

Therapy with NSAIDS coxibs & aspirin

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An overview

Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and more recently coxibs have revolutionised management of inflammatory and other connective tissue disorders.

They have made a major contribution in their analgesic or pain relieving effect and also many are valuable in conditions such as migraine and dysmenorrhoea, while aspirin has useful antithrombotic actions in ischaemic heart disease.

Anti-inflammatories are the third most commonly prescribed group of drugs in Australia. Recently the association of Coxibs with the development of significant heart disease has resulted in the withdrawal of rofecoxib.

The rate of anti-inflammatory use is increasing now that musculo-skeletal conditions account for 17.7% of all GP consultations. Aspirin has been available over the counter for many years and its use is high and probably underestimated.

The widespread use of these medications means that their side effects present a common problem.

To balance benefits and risks, all medications need continuous review. Accumulating information about the risks associated with anti-inflammatories means their use needs careful justification. With traditional NSAIDs, prophylaxis to prevent ulcers and complications may need consideration. Even low dose aspirin has a significant risk of causing peptic ulceration and bleeding.

The COX-2 selective inhibitors have an improved gastrointestinal safety profile than non selective NSAIDs. These issues are particularly important in patients with existing or previous peptic ulcers if they need anti-inflammatories or aspirin.

This overview discusses the benefits and risks of these anti-inflammatory agents and has been written to help doctors and pharmacists decide on their use in individual patients.

Comparative deaths: NSAID ulcers vs other causes

Number of deaths per year



Arthroscopy 1998

How anti-inflammatory drugs work

Anti-inflammatory drugs (NSAIDs and selective COX-2 inhibitors) inhibit the enzyme cyclooxygenase (COX) which converts arachidonic acid to prostaglandins.

These substances are major mediators of inflammation and also play other important non-inflammatory roles in maintaining the body's normal physiology. Prostacyclin inhibits platelet aggregation and promotes vasodilation. Prostaglandin E2 suppresses the formation of acid in the stomach and thromboxane promotes aggregation of platelets. COX exists in two forms. COX-1 is found throughout the body and is the main form responsible for the production of prostaglandins involved in normal body functions. COX-2 is normally present in small amounts in a number of tissues, but is mainly induced when there is inflammation and tissue damage.

Selective inhibition of COX-2 with drugs such as celecoxib prevents the formation of prostaglandins at sites of inflammation, but avoid the potential gastrointestinal toxicity that may occur if gastric prostaglandin E2 were reduced and platelet function impaired. Inhibiting COX-2, with or without inhibition of COX-1, may have adverse effects in the kidney and

blood vessels leading to poor renal function, hyperkalemia, fluid retention and elevated blood pressure. These effects are most likely in elderly patients and in patients with renal impairment or cardiovascular disease.

COX-2 inhibitors such as celecoxib are highly selective for inhibiting only the COX-2 isoenzyme. NSAIDs have varying degrees of COX-2 selective inhibition compared with COX-1. Whether NSAIDs selectively inhibit COX-1 or COX-2 is often dose dependent. For example, meloxicam is relatively COX-2 selective at lower doses but loses this selectivity at higher doses.

Who benefits from anti-inflammatories?

Anti-inflammatory agents are useful in various musculo-skeletal conditions. The newer coxibs have similar efficacy to the traditional NSAIDs in these conditions. Aspirin is widely recognised as effective for prophylaxis against thromboembolic events in patients as secondary prevention after myocardial infarction and thrombotic stroke.

Possible indications for use

1] Rheumatic

Inflammatory joint and connective tissue diseases such as rheumatoid arthritis, gout, seronegative arthropathies, SLE

Short term use in sporting injuries

Osteoarthritis and degenerative diseases of the spine where simple analgesics have failed and inflammation is a component of joint pathology

2] Non-Rheumatic

Pain following surgery, primary or metastatic carcinoma, post-herpetic neuralgia and renal colic

Migraine and dysmenorrhoea

Transient ischaemic attacks to prevent cerebral infarction (low-dose aspirin)

Post myocardial infarction and unstable angina (low-dose aspirin)

Pleuritic pain

If possible, anti-inflammatories should only be used in short courses for relief of symptoms. In musculo-skeletal disease such as osteoarthritis, always consider alternative forms of treatment first, such as paracetamol for pain relief, physiotherapy, hydrotherapy, local corticosteroid injections and exercise programs. Spinal pain may respond to TENS (transcutaneous electrical nerve stimulator). Surgery may also be necessary – for example knee and hip replacement.



