

COX-2 INHIBITORS : NEW NON-STEROIDAL ANTI- INFLAMMATORY DRUGS

SUMMARY

☐ The rationale for the COX-2 selective drugs is that they cause less gastrointestinal damage than the NSAIDs because they do not inhibit the COX-1 enzyme which synthesises prostaglandins that protect the lining of the gastrointestinal tract.

☐ While selective COX-2 inhibitors are an advance in therapy, they are no more potent as anti-inflammatory drugs.

☐ The limited available data does suggest improved gastrointestinal outcomes with the selective COX-2 inhibitors but further studies are awaited.

☐ The higher cost and improved gastrointestinal side-effect profile of the new COX-2 inhibitors must be weighed against the lower cost and equivalent efficacy of the traditional NSAIDs.

INTRODUCTION

The therapeutic effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are mediated primarily through inhibition of cyclooxygenase (COX) and prevention of subsequent formation of prostaglandins and related inflammatory mediators. They are one of the most widely used class of drugs and commonest cause of adverse gastrointestinal events resulting in substantial morbidity and mortality. In selected groups of patients the risk of gastric toxicity is significant. It is thought that nonspecific COX inhibition is responsible for much of the toxicity of NSAIDs. The promise of specific COX -2 inhibitors is that they will be as effective as traditional NSAIDs at relieving inflammation and pain but will cause less gastrointestinal adverse effects.¹⁻³

Celecoxib and rofecoxib are selective COX - 2 inhibitors approved in Ireland in recent months. They are a new type of NSAID specifically designed to block COX-2 enzyme rather than COX-1 and so according to theoretical predictions to reduce gastrointestinal toxicity associated with NSAIDs. They are not the first NSAIDs with selective activity - others including meloxicam and nimesulide have a greater effect on COX-2 than COX-1 but the selectivity with celecoxib and rofecoxib is claimed to be considerably higher. Celecoxib is licensed for the treatment of osteoarthritis and rheumatoid arthritis. Rofecoxib is licensed for the treatment of osteoarthritis.

EFFICACY

Celecoxib has been compared with placebo and active comparators in osteoarthritis and rheumatoid arthritis. Dosage ranges of 100 to 400mg/day for osteoarthritis and 200 to 800mg/day for rheumatoid arthritis have been shown to be of similar efficacy to naproxen 1000mg/day or diclofenac 150mg/day.⁴⁻⁷ The usual dose for celecoxib is 200mg daily with a maximum dose of 400mg daily for both osteoarthritis and rheumatoid arthritis.

Rofecoxib 12.5 to 25mg/day for patients with osteoarthritis has similar efficacy to ibuprofen 2400mg/day or diclofenac 150mg/day.^{8, 9,10} Higher doses are as yet unlicensed.^{11,12}

GASTROINTESTINAL SAFETY

Clinical data on the gastrointestinal toxicity of celecoxib and rofecoxib is limited and has been presented mostly in abstract form and in manufacturers Summary of Product Characteristics (SPCs).

Endoscopic data on the incidence of ulcers with celecoxib was gathered from efficacy studies rather than specifically designed toxicity studies.^{6,13,14} Of the peer-reviewed studies published to date, the rate of ulceration with celecoxib was similar to that found with placebo. It remains to be seen whether the reduction in endoscopic ulcer rate observed with celecoxib will translate into clinical benefit. In the study comparing celecoxib to diclofenac, the only significant between - group difference in other gastrointestinal related adverse events was for abdominal pain which occurred in significantly fewer celecoxib recipients (11 v's 21%).

The results of the Celecoxib Long Term Arthritis Safety Study (CLASS) which included a broad spectrum of nearly 8,000 patients with rheumatoid arthritis and osteoarthritis, including those taking low-dose aspirin for cardiovascular prophylaxis, have recently been published.^{15,16} The results show that celecoxib was associated with fewer symptomatic gastrointestinal ulcers and ulcer complications than ibuprofen or diclofenac in both arthritis groups but this finding was only significant in those who were not taking aspirin. However the rate for ulcer complications alone, the primary endpoint of the study, only showed a nonsignificant trend in favour of celecoxib. The ulcer complication rate associated with celecoxib could have been increased by the supratherapeutic dosages used in the study or as a result of the high number of patients taking low-dose aspirin concomitantly. Low-dose aspirin appears to have offset any potential protective effect of COX-2 selectivity for celecoxib in this trial. The results of this study provide promising data to suggest that celecoxib is effective in reducing, but not eliminating, the risks of symptomatic ulcers and ulcer complications, at least among individuals who do not take aspirin. Further large-scale outcome analyses of COX-2 selective NSAIDs will be required to determine their ultimate benefit and safety profile.

