

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 use of 'as required' NSAIDs should be considered where appropriate.
- The preferred non-selective NSAIDs are ibuprofen or naproxen. A proton pump inhibitor (PPI) may be required depending on GI risk.

Introduction

Oral non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of arthritis and other painful conditions. Refer to the NHSGGC oral non-steroidal anti-inflammatory guideline available on StaffNet for further information.¹

Background to Safety Issues

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 the time, they concluded that the overall benefit-risk balance of these medicines was positive, but a small increased CV risk could not be excluded.² As the data were limited, the CHMP therefore 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 which was published in October 2012.²

The CHMP concluded that the latest evidence confirmed findings from the 2005 and 2006 reviews. They reported a small but consistent increase in the risk of CV side effects with diclofenac, compared with

other NSAIDs. Following this review, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) assessed the available data on diclofenac and concluded that the CV risk with diclofenac is similar to that of the selective COX-2 inhibitors. As a result, diclofenac is contraindicated in patients with established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.³

In 2015, PRAC assessed further evidence on the CV safety of ibuprofen and concluded that high daily doses of ibuprofen (≥ 2.4 g daily) are associated with an increased risk of CV events which may be similar to COX-2 inhibitors and diclofenac. This review confirmed the findings of previous EU reviews and does not suggest that ibuprofen at low doses (≤ 1.2 g daily) is associated with an increased risk of CV events.⁴ The MHRA confirmed these findings in a drug safety update bulletin in June 2015.⁵

Efficacy

Conventional non-selective NSAIDs have a similar analgesic efficacy.⁶ Single dose trials have shown there is no significant difference in post-operative analgesia between diclofenac 50mg and ibuprofen 400mg.⁷ 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.^{8,9} The use of 'as required' NSAIDs should be considered where appropriate. 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.¹⁰ All NSAIDs are contraindicated in patients with active gastro-intestinal ulceration or bleeding.⁹ Risk factors for NSAID induced GI adverse effects include:^{6,10,11,12}

- 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 – alcohol consumption and cigarette smoking, possibly contribute to risk

All NSAIDs are associated with serious GI toxicity and the risk is higher in the elderly. NSAIDs vary in their propensity to cause serious GI effects. Of the non-selective NSAIDs, naproxen and diclofenac are associated with an intermediate risk of serious GI side effects and low dose ibuprofen is associated with the lowest risk. COX-2 selective inhibitors are associated with a lower risk of serious upper gastrointestinal side-effects than non-selective NSAIDs.⁹

CV Safety

All NSAIDs are contraindicated in severe cardiac failure.⁹

As described in the introduction, diclofenac has a consistent but small increase in the risk of CV side effects compared with other NSAIDs, similar to the CV risks of the COX-2 inhibitors. Diclofenac is therefore contraindicated in patients with established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.³

Of the other non-selective NSAIDs, high dose ibuprofen (≥ 2.4 g daily) is associated with an increased risk of CV events. CV events may be higher in patients with cardiovascular disease (CVD), and high ibuprofen doses should be avoided in this population. Similarly, high daily doses of ibuprofen should not be recommended to patients with risk factors for CVD.⁴

A European case-control study was published in 2016 as part of the SOS project. This study reported that current use of any NSAID (use in preceding 14 days) was associated with a 19% increased risk of hospital admission for heart failure compared with past use of any NSAIDs (use > 183 days in the past). The risk varied between NSAIDs and was dose dependent. The risk was doubled with very high doses (≥ 2 defined daily dose equivalents) of diclofenac, etoricoxib, indometacin and piroxicam.¹³

Following publication of the EU reviews, a Bayesian meta-analysis of almost 450000 individuals from Canadian and European databases was published in 2017. This meta-analysis reported that current use of all NSAIDs was associated with an increased risk of myocardial infarction (MI) compared with non-use in the preceding year. The onset of risk occurred in the first week of NSAID use and the risk was greatest during the first month and with the use of higher daily doses (of celecoxib >200mg, diclofenac >100mg, ibuprofen >1200mg, and naproxen >750mg). With use longer than one month, the risks

did not appear to exceed those associated with shorter durations.¹⁴

Another recent Danish case-control study reported that the use of any NSAID (use in preceding 30 days) was associated with an increased risk of cardiac arrest. The result was primarily driven by an increased risk with diclofenac and ibuprofen. No information on doses was provided.¹⁵

These recent studies confirm the need to consider individual risk factors prior to initiating patients on an NSAID. Avoid NSAIDs if possible in patients with CVD.

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.¹⁶ NSAIDs should therefore be used with caution in patients with hepatic impairment and are contraindicated in severe liver disease.⁹

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.¹² NSAIDs should be avoided if possible or used with caution in patients with renal impairment.⁹ Concomitant use of NSAIDs and other nephrotoxics (e.g. ACE inhibitors, Angiotensin Receptor Blockers (ARBs), diuretics and lithium should be avoided where possible to avoid the risk of acute kidney injury (AKI). Also note, when NSAIDs are given with lithium there is an increased risk of lithium toxicity as lithium excretion is reduced.⁹

Place in Therapy

Refer to the NHSGGC oral non-steroidal anti-inflammatory guideline on StaffNet for full information.¹

What NSAID should I prescribe if indicated?

In NHSGGC, the non-selective NSAIDs of choice are naproxen or ibuprofen.¹

If my patient has GI risk factors (without a history of vascular disease or low risk of CVD) what NSAID should I prescribe?