Anti-inflammatories in non-inflammatory joint problems

If the joint problem is non-inflammatory, it may be difficult to understand how an anti-inflammatory will help other than for pain relief. However, minor and subtle inflammatory changes have been demonstrated in osteoarthritis and anti-inflammatories may be useful if simple analgesics have not worked.

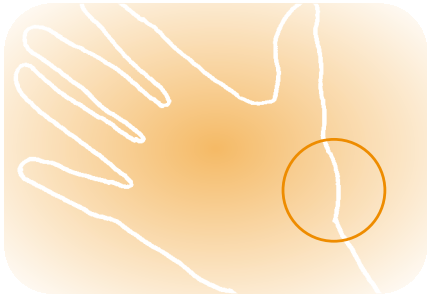
Adverse effects of anti-inflammatories

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce pain and improve function in patients with mechanical and inflammatory arthropathies. They are also helpful in many other conditions, but these benefits come at a price.

In Canada annual statistics show that NSAIDs cause more deaths from GI bleeding than motor vehicle accidents. In the United Kingdom, every year over 2000 people die from the complications of gastrointestinal damage induced by NSAIDs.

These agents can also have unwanted effects on the cardiovascular system, small intestine, colon, lungs and kidneys. However evidence shows that anti-inflammatories may inhibit colonic neoplasia and other gastrointestinal cancers.

The introduction of COX-2 inhibitors promised equivalent efficacy with greater safety and tolerability.

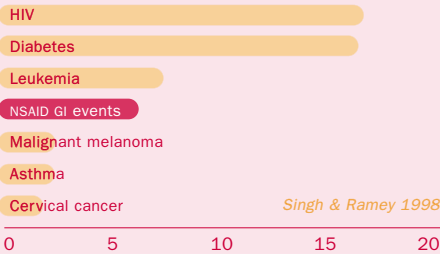


Cardiovascular

The selective COX-2 inhibitor rofecoxib, which at present is withdrawn from the market, has been associated with an increased risk of myocardial infarction and other serious vascular events in a long term placebo controlled study. This result has been supported by findings of an increased risk of myocardial infarction in rofecoxib users compared with non users and users of certain other non-selective COX inhibitors, particularly at higher doses. Celecoxib therapy at a dose of 800 mg per day has been associated with an increased risk of myocardial infarction compared with placebo in one long term study, while similar studies at doses of 400 mg and 200 mg daily have found no significant increase. Celecoxib has not been associated with an increase in the risk of serious cardiovascular events compared to non-users or uses of non-selective COX inhibitors in population studies, except for one powerful study in which a

Causes of death in the USA

Death rate per 100,000



small increase in risk of minimal clinical significance was demonstrated. The effects of non-selective COX inhibitors on serious cardiovascular events have not been studied in placebo controlled studies, with the exception of one study using naproxen that suggested a trend for an increase in cardiovascular risk following analysis at an interim stage of the study. Several population studies have reported an increased risk of cardiovascular events for certain non-selective COX inhibitors, including diclofenac and indomethacin, compared to non-users.

These data suggest that COX inhibitor therapy, whether selective or not, may be associated with an increased risk of cardiovascular events. The extent of this risk and the manner in which it varies between different anti-inflammatory drugs is not able to be determined accurately from the data currently available. However, the relative risk for cardiovascular events associated with COX inhibitor drugs (selective or non-selective, appears to be of the order of 2 or less. The mechanisms associated with an increased risk of cardiovascular events during COX inhibitor therapy are not known and are likely to be multifactorial.

COX inhibitor anti-inflammatory drugs, whether selective or non-selective, should be used with caution in patients who have an increased risk of cardiovascular disease, and an assessment of a

patients' cardiovascular risk should be undertaken and taken into account before prescribing any of these drugs.

Renal

Adverse renal effects of anti-inflammatory drugs are most likely to occur in elderly patients with renal impairment, diabetes or other vascular diseases. Selective COX-2 inhibitors are just as likely to produce problems as NSAIDs. Check serum creatinine levels and electrolytes before prescribing anti-inflammatory drugs in high-risk patients and one week after commencing treatment. Creatinine and electrolytes should be measured at reasonable intervals depending on the age and risks of the patient. Elderly patients and those with compromised renal function or renal perfusion who are on anti-inflammatory therapy may be at risk of renal failure or other renal complications if they become dehydrated or hypotensive.

