

Oral NSAIDs – An Update

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- There is considerable variation in individual response and tolerance to NSAIDs, but little difference in anti-inflammatory activity.
- All NSAIDs should be avoided if possible in patients with a history of vascular disease, a high risk of cardiovascular disease (CVD), or gastrointestinal (GI) risk factors.
- Treatment choice depends on individual response, risk factors and adverse effects, particularly GI and cardiovascular (CV) complications.
- The lowest effective dose to control the patient's symptoms, for the shortest duration possible, should be used.
- The preferred non-selective NSAIDs are low dose ibuprofen or naproxen, in combination with a proton pump inhibitor (PPI) depending on GI risk.

Introduction

Oral non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of arthritis and other painful conditions. The NHSGGC oral anti-inflammatory guideline has been updated to reflect the most recent evidence.¹

In 2005 and 2006, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) reviewed NSAIDs in relation to possible CV risks, GI side effects and serious skin reactions. At this time, they concluded that the overall benefit-risk balance of these medicines was positive, but a small increased CV risk could not be excluded. As the data were limited, the CHMP suggested that the European commission fund independent epidemiological studies on the safety of NSAIDs in order to generate robust evidence for the Committee's decision making. The safety of non-steroidal anti-inflammatory drugs (SOS) project was set up, with the aim of assessing and comparing the risk of CV and GI events with NSAIDs. The accumulated findings from published studies and the results of the SOS form the basis of the CHMP review that was published in October 2012.²

The CHMP concluded that the latest evidence confirms findings from the 2005 and 2006 reviews. They report a small but consistent increase in the risk of cardiovascular side effects with diclofenac, compared with other NSAIDs. To follow-on from this review, the

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) are in the process of assessing the available data on diclofenac and will consider the need for updated treatment advice, which should be available in 2013.²

Efficacy

Conventional non-selective NSAIDs have a similar analgesic efficacy.^{3,4} Single dose trials have shown there is no significant difference in post-operative analgesia between diclofenac 50 mg and ibuprofen 400 mg.⁵ Treatment of choice depends on individual response, risk factors and adverse effects, particularly GI and CV complications.

Safety

The lowest effective dose for the shortest duration possible should be used to control the patient's symptoms and minimise adverse effects.^{6,7}

GI and CV side effects are of particular concern.

GI Safety

The use of NSAIDs is associated with around a fourfold increase in the incidence of severe upper GI ulcer complications compared to non-users of NSAIDs.³ Risk factors for NSAID induced GI adverse effects include:^{3,4,8,9}

- Age ≥ 65 years
- History of gastroduodenal ulcer, perforation or GI bleeding
- Concomitant medication known to increase risk of upper GI adverse effects e.g. aspirin, anticoagulants, corticosteroids, SSRIs
- Serious co-morbidity
- Prolonged duration of NSAID use
- High dose NSAID use
- Lifestyle factors possibly contribute to risk – alcohol consumption and cigarette smoking.

NSAIDs vary in their propensity to cause serious GI effects. Low dose ibuprofen and the COX-2 selective inhibitors are associated with the lowest risk; naproxen and diclofenac are associated with an intermediate risk of GI side effects.⁷

CV Safety

The updated EMA review was published in October 2012. Most of the data related to the three most

widely used NSAIDs: diclofenac, ibuprofen and naproxen. The CHMP concluded that current treatment advice adequately reflects the knowledge regarding the safety and efficacy of naproxen and ibuprofen.² Diclofenac had a consistent but small increase in the risk of CV side effects compared with other NSAIDs, similar to the risks of the COX-2 inhibitors.

For non-selective NSAIDs, the risk of arterial thrombotic events is increased with diclofenac (150 mg daily) and ibuprofen (2.4 g daily). Naproxen (1 g daily) is associated with a lower thrombotic risk, and low doses of ibuprofen (1.2 g daily or less) have not been associated with an increased risk of myocardial infarction.⁷

Other side effects

Other serious side effects of all NSAIDs include hypersensitivity (e.g. asthma), hepatotoxicity and nephrotoxicity. Hepatotoxicity is an extremely rare and unpredictable side effect associated with NSAIDs, including those that are COX-2 selective. It has been suggested the risk of hepatotoxicity is more common with diclofenac and sulindac, and lowest with ibuprofen.¹⁰

NSAIDs inhibit prostaglandin induced vasodilation, and this can lead to reduced renal blood flow, which rarely precipitates renal failure. The non-selective NSAIDs inhibit two isoforms of the enzyme cyclo-oxygenase (COX) – COX-1 and COX-2. Both COX-1 and COX-2 are involved in regulation of renal blood flow, and there is no advantage between COX-2 selective NSAIDs and non-selective NSAIDs in terms of renal toxicity.³

All NSAIDs are contraindicated in patients with active gastro-intestinal ulceration or bleeding, and severe cardiac failure. NSAIDs should be avoided if possible or used with caution in patients with renal impairment.⁷

Place in Therapy

Refer to the NHSGGC guideline for full information.¹

What NSAID should I prescribe if indicated?

In NHSGGC, the non-selective NSAIDs that are on the Formulary are ibuprofen, naproxen and diclofenac. The preferred non-selective NSAIDs are naproxen or low dose ibuprofen (1.2 g daily); diclofenac is no longer a preferred drug due to CV risk.¹

If my patient has GI risk factors what NSAID should I prescribe?

