Newer Non-steroidal Anti-inflammatory Drugs – A Review of their Therapeutic Potential and Adverse Drug Reactions

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Abstract

Use of non-steroidal anti-inflammatory drugs for the treatment of painful joint conditions like osteoarthritis, rheumatoid arthritis, arthritis of systemic lupus erythematosus, psoriasis, and other seronegative spondyloarthropathies is ubiquitous. They are the most commonly employed first line drugs for all these conditions and many others – like musculoskeletal trauma, minor aches and pains, and dysmenorrhoea. Several newer applications like prophylaxis of stroke with aspirin is now common place. Use of these drugs for the prophylaxis of conditions like Alzheimer’s disease and colorectal cancer is being evaluated. Unfortunately, they have several toxicities ranging from minor heartburn to severe gastrointestinal haemorrhage and perforation. Therefore, newer NSAIDs have been introduced in recent years to circumvent this problem. In preliminary studies, these have shown better safety, efficacy, and tolerability but the full spectrum of adverse reactions of these drugs is yet to be fully known. Moreover, these are much more costlier than conventional NSAIDs. Short acting drugs like ibuprofen and diclofenac are safer than longer acting ones like indomethacin and phenylbutazone and should be preferred over them. Newer NSAIDs should not, therefore, be used indiscriminately in all situations, but they should hesitantly be prescribed wherever patient is intolerant to conventional NSAIDs, or there is some contraindication or if patient is willing to accept expensive long-term treatment.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed drugs in the treatment of pain and inflammation in many conditions, including osteoarthritis and rheumatoid arthritis. These are a group of drugs that inhibit both isoforms of cyclooxygenase enzyme (COX-1 and COX-2). Conventional NSAIDs are nonselective that bind and inhibit both isoforms but COX-1 is inhibited more avidly than COX-2. Inhibition of COX-1 is responsible for side effects and of COX-2 for therapeutic effects. This has resulted in the introduction of the COX-2 selective drugs1. These are the newer drugs that have recently been made available in the Indian drug market. Their examples include nimesulide, nabumatone, meloxicam, etodolac, celecoxib, and rofecoxib. Last two have especially become popular amongst clinicians. These are generally considered to be more safe and tolerable and at least equally efficacious. There, however, are many issues that need to be addressed before their widespread usage can be recommended in situations where conventional NSAIDs are helpful.

Need for newer NSAIDs

It is now known that the inhibition of the COX-1 isomer is responsible for the side effects of the conventional NSAIDs and of the COX-2 is responsible for the beneficial effects (e.g., anti-inflammatory effects and analgesia). These have been developed with the conviction that COX-2 is an inducible isomer and its synthesis is increased at the sites of inflammation. These are, however, early days of the release of this group of drugs. Therefore, many concerns are being raised regarding these drugs. There is evidence that these are already becoming the popular drugs in many countries in spite of being expensive. This practice is likely to affect the dental prescriptions also. A closer look at their pharmacology is therefore necessary to understand their therapeutic usefulness and limitations at this moment. A comparison of these drugs with the older ones is necessary. Following are some of empirical guidelines that can help clinicians in choosing an appropriate NSAID wherever indicated.
How to choose NSAIDs in clinical situations?

Why to choose? The question arises as to why it is necessary to choose a particular NSAID when all have similar pharmacological profile? The answer is that their safety, tolerability, and efficacy differ in clinical situations. Aspirin has dominated the pharmaceutical market for more than 50 years ever since its synthesis in 1899, and physicians had no other choice but to go for it. The scenario had only started changing in the early 1950s when other NSAIDs started hitting the drug stores and the question of choosing a particular drug started getting importance. NSAIDs presently are the most widely used drugs in medicine and their annual sales in the world is more than 6 billion dollars. Presently, more than 100 NSAIDs have been tested clinically and more than 50 are there in the world market. Nearly 35 million people are taking them on daily basis and FDA has ranked them the most frequent cause of adverse drug reactions.

