Counselling on non-steroidal anti-inflammatory drugs

By Megan Deldot and Associate Professor Lisa Nissen

Case study

A 72-year-old man, Mr BK, presents to the pharmacy requesting Voltaren Rapid for his ‘bad arthritis’. He states that a friend has used Voltaren Rapid for arthritis pain and has found that it has really helped. Mr BK usually takes regular Panadol Osteo as prescribed by his doctor; however, this medication is not controlling his pain adequately at present. He was diagnosed with osteoarthritis several years ago by his GP, and the pain is usually well controlled.

Learning objectives

After reading this article you should be able to:

• Provide information on the potential adverse effects of NSAIDs
• Counsel appropriately on diclofenac
• Provide lifestyle advice on ways to minimise pain resulting from osteoarthritis.

Competency standards (2010) addressed:
6.1.1, 6.1.2, 6.2.1, 6.2.2, 6.3.3, 7.1.2, 7.1.3, 7.1.4

Accreditation number:
CAP110101a

What is osteoarthritis?

Osteoarthritis is a common chronic joint disease which is becoming more prevalent in our community due to the obesity epidemic and the ageing population. Pain and loss of function are the main clinical features and the aims of treatment should be the reduction of this pain and stiffness and the maintenance and improvement of the patient’s functional capacities.

Paracetamol is the first choice analgesic for osteoarthritis because it is effective with regular dosing throughout the day and has a good safety profile. However, often, despite optimal dosage regimens of paracetamol, other drugs like Voltaren Rapid, a non-steroidal anti-inflammatory drug (NSAID), are added to therapy.

How do NSAIDs work?

Traditional (non-selective) NSAIDs inhibit the synthesis and release of prostaglandins by inhibiting, to variable degrees, the enzyme cyclo-oxygenase (COX), present as COX-1 and COX-2. Newer selective COX-2 inhibitors primarily antagonise COX-2 at therapeutic doses (see Table 1). Prostaglandins are chemicals which are released by cells when tissue is damaged or injured. They cause inflammation and swelling and sensitise the nerve endings, which can cause pain. NSAIDs block the production of prostaglandins, resulting in less inflammation and less pain (see Figure 1).

COX-1 is expressed in most tissues and in particular is responsible for the synthesis of protective mucosal prostaglandins in the gastrointestinal tract to maintain the normal lining of the stomach. The enzyme is also involved in kidney and platelet function. The COX-2 enzyme is also expressed in many tissues, including the brain, kidney, placenta and gastrointestinal tract (often at low
## Table 1. Selective and non-selective NSAIDs

<table>
<thead>
<tr>
<th>Traditional (non-selective) NSAIDs (COX-1 and COX-2 inhibitors)</th>
<th>Selective NSAIDs (COX-2 inhibitors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Mefenamic Acid</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Naproxen</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Sulindac</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Tiaprofenic acid</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Celecoxib</td>
</tr>
<tr>
<td></td>
<td>Etoricoxib</td>
</tr>
<tr>
<td></td>
<td>Meloxicam</td>
</tr>
<tr>
<td></td>
<td>Parecoxib</td>
</tr>
</tbody>
</table>

## Table 2. Consequences of inhibition of COX-1 and COX-2

<table>
<thead>
<tr>
<th>Desirable</th>
<th>Undesirable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased inflammation</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Decreased fever</td>
<td>Gastrointestinal ulcers</td>
</tr>
<tr>
<td>Decreased pain</td>
<td>Decreased renal function</td>
</tr>
<tr>
<td></td>
<td>Increased sodium retention</td>
</tr>
<tr>
<td></td>
<td>Decreased vasodilation</td>
</tr>
<tr>
<td></td>
<td>Increased production of thromboxane A2 (increased platelet aggregation and vasoconstriction)</td>
</tr>
</tbody>
</table>

levels), and is upregulated in cancer tissue and by inflammatory cytokines. It is induced during inflammation and tissue repair and may also have a significant role to play in renal function.

