Prescribing Oral Analgesia for Osteoarthritis — Post-rofecoxib Era

Prof. Kenneth KC Lee
BSc(Pharm), MPhil, PhD
Professor, School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong

Osteoarthritis (OA) is estimated to affect 1 in 3 people aged 70 years and older in Hong Kong, with over 80% of them suffering from OA of the knee. Lateral OA of the knee is twice as frequent in the Chinese population, aged 60 years or older, than in the Caucasian population. Women are nearly four times more likely to suffer from OA than men. In addition to common risk factors, such as weight, age and gender, recent studies have identified a relationship between chopstick use and increased prevalence of OA in the hand. Prolonged squatting among elderly Chinese is also said to be a strong risk factor for knee OA.

Management of osteoarthritis

OA is a widespread, chronic condition that requires an individualised management plan involving multiple kinds of treatment; optimal management remains a challenge for many physicians. The goals of managing OA include:

- Controlling pain
- Maintaining and improving the range of movement and stability of affected joints
- Limiting functional impairment.

All therapies for OA should ideally produce minimum side effects. Management should be individualised and patient-centred, and clinicians have a variety of pharmacological and non-pharmacological treatments to choose from. Non-pharmacological strategies involve patient education, weight loss and mechanical aids, such as walking sticks. Alternative or complementary supplements for OA include glucosamine and chondroitin. Chondroitin exhibits a wide range of biological activities, producing a slow but gradual decrease of clinical symptoms associated with OA. These benefits are said to last for a long period after treatment. A study published in July 2004 found that glucosamine plus methylsulfonylmethane provided rapid improvement in pain and inflammation for OA patients and was more effective than either nutrient alone. Researchers also believe that leeches show promising signs for OA treatment. However, patients with more severe disease and higher pain scores should receive pharmacological therapy.

Oral analgesics

The aim of therapy is to relieve OA symptoms in patients. Traditional non-steroidal anti-inflammatory drugs (NSAIDs) and the more recent cyclooxygenase-2 (COX-2) selective inhibitors are effective analgesics for providing pain relief in OA sufferers. However, conventional NSAIDs are associated with an increased risk of upper gastrointestinal (GI) complications, such as ulcers, perforation, obstruction and GI bleeding. Since the withdrawal of the COX-2 selective inhibitor rofecoxib (Vioxx®, MSD), due to concerns about cardiovascular toxicity, other available and more cost-effective analgesics indicated for OA are now being re-assessed.

Paracetamol — recommended first-line therapy for mild to moderate OA

Paracetamol (acetaminophen) is consistently chosen as a suitable first-choice analgesic for most patients suffering mild to moderate pain. Patient preference studies have shown that 40 — 45% of patients find their OA pain is satisfactorily relieved by paracetamol. There is also evidence that at doses of 4 g/day, paracetamol can offer the same pain relief as conventional NSAID therapy in patients with mild-to-moderate joint pain. Two recent studies have also shown that more than 40% of patients with OA either prefer paracetamol to NSAIDs, or find no difference between the two. Based on evidence of paracetamol’s long-term safety profile and efficacy in relieving OA pain, the EULAR (European League Against Rheumatism) guidelines recommend that it should be the preferred long-term analgesic for OA. However, if paracetamol alone fails to give sufficient pain relief, conventional NSAIDs and COX-2 inhibitors should be considered as supplementary or alternative therapy.

The importance of safety and tolerability

With the recent withdrawal of rofecoxib as a result of increased CV risk, physicians should be more alert to the safety profile of other analgesics when deciding on an appropriate OA medication. Recent publications highlight that paracetamol:

- Is generally well tolerated
- Appears to act centrally
- Has minimal effect on the GI tract.

While some research indicates that paracetamol at relatively modest doses may be associated with fatal hepatic toxicity, other studies support the safety of paracetamol in patients with established liver disease, making it the preferred analgesic for these patients, especially compared with
NSAIDs. Similarly, the Scientific Advisory Board of the National Kidney Foundation recommends paracetamol as the preferred analgesic in patients with renal impairment. Indeed paracetamol’s safety records should encourage the first-line use of this analgesic for mild to moderate OA, before other pharmaceutical interