COX-2 selective non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis

Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation

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Executive summary

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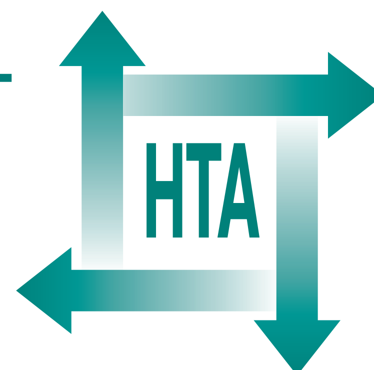

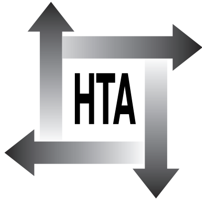

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Executive summary

Objectives

The objectives were to review the clinical effectiveness and cost-effectiveness of cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs) (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis (OA) and rheumatoid arthritis (RA).

Epidemiology and background

OA and RA are common conditions that cause pain, disability and reduced physical function. Treatment costs of arthritis to the NHS are substantial, and rising. NSAIDs are effective treatments for symptomatic relief of arthritis. COX-2 selective NSAIDs have the potential for maintaining symptomatic benefits but also may reduce the adverse gastrointestinal (GI) effects associated with non-selective NSAIDs.

Methods

Clinical effectiveness

Systematic reviews of randomised controlled trials (RCTs) were undertaken. Electronic databases were searched up to November 2003. Industry submissions to NICE in 2003 were also reviewed. Meta-analyses were undertaken for each COX-2 selective NSAID compared with placebo and non-selective NSAIDs.

Cost-effectiveness

A new modelling exercise was undertaken that used the Markov model developed originally by Maetzel and colleagues (2001) as a starting point. The model was designed to run in two different forms: the 'full Assessment Group Model (AGM)', which includes an initial drug switching cycle, and the 'simpler AGM', where there is no initial cycle and no opportunity for the patient to switch NSAID.

The main data sources for clinical parameters were the meta-analysis results from this systematic review. Where necessary, other sources have been used.

Results

Clinical effectiveness

Etodolac

Twenty-nine RCTs were included. Studies compared etodolac with either placebo or non-selective NSAIDs. Compared with non-selective NSAIDs (naproxen, piroxicam, diclofenac, indomethacin, tenoxicam, ibuprofen, nabumetone or nimesulide), etodolac (600–1000 mg/day) was equally efficacious and of equivalent or superior gastrointestinal (GI) tolerability. Pooled analysis did not show a difference in complicated upper gastrointestinal (UGI) events (POBs) [relative risk (RR) 0.39, 95% confidence interval (CI) 0.12 to 1.24]. Etodolac was associated with significantly fewer clinical UGI events (PUBs) (RR 0.32, 95% CI 0.15 to 0.71). No myocardial infarctions (MIs) were reported.

Meloxicam

Sixteen RCTs were included (plus 11 trials available only in abstract form that were included in sensitivity analysis). Studies compared meloxicam with either placebo or non-selective NSAIDs. Compared with non-selective NSAIDs (naproxen, diclofenac, nabumetone or piroxicam), meloxicam (7.5–22.5 mg/day) was of inferior or equivalent efficacy and superior GI tolerability. Pooled analysis did not show a difference in complicated UGI events (RR 0.56, 95% CI 0.27 to 1.15). Meloxicam was associated with significantly fewer clinical UGI events (RR: 0.53, 95% CI: 0.29 to 0.97). There were insufficient events to comment on MI risk. Inclusion of abstract-only data made no difference to these conclusions.

Celecoxib

Forty RCTs were included. Studies compared celecoxib with placebo, non-selective NSAIDs or other COX-2 selective NSAIDs. Compared with non-selective NSAIDs (naproxen, diclofenac, ibuprofen or loxoprofen), celecoxib (200–800 mg/day) was equally efficacious and of superior GI tolerability. Celecoxib was associated with significantly fewer clinical UGI events (RR 0.55, 95% CI 0.40 to 0.76) and complicated UGI events (RR 0.57, 95% CI 0.35 to 0.95) and a significantly higher risk of MI (RR 1.77, 95% CI 1.00 to 3.11).