The inhibition of COX-1 and COX-2 by traditional NSAIDs may result in both desirable and undesirable effects (see Table 2). Inhibition of COX-1 results in impaired gastric cytoprotection and antiplatelet effects whereas inhibition of COX-2 results in analgesia and reduction of inflammation. Reductions in glomerular filtration rate and renal blood flow occur with both COX-1 and COX-2 inhibition.

The anti-inflammatory and analgesic properties of traditional NSAIDs result from the inhibition of prostaglandin synthesis mediated by COX-2 at the site of tissue injury. Selective COX-2 inhibitors were developed initially with the aim of treating pain without causing gastrointestinal toxicity.

### How effective are NSAIDs?

NSAIDs are effective at relieving pain and stiffness. They usually work quickly, within a few hours, but their maximum anti-inflammatory and analgesic benefits may not be felt for two to four weeks or sometimes longer. If no improvement is seen after this timeframe then a different NSAID may be tried.

### Case study

As inhibition of COX-1 and COX-2 can be associated with serious health risks, no NSAID should be considered safe. Potential health risks need to be assessed by the pharmacist, in the context of patient need and individual risk, before a product can be recommended.

The pharmacist should ask the following questions to help with this assessment.

### Are you taking any other medications?

There are numerous documented drug-drug interactions between NSAIDs (both selective and non-selective) and prescription (e.g. warfarin, ACE inhibitors, diuretics and lithium), over-the-counter and complementary medicines. It is essential to take a thorough medication history before considering a NSAID.

### Do you have any kidney problems?

The decision to use a NSAID should take into consideration the patient’s renal function status. COX-1 inhibition by traditional NSAIDs has been associated with adverse renal effects such as:

- decreased renal blood flow and perfusion
- decreased glomerular filtration (GFR)
- oedema
- increased blood pressure
- interstitial nephritis.

There is also some evidence to suggest that COX-2 inhibition may
induce renal ischaemia, electrolyte imbalance and abnormal blood pressure.\textsuperscript{3, 5} This may lead to fluid and sodium retention and ultimately a decreased GFR.\textsuperscript{3}

Pre-existing renal dysfunction may increase the risk of NSAID-induced impairment and NSAIDs should be avoided in patients with a creatinine clearance (CrCl) <25 mls/min.\textsuperscript{2} The patient’s renal function may need to be monitored if they have other risk factors for reduced renal function such as being over the age of 65 years, taking blood pressure medications (e.g. ACE inhibitors/angiotensin receptor antagonists, diuretics) or if they are likely to be taking the NSAID for a prolonged period of time.\textsuperscript{2, 4} For patients on continued long term treatment with NSAIDs, renal function should be measured before starting and then at least once a year.\textsuperscript{2}

The patient should be advised to immediately report to their doctor any unusual weight gain, swelling of their ankles or legs, or blood in their urine.

**Do you have any heart problems?**

All NSAIDs should be used with caution and may be contraindicated in patients with cardiovascular risk factors. In 2004, rofecoxib, a selective COX-2 inhibitor, was withdrawn from the market due to an increased risk of cardiovascular events, including myocardial infarction and strokes.\textsuperscript{7} Since this time, a number of systematic reviews have found that cardiovascular events, including cardiovascular death, were increased with diclofenac, indomethacin, ibuprofen, celecoxib at doses above 200 mg/day, etoricoxib and probably meloxicam.\textsuperscript{7, 9} Naproxen seems to be the least harmful in terms of cardiovascular events.\textsuperscript{7, 9}

The mechanism of cardiovascular toxicity is not fully understood but may involve an imbalance between thromboxane A\textsubscript{2} and prostacyclin resulting from inhibition of COX-2. With the loss of prostacyclin antplatelet and vasodilatory effects, a relative excess of thromboxane A\textsubscript{2} may result in vasoconstriction, platelet aggregation and thrombosis.\textsuperscript{7}