Gastrointestinal

Risk data suggest a hierarchy of NSAID toxicity with ibuprofen and diclofenac being less toxic and ketoprofen, indomethacin and piroxicam being more toxic, particularly for gastrointestinal side effects. While coxibs are associated with a similar spectrum of gastrointestinal symptoms, these are less common and there is a lower incidence of ulcers and ulcer complications than those associated with NSAIDs. Coxibs also cause less small intestinal erosive problems.

Aspirin, even in low dose, may cause erosions, ulcers and gastro-intestinal haemorrhage.

The incidence of gastric ulceration in patients receiving particularly low dose aspirin is significantly lower than at 150–300mg doses. (See Figure).

Only 60% of GI bleeding complications occur in the oesophagus, stomach and duodenum. The remainder occur in the small intestine and colon and cannot therefore be prevented by cc-therapy with PPI'.

Ulcer disease and traditional NSAIDs

- Gastro-duodenal ulceration with aspirin or NSAID therapy is part of the spectrum of disease that includes erosion and chronic ulceration.
- 10% of patients will stop NSAID therapy because of dyspeptic side effects.
- 1–6% will develop serious side effects, most commonly peptic ulcer disease.
- 30% of all complications of peptic ulcers are the result of NSAIDs.

NSAIDs/aspirin may cause:

- Acute ulcers (erosions)
- Complications of pre-existing “silent” chronic ulcers
- New chronic gastric and duodenal ulcers.

Erosions

- May be a local effect of NSAIDs
- Usually of little significance, but may cause bleeding
- May predict subsequent ulcer

Chronic gastric and duodenal ulcers

Some patients on NSAIDs have:

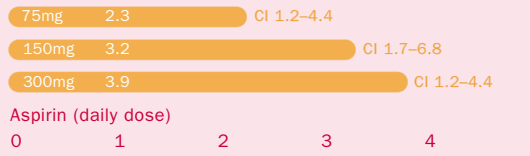
- Dyspepsia but no ulcer
- Dyspepsia and ulcer
- Ulcer but no dyspepsia or any other symptom
- 60–80% of patients on NSAIDs who develop major complications including haemorrhage or perforation have had no prior symptoms.

NSAID induced ulcers are:

- More likely to be symptomatically silent
- More likely to bleed
- More likely to perforate
- More likely with increasing frequency at higher doses and longer duration of drug therapy
- More likely to cause death.

Risk of upper GI bleeding related to Prophylactic Aspirin

Risk of GI complications is dose-dependent and is the same regardless of use of plain, buffered, or enteric-coated aspirin^{1,2}



CI: Confidence interval

1. Weil et al. *BMJ* 1995;310:827–830

2. Sorensen et al. *Am J Gastroenterol* 2000;95:2218–2224

Definite risk factors for NSAID ulcer development:

- Prior peptic ulcer disease
 - High dose NSAIDs
 - Multiple NSAIDs
 - Helicobacter pylori infection
 - Concomitant corticosteroid medication
 - Age >65 years.
- Pro-drugs, enteric-coated salicylates or NSAIDs or NSAID suppositories can still result in increased complications of chronic peptic ulcer. These dangers arise from the systemic effects of NSAIDs.
- Topical NSAIDs (sprays and gels) appear to be safe.
 - The use of low dose of aspirin has a risk of causing peptic ulceration and bleeding.
 - The combination of aspirin (including low dose aspirin down to 75mg) and NSAIDs increase the risk of peptic ulcer 2–3 fold.
 - The combination of NSAIDs with anti-coagulants (eg. Warfarin and anti-thrombotic agents (eg. Plavix) significantly increase the risk of major haemorrhage from NSAID-induced ulcers.
 - No NSAID is free of risk but some are more risky than others.

Nsaids and *helicobacter pylori*

Helicobacter pylori infection and the use of NSAIDs are common.

Data on their interactions in causing damage to the upper gastrointestinal tract conclude that:

1] In NSAID-users, peptic ulcer occurs in 42% who are H.pylori positive and 26% of those who are H.pylori negative.

2] NSAID-users who are H.pylori positive are 60 times more likely to have peptic ulcer than those who do not take NSAIDs and are H.pylori negative.