Unfortunately, they also cause most frequently lethal drug toxicity such as gastrointestinal haemorrhage. Importantly, nonprescription use, that is often ignored, is considered to be seven folds higher than the prescription use. Advent of newer drugs in the market makes the question of NSAID choice all the more important as exemplified by the fact that 2.5 million prescriptions were written for celecoxib alone in just 3 months of its release. Decision of using NSAIDs in most therapeutic situation is empirical, but certain principles can help clinicians prescribing them safely and effectively. We review some of them.

1. Clinicians should familiarise themselves with minimal number of drugs: Most rheumatologists feel that clinicians should familiarise themselves with a dozen of NSAIDs and try to get full information about them. Under most circumstances, this list should not generally exceed 20 drugs so that safe and effective use of the drugs can be achieved.

2. Analgesia and antipyretic uses: Choosing a NSAID for its analgesic and antipyretic effect in indications like fever, common cold, dental pain, minor soft tissue injuries, musculoskeletal pain, and non-specific body aches is not difficult as in most circumstances the drug is to be used for a short duration only. Both newer drugs, e.g., celecoxib and rofecoxib have now been approved by FDA for short-term relief of pain and inflammation.

3. Anti-inflammatory use: Choice of NSAID for chronic and disabling inflammatory joint diseases like rheumatoid arthritis and osteoarthritis is governed by age, diagnosis, degree of severity, relative gastrointestinal safety, tolerability, and relative efficacy in the given clinical situation. It is a common misconception that all NSAIDs are therapeutically equally efficacious and any one of them could be used for the given indication. Use of multiple NSAIDs should be discouraged. An agent with comparatively less GI side effects like ibuprofen and diclofenac should be preferred in place of indomethacin, piroxicam, or naproxan, which are more gastrotoxic. In situations, e.g., osteoarthritis where inflammation of joints is minimal analgesics, like paracetamol should be preferred over anti-inflammatory drugs like ibuprofen. American Rheumatological Association recommends use of 1 gm of paracetamol every 6 hours for pain relief in osteoarthritis. In situations where diagnosis is uncertain, the drug should be empirically chosen and given for a week or so and if the response is adequate it should be continued until side effects mandate its withdrawal. Ankylosing spondylitis, for unknown reasons, responds better to a particular NSAID like indomethacin. It is probably related to its stronger inhibition of prostaglandin synthesis.

Under some situations, choice of NSAIDs is very obvious. Stroke prevention, post-myocardial infarction prophylaxis, and patient with atrial fibrillation are therapeutic situations where aspirin is the drug of choice because of its unique
antiplatelet property of acetylating and causing irreversible inactivation of cyclooxygenase –1 isoform in the platelets. Other NSAIDs inactivate this enzyme reversibly and therefore do not cause sustained antiplatelet effects. Aspirin has also been adequately studied in the chemoprevention of colon cancer. Mefenamic acid is supposed to relieve the pain of dysmenorrhea better than other NSAIDs, although GI side effects often limit its use.

4. Consider substitution, if there is no response with one drug: Surprisingly, NSAIDs have large inter-patient variations, reasons of which are not entirely clear. Even when drugs are from the same chemical family or are structurally similar, they can be substituted. One patient may respond to one agent of one class but may not respond to another agent of the same class. Determination of the therapeutically effective dose for a particular patient is difficult and is often based on ‘hit and trial’ method. Treatment should be started on low dose and response should be awaited. If response is adequate, treatment is continued for one week as most side effects of NSAIDs appear in the first week. In case of no response, change of NSAIDs should be considered. Persistent dyspepsia is one of the most frequent side effects of NSAIDs and with few exceptions it can be an indicator of onset of future gastrointestinal (GI) toxicity. Newer agents like celecoxib, nabumatone, and etodolac have been shown to be almost 4-fold less GI toxic than the older ones. Studies regarding the GI safety of nimesulide have not shown the reduced risk of complications.

