



Therapeutic brief

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Clinical Risk Management: NSAIDs

The withdrawal of rofecoxib (Vioxx®) in September 2004 ignited debate regarding the safety of all non-steroidal anti-inflammatory drugs (including selective COX-2 and non-selective NSAIDs). Drug regulatory agencies^{1,2} have since formulated recommendations on appropriate use of NSAIDs.

This therapeutic brief asks you to review the clinical risk management of your veteran patients who use NSAIDs (excluding low dose aspirin), particularly those with diabetes and heart failure.

NSAIDs: Think clinical risk management of high risk patients

- Choice of NSAID
- Review dose and duration of use regularly
- Consider a gastroprotective agent
- Assess & monitor renal, cardiovascular and gastrointestinal risk

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NSAIDs have effective analgesic and anti-inflammatory properties but their potential to cause serious adverse effects is well known. Patients with heart failure, diabetes, and those aged over 65 years are at particular risk of cardiovascular and renal adverse effects.

In the year April 2004 to March 2005, 105,476 of the 317,908 veterans who were dispensed at least one medicine also received a NSAID (33%).³ 34% of veterans dispensed medicines for diabetes and 33% of veterans dispensed medicines for heart failure were also dispensed at least one NSAID.³

Osteoarthritis is a common reason for use of NSAIDs. Paracetamol is first-line pharmacological treatment for osteoarthritis.⁴ For patients whose pain is not adequately relieved by regular paracetamol, NSAIDs may be considered.

Key Points

- Many veterans are at increased risk of an NSAID adverse effect due to their age (>65 years).
- Veterans with heart failure and/or diabetes are at particular risk of the cardiovascular and renal adverse effects from NSAIDs.
- Both selective COX-2 and non-selective NSAIDs can exacerbate heart failure and hypertension.
- Selective COX-2 NSAIDs show an increased risk of thrombotic events such as heart attack and stroke, particularly when used in high doses.
- Selective COX-2 NSAIDs are no more effective than non-selective NSAIDs for the treatment of inflammatory conditions.
- NSAIDs should only be considered for treating osteoarthritis after a trial of regular paracetamol.



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NSAIDs: Major risks

Gastrointestinal (GI) effects

GI complications can occur with all NSAIDs, including the selective COX-2 NSAIDs.⁽⁵⁻⁷⁾ Avoid use in patients with active peptic ulcer or GI bleeding and, where possible, in those with a past history of peptic ulcer disease.⁸

Cardiovascular and renal effects

Because there is an increased risk of thrombotic events with COX-2 selective NSAIDs, particularly at high doses, the Therapeutic Goods Administration in Australia advises that they should not be prescribed for patients with increased risk of cardiovascular events, such as heart attacks.¹

Similarly, European authorities state that COX-2 selective NSAIDs are contraindicated in patients with established ischaemic heart disease and/or cerebrovascular disease or peripheral arterial disease, and that caution is necessary if prescribing COX-2 selective NSAIDs to patients with risk factors for heart disease such as hypertension, hyperlipidaemia, diabetes, or smoking.²

All NSAIDs, including selective COX-2 NSAIDs, inhibit prostaglandin synthesis thereby causing salt and water retention. This can worsen heart failure or hypertension.

The beneficial effects of diuretics and ACE inhibitors/angiotensin II receptor blockers (A2RB) for heart failure and hypertension can be antagonised by NSAIDs.

NSAIDs, including COX-2 NSAIDs, may cause or exacerbate kidney impairment. NSAIDs, ACE inhibitors, and diuretics, individually or in combination, are implicated in the majority of cases of iatrogenic

acute renal failure and the combination of these three drug groups (the “triple whammy”) should be avoided. Reduced renal blood flow due to heart failure, dehydration, or renal disease increases the risk of this effect.⁹

NSAIDs increase the risk of hyperkalaemia in patients on ACE inhibitors and A2RB, particularly those with diabetes or renal impairment.

Why are patients with heart failure or diabetes at higher risk from NSAIDs?

Heart failure:

May be exacerbated by the salt and fluid retention caused by NSAIDs. NSAIDs have been associated with substantially increased hospital admission due to heart failure. The heart failure disease burden from these drugs may be similar to that for serious GI complications.¹⁰

Diabetes:

The American Heart Association indicates that patients with diabetes belong in the same risk category as patients with known cardiovascular disease.¹¹ Concurrent use of an NSAID with an ACE inhibitor may increase the risk of renal impairment. NSAIDs can increase blood pressure¹² and small increases in blood pressure in hypertensive diabetic patients are associated with a substantial increase in the risk of cardiovascular morbidity.¹³



NSAIDs: Alternatives in osteoarthritis

- **Non-pharmacological measures:**

Weight loss, exercise and physiotherapy. Continue once drug therapy is introduced.

- **Paracetamol:**

Comparable efficacy and better safety profile than NSAIDs for patients with mild to moderate joint pain.⁴

Is first-line treatment and should be used regularly - ie 1000mg (2x500mg) four times daily for standard paracetamol tabs.