3] Taking NSAIDs or being H.pylori positive increases the risk of peptic ulcer 20 fold.

4] The increased risk of upper gastrointestinal bleeding is:

H.pylori positive	1.8
NSAID-user	4.9
H.pylori & NSAID	6.1

Recent data from Hong Kong show that in those who are H.pylori positive, eradicating H.pylori when starting an NSAID reduced peptic ulcer incidence from 34% to 12% and symptomatic upper GI bleeding from 27% to 4%. Because of the risk of GI bleeding, particular in the elderly – some suggest.

A] Before prescribing NSAIDs determine H. pylori status by serology or C14 or C13 urea breath test; if positive eradicate the H. pylori.

AND/OR

B] Prescribe a proton pump inhibitor with an NSAID if *H.pylori* positive.

(Note – unless the patient has gastro-oesophageal reflux disease or proven peptic ulcer this is not covered by the PBS in Australia).

Co-prescription of a proton pump inhibitor with any NSAID following *H.pylori* eradication may be considered in particularly high risk patients such as those who have had previous symptomatic or complicated gastrointestinal ulcers. (Class 2 to 4 see RAPID Chart).

The above scenarios assume that the patient has had an inadequate response to COX-2 selective inhibitors and therefore requires the use of NSAID therapy.

Helicobacter pylori and Cox-2 inhibitors

The interaction between *H.pylori* and the newer COX-2 inhibitors has not been examined in any large studies but appears to pose a significantly lower, but still measurable, increase in the risk of ulceration.

Eradication of *H.pylori* infection should be considered and also some advocate continued co-prescription of a proton pump inhibitor. This seems reasonable in those with a previously documented peptic ulcer and essential in those with a past history of a bleeding peptic ulcer.



COX-2 selective inhibitors

The coxibs have equal efficacy to standard NSAIDs but are associated with a significantly lower risk of gastric and duodenal ulcers. The background prevalence of peptic ulcer disease varies in different populations depending on the prevalence of *H.pylori* infection, ethnic factors, smoking and the use of corticosteroids. Any increased risk of peptic ulcer with COX-2 selective inhibitors, is significantly lower than with traditional NSAIDs.

Life-threatening complications of peptic ulcer disease, perforation and bleeding, occur in about 2–4% per year of patients taking NSAIDs. COX-2 selective inhibitors reduce this risk by 50–70%. The potential seriousness of the complication warrants the use of a COX-2 selective inhibitor. In high-risk patients, the argument to use a COX-2 selective inhibitor over an NSAID as first line therapy is compelling.

Risk Assessment Pathway for anti-Inflammatory Drugs (RAPID)

Have all therapies for the condition been optimised? Eg.
(a) non-pharmacological: exercise, weight loss, other physical therapies and surgery.
(b) pharmacological: paracetamol, anti-inflammatory gels and creams, glucosamine

Assess contraindications to non selective NSAIDs and coxibs

Non selective NSAIDs and coxibs should be used with caution where the patient is dehydrated, on diuretics, ACE inhibitors, angiotension 2 receptor antagonists, steroids, anti-thrombotics or where there is a history of hypertension, renal impairment, heart failure or asthma

Decision made to use non selective NSAID or coxib

Assess cardiovascular risk as per New Zealand Heart Foundation and gastrointestinal risk as per SCORE (insert hyperlinks)

Cardiovascular Risk Summary

Chronic use of both non-selective NSAIDs and coxibs may increase the risk of serious cardiovascular events

Cardiovascular risk can be reduced by optimising lipid profile, blood pressure, diabetes control, and smoking cessation

Cardiovascular risk can be reduced by optimising lipid profile, blood pressure, diabetes control, and smoking cessation

NSAIDs and coxibs should be used with extreme caution in those at high cardiovascular risk i.e. those at greater than 15% 5 year risk or those with established cardiovascular disease

Gastrointestinal Risk Summary

For gastrointestinal risk level 1 patients if a non-selective NSAID is indicated, consider initial H pylori eradication

In those at gastrointestinal risk level 2, 3 and 4 consider risk reduction strategies such as: Coxibs, or non-selective NSAIDs with concomitant proton pump inhibitors*
Consider initial H pylori eradication

The use of low dose aspirin, independently increases the risk of gastrointestinal bleeding.