5. Avoid using multiple NSAIDs and consider ulcer prophylaxis in high-risk groups: Some physicians consider combination of NSAIDs in the treatment of inflammatory joint diseases. There is little evidence to support this practice because therapeutic benefits do not add but side effects do. Moreover there is no evidence that fixed dose combinations of NSAIDs are superior to individual drugs in the long-term management of arthritis. Similarly, use of concomitant gastrotoxic drugs should be avoided, e.g., corticosteroids and NSAIDs. Patients at high risk may require ulcer prophylaxis and these are summarised in table I. Ulcer prophylaxis can be started with misoprostol (PGE1) 100 microgram daily in four divided dosages. An increasing dosage schedule results in side effects like diarrhoea in up to 25% of patients and often limits the dose. Omeprazole has been found to be protective in a large international study (73 centers, 15 countries) involving 541 patients. Omeprazole (20 mg/40 mg/d) was compared in a double-blind manner with ranitidine 150 mg twice daily. Ulcer healing rates in patients on omeprazole were 80% and all were taking NSAIDs concomitantly. Similarly, in another study, omeprazole (20/40 mg/d) was compared with misoprostol 200 microgram four times daily. Results are summarised in table II. The common outcomes of these studies were as follows:

- Omeprazole was clearly superior to other agents for both prophylaxis and treatment of NSAID-induced gastrointestinal injury.
- H₂ blockers like ranitidine have yielded disappointing healing rates.
- Effects of omeprazole were unrelated to dose. Maximum effects seen were at 20 mg daily dose. Further increase did not lead to increase in therapeutic benefits.

Table I: Predisposing factors for NSAID induced GI ulceration.

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<th>Factor</th>
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<tr>
<td>Female gender</td>
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<tr>
<td>Advanced age (&gt; 65)</td>
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<tr>
<td>Previous history of active peptic ulceration</td>
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<tr>
<td>Smoking, alcoholism</td>
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<tr>
<td>Heavy coffee consumption</td>
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<tr>
<td>Concomitant ingestion of GI toxic drugs</td>
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<tr>
<td>Prolonged use of heavy doses of NSAIDs</td>
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Use of multiple NSAIDs.

Table II: Success rates for ulcer healing by various agents.

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<tr>
<th>Drug, dose, and duration</th>
<th>Healing rate</th>
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<tr>
<td>Omeprazole 20/40 mg/d x 4 weeks</td>
<td>80% (140/174)</td>
</tr>
<tr>
<td>Omeprazole 40 mg/d x 8 weeks</td>
<td>79% (148/187)</td>
</tr>
<tr>
<td>Ranitidine 150 mg BD x 4 weeks</td>
<td>63% (110/174)</td>
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For prevention of ulcers, lowest dose of NSAID should be used for short duration, less gastrotoxic drugs like paracetamol, ibuprofen, and diclofenac should be preferred over potent NSAIDs like indomethacin and phenylbutazone. Use of antacids and H$_2$-blockers like ranitidine for the prevention of NSAID-induced ulcers should be avoided as it is not only without any benefits but may also be harmful as they may mask early warning symptoms of ulcer, thereby delaying the diagnosis. In their presence, ulcer may perforate asymptptomatically. Moreover, reduction of gastric acid output to minimal leads to colonization by *H. pylori* – a known predisposing factor for ulcer genesis.

6. NSAID use in children: Choice of NSAIDs in children is generally restricted to paracetamol, aspirin, naproxen, and now nimesulide. Although nimesulide has been shown to be superior to the existing drugs in childhood febrile illnesses like upper respiratory infections, but it is costlier than the conventional NSAIDs. Aspirin is not recommended as a routine analgesic and antipyretic drug in childhood viral illness because of fear of Reyes syndrome. However, it enjoys its reputation as an anti-inflammatory agent in the management of rheumatic fever and childhood arthropathies.

6. Topical or systemic administration?
Topical NSAIDs represent an attractive alternative to systemically administered drugs. Studies have shown that topically applied NSAIDs directly reach to the synovial fluid, menisci, and articular cartilages. Generally, 70-80% of the plasma concentration reaches the articular tissues. Interestingly, in one study, the topically applied NSAID concentrated in the menisci and cartilage to about 20-30 folds of the systemic concentration. Although the mechanisms through which they reach the joints remain to be exactly determined, the reported plasma concentration is generally less than 15% of the systemic concentration. Moreover, maximal concentration after topical administration is uniformly below the accepted therapeutic concentration for NSAIDs, at which systemic toxicity appears. Bioavailability studies have shown that NSAIDs administered topically achieve only 3-5% of the systemic concentration when compared with oral administration. This, therefore, affords major protection from life-threatening toxicities.