More recently, NSAIDs have been associated with an increased risk of atrial fibrillation and flutter, possibly through their adverse renal effects (e.g. fluid retention, electrolyte disturbances and blood pressure destabilisation).\textsuperscript{10} COX-2 inhibitors and in particular diclofenac were associated with higher risk of atrial fibrillation and flutter than the non-selective NSAIDs.\textsuperscript{10}

Cardiovascular risk, including atrial fibrillation and flutter, need to be taken into consideration before recommending any NSAID, particularly in the older patient. A quick reference guide to assess a patient’s absolute cardiovascular disease can be found on the National Heart Foundation website at: www.heartfoundation.org.au/SiteCollectionDocuments/absolute-risk-assessment.pdf

**Do you have high blood pressure?**

All NSAIDs in doses adequate to reduce inflammation and pain can increase blood pressure\textsuperscript{11} and should be used cautiously in patients with pre-existing hypertension, oedema, diabetes, mild kidney disease or congestive heart failure.\textsuperscript{12} COX-2 inhibition results in a reduction in prostaglandin synthesis and is associated with both sodium and water retention and vasoconstrictor effects.\textsuperscript{12} Use of NSAIDs and COX-2 inhibitors may lead to increased systemic vascular resistance and a subsequent increase in blood pressure.\textsuperscript{12}

Hypertensive patients who are started on a NSAID should be advised to have their blood pressure checked within one to three weeks of initiation\textsuperscript{12} and then every three to six months should therapy continue.\textsuperscript{4}

**Do you have any stomach problems?**

All NSAIDs can cause serious gastrointestinal adverse effects.\textsuperscript{2} The inhibition of COX-1-mediated prostaglandin synthesis results in impaired gastric cytoprotection and may lead to the development of gastric pain, distress and/or ulceration, gastrointestinal bleeding and perforation.\textsuperscript{5} The risk appears to be higher with indomethacin, ketoprofen, naproxen and piroxicam and lower with ibuprofen and diclofenac (although the advantage for the latter two may be lost when they are taken at full doses).\textsuperscript{5} Selective NSAIDs are generally associated with a lower risk of GI complications than non-selective NSAIDs.\textsuperscript{2}

The risk of severe gastrointestinal adverse effects with NSAIDs is increased in patients who;\textsuperscript{2, 4}

- are over 65 years of age;
- have had a previous stomach or duodenal ulcer;
- are taking warfarin, corticosteroid tablets, low-dose aspirin or other antiplatelet medicines, or SSRIs.

NSAIDs are contraindicated in patients who have active peptic ulcer disease or gastrointestinal bleeding.\textsuperscript{2}

The patient should be advised to look out for any signs of gastrointestinal bleeding including:\textsuperscript{4}

- severe stomach pains
- passing blood or black/tarry stools
- vomiting blood.

If any of these symptoms occur, the NSAID should be stopped immediately and the patient should be advised to seek immediate medical attention.

**Do you have haemophilia or any other bleeding disorder?**

There is an increased risk of bleeding with non-selective NSAIDs due to antiplatelet effects and the possibility of thrombosis in patients taking COX-2 inhibitors.\textsuperscript{2} Patients who have any underlying coagulation disorder should be advised to speak with their doctor prior to starting any of these medicines.

**Are you likely to be having surgery or dental work done soon?**

Patients should be advised to let their doctor or dentist know that they are taking a NSAID before any medical or dental procedure, because of the increased risk of bleeding with non-selective NSAIDs and thrombotic events with COX-2 inhibitors, as well as the possibility of renal impairment after surgery.\textsuperscript{2} It may be advisable to stop the NSAID two to three days before surgery, especially if there is a significantly increased risk of post-operative bleeding,\textsuperscript{2} but this will depend on the type of surgery performed and the preference of the surgeon or dentist.