NSAIDs and Coxibs should be used in the lowest effective dose or shortest duration possible. Chronic use of NSAIDs or coxibs should be monitored e.g. blood pressure and renal function. The need for ongoing use should be regularly reviewed.

*Not available on the PBS for this indication

ASSESSING CARDIOVASCULAR RISK AND TREATMENT BENEFIT

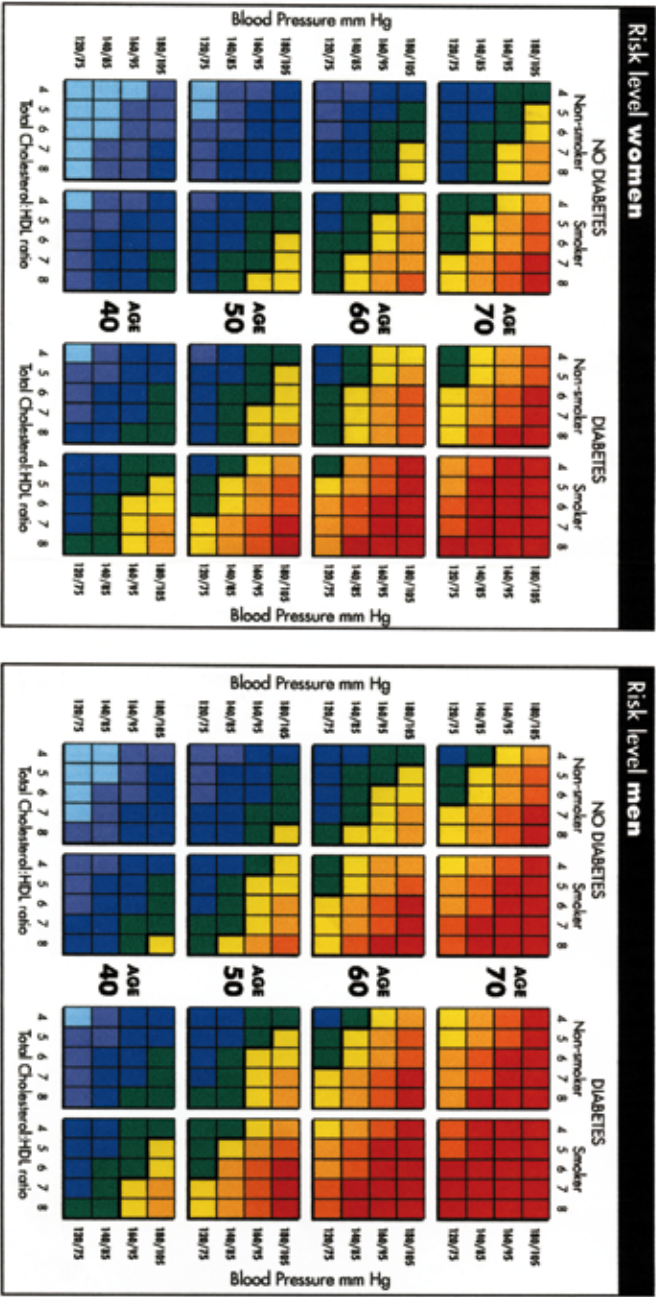
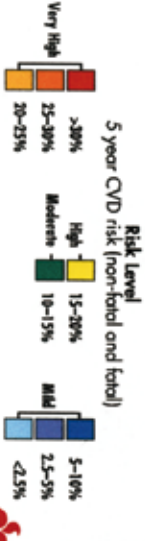


Figure 2: Assessing 5-year cardiovascular risk and treatment benefit



How to use the Tables.

- Identify the table relating to the person's sex, diabetic status, smoking history and age.
- Within the table choose the cell nearest to the person's age, blood pressure and TC:HDL ratio.
- When the systolic and diastolic values fall in different risk levels, the higher category applies.
- For example, the lower left contains all non-smokers without diabetes who are less than 45 years and have a TC:HDL ratio less than 4.5 and a blood pressure less than 130/80 mm Hg. People who fall exactly on a threshold between cells are placed in the cell indicating higher risk.

Do you know your SCORE?

Use this test to determine your **S.C.O.R.E.** (**S**tandardised **C**alculator **O**f **R**isk for **E**vents), the estimated risk profile for serious NSAID-induced GI toxicity (eg. stomach ulcer or bleeding ulcer).