If the patient has GI risk factors, a non-selective NSAID (naproxen or low dose ibuprofen) can be used with extreme caution, in combination with a PPI.¹

If my patient has vascular disease or a high risk of CVD what NSAID should I prescribe?

If the patient has a history of vascular disease or high risk of CVD, NSAIDs should be avoided if possible. If an NSAID must be used, naproxen is the preferred drug. In these patients, NSAIDs should be used with extreme caution and in combination with a PPI.¹

Is there any difference in GI adverse effects with naproxen enteric coated (EC) tablets and naproxen standard release tablets?

Naproxen EC and standard naproxen have both been shown to be efficacious and well tolerated in rheumatoid arthritis and osteoarthritis.¹¹ Enteric coatings generally do not protect against systemic adverse effects. It may be that the EC formulation causes fewer GI side effects however literature is conflicting. If patients have GI risk factors, they should be prescribed a PPI in combination with an NSAID. An EC preparation alone may not provide sufficient protection against systemic effects.

What PPI should I prescribe?

The NHSGGC Formulary PPIs are either omeprazole (20 mg daily) or lansoprazole (15-30 mg daily).¹

What if my patient is on low dose aspirin and needs an NSAID?

It is recommended that other analgesics should be considered before adding in an NSAID. The combination of aspirin with NSAIDs increases the risk of upper GI complications and they should only be prescribed together if absolutely necessary.^{7,12} A PPI is indicated in these patients if an NSAID is co-prescribed.¹

There is inadequate evidence of an interaction between NSAIDs and low dose aspirin, although it has been suggested that all non-selective NSAIDs antagonise the cardio-protective effects of low dose aspirin.¹³ Local guidance states aspirin should be taken 1 hour before ibuprofen if co-administration is necessary.^{1,14}

Are the CV risks present if my patient only needs short term treatment with NSAIDs?

A cohort study has shown in the healthy population the absolute risk of CV events was very low, however a dose-dependent increase in CV risk was seen with NSAIDs, especially diclofenac, even in the short term.¹⁵ Another cohort study in patients with prior MI reported that the harmful CV effects of NSAIDs were evident after short-term use.¹⁶ It is therefore recommended that NSAIDs are prescribed for the shortest duration possible.¹

Can I prescribe an NSAID if my patient is elderly?

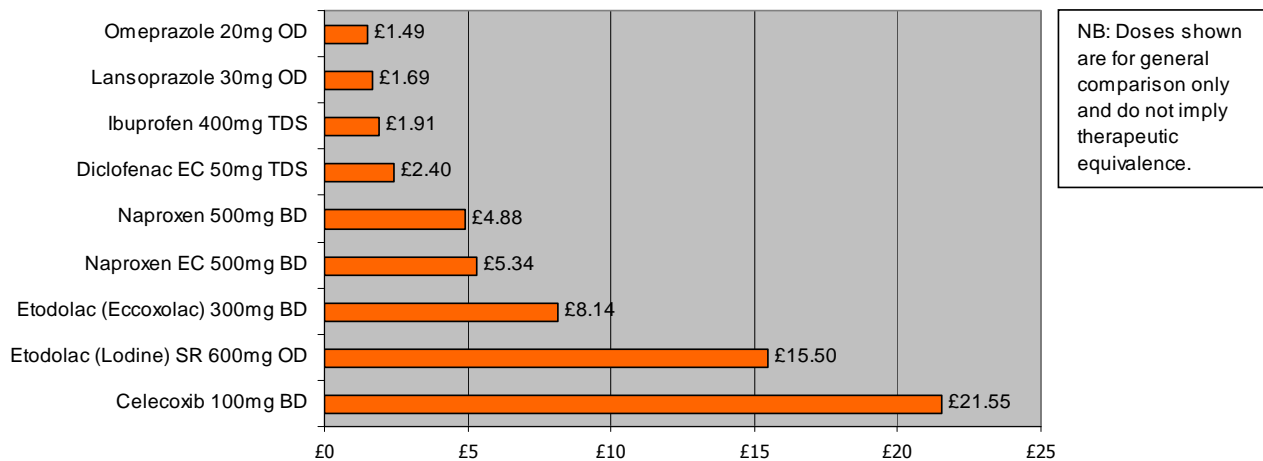
The risk of serious GI toxicity is higher in the elderly and therefore, should be avoided if possible. NSAIDs should be used with caution in the elderly due to the

risk of serious side effects.⁷ If NSAID treatment is necessary a PPI should be used to help prevent ulcers.¹ The risk of NSAID induced renal toxicity is increased in those aged over 60 years and in those with pre-existing renal disease.¹²

What about the COX-2 selective inhibitors?

COX-2 selective inhibitors have been associated with an increased risk of CV events.⁸ The COX-2 selective inhibitors included on the NHSGGC formulary are celecoxib and etodolac. They are only indicated for use in patients with a high GI risk and low CV risk where a non-selective NSAID and PPI is unsuitable and an anti-inflammatory agent is desirable.¹

Cost for 28 days treatment (Scottish Drug Tariff/MIMS January 2013)



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