active compound, salicylate. Thus, the half-life of elimination of salicylate varies from three hours at low dose (one gram) to 16-20 hours at recommended anti-inflammatory doses (three to six grams a day).

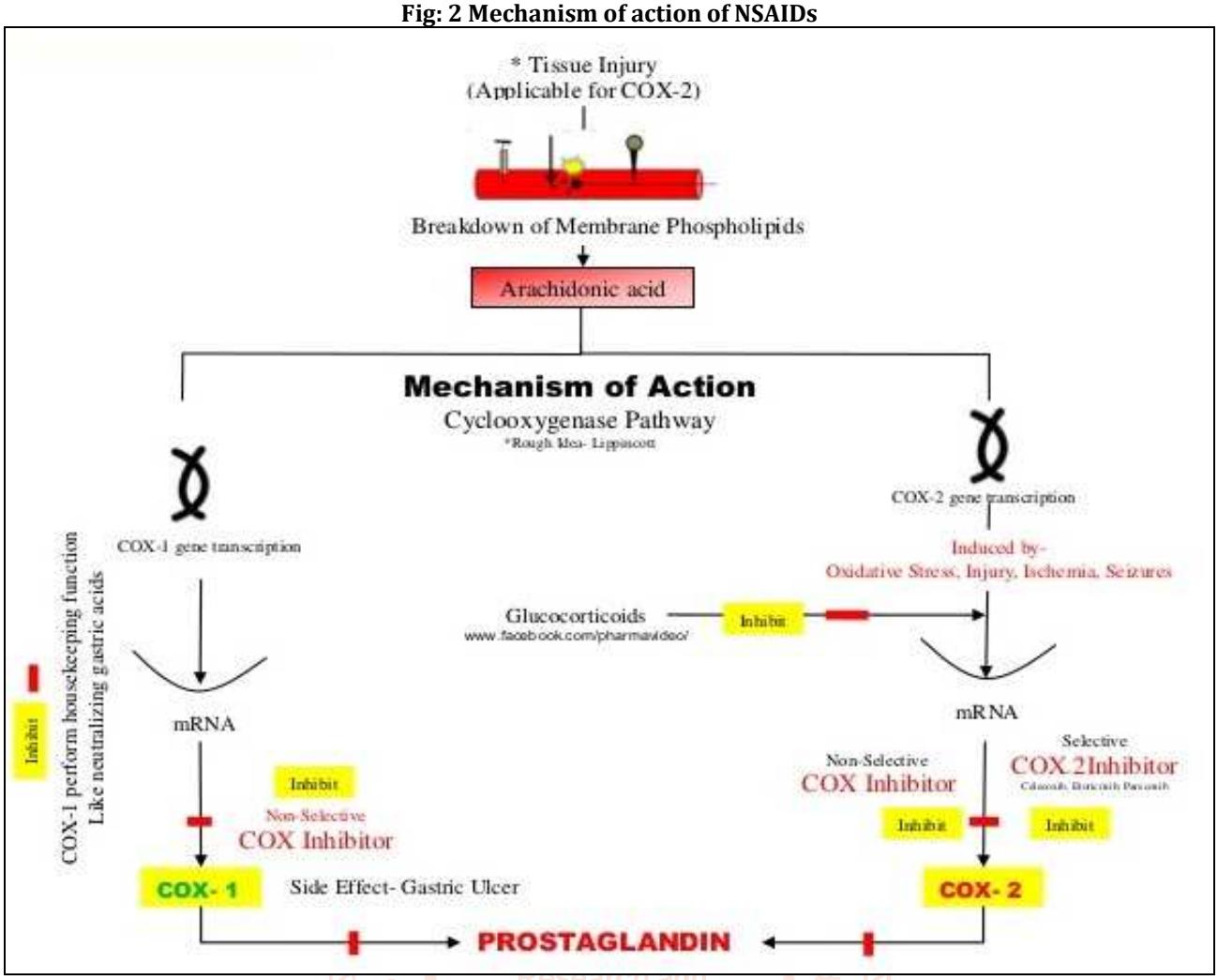
Half life

The half life of a drug is the time it takes for the serum concentration to be reduced by half. This may or may not correlate with the length of time between doses. In the case of NSAIDs, direct correlation is rare; diclofenac for example, has a half life of one hour, but clinical experience has shown that it can be effective when given twice or even once a day. Similarly, manufacturers claims about the benefits of a drug with a longer half life should be interpreted cautiously; only randomized controlled trials can determine optimal dosage regimens.

MECHANISM OF ACTION

NSAIDs acts by the inhibition of COX no matter what structural diversity they have. Prostaglandins are produced by the COX pathway which are the end products of fatty acid metabolism. They are the major physiological mediators in the therapeutic areas like pain, inflammation, cancer, pyrexia and neurological disease.

Fig: 2 Mechanism of action of NSAIDs



SIDE EFFECTS

All NSAIDs causes side effects. These side effects should be identified as those that virtually prohibit drug use, those for which patients should be closely monitored and those which are common but not life-threatening.

