Etoricoxib for osteoarthritis, gout and pain

PATRICK HANRAHAN BSc, MB BS, FRACP **JOHN HANRAHAN** MB BS

Etoricoxib is an effective and well-tolerated analgesic for acute pain and is also used for the relief of chronic pain in osteoarthritis. Although it shares the increased cardiovascular risks of most other coxibs and NSAIDs, this does not usually become apparent until after at least a month of treatment so is of more concern if the drug is used for longer periods.

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Figure. Inflamed toe in a patient with gout.

Etoricoxib (Arcoxia) is an anti-inflammatory analgesic of the coxib class. It is not on the Pharmaceutical Benefits Scheme (PBS) but is approved in Australia for the symptomatic treatment of osteoarthritis, the treatment of acute gout (Figure) and the relief of short-term pain, including that associated with menstruation and minor dental procedures. It is available on private prescription in doses of 30 mg and 60 mg in blister packs of five, 10 and 30 tablets and in a dose of 120 mg in blister packs of five and 10 tablets.

Coxibs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used in the treatment of arthritis and pain for many years. Recently they have been divided into nonselective (or traditional) NSAIDs (tNSAIDs) and selective NSAIDs (otherwise termed coxibs), based on the relative inhibitions of the cyclo-oxygenase isoenzymes COX-1 and COX-2. Coxibs such as etoricoxib selectively inhibit the inducible inflammation-associated COX-2 while sparing COX-1, whereas nonselective NSAIDs such as naproxen inhibit both isoforms.

Coxibs were initially posited as being much safer than tNSAIDs based on a message that their inhibition of COX-2 resulted in their having similar efficacies to tNSAIDs while their relative lack of inhibition of gastroprotective COX-1 reduced the incidence of ulcers, gastroduodenal bleeding, perforation and obstruction. Unfortunately, initial concerns about an increased incidence of adverse cardiovascular events were confirmed in a placebo comparison with 25 mg of rofecoxib (Vioxx) in a colorectal adenoma prevention trial in 2005.[1] As a result, the manufacturer voluntarily removed rofecoxib from the market.

Coxibs and cardiovascular risk

The increased cardiovascular system risk associated with coxibs was thought to be due to the relatively unopposed action of the platelet aggregating and COX-1-dependent thromboxane TXA-2. Rofecoxib has a COX-2 to COX-1 selectivity ratio of 35,[2] and this hypothesis therefore raises questions about the potential adverse risk of etoricoxib, which has a much greater selectivity for COX-2 of 106.

This explanation is, however, an oversimplification of cardiovascular risk and anti-inflammatory therapy. COX-2 is expressed in atheromatous plaques and there is evidence that the variable risk of myocardial infarction among coxibs relates to the degree of COX-2 suppression rather than the relative ratio of Cox-2 to COX-1 inhibition.[3] There is also an increased risk of myocardial infarction with the use of some tNSAIDs – for example, a relative risk (RR) of myocardial infarction of 1.44 has been shown for diclofenac use compared with no NSAID use.[3,4] Naproxen, however, does not have an increased risk (RR, 0.98),[4] and the use of this NSAID at full dose may confer slight cardioprotection. Interestingly, the RR for the use of the COX-2 selective inhibitor celecoxib has been shown to be only 0.96. However, as with rofecoxib, there is a dose-related increase in risk at greater than the recommended celecoxib dose of 200 mg per day, and it should be used with caution.[4]

Etoricoxib and cardiovascular risk

The cardiovascular risks of etoricoxib 60 mg and 90 mg were assessed by comparison with 150 mg of diclofenac in

Dr Patrick Hanrahan is a Rheumatologist in Perth, and Dr John Hanrahan is an Intern at Royal Perth Hospital, Perth, WA.

patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program.[5,6] Nearly 35,000 patients were enrolled for an average duration of 18 months. There was no increase in the rate of thrombotic cardiovascular events compared with diclofenac. There was, however, a significant increase in cessations due to oedema with 90 mg of etoricoxib and with both doses due to hypertension. There were significantly less discontinuations due to gastrointestinal or liver problems with etoricoxib.