Topically applied NSAIDs rarely exhibit systemic side effects and most (95%) of the side effects are dermatological in nature-like rashes and/or pruritis. Topical administration of NSAIDs offers advantage of local, enhanced delivery of drugs to affected tissues with a reduced incidence of systemic effects. Empirical clinical evidence suggests that topical NSAIDs are as effective as oral ones in the treatment of rheumatic disease. Positive treatment outcome ranges from 30 to 95% with considerable inter-patient variability. So the question arises – should topical NSAIDs be preferred in these situations over oral ones? The answer is difficult at the moment as their efficacy needs to be evaluated in large placebo-controlled double blind studies before we can actually reach this conclusion. Nevertheless, if patients cannot tolerate the oral NSAIDs or if these are contraindicated, then topical NSAIDs are a safe and viable therapeutic option.

7. NSAIDs in pregnancy: All NSAIDs in general are to be avoided in pregnancy. If NSAID is required, then a low dose of aspirin is probably the safest. Paracetamol is another drug of this class that can be used for the same purpose.
Aspirin should be stopped prior to delivery to avoid complications like prolonged labour, increased post-partum haemorrhage, and premature closure of ductus arteriosus. Cost effectiveness of individual NSAIDs should be considered as newer agents are considerably more expensive than conventional ones.

Adverse effects of the selective COX-2 inhibitors

Adverse effects of the NSAIDs are usually dose related, although many dose unrelated effects like idiosyncratic effects also appear. These include urticarial rashes, angioedema, and bronchospasm, etc. These drugs are selective antagonists and the general principle of the use of the antagonist is that they tend to lose the selectivity if the dose range for which they exert their actions on the selective targets is exceeded. Usually this dose range is narrow. These drugs have a high degree of selectivity that ranges from 1.3 to 2350 times more than the conventional NSAIDs.

This high degree of the selectivity is consistent with the fact that they exhibit lesser degree of gastrotoxicity as compared to the conventional NSAIDs. Indeed, the early preclinical and clinical studies have shown that the drugs have minimal effects on the prostaglandin synthesis in stomach and renal parenchyma. In addition, these drugs do not interfere with the synthesis of the thromboxanes. These, therefore, do not share the tendency to cause platelet inhibition and consequent bleeding. Moreover, the risk of the drug interactions of the older NSAIDs is considerably higher as compared to the newer NSAIDs. One reason is that the newer drugs have not been available in the market for too long. That is why the interactions of this group of drugs have been studied inadequately. Several large studies have shown that the risk of adverse reactions with these drugs is low. These include both, milder adverse effects like nausea, vomiting, and anorexia as well as severe ones like peptic ulceration and upper gastrointestinal haemorrhage. For rofecoxib, this risk has been shown to be comparable to the placebo in one study. However, clinical experience is limited with these drugs and a complete list of the adverse reactions including that of the drug interactions is not yet completely known.

There is already a suspicion that the drugs may have many of the side effects of the older NSAIDs. Although the risk of serious gastrointestinal complications like peptic ulceration and haemorrhage is 4-5 times lesser than that of the older NSAIDs, the potential of the renal side effects like hypernatraemia, potentiation of the hyperkalaemia, and peripheral oedema is indeed there. This reduced risk is in comparison to ibuprofen or diclofenac, which are otherwise considered to be safe drugs for the gastrointestinal tract. Renal side effects can lead to the diminution of the antihypertensive effect of the antihypertensive medications. Therefore, it is recommended that the same precautions that are used for the conventional NSAIDs during their administration in the patient with hypertension should be used in case of the newer drugs like celecoxib and rofecoxib also. Lesser risk of the gastrointestinal haemorrhage has been shown to occur in the healthy volunteers taking the drugs in small clinical trials upto 7 days and those taking the drugs for 6 months. The reduced risk is not accompanied by the reduced efficacy. Several studies have shown that these drugs are equally efficacious and better tolerable as compared to the older drugs like ibuprofen, diclofenac, piroxicam, and naproxan.