There may be a risk of renal impairment after surgery, especially if the patient is not adequately hydrated or has renal hypoperfusion. The patient should be adequately hydrated before surgery, particularly if a NSAID
is to be used in the post-operative management of pain.²

Do you have asthma?
In some patients with asthma, symptoms such as wheeze or breathlessness are made worse by NSAIDs.³,⁴ Patients with asthma should be advised to seek medical attention if their asthma suddenly becomes worse after taking a NSAID.⁴

Do you drive or operate machinery?
NSAIDs can cause dizziness, light-headedness, tiredness, ringing in the ears (tinnitus) and headache.⁴ The extent to which these occur varies between individual NSAIDs. Patients should be advised to monitor their response to the medication before driving, operating heavy machinery or doing jobs that may require them to be alert.

Case study
Once an assessment has been made on whether the patient should use NSAIDs the following counselling questions will assist them in understanding how to take the medicine correctly and when to get more information should they want it.

Do you know how to take Voltaren Rapid?
NSAIDs should preferably be taken at the lowest effective dose and for the shortest possible duration to minimise the risk of developing side effects.¹ The patient should be advised to swallow the tablets whole with a full glass of water.¹³ The tablets should not be broken or chewed.¹³ The tablets should preferably be taken before meals to speed their onset of action. However, if they cause stomach upset, they may be taken with or immediately after food.¹³

Are you aware of any other techniques which may help to reduce or control arthritic pain?

Lifestyle modifications
Exercise and physical therapy are important components for both prevention and symptom relief. There is evidence for a positive effect of regular exercise, in particular exercises that strengthen muscles, improve joint stability and improve aerobic condition.¹ A referral to a physiotherapist may also be useful as they can show the patient the most appropriate techniques to relieve their pain.

Weight control
Weight reduction has proven to be beneficial especially in lessening pain and improving physical activity in osteoarthritis of the knee.¹ Recommendations should be relevant to the individual and specific with achievable, measurable short and long term goals. Keeping to a healthy weight limits the stress on weight-bearing joints. Recommend eating a healthy diet including plenty of fruits, vegetables and whole grains and limiting foods high in fat, salt or sugar.
Other non-pharmacological therapies that may be considered in the management of osteoarthritis include:
• Thermotherapy
Ice packs may be beneficial for acute flare-ups, when minor joint inflammation is present. Heat (e.g. rubs, plasters, packs, pads) may promote relaxation and improve joint flexibility and blood flow to the joint, thereby reducing pain and stiffness, although evidence for these strategies is limited.¹⁴
• Electrotherapy
Transcutaneous electrical nerve stimulation (TENS) is the use of an electrical current produced by a device worn and operated by the patient, to stimulate nerves, inhibit pain signals and reduce pain. Treatment with high frequency and strong burst modes for at least four weeks may be beneficial in osteoarthritis of the knee.¹⁴
• Acupuncture
There is some evidence to suggest that a six to 12 week course of acupuncture may reduce pain and improve function in some patients with osteoarthritis of the knee.¹⁴
• Aids and devices
Footwear with shock-absorbing properties, laterally wedged insoles, knee braces, patellar taping, thumb splints and walking aids may reduce pain and improve function.¹⁴

Do you know where to find more information on osteoarthritis?
Pharmacists are in an ideal position to contribute to the ongoing management of osteoarthritis by educating patients and encouraging them to become more active in the management of their condition. The following PSA Self Care Fact Cards may be relevant for patients with osteoarthritids:
• Weight and health
• Relaxation techniques
• Preventing falls
• Exercises for flexibility
• Osteoarthritis
• Pain relievers.
A variety of online patient resources can be used to complement the information in the PSA Self Care fact cards.
Arthritis Australia has useful information sheets, booklets, programs and support services available at: www.arthritisaustralia.com.au
The Health Insite website: www.healthinsite.gov.au provides useful links to information fact sheets on osteoarthritis and NSAIDs.
The NPS also has multiple information sheets and resources for pharmacists and consumers at: www.nps.org.au