Table1: Adverse effects of NSAIDs on various systems

Cardiovascular side effects	➢ Edema ➢ Hypertention ➢ Congestive heart failure ➢ Myocardial infarction ➢ Stroke and other thrombotic events
Gastrointestinal toxicity	➢ Dyspepsia ➢ Gastroduodenal ulcer ➢ GI bleeding and perforation
Nephrotoxicity	➢ Electrolytic imbalance ➢ Sodium retention ➢ Edema ➢ Reduce glomerular filtration rate ➢ Nephrotic syndrome ➢ Acute interstitial nephritis ➢ Renal papillary necrosis ➢ Chronic kidney disease

Side effects that virtually prohibit use

Blood dyscrasias (aplastic anemia and agranulocytosis) may occur with phenylbutazone and fall into the first category.It has been estimated that there is one fatal blood dyscrasia for every 250,000 patient/months with this drug. Oxyphenbutazone is probably no safer than phenylbutazone and both these drugs should be used as a last resort for patients who have not responded to any other NSAID after an appropriate therapeutic trial.

Side effectsfor close monitoring

Fenoprofen has also been linked with aplastic anemia, but to date only two cases have been reported. This drug should be used cautiously, and patients should be closely monitored. Virtually all NSAIDs may precipitate asthma in susceptible

patients that is, 8.2% of patients with pre-existing asthma or sensitivity to ASA (rhinitis and nasal polyps). Patients who have asthma, or patients in whom asthma has developed following the use of NSAIDs, should be referred to a pulmonary function laboratory for sensitivity testing. While the exacerbation of asthma by NSAIDs is rare, it can be fatal in highly sensitive patients. Acetaminophen and non-acetylated salicylate (e.g., choline magnesium trisalicylate) can be tried in most of these patients. It is safest to start with half a tablet and to observe the patient for two to three hours. Four percent of patients who are sensitive to ASA will also be sensitive to acetaminophen. Renal dysfunction has been reported as a side effect for virtually all NSAIDs. Monitoring serum creatinine and urine protein should be started when therapy begins, and then at three to six month intervals. Patients should be instructed to notify the physician if they gain weight, or develop edema, muscle weakness, anorexia or decreased micturition. It is not clear from the literature whether patients who develop renal impairment can be safely treated with alternative NSAIDs. A reasonable approach is a cautious trial with an NSAID from a different chemical class (see Table 1), with close monitoring of renal function.

Idiosyncratic adverse effects

Two NSAIDs have been reported to cause idiosyncratic adverse effects that are not typical of this group of drugs. Tolmetin has been reported to produce a much higher incidence of anaphylactoid reactions than any of the other NSAID's. This reaction usually appears after an uneventful first course of treatment. Sulindac has been associated with a variety of rare multisystem adverse reactions, including hypersensitivity, pneumonitis, fever, abnormal liver function, lymphadenopathy and bone marrow and skin involvement. Of the four patients reported to have developed these adverse reactions to sulindac, one died of coagulopathy. Pancreatitis associated with sulindac has also been reported.

Non life-threatening side effects

Adverse reactions that are common and not life-threatening, are well known to most clinicians. Gastrointestinal upset of varying severity is common with all NSAIDs. Gastrointestinal (GI) ulceration is associated with NSAID use, but it is not clear whether ulceration is a manifestation of rheumatoid arthritis as a multisystem disease process, or ulceration is caused by the inhibition of prostaglandins, which are cytoprotective in the gastric mucosa, or ulcers are present but asymptomatic until NSAIDs exacerbate them. Thus, although patients who develop gastric or duodenal ulceration while receiving NSAIDs should receive anti-ulcer treatment, the presence of ulceration does not necessarily preclude use of NSAIDs. In a study of healthy volunteers, enteric-coated ASA caused fewer endoscopically apparent gastric erosions than uncoated or 'buffered' ASA, but the relevance of this to patients with rheumatic disease is not known. Gastrointestinal bleeding at the rate of one to two milliliters a day is common with all NSAIDs. However, frank gastrointestinal hemorrhage is probably rare. Duggan has estimated the risk of serious gastrointestinal hemorrhage to be one episode per two million doses of ASA. It has also been estimated that there are 1 5 episodes of major bleeding per 100,000 patients taking ASA more frequently than four days per week, and frank GI bleeding may also be a particular concern when patients are taking piroxicam. GI distress may be reduced if the medication is taken with meals. Severe frontal headache is more common than GI distress in patients taking indomethacin, but it may be less severe at lower doses. Tinnitus may occur frequently with ASA use and we have observed that hyperventilation and deafness may also be a side effect in elderly patients. ASA-induced tinnitus and deafness may respond to a lower dose of ASA, but a different agent may be required if a therapeutic effect cannot be elicited at the lower dose. All NSAIDs except ibuprofen22 and naproxen have clinically significant antiplatelet effects. Because all NSAIDs can produce adverse effects, all patients-especially elderly ones-should be selected carefully for treatment. It is also important to limit the use of NSAIDs to conditions for which they are clearly indicated. Indiscriminate prescribing will increase the frequency of adverse reactions in a population for whom the drug was never intended.