Unresolved issues regarding the adverse reactions of the COX–2 inhibitors

Are these drugs a real therapeutic breakthrough? Vane in 1971 discovered that NSAIDs act by inhibition of synthesis of prostaglandins. Role of the prostaglandins, in the health and disease, is now better understood and NSAIDs are now being actively investigated for their chemopreventive potential in colon cancer,
Alzheimer’s disease, and in many other diseases. COX-2 is now considered to be an inducible isoform that has higher expression in the inflammatory areas. Expression of this enzyme is low even in organs like brain, kidneys, and reproductive tract. This is now known to mediate several physiological functions, inhibition of which in theory might have many adverse effects unknown to us at this moment. Inspite of their remarkable safety in preliminary studies, several questions about the safety, efficacy, and tolerability need to be answered:

- Are these drugs safe in the presence of inflammatory GI problems like H. pylori gastritis and inflammatory bowel disease? Enhanced COX-2 expression has been shown to occur in these diseases. There is minor risk that these conditions could be worsened.
- Do they retard the ulcer healing? In the animal studies, many of the drugs of this group have been shown to be doing so. In humans, sufficient data is not available in this respect. This needs to be tested in the long-term endoscopic studies.
- Do they cause ulcers? Yes, they do so; but the frequency is considerably less as compared to the conventional NSAIDs. The mechanisms are not known. It is, at least in part, due to COX-1 inhibition as the selectivity of these agents is lost in higher doses and they inhibit the COX-1 also.
- Are these agents nephrotoxic? There is small evidence that the drugs can cause the same renal effects as that of the conventional NSAIDs, i.e., they can cause hypernatraemia, hyperkalaemia, and diminution of the therapeutic effects of antihypertensive drugs.
- Will these drugs affect labour? Cyclical induction of the COX-2 plays a role in the induction of hormones of ovulation. Moreover, it is also expressed by gravid uterus where it is important for the onset of labour. Therefore, there is risk of side effects like preterm labour.
- Is there any risk of teratogenicity? COX-2 selective agents have been shown to hamper the development of foetal kidneys and brain in experimental animals. Moreover, the safety of these agents is not confirmed in pregnant women. These are not recommended in pregnant women.
- Is the risk of side effects sufficiently low to recommend them for prophylaxis? Adverse effects associated with the use of low doses of COX-2 selective drugs for potential application like the prevention of Alzheimer’s disease and colorectal cancers are not known.
- Do they provide adequate analgesia? Expression of the COX-1 at the sites of inflammation has been identified. This means that these drugs may not be able to produce full anti-inflammatory effects. This is consistent with the findings that many patients report reduced pain relief with these drugs.
- Do they have the potential to cause cardiovascular diseases? Recent studies have shown that COX-2 can be induced in the vascular tissues. Therefore, selective COX-2 inhibitors may theoretically cause the increased risk of vascular disease. Since information available at this time is limited; it can be presumed that they can be neutral, beneficial, or harmful in patients with cardiovascular diseases.
- Is over-the-counter (OTC) status for these drugs justified? Availability of the COX-2 inhibitors has brought new problems to our notice. In many countries these drugs are available on the over-the-counter basis. This may contribute to the increased risk of the ulcer complication in the patients taking these drugs on the non-prescriptional basis.

**Conclusions**

It is clear that the COX-2 inhibitors are safer, better tolerated, and equally efficacious, but many clinical issues need to be fully resolved. Numbered compounds such as SC58125 have been now
synthesised and being tested clinically. Early results show that these do not have significant gastrototoxicity or nephrotoxicity even in doses greater than those required for anti-inflammatory effects. Similarly, compounds such as 1.475.337 and flusolide (CGP28258) are COX-2 inhibitors that are being developed and have more than 1,000 times selectivity for COX-2. It is, however, evident that such high degree of selectivity will not offer any advantage over the conventional NSAIDs, unless full information about their side effects is known. Nimesulide is one such example, which, inspite of being a selective COX-2 inhibitor, has recently been shown to have the same spectrum of adverse events as compared to the conventional NSAIDs in a large study from Italy. Presently, adverse reactions because of selective COX-2 inhibition are being studied, and whether these agents are real advancement or not, only time will tell; but early results show promise. Proper clarification of these issues is important because these drugs are now being used increasingly instead of the conventional NSAIDs in spite of being many times expensive.

References