

DRUG UPDATE

No.5

May 2006

NON-SELECTIVE NSAIDS AND CARDIOVASCULAR RISK

The cardiovascular (CV) safety of non-selective NSAIDs has been examined in the light of the recognised risks of COX-2 selective NSAIDs. Randomised controlled trial evidence of increased CV risk has led to prescribing restrictions for all COX-2 selective NSAIDs. Studies examining a possible link between non-selective NSAIDs and thrombotic events have produced inconsistent results, but a small increase in risk of cardiovascular events cannot be excluded. However, the evidence is insufficient to change the balance of risks and benefits of non-selective NSAIDs and no changes to current prescribing practice have been recommended. All NSAIDs should be used only where there is a clear indication, at the lowest effective dose and for the shortest time period, employing intermittent therapy where possible.

What are non-selective NSAIDs?

Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) are used widely for the treatment of acute and chronic pain.

Commonly used examples are ibuprofen, diclofenac and naproxen. Less commonly prescribed non-selective agents include indometacin, ketorolac, nabumetone and piroxicam.

What are the cardiovascular risks?

Randomised controlled trials (RCTs) have shown an increase in cardiovascular events, including myocardial infarction and stroke, associated with several COX-2 selective NSAIDs (rofecoxib, celecoxib and etoricoxib).^{1,2,3} Event rates in patients taking etoricoxib, celecoxib and lumiracoxib were not significantly different (RR=1.49, 0.95, 1.18 respectively)^{3,4,5} compared with non-selective NSAIDs.

Twelve published observational studies have considered the risk of cardiovascular events with non-selective NSAIDs.⁶⁻¹⁷ A summary of the risk estimates obtained from these studies is available http://www.nyrdtc.org/GMMMMG/Groups/Publications/GM_DUD/GM_DU_CV_risk_table.pdf. The results are inconsistent and it is not currently possible to draw conclusions as to whether commonly used non-selective agents increase risk, or if the risk varies according to the agent used.

Platelet studies have suggested that ibuprofen can interfere with the anti-platelet effect of aspirin.¹⁸ However, a clinically important effect has not been clearly demonstrated in epidemiological studies or clinical trials.¹⁸

The majority of available observational information relates to the most commonly used non-selective NSAIDs (ibuprofen, diclofenac and naproxen). It is worth noting that NICE classified meloxicam and etodolac as COX-2 selective agents whereas the MHRA included them in their review of

non-selective agents. Irrespective of their COX-2 selectivity, the absence of data for these and other NSAIDs should not be interpreted as a lack of cardiovascular risk.

Other adverse effects associated with all NSAIDs include raised blood pressure as well as precipitation of heart and renal failure.¹⁹

What did the MHRA conclude from its recent review?

The Medicines and Healthcare Regulatory Authority (MHRA) has issued guidance on the use of non-selective NSAIDs, which states:^{18,20}

- The evidence for non-selective NSAIDs is less clear than that for COX-2 inhibitors in relation to increased thrombotic events
- The evidence is insufficient to change the balance of risks and benefits of non-selective NSAIDs and no changes to current prescribing practice have been recommended.

When should they be used?

Currently available evidence does not enable one non-selective NSAID to be recommended over another with respect to cardiovascular risk. However, there is evidence of differences in gastrointestinal (GI) risks at commonly used doses. These are summarised in the table below.²¹

Non-selective NSAID	Pooled relative risk of upper GI bleed compared with placebo (95% Confidence Interval)	No. of studies
Ibuprofen	1.9 (1.6-2.2)	9
Diclofenac	3.3 (2.8-3.9)	11
Naproxen	4.0 (3.5-4.6)	12
Indometacin	4.6 (3.8-5.5)	10
Ketoprofen	4.6 (3.3-6.4)	6
Piroxicam	6.3 (5.5-7.2)	12