INSTRUCTIONS

Answer each question, then write the appropriate points in the right hand column. After answering all the questions, add up the points and see the bottom of this sheet for **treatment guidelines**.

				Points
1. How old are you?				
Age 20 or under	0 points	Age 51–55	9 points	<input style="width: 50px; height: 50px; border: 1px solid black;" type="text"/>
Age 21–25	3 points	Age 56–60	10 points	
Age 26–30	3 points	Age 61–65	12 points	
Age 31–35	4 points	Age 66–70	13 points	
Age 36–40	5 points	Age 71–75	14 points	
Age 41–45	6 points	Age 76–80	16 points	
Age 46–50	8 points	Age 81–85	17 points	
		Over Age 85	18 points	
2. How do you rate your current health status on the following scale?				
Very poor			4 points	<input style="width: 50px; height: 50px; border: 1px solid black;" type="text"/>
Poor			3 points	
Fair			2 points	
Well			1 points	
Very well			0 points	
3. Do you have <i>rheumatoid</i> arthritis (not osteoarthritis, also known as “wear and tear” arthritis, or other forms of arthritis)?				
No	0 points	Yes	2 points	<input style="width: 50px; height: 50px; border: 1px solid black;" type="text"/>

4. If you are taking prednisone or other corticosteroids by mouth (not by oral inhaler) or by injection, for how many months have you taken them in the past year?

0 months	0 points	4–6 months	3 points	<input type="checkbox"/>
1–3 months	1 point	7–10 months	4 points	
		11–12 months	5 points	

5. Have you ever been hospitalised for a stomach or intestinal problem such as bleeding or an ulcer (if “yes”, skip next question)?

No	0 points	Yes	2 points	<input type="checkbox"/>
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6. (If answer to #5 is “No”) Have you ever had gastrointestinal side effects (heartburn, stomach pain, nausea, vomiting) when taking NSAIDs?

No	0 points	Yes	2 points	<input type="checkbox"/>
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ADD UP THE TOTAL SCORE

What your **S.C.O.R.E.** means

- RISK LEVEL 1** **Up to 10 points** Risk of a serious GI side effect (eg. stomach ulcer or bleeding) is *not significantly increased* by taking NSAIDs, if taken as recommended in product labelling.
- RISK LEVEL 2** **11 to 15 points** Risk of a serious GI side effect is *moderately increased* by taking NSAIDs. Consultation with a medical professional is recommended, especially if you need to take NSAIDs regularly.
- RISK LEVEL 3** **16 to 20 points** Risk of a serious GI side effect is *significantly increased* by taking NSAIDs. Consultation with a medical professional is advisable.
- RISK LEVEL 4** **Over 20 points** Risk of a serious GI side effect is *substantially increased* by taking NSAIDs. Consultation with a medical professional is strongly encouraged.

NOTE: This scoring tool/risk calculator is based on work done using the ARAMIS data base (prospective data on >11,000 patients with arthritis) by Dr Gurkirpal Singh and colleagues at Stanford University Division of Immunology, and is provided for educational purposes only. For licensing information, email Dr Singh at gsingh@stanford.edu

Oesophageal ulceration

“Pill ulceration” is not uncommon and occurs with tetracycline, potassium and other medications as well as NSAIDs. Ulceration associated with NSAIDs is particularly likely if there are oesophageal strictures or motility disorders. Patients with oesophageal disease should use soluble tablets or make sure they are upright when swallowing tablets, washing them down with plenty of water.

Other gastrointestinal effects of NSAIDs

Small bowel enteropathy may affect anyone who has taken NSAIDs or coxibs. More than two-thirds of patients on NSAIDs may have some small intestinal ulceration and occult blood loss seen with video capsule endoscopy although most remain free of symptoms. Some may develop diarrhoea and bile acid malabsorption may contribute to this. A few patients develop strictures or frank ulceration resembling Crohn’s disease.

In the colon, there may be exacerbation of existing ulcerative colitis and NSAIDs may induce new cases. Suppositories may cause a non-specific proctitis and colonic ulceration with haemorrhage, stricture and perforation of diverticula with subsequent fistulae may occur.

Little information on the risk of these complications with COX-2 selective inhibitors is available, but short-term studies indicate significantly less microscopic blood loss than with NSAIDs and less small intestinal erosions.