The MEDAL study showed that there is no difference in the rate of thrombotic cardiovascular events between a highly selective coxib and what is generally regarded as a tNSAID, albeit one with an increased risk compared with nonuse.

Osteoarthritis and etoricoxib

Etoricoxib in doses of 30 and 60 mg once daily is effective in the treatment of osteoarthritis.[7] Both doses are more effective than placebo with no increased efficacy at doses higher than 60 mg. Etoricoxib 30 mg has been shown to be as effective as ibuprofen 800 mg three times daily and celecoxib 200 mg once daily, and 60 mg once daily as effective as diclofenac 50 mg three times daily and naproxen 500 mg twice daily. There is probably a slight dose response from 30 mg to 60 mg.

Although etoricoxib is registered in Australia for use in osteoarthritis, an application for listing on the PBS was rejected in 2008 because of 'a lack of demonstrated clinical need for etoricoxib in the context of an inferior safety profile in terms of hypertensive related adverse events, compared to celecoxib'.[8] Nevertheless, etoricoxib does provide an alternative agent for the management of osteoarthritis; if used, it should be started at 30 mg once daily and increased to 60 mg once daily if necessary, while observing blood pressure, renal function and oedema.

Gout and etoricoxib

Two randomised, controlled trials have demonstrated efficacy of etoricoxib comparable to indomethacin in the reduction of pain in acute gout.[9,10] The first study, published in 2002, consisted of 142 patients, and the second, published in 2004, comprised 189 patients. Both studies involved patients experiencing an acute attack of gout receiving eight days of either 120 mg etoricoxib once daily or 50 mg indomethacin three times daily. Pain scores in both treatment groups in both studies were significantly improved by four hours after the first dose and throughout this period, with no significant difference between the two groups. The second study also showed a similar reduction in inflammation in both groups. Both drugs were well tolerated, but etoricoxib was associated with less dizziness, headache and somnolence.

These studies suggest that etoricoxib at a dose of 120 mg once daily is a suitable alternative to the widely used treatment of indomethacin for attacks of acute gout.

Etoricoxib in acute pain

Randomised controlled trials have demonstrated the efficacy of etoricoxib for pain relief in chronic back pain, dysmenorrhoea, dental surgery and arthroplasty.

A Cochrane review of five randomised, placebo-controlled trials with a total of 880 participants demonstrated that etoricoxib is an effective postoperative analgesic.[11] Patients undergoing dental surgery and arthroplasty received either etoricoxib 120 mg or placebo, with some trials including treatment arms with 60 mg, 180 mg and 240 mg. There was a suggestion of increasing efficacy with increased doses, but a definitive dose response could not be demonstrated. About 70% of participants experienced useful pain relief for over 24 hours postoperatively. The number needed to treat (NNT) for at least 50% pain relief was 1.9. The authors of the review noted that, indirectly compared, this NNT is better than that of traditional NSAIDs (ibuprofen, naproxen, diclofenac) and other COX-2 inhibitors (rofecoxib, lumiracoxib, celecoxib) in similar circumstances.

The analgesic efficacy of etoricoxib in the treatment of primary dysmenorrhoea was demonstrated in a randomised controlled trial consisting of 73 patients receiving either etoricoxib 120 mg, naproxen sodium 550 mg or placebo.[12] Etoricoxib was well-tolerated and found to provide a rapid (median time of onset 1.5 hours) and sustained level of pain relief similar to naproxen and superior to placebo.

Summary

Etoricoxib is effective and well-tolerated for the treatment of the acute pain and inflammation of gout. It is also an extremely effective analgesic for the short-term treatment of acute pain. Although etoricoxib shares the increased cardiovascular system morbidity of most other coxibs and tNSAIDs, this is usually not manifest until after at least a month of treatment[3] and is of more concern should the drug be used to treat the symptoms of osteoarthritis for longer periods. Etoricoxib's long half-life of 22 hours allows once daily dosing. MT

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A list of references is available on request to the editorial office.

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