Of the peer-reviewed published studies the safety of rofecoxib has been compared to aspirin and ibuprofen.^{5,9,17} There were significantly fewer endoscopic gastrointestinal ulcers in patients receiving rofecoxib compared to the comparator

NSAIDs. It remains to be seen whether the reduction in endoscopic ulcer rate will translate into clinical benefit.

Preliminary data on ulcer complications occurring with rofecoxib in phase III studies have been published.¹⁸ This analysis demonstrated a statistically important decrease in perforations, ulcerations and bleeds (PUBs) for rofecoxib-treated patients compared with NSAID-treated patients. However this study was a retrospective analysis and patients were not taking concomitant aspirin. Further data from clinical studies are awaited.

ADVERSE EFFECTS

Despite being postulated that selective inhibitors of COX-2 would spare patients the adverse renal effects associated with nonspecific inhibition of COX enzyme, findings from trials are not consistent with these expectations.^{19,20} Clinicians must assume that all NSAIDs including the selective COX-2 inhibitors, have the same risk for adverse effects on renal function.

Prolongation of bleeding time is a potentially serious side effect of conventional NSAID therapy and is ascribed to the inhibition of platelet COX-1 activity. The selective COX-2 inhibitors do not interfere with normal mechanisms of platelet function as platelets lack COX-2.^{20,21} The clinical effect is a reduced tendency toward bleeding.

INTERACTIONS

Similar to other NSAIDs, celecoxib and rofecoxib may interact with many drugs; they may, for example, decrease the effectiveness of diuretics, beta-blockers, ACE inhibitors and some other antihypertensive drugs (see Summary of Product Characteristics). Both increase prothrombin time and the risk of bleeding if given with warfarin and hence need monitoring.^{20,22}

CONCLUSION

☐ The COX-2 inhibitors have similar efficacy to the comparator NSAIDs that have been used. They have not so far been compared with other NSAIDs such as indomethacin in arthritis.

☐ Detailed published peer-reviewed evidence to support the manufacturers claims of an improved safety profile over existing NSAIDs particularly with regard to gastrointestinal adverse effects is currently limited. So far the majority of gastrointestinal safety data has come from studies in which patients had regular endoscopies. Although these showed significantly less gastrointestinal damage on endoscopy with the COX-2 inhibitors, the relevance of these findings to serious clinically significant gastrointestinal events is not known as most people are asymptomatic before presenting with a catastrophic upper gastrointestinal event. Despite selectivity PUBs have

occurred with COX 2 specific NSAIDs and they carry the standard NSAID warning about gastrointestinal effects.

☐ The new drugs are significantly more expensive than other NSAIDs many of which are now available as generics. There is as yet no pharmacoeconomic data on these new drugs or data as to whether gastroprotective agents should be co-prescribed. Overall cost-effectiveness of COX-2 inhibitors will be heavily influenced by the rates of co-prescribing of gastroprotective agents and potential savings in treatment of adverse events. Greatest economies will be made by ensuring that anti-inflammatory drugs are prescribed appropriately.