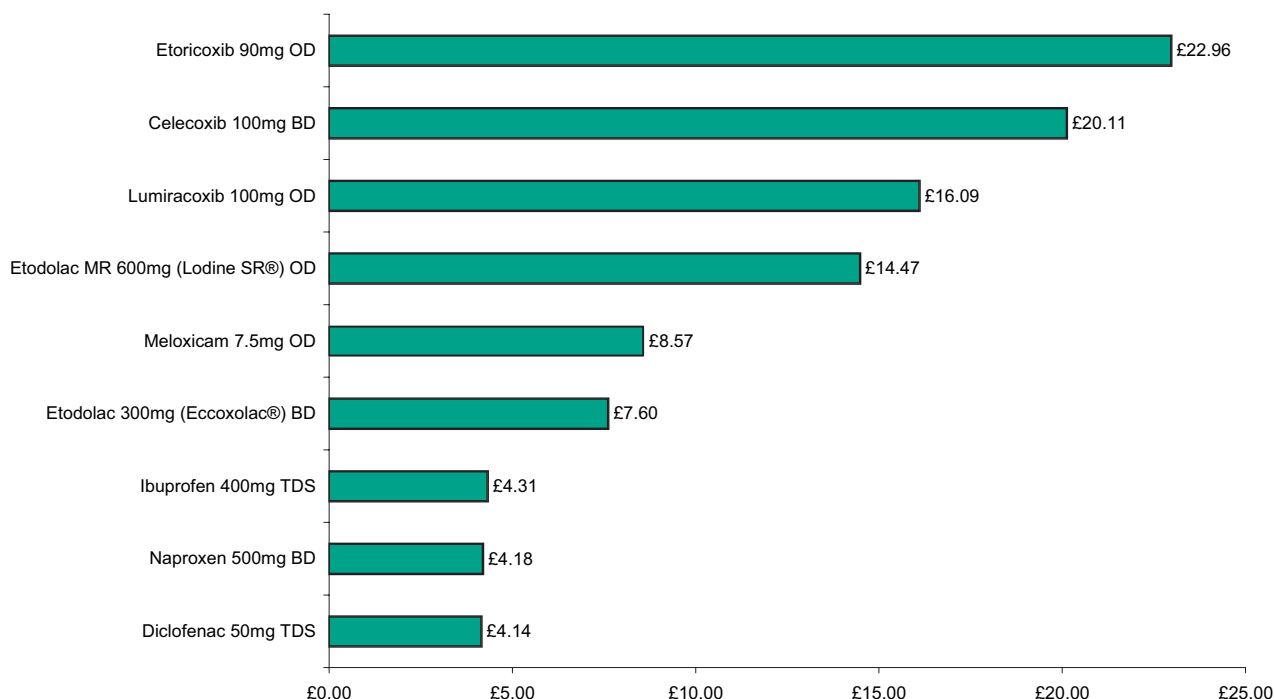
If NSAID therapy is necessary, a non-selective NSAID with a low risk of GI toxicity (e.g. ibuprofen) should be the agent of first choice. NSAIDs should be used for the shortest time possible and at the lowest effective dose to minimise adverse effects. In patients at high risk of GI bleed, use of a gastroprotective agent (e.g. proton-pump inhibitor) may be appropriate if a non-selective NSAID is to be prescribed.²²

What other options are there?

Simple analgesia (e.g. paracetamol, codeine) and non-drug interventions may be appropriate for patients requiring pain relief.²²

How much do NSAIDs cost?

Approximate costs for 28 days treatment (Drug Tariff/eMIMS April 2006)



REFERENCES

- Juni P et al. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004;364:2021-9 (MA)
- Solomon SD et al. Cardiovascular risks associated with celecoxib in a clinical trial for colorectal adenoma prevention. *NEJM* 2005;352(11):1071-80 (RCT)
- Adlington S et al. Systematic review and meta-analysis of the risk of major cardiovascular events with etoricoxib therapy: a RCT. *NZ Med J* 2005;118(1223):U1684 (Abs)
- Silverstein FE et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: A randomised controlled trial. *JAMA* 2000;284(10):1247-55 (RCT)
- Farkouh ME et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004;364:675-84 (RCT)
- Ray WA et al. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. *Lancet* 2002;359(9301):118-23 (CT)
- Garcia Rodriguez LA. The effect of NSAIDs on the risk of coronary heart disease: fusion of clinical pharmacology and pharmacoepidemiologic data. *Clin Exp Rheum* 2001;19(6 suppl 25):S41-4 (R)
- Garcia Rodriguez LA et al. Non steroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population. *Circulation* 2004;109:3000-6 (CT)
- Graham DJ et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 2005;365:475-81 (CT)
- Hippisley-Cox J et al. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 2005;330:1366-73 (CT)
- Johnsen SP et al. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib and other NSAIDs. *Arch Intern Med* 2005;165:978-84 (CT)
- Kimmel SE et al. The effects of non-selective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. *J Am Coll Cardiol* 2004;43(6):985-90 (CT)
- Mamdani M et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. *Arch Intern Med* 2003;163(4):481-6 (CT)
- Ray WA et al. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002;360(9339):1071-3 (CT)
- Schlienger RG et al. Use of nonsteroidal anti-inflammatory drugs and the risk of first-time acute myocardial infarction. *Br J Clin Pharmacol* 2002;54:327-32 (CT)
- Solomon DH et al. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. *Arch Intern Med* 2002;162:1099-104 (CT)
- Watson DJ et al. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. *Arch Intern Med* 2002;162:1105-10 (CT)
- Medicines Healthcare Regulatory Authority. Cardiovascular safety of non-steroidal anti-inflammatory drugs- overview of key safety data. August 2005. <http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con2022711.pdf> (last accessed 10/04/06)
- BMA and RPSGB. British National Formulary – Section 10.1.1 Non-steroidal anti-inflammatory drugs. No. 50 2005 (September)
- Medicines Healthcare Regulatory Authority. Letter to healthcare professionals including question and answers August 2005. <http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con2022710.pdf> (last accessed 10/04/06)
- Hernandez-Diaz S et al. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation. *Arch Intern Med* 2000;160(14):2093-9 (MA)
- Former Northern and Yorkshire Regional Drug and Therapeutics Centre. COX-2 selective inhibitors. Drug Update No. 41 (April 2005) (R)

KEY MA-meta analysis, RCT-randomised controlled trial, Abs-Abstract, CT-controlled trial, R-review