Modified-release paracetamol tablets eg Panadol Osteo® & Duatrol SR® may aid compliance (1330mg (2 x 665mg tabs) three times daily).^{† 14}

- **Topical NSAIDs:**

Can help if symptoms are mild and may be used with regular paracetamol; serious systemic adverse effects are less likely than with oral NSAIDs.⁸

- **Paracetamol + low-dose/intermittent NSAID**

- **Intra-articular corticosteroids:**

Useful for localised inflammatory disease in selected patients.

- **Glucosamine:**

Symptom relief in mild to moderate osteoarthritis of the knee. Additional monitoring of blood glucose may be warranted in people with diabetes.¹⁵



† Available under the PBS as a restricted benefit for the relief of persistent pain associated with osteoarthritis.



NSAIDs: Clinical risk management of high risk patients

NSAIDs: Think clinical risk management of high risk patients

- Choice of NSAID
- Review dose and duration of use regularly
- Consider a gastroprotective agent
- Assess & monitor renal, cardiovascular and gastrointestinal risk

Choice of NSAID

There is little difference in efficacy between agents.⁸ Maximal analgesic and anti-inflammatory effects of NSAIDs are usually seen in 2 weeks; if no response in 3 weeks, try a different NSAID.⁸

Use the lowest effective dose for the shortest duration possible

The incidence of adverse effects of NSAIDs increases in a linear fashion with dose.¹⁹ For patients whose symptoms are well controlled, attempt NSAID dose reduction and try on an as-needed basis.⁴

Both high-dose and long plasma half-life NSAIDs (eg naproxen, piroxicam) have been associated with an increased risk of precipitation of heart failure¹⁰ or renal impairment.¹⁶

Choose an NSAID with a lower risk of adverse GI events, eg low-dose ibuprofen (<1200mg/day) or diclofenac^{8,17} or celecoxib.

Do not use more than one oral NSAID at the same time; only use in patients on low-dose aspirin if absolutely necessary.⁷ Regardless of which NSAID is used (including the more selective COX-2 NSAIDs) co-administration with low dose aspirin increases the risk of GI events.

Consider a gastroprotective agent

Consider a proton pump inhibitor^{††} or misoprostol (not H₂- antagonists¹²) in those at moderate or high risk of GI adverse events:

- age over 65 years
- concomitant medications known to increase upper GI adverse events (e.g. anticoagulants, steroids, low-dose aspirin, and bisphosphonates)
- serious co-morbidity (e.g. cardiovascular disease), or
- prolonged use of maximum recommended doses of non-selective NSAIDs.¹⁸

Assess and monitor renal, cardiovascular and gastrointestinal risk

Current expert opinion suggests:

Check renal function, electrolytes and blood pressure at baseline. Repeat after one week (high risk patients) or 2 to 4 weeks (standard monitoring).

- Estimate glomerular filtration rate (GFR) by calculating creatinine clearance (see below).
- Check electrolytes, with particular attention to hyperkalaemia which may occur in the absence of marked renal dysfunction.
- Monitor for marked weight gain or increased oedema.
- Ask your patient to weigh themselves daily and to report an increase in weight of 1.5kg or more over 24 hours.
- Monitor for signs and symptoms of GI complications.
- Measure complete blood count and liver function and repeat at least once a year.

Calculate creatinine clearance (Cl_{cr}) in mL/min using Cockcroft-Gault equation

Males:

$$\text{Creatinine Clearance (ml/minute)} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{0.815 \times \text{serum creatinine (micromol/L)}}$$

Females:

as above then multiply result by 0.85

†† The prescriber must certify that the patient satisfies criteria set out in the Pharmaceutical Benefits Schedule.

Emerging Issues



At the time of publication, the majority of evidence of thrombotic risk has been for the selective COX-2 NSAIDs. However, knowledge of the role of the cyclo-oxygenases in thrombosis and of the cardiovascular safety of NSAIDs is not fully understood.²⁰

There have been suggestions that NSAIDs, in particular ibuprofen, may inhibit the anti-platelet effect of aspirin. However, reports are conflicting and further trials are required before recommendations can be made.

For the latest news:

For general advice contact NPS Medicines Line on 1300 633 424 or see the webpage at: <http://www.nps.org.au/>

What to tell my patient

- Instruct patients on how to use paracetamol appropriately and discuss alternative ways to manage pain.
- Explain that anti-inflammatory medicines can affect the heart by increasing fluid and salt retention, and that they can cause or worsen heart and kidney disease.
- Advise patients to stop the NSAID and contact you immediately if they notice sudden weight gain, swollen feet or ankles, increased tiredness or breathlessness, gastrointestinal problems (e.g. black stools or dark, coffee-coloured vomit) or any other unwanted effects.
- For diabetic patients, emphasise their increased risk of cardiovascular & kidney problems, which can be further increased by the use of NSAIDs.
- Encourage patients to discuss with you their use of over-the-counter medicines, including those for pain or arthritis e.g. paracetamol, ibuprofen.
- Advise that lifestyle interventions (physical activity, maintaining a healthy bodyweight and healthy eating) are life-long.

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