

SAFER MEDICATION USE

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NON-SELECTIVE NSAIDS AND THROMBOTIC RISK

Further evidence has been published indicating that some non-selective NSAIDs may be associated with a small increase in risk of thrombotic events such as MI and stroke, particularly when used long term in high doses. Most evidence relates to diclofenac, ibuprofen and naproxen compared to COX-II inhibitors. Diclofenac in high doses appears to carry the greatest risk and naproxen the lowest. High dose ibuprofen may also confer a small thrombotic risk; whilst low dose ibuprofen is not associated with an increased risk. While the overall benefit-risk remains favourable, all NSAIDs (including COX-II inhibitors) should be used only where there is a clear indication, at the lowest effective dose and for the shortest time period, reviewing the need for long-term treatment periodically. Ibuprofen (low dose) remains a suitable first choice NSAID, with naproxen as an alternative.

Background

Cyclo-oxygenase-2 (COX-II) selective non-steroidal anti-inflammatory drugs (NSAIDs) (rofecoxib, celecoxib and etoricoxib) are associated with a small increase in cardiovascular (CV) events, including myocardial infarction (MI) and stroke.^{1,2,3} The thrombotic risk of non-selective NSAIDs was discussed in a previous Drug Update in May 2006.⁴ Recently published data adds weight to earlier assessments of CV safety of non-selective NSAIDs.

What is the new evidence around cardiovascular risks?

In a recent systematic review, diclofenac was shown to have the highest risk of CV events, whilst naproxen was associated with no apparent increase in risk.⁵ A detailed discussion of the results is available in Rapid Appraisal No. 13.⁶

A meta-analysis has indicated that COX-II inhibitors are associated with a small increased incidence of serious vascular events (mainly due to an increased risk of MI) compared with placebo and naproxen, but not with other non-selective NSAIDs.⁷ When non-selective NSAIDs were compared with placebo, similar levels of increased risk to those observed with COX-II inhibitors were seen with diclofenac and high dose ibuprofen (2400 mg daily) but not with naproxen (rate ratios 1.63 [95% CI; 1.12 to 2.37], 1.51 [0.96 to 2.37], 0.92 [0.67 to 1.26] respectively.)

Further evidence for an increased CV risk with diclofenac comes from recent studies. The MEDAL programme suggested a small thrombotic risk for diclofenac (150mg daily), similar to that of licensed doses of etoricoxib.⁸ The use of diclofenac is associated with about four extra CV events (mainly non-fatal and fatal MI) for every 1,000 patients treated for one year,⁸ which is consistent with the increased risk for COX-II inhibitors.⁷ Secondly, an epidemiological study of NSAID use following acute MI demonstrated a dose-related excess mortality associated with the short term use of diclofenac, and to a lesser extent ibuprofen, compared with non-exposure to NSAIDs.⁹

Some in-vitro studies have shown diclofenac to have similar COX-II selectivity to celecoxib, whereas ibuprofen and

naproxen exhibit little or no COX-II selectivity.¹⁰ The relevance of COX-II selectivity as a sole determinant of CV risk is unclear. In the absence of study outcomes, COX-II selectivity cannot be used to predict the CV risk profile of other non-selective NSAIDs e.g. meloxicam and etodolac.

A recently published RCT investigating the reduction in incidence of Alzheimer's disease with naproxen or celecoxib suggested that low dose naproxen may have an increased CV and cerebrovascular risk (hazard ratios 1.63 [95% CI; 1.04 to 2.55] and 1.10 [0.67 to 1.79] respectively.)¹¹ However data from this trial must be interpreted with caution as the trial was not sufficiently powered or designed to examine CV safety; in addition the study was stopped early due to mounting fears over increased CV risks of COX-II inhibitors. Overall the evidence for naproxen (1000 mg daily) shows that it is associated with a lower thrombotic risk than COX-II inhibitors.⁷

It has been suggested that ibuprofen may interfere with the anti-platelet activity of low dose aspirin, although the clinical relevance of this has not been clearly demonstrated in epidemiological and clinical trials.¹² Recent data indicated the CV effects of ibuprofen did not differ among aspirin users and non-users.⁵ This was also true for COX-II inhibitors.⁷ However, with other non-selective NSAIDs the effects of concomitant aspirin on CV risks were inconsistent.⁵

What did the MHRA and EMEA conclude from their recent review in October 2006?