When should the pharmacist refer?
Patients should be referred to their doctor for assessment if:¹⁵
• symptoms developed rapidly (e.g. signs of systemic illness)
• symptoms occur in younger patients
• symptoms affect the same joints on both sides of the body
• symptoms are not localised to the affected joint
• other symptoms are present (e.g. warmth, swelling of joint, morning stiffness lasting >30 mins)
• joint function is affected
• pain is moderate to severe.

Case study
Osteoarthritis is the most common form of arthritis and its prevalence increases with age.¹⁴ In reality the
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The majority of patients with moderate to severe osteoarthritis who might benefit from the use of a NSAID or COX-2 inhibitor are likely to be elderly, like Mr BK, and are therefore at higher risk for the development of gastrointestinal, renal and cardiovascular adverse effects.

Regular paracetamol is the first choice analgesic, which Mr BK has tried, but despite this he has ongoing pain. NSAIDs have an important role to play as they are effective analgesics and have a low risk of serious adverse effects if used appropriately in carefully selected patients.

Topical NSAIDs may be considered before the use of oral NSAIDs in patients like Mr BK, who have tried regular paracetamol and are still experiencing pain. However, it must be remembered that systemic side effects can still occur, though the risk is significantly less than with oral NSAIDs due to their reduced systemic absorption.

Oral NSAIDs may be used after careful consideration of the patient’s need and risk of developing adverse effects and may produce additive benefit in patients who are already taking regular paracetamol and who have tried a topical NSAID with little effect. In Mr BK, who has no other co-morbidities, Voltaren Rapid could be recommended for up to seven days. If his pain has not resolved satisfactorily after seven days, he should be advised to consult his doctor for further assessment.

Key learning points

Inhibition of COX-1 and COX-2 is associated with serious health risks; no NSAID should be considered safe. Pharmacists are encouraged to consider carefully the patient benefits versus the individual risk of taking a NSAID before recommending their use.

Potential toxicity from NSAIDs may be minimised by:

- considering the use of topical NSAIDs before oral
- ensuring an adequate trial of regular paracetamol before starting a NSAID
- using the lowest effective dose for the shortest period of time
- selecting NSAIDs with the lowest risk, e.g. diclofenac and ibuprofen – lowest gastrointestinal risk; naproxen – lowest cardiovascular risk
- not using more than one NSAID at a time.

References


Questions

1. The maximum anti-inflammatory and analgesic effect of NSAIDs may not be felt for:
   a) 1 to 2 days.
   b) 3 to 4 days.
   c) 2 to 4 weeks.
   d) 4 to 6 months.

2. In which ONE of the following scenarios would you refer the patient to the doctor?
   a) Pain is mild with no other symptoms.
   b) Symptoms affecting the same joints on both sides of the body.
   c) Symptoms are localised to the affected joint.
   d) Patient with osteoarthritis not taking paracetamol regularly and experiencing ongoing pain.

3. Which ONE of the following may increase the risk of gastrointestinal side effects with NSAIDs?
   a) Age <65 years.
   b) Taking regular paracetamol.
   c) Previous stomach or duodenal ulcer.
   d) Having asthma.

4. Potential toxicity associated with NSAIDS can be minimised by which ONE of the following?
   a) Using the lowest effective dose for the shortest period of time.
   b) Taking ibuprofen and diclofenac together to decrease pain.
   c) Taking on an empty stomach.
   d) Using high dose NSAIDs for as long as possible.

5. Which ONE of the following may also be beneficial in easing the pain and stiffness associated with osteoarthritis?
   a) Leading a sedentary lifestyle.
   b) Wearing a copper bracelet.
   c) Alternative remedies like cranberry extract.
   d) Exercise and physical therapy.