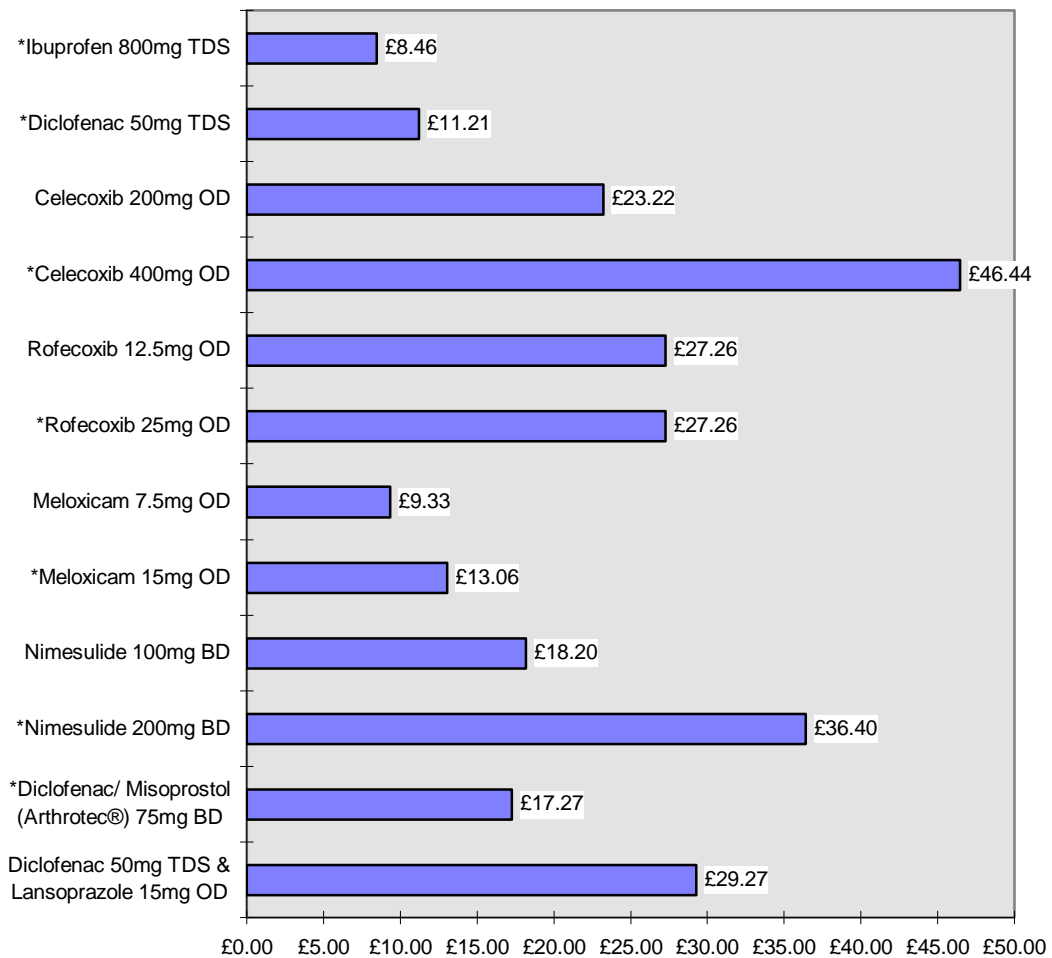
☐ The major determinant in deciding whether to use the new agents should be the risk for serious gastrointestinal toxicity. While COX-2 inhibitors are an advance in therapy the results of ongoing studies are awaited. On the basis of available data it would seem reasonable to confine these new agents for use in the elderly and those with a history of upper gastrointestinal bleed or ulcer ; additional risk factors include anticoagulation, corticosteroid therapy, cardiac disease and high-dose NSAIDs.

COSTS

- Almost £10 million was spent by the General Medical Services (GMS) on anti-inflammatory and anti-rheumatic medicines in 1999.

Comparative Costs for 28 Days Therapy

Drug costs are based on data from GMS 2000



* Maximum recommended daily dose

References

1. Am J Med 1999;107(6A):72S-75S
2. Lancet 1999;353:307-14
3. Drugs Jun 2000;59(6):120
4. Arthritis Rheum 1998;41(9):1591-602
5. Arthritis Rheum 2000;43(2):370-7
6. Mayo Clin Proc 1999;74(11):1095-105
7. JAMA 1999;282(20):1961-3
8. J Rheumatol 1999;26(11):2438-47
9. Gastroenterology 1999;117:776-783
10. Arthritis Rheum 2000;43(5):978-87
11. Clin Ther 1999;21(6):943-53
12. Clin Pharmacol Ther 1999;65(3):336-47
13. JAMA 1999;282:1921-28
14. Lancet 1999;354:2106-11
15. JAMA 2000;284:1297-1299
16. JAMA 2000;284:1247-1255
17. Aliment Pharmacol Ther 1999;13:761-7
18. JAMA 1999;282(20):1929-33
19. Am J Med 1999;107(6A):655-715
20. Med Lett 2000;42(1082):57-64
21. J Clin Pharmacol 2000;40:124-132
22. Ann Pharmacother 2000;34:325-7

Every effort has been made to ensure that this information is correct and it is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet for specific information on drug use.