Hepatitis

Acute hepatitis reflected by a rise in liver enzymes, occurs as a complication of NSAID therapy.

It is frequently cholestatic (high alkaline phosphatase and gamma GT) and rarely may be fatal.



Inflammatory bowel disease (IBD)

Despite increased quantities of prostaglandins being expressed by the mucosa in inflammatory bowel disease (IBD), NSAIDs do not help in its management and may be associated with the onset of IBD or cause re-activation of quiescent disease. Patients admitted to hospital for flare-ups of IBD have a higher than expected use of NSAIDs.

Why NSAIDs may cause problems is not clear but this may relate to the inhibition of both COX-1 and COX-2.

By reducing the production of protective prostanoids to the same extent as traditional NSAIDs, COX-2 selective inhibitors theoretically would aggravate mucosal damage to a similar degree. This has been seen in animal models of colitis where COX-2 selective inhibitors have exacerbated the disease.

There have been no clinical trials of COX-2 selective inhibitors to confirm similar findings in patients with inflammatory bowel disease.

Recommendation: Like NSAIDs, COX-2 selective inhibitors should be used with caution in patients with inflammatory bowel disease because of the risk of possible exacerbation of the disease.

Bleeding

Due to their effect on platelet aggregation and bleeding time via an action on COX-1, NSAIDs should be stopped 7 days prior to surgery.

The coxibs on the other hand do not prolong bleeding time and have no effect on platelet aggregation. As a result they are a better choice when anti-inflammatory cover is required in arthritis patients who need to undergo a surgical procedure, since they do not require discontinuation before surgery.

Asthma

Some people with asthma are sensitive to aspirin and other NSAIDs that can cause acute severe bronchospasm from an excess of bronchoconstrictor leukotrienes. Those with asthma and a history of aspirin allergy (particularly in association with nasal polyposis) should not be given these agents. Aspirin sensitivity appears to be a class effect extending to most NSAIDs. In theory coxibs should not precipitate asthma, but until this is clarified these drugs should be avoided in those patients with a history of aspirin-induced asthma. If aspirin tolerance is unknown, consider alternative analgesics or anti-inflammatories in asthmatic patients.

Before prescribing anti-inflammatories or aspirin, always ask a patient about a history of asthma.



management strategies

- **Are anti-inflammatories needed?**

Simple analgesia with paracetamol, weight loss and physical therapies can often be used instead of anti-inflammatories for relief of musculoskeletal pain. Published guidelines for the management of osteoarthritis recommend medication paracetamol (up to 4g/day) as the first choice.

- **Is the patient in a high-risk group?**

High risk groups for ulcer complications include those taking multiple or high dose NSAIDs, those with an active or previous peptic ulcer, or anyone taking corticosteroids. Elderly patients are at higher risk and are also more likely to require NSAIDs. Cardiovascular risk includes hypertension, ischaemic heart disease and cardiac failure. Monitoring of blood pressure and renal function is essential. Doctors should identify high-risk patients and consider co-prescription of gastro-protective agents if using traditional NSAIDs. Coxibs should be considered as first-line agents in the high-risk group.

- **Which anti-inflammatory?**

All anti-inflammatory agents have the potential to cause gastrointestinal and other complications but coxibs have

a significantly lower rate of ulcers and complications such as perforation and bleeding. All anti-inflammatory agents may cause gastric micro bleeding and/or anaemia although there are differences in their association with chronic gastric ulcer. Ketoprofen and piroxicam have a higher risk than ibuprofen and diclofenac. Considerable caution should be used in any patient with increased cardiovascular risk.

In spite of subtle differences in mode and mechanism of action, comparative trials of anti-inflammatory agents including coxibs have not shown significant differences in effectiveness. However there can be marked individual differences in clinical response to different agents. Selecting an anti-inflammatory for a particular patient is still an art rather than a science.

There is no advantage in using more than one anti-inflammatory at any one time in an individual patient and there is strong evidence this may increase the risk of ulcer complications. Beware of OTC use of aspirin or NSAIDs while using a coxib.

- **Is surgery indicated?**

Joint replacement may provide the solution for some patients with chronic joint disease.