DRUG INTERACTION OF NSAIDs

Adverse drug reactions are very commonly shown in NSAIDs so as the age and no. of medication increases NSAIDs should prescribe with caution.

Table2: Drug interactions with NSAIDs

Medicaments	Interactions
Antiplatelets (aspirin, clopidogrel)	Risk of GI bleeding
Angiotensin-converting-enzyme inhibitor (ACEI) and Angiotensin Receptor Blockers (ARB)	Increases in blood pressure by attenuating antihypertensive effects
Beta blockers	Increases in blood pressure by attenuating antihypertensive effects
Calcium antagonists	Increases in blood pressure by attenuating antihypertensive effects
Corticosteroids	Increases risk of GI bleeding
Digitalis glycosides	Increase serum digoxin level
Diuretics	Increases in blood pressure by attenuating antihypertensive effects
Methotrexate	NSAIDs reduce renal excretion of methotrexate, causing ethotrexate toxicity.
Selective serotonin reuptake inhibitors (SSRIs)	Increases risk of GI bleeding
Warfarin and other anticoagulants	Increases risk of GI bleeding

COMPLIANCE

It is important to remember that NSAIDSs reduce joint inflammation, but do not alter the course of rheumatoid arthritis, that their side effects range from distressing to disastrous, and that if symptoms are reasonably controlled with a lower dose, it is pointless to insist on 'full compliance'. With this in mind, however, it is obvious that patients who never take their drugs or who take them inefficiently, will not gain optimum benefits. Factors which affect compliance in patients with rheumatoid arthritis have not been extensively studied. Overall drug compliance has been reported as 64%, a figure similar to the compliance rate of patients taking antihypertensive medications. Demographic factors such as age, sex, race and socioeconomic status appear to have no effect on compliance. In general, there is no clear relationship between disease severity and compliance for conditions other than rheumatic diseases, and while evidence suggests that a complex drug regimen makes patients with other diseases less compliant, this evidence has not been consistently reproduced in patients with rheumatoid arthritis. Nor is it clear that the length of time between doses has any effect on compliance contrary to the claims of many manufacturers. However, patient compliance does appear to vary according to the drug used; mean drug specific compliance rates for the major anti-inflammatory drugs prescribed over a six-month period have been reported as follows: penicillamine, 84%; prednisone 82%; naproxen 72%; ASA 69%; ibuprofen 61 %; and indomethacin 58%. In one study which documented drop-out rates at the end of one year of treatment, 84% of patients taking ASA had stopped taking their medication, compared to 64% of patients taking indomethacin or naproxen and 57% of patients taking flurbiprofen. Finally, diagnosis appears to have an effect on compliance: the compliance rate was 73% for patients with rheumatoid arthritis; 53% for patients with osteoarthritis; 51 % for patients with ankylosing spondylitis, and 65% for patients with gout.

PRACTICAL PRISCRIBING

The practical prescribing of NSAIDs has been covered in depth in recent publications. The following steps may be useful for prescribing NSAIDs:

1. Determine if the patient responded to a particular NSAID previously. If so, prescribe it again unless the patient suffered an adverse effect that precludes its use.
2. Select an NSAID based on your experience, the cost to the patient, and how likely the patient is to experience an adverse effect.
3. Choose a dose appropriate to the patient's symptoms. There is no point in prescribing maximum doses of NSAIDs if the patient has only mild or moderately severe symptoms. Moreover, the likelihood of side effects may be increased at higher doses. In patients with severe symptoms, titrate medication against pain, disability and side effects.
4. In general, avoid combinations of NSAIDs. Naproxen or ibuprofen may be more effective when given with ASA, but other combinations have not been shown to be more effective than single agents. Again, the likelihood of side effects is increased with combination therapy, and the cost may be prohibitive.
5. Do not change from one NSAID to another until the patient has received treatment for at least one week. Optimum results may not be achieved until he has been taking the NSAID for one to three weeks.
6. Patients may believe that drug therapy has failed when, in fact, their disease has become more severe. A short drug holiday followed by reinstatement of the same drug may help to determine whether the disease is more severe, or the drug therapy is ineffective. It may be appropriate to temporarily increase doses or to add analgesics to control symptoms.
7. Be alert for adverse effects from NSAIDs. When you suspect there are adverse effects, take the patient off the drug and select another, (see Adverse Effects'). Suspected adverse reactions should also be reported to the provincial Medical Association or to the Health Protection Branch.

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no conflicts of interest

COCNCLUSION

In order to provide an instant remedy and comprehensive care to the patient by knowing the exact mechanism of action, adverse drug reactions and pleiotropic effects are very important. Non – steroidal anti-inflammatory drugs are the mostly common drugs which are prescribed. And by the clinical study it was revealed that these drugs should be prescribed for the shorter duration of time as well with lowest effective dose and under the care with monitoring GI, renal and cardiovascular toxicity.

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