Ibuprofen, with a PPI may be used with extreme caution.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 or low dose ibuprofen (up to 1.2g daily) may be used in combination with a PPI with extreme caution.¹

Does ibuprofen 1.8g daily infer an additional CV risk similar to a dose of 2.4g daily?

In 2015, the EMA's PRAC review of ibuprofen, reported that there are no or limited data on the arterial thrombotic risk of ibuprofen at doses between 1.2g and 2.4g daily and therefore it cannot be determined exactly how the risk changes over this dosage range. It is likely, however, that there is a dose-dependent increase in risk with increasing doses between 1.2g and 2.4g daily.⁴

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.¹⁷ Enteric coatings generally do not protect against systemic adverse effects, however it may be that the EC formulation causes fewer GI side effects though literature is conflicting. If patients have GI risk factors, they should be prescribed a PPI in combination with an NSAID, as an EC preparation may not provide sufficient protection against systemic effects.¹

What PPI should I prescribe for gastroprotection?

The NHSGGC Formulary PPIs are either omeprazole 20mg daily or lansoprazole 15-30mg daily.^{1,18}

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

If patients are taking low dose aspirin, it is recommended that alternative 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.^{9,19} A PPI is indicated in these patients if an NSAID is co-prescribed.¹

It has also been suggested that all non-selective NSAIDs may antagonise the cardio-protective effects of low dose aspirin, however, there is conflicting evidence for this.²⁰ The potential interaction with ibuprofen and aspirin may be related to the timing of administration and it has been suggested that taking ibuprofen two hours after aspirin may negate this effect, however, evidence is limited to support this practice. Evidence for the interaction is limited to pharmacokinetic (PK) and pharmacodynamic (PD)

studies. These studies have shown that ibuprofen inhibits the antiplatelet effect of aspirin when it is administered concurrently or 2 hours before aspirin, however, there are no *in vivo* data to support the practice of dosing ibuprofen 2 hours after aspirin. The PK/PD data do not provide information on what impact the order and timing of dosing would have if patients are taking multiple doses of ibuprofen on a daily basis.⁴ Overall, the impact of using an NSAID on the antiplatelet effect of low dose aspirin remains uncertain. The possibility that this long term combination may reduce the cardioprotective effects of low dose aspirin cannot be excluded. Available data is insufficient to justify specific dose order and time interval for these patients.

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.²¹ Another cohort study in patients with prior MI reported that the harmful CV effects of NSAIDs were evident after short-term use.²²

The EMA's PRAC review of ibuprofen in 2015 concluded that the effect of ibuprofen treatment duration on CV risk has not been extensively studied and is therefore uncertain.⁴ However, since then further evidence published in 2017 has shown that short term use of ibuprofen was associated with an increased risk of cardiac arrest¹⁵ and in another study all NSAIDs exhibited a rapid onset of risk for MI in the first week of use.¹⁴ Therefore the risk of CV events should be borne in mind even when intended for short term use. Individual patient risk factors should be considered prior to initiating patients on an NSAID. Avoid NSAIDs if possible in patients with CVD.

Can I prescribe an NSAID if my patient is elderly?

The risk of serious GI toxicity associated with NSAIDs is higher in the elderly and therefore, they should be avoided if possible. If prescribed in the elderly, NSAIDs should be used with caution due to the risk of serious side effects and fatalities and the use of 'as required' doses should be considered where appropriate.¹⁰ If NSAID treatment is considered necessary a PPI should be used to help prevent ulcers.¹ The risk of NSAID induced renal toxicity is increased in those aged 60 years or over and in those with pre-existing renal or hepatic disease.¹⁹

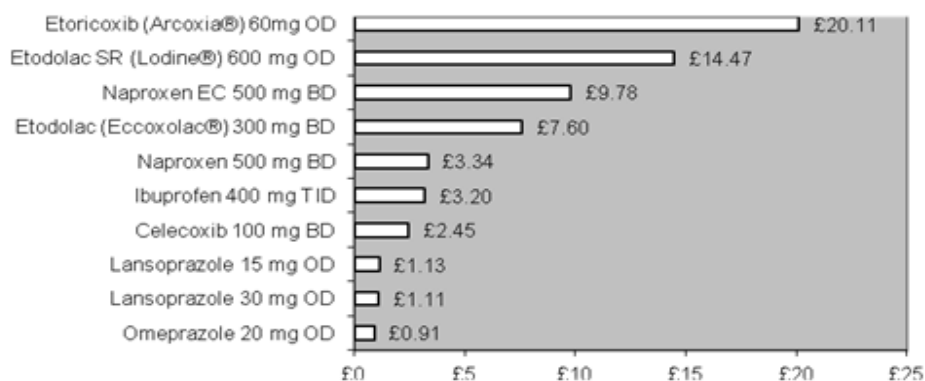
What about the COX-2 selective inhibitors?

COX-2 selective inhibitors have been associated with an increased risk of CV events.¹⁰ The COX-2 selective inhibitors included on the NHSGGC formulary are celecoxib and etoricoxib.¹⁸ Etodolac is also on the formulary¹⁸ and is believed to be selective for the inhibition of COX-2.²³ The COX-2 selective inhibitors

and etodolac 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. Etoricoxib has an additional restriction for the use in acute gout only.¹⁸

Cost for 28 days treatment (Scottish Drug /eMIMS Aug 2017)



NB: Doses shown are for general comparison only and do not imply therapeutic equivalence.

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