Ulcer Prophylaxis

- Patients with NSAID ulcer risk factors
 - *Prior ulcer disease or history of complications*
 - *High dose NSAIDs*
 - *Multiple NSAIDs*
 - *Helicobacter pylori infection*
 - *Concomitant corticosteroid therapy*
 - *Age > 65 years*
 - Patients on warfarin, anti-thrombotic agents and aspirin.
 - If clinical efficacy dictates NSAID prescribing rather than COX-2 selective inhibitors, prophylaxis is recommended with a proton pump inhibitor.
 - Patients on COX-2 selective inhibitors without risk factors do not need proton pump inhibitor prophylaxis.
 - There is as yet insufficient evidence to decide if low-risk patients on COX-2 inhibitors plus aspirin, or anti-coagulants should have proton pump inhibitor prophylaxis, though this may be shown to be necessary.
- However, detection and eradication of *H.pylori* should be considered.

Guidelines for pain management

1] Do not use NSAIDs and aspirin initially to treat pain in those with non-inflammatory diseases.

2] Simple analgesia, such as paracetamol, should be first-line therapy.

3] Avoid using more than one NSAID at a time.

If possible avoid therapy with NSAIDs and steroids. For patients with an active gastric or duodenal ulcer who are being treated with COX-2 selective inhibitors or NSAIDs, prescribe a proton pump inhibitor until healed. Following healing of the ulcer, prophylactic therapy with a proton pump inhibitor should be continued indefinitely if NSAIDs, rather than a COX-2 selective inhibitor, must be used. An exception would be those first seen with a serious complication, in which case NSAIDs should be stopped until the ulcer heals or is excised.

Patients with a history of ulcer disease or gastrointestinal haemorrhage of unknown cause regardless of age, or those with erosive oesophageal disease or strictures, or anyone aged over 60 and needing long-term anti-coagulant therapy, should be treated prophylactically with proton pump inhibitors if treated with NSAID or COX-2.

Over-the-counter dispensing (OTC)

As NSAIDs are increasingly available OTC and widely advertised, it is essential to educate patients to ensure that the effectiveness of treatment with NSAIDs is balanced by discussing their risks.

The pharmacist should ask:

- Have you had a stomach or duodenal ulcer or do you suffer from indigestion/heartburn?
- What other medications are you taking?

NSAIDs/aspirin

Steroids (cortisone)

Asthma drugs

Blood pressure drugs

Blood thinning drugs

- Are you taking any other pain relief medicines?
- Do you suffer from asthma?
- Are you pregnant?

NSAIDs in children

The commonest situation when the use of NSAIDs is considered is fever. Most children tolerate low-grade fever well and do not necessarily require intervention.

However, temperatures above 38.0°C require consideration of either paracetamol or ibuprofen suspension.

Paracetamol given for a short duration at the recommended dose is almost certainly the medication of choice particularly in view of its safety profile.

Ibuprofen has equivalent efficacy to paracetamol in controlling fever and appears safe provided it is used for a short period of time. Longer-term use of both paracetamol and ibuprofen is not indicated without a definite diagnosis of the cause of the fever.

A common indication for long term NSAID therapy in children is chronic inflammatory arthritis where NSAIDs provide both symptomatic pain relief together with an anti-inflammatory effect. Acute injuries in children should not be treated with NSAID therapy.

Adverse events

Adverse events with NSAIDs appear much less common than in adults.

Gastrointestinal events are much less common than in adults and this may be attributed to the absence of concurrent *Helicobacter pylori* infection.

Hepatitis may occur with any NSAID but most frequently with aspirin. Hepatitis almost always resolves spontaneously on discontinuation of the drug.

Renal adverse events are also uncommon especially with short-term use. A number of cutaneous reactions have been reported including pruritus, morbilliform rashes, photosensitivity and urticaria.

No COX-2 selective inhibitors have been approved for use in children in Australia.

Safety check list

Questions the physician or pharmacist should consider before prescribing or recommending an NSAID.

- **Could there be drug interactions?**
Consider ACE-inhibitors, beta-blockers, thiazides, frusemide, warfarin and lithium.
- **Can NSAIDs exacerbate pre-existing disease?**
Peptic ulcer, oesophagitis, asthma, hypertension, renal failure, cardiac failure and ascites.
- **What concurrent medications are being used?**
Aspirin, steroids and, even more important, other NSAIDs, including those purchased OTC.
- **Review the risk factors.**
Have you discussed possible side-effects with the patient?



Additional copies of Therapy with NSAIDs coxibs & aspirin are available from:

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Notes