▶

Rofecoxib

Twenty-seven RCTs were included. Studies compared rofecoxib with placebo, non-selective NSAIDs, Arthrotec or other COX-2 selective NSAIDs. Compared with non-selective NSAIDs (naproxen, ibuprofen, or nabumetone), rofecoxib (12.5–50 mg/day) was equally efficacious and had superior GI tolerability. Rofecoxib was associated with significantly fewer clinical UGI events (RR 0.43, 95% CI 0.32 to 0.57) and complicated UGI events (RR 0.40, 95% CI 0.23 to 0.70) and a significantly higher risk of MI (RR 2.92, 95% CI 1.36 to 6.28) compared with non-selective NSAIDs.

Etoricoxib

Seven RCTs were included. Studies compared etoricoxib with either placebo or non-selective NSAIDs. Compared with non-selective NSAIDs (naproxen, diclofenac and ibuprofen), etoricoxib (60–120 mg/day) was equally efficacious and of equivalent or superior GI tolerability. Pooled analysis did not show a significant difference in clinical UGI events (RR 0.23, 95% CI 0.05 to 1.08) and complicated UGI events (RR 0.46, 95% CI 0.07 to 3.10). MI events were reported in only one trial (RR 1.58, 95% CI 0.06 to 38.66).

Valdecoxib

Eleven RCTs were included. Studies compared valdecoxib with either placebo or non-selective NSAIDs. In comparison with non-selective NSAIDs (naproxen, diclofenac or ibuprofen), valdecoxib (10–80 mg/day) was equally efficacious and had equivalent or superior GI tolerability. Pooled analysis did not show a significant difference in clinical UGI events (RR 0.20, 95% CI 0.03 to 1.46). Valdecoxib was associated with significantly fewer complicated UGI events (RR 0.43, 95% CI 0.19 to 0.97) and lower risk of MI (RR 0.25, 95% CI 0.06 to 1.00). The latter estimate was based on a total of six MI events and needs to be interpreted with great caution.

Lumiracoxib

Fifteen RCTs were included. Studies compared lumiracoxib with either placebo, non-selective NSAIDs or other COX-2 selective NSAIDs. Compared with non-selective NSAIDs (diclofenac, ibuprofen or naproxen), lumiracoxib (100–1200 mg/day) appeared to be equally efficacious and of significantly superior GI tolerability. Lumiracoxib was associated with significantly fewer clinical UGI events (RR 0.47, 95% CI 0.37 to 0.61) and complicated UGI events (RR 0.34, 95% CI 0.23 to 0.52) and a statistically non-significant increase in clinically confirmed MI risk (RR 1.71, 95% CI 0.86 to 3.37), particularly compared with naproxen. Lumiracoxib at 400 mg/day was associated with significantly increased hepatotoxicity compared with naproxen and ibuprofen.

There is a need for caution in the interpretation of the above meta-analysis results as relatively small numbers of clinical GI and MI events were reported across trials.

Subgroup analyses

Celecoxib appears to reduce clinical GI events and significantly increase MI risk, relative to non-selective NSAIDs, in both aspirin users and non-users. Rofecoxib appears to reduce clinical GI events, relative to non-selective NSAIDs, in both patients with prior GI history and no prior GI history, steroid users and non-users and patients positive and negative for *Helicobacter pylori*. The GI protective effect of lumiracoxib appeared to be reduced in aspirin users. These subgroup analyses are based on small numbers and need confirmation. It is not possible to comment on the effect of the use of anticoagulants and age on clinical GI or MI risk of COX-2 selective NSAIDs.

Direct COX-2 comparisons

Fourteen RCTs were included. Studies compared rofecoxib (12.5–25 mg/day) with celecoxib (200 mg/day) or valdecoxib (10 mg/day) or lumiracoxib (200–400 mg/day) and celecoxib (200–400 mg/day) with lumiracoxib (200–800 mg/day). Compared drugs were equally tolerated and of equal efficacy. Trials were of insufficient size and duration to allow comparison of risk of clinical UGI events, complicated UGI events and MIs.