Both the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Authority (MHRA) have issued guidance on the use of non-selective NSAIDs. They concluded diclofenac (150 mg daily) and ibuprofen (2400 mg daily) may be associated with a small increased risk of thrombotic events when used for long-term treatment.^{13,14} Low dose ibuprofen (1200 mg daily or below) is not associated with an increased risk of MI.¹³ A small increased thrombotic risk cannot be excluded for other NSAIDs. However, the overall benefit-risk balance for non-selective NSAIDs remains favourable; on the basis of overall safety and taking into account the patient's individual risk factors.¹⁴

Implications for practice.

- NSAIDs should be used at the lowest effective dose, for the shortest time possible to minimise adverse effects. The need for long-term treatment should be reviewed periodically.¹³
- When NSAID therapy is indicated, the CV and gastrointestinal (GI) risks should be taken into account.¹³ Differences in GI and other adverse effects, plus the use of gastroprotective agents have been discussed in a previous Drug Update.⁴
- Ibuprofen at low doses (<1200 mg daily) is the agent of first choice. Naproxen can be considered as an alternative.
- Patients prescribed diclofenac (150 mg daily) or high dose ibuprofen (2400 mg daily) should be reviewed, bearing in mind drug safety profile, patients' individual risk factors and patient preference, before considering switching to an alternative.^{13,14}

- Combination of NSAIDs and low dose aspirin (and possibly other antiplatelet drugs) significantly increase the GI risks. This combination should be avoided unless absolutely necessary;¹³ in patients at high risk of GI bleed, use of a gastroprotective agent (e.g. proton-pump inhibitor) may be appropriate.

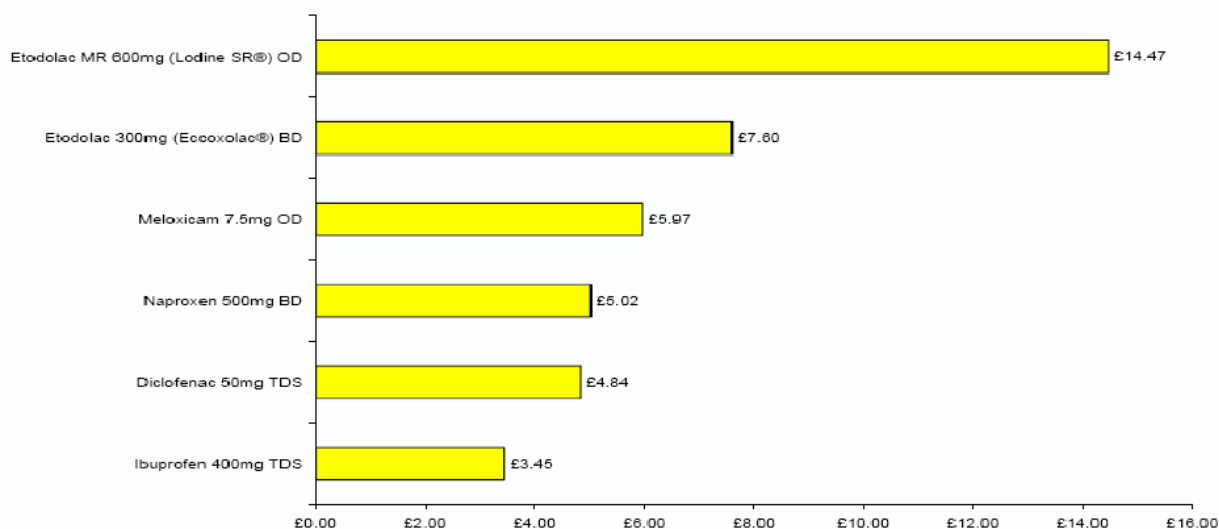
When should adverse reactions be reported to the CHM?

All serious suspected adverse reactions to any NSAID or COX-II inhibitor should be reported to the Commission for Human Medicines (CHM) via the Yellow Card Scheme. (www.MHRA.gov.uk). This includes CV events suspected to be related to NSAID use.

All adverse reactions to black triangle drugs (which include the COX-II inhibitors etoricoxib, lumiracoxib and parecoxib¹⁵) should be reported, as should all suspected serious reactions to any drug, herbal or OTC medicine.

The Yellow Card Centre Northern and Yorkshire can provide support and guidance on any adverse reaction related enquiry or completion of a Yellow Card.

Cost of 28 days treatment (Drug Tariff March 2007)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT - randomised controlled trial, MA-meta analysis, R-review, ES-epidemiological study

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