COX-2 versus non-selective NSAID combined with a gastroprotective agent

One RCT directly compared celecoxib with diclofenac combined with omeprazole. Arthritis patients who had recently suffered a GI haemorrhage were included. Although no significant difference in clinical GI events was reported, the number of events was small and more such studies, where patients genuinely need NSAIDs, are required to confirm these data. A second trial showed that rofecoxib was associated with fewer diarrhoea events than Arthrotec.

Cost and cost-effectiveness

A review of previous published cost-effectiveness analyses, principally comparing either

celecoxib or rofecoxib with non-selective NSAIDs, indicated a wide range of possible incremental cost per quality-adjusted life-year (QALY) gained estimates.

Using the simpler AGM, with ibuprofen or diclofenac alone as the comparator, all of the COX-2 products are associated with higher costs (i.e. positive incremental costs) and small increases in effectiveness (i.e. positive incremental effectiveness), measured in terms of QALYs. The magnitude of the incremental costs and the incremental effects, and therefore the incremental cost-effectiveness ratios, vary considerably across all COX-2 selective NSAIDs.

The base-case incremental cost per QALY results for COX-2 selective NSAIDs compared with diclofenac for the simpler model are as follows: celecoxib (low dose) £68,400; celecoxib (high dose) £151,000; etodolac (branded) £42,400; etodolac (generic) £17,700; etoricoxib £31,300; lumiracoxib £70,400; meloxicam (low dose) £10,300; meloxicam (high dose) £17,800; rofecoxib £97,400; and valdecoxib £35,500.

When the simpler AGM was run using ibuprofen or diclofenac combined with proton pump inhibitor (PPI) as the comparator, the results change substantially, with the COX-2 selective NSAIDs looking generally unattractive from a cost-effectiveness point of view (COX-2 selective NSAIDs were dominated by ibuprofen or diclofenac combined with PPI in most cases). This applies both to 'standard' arthritis patients and to 'high-risk' arthritis patients defined in terms of previous GI ulcers.

The full AGM produced results broadly in line with the simpler model.

Limitations of the calculations

There are substantive differences in the incremental costs per QALY results in this report compared with industry submissions. These differences reflect, principally, variations in parameter values for clinical GI events and MI risk. There are also key differences in the choice of comparator non-selective NSAIDs and costs, and whether cardiovascular risks are included within the model.

Conclusions

The COX-2 selective NSAIDs examined in this report (i.e. etodolac, meloxicam, celecoxib, rofecoxib, valdecoxib, etoricoxib and lumiracoxib) were found to be similar to non-selective NSAIDs for the symptomatic relief of RA and OA and to provide superior GI tolerability (the majority of evidence is in patients with OA). Although COX-2 selective NSAIDs offer protection against serious GI events (i.e. PUBs and POBs), the amount of evidence for this protective effect varied considerably across individual drugs. The volume of trial evidence with regard to cardiovascular safety also varied substantially between COX-2 selective NSAIDs. Increased risk of MI compared to non-selective NSAIDs was observed among those drugs with greater volume of evidence in terms of exposure in patient-years.

Economic modelling shows a wide range of possible costs per QALY gained in patients with OA and RA. Costs per QALY also varied if individual drugs were used in 'standard' or 'high'-risk patients, and according to the choice of non-selective NSAID comparator and whether that NSAID was combined with a PPI.

Need for further research

With reduced costs of PPIs, future primary research needs to compare the effectiveness and cost-effectiveness of COX-2 selective NSAIDs relative to non-selective NSAIDs with a PPI. Direct comparisons of different COX-2 selective NSAIDs, using equivalent doses, that compare GI and MI risk are needed. Pragmatic studies that include a wider range of people, including the older age groups with a greater burden of arthritis, are also necessary to inform clinical practice.

Publication

Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2008;**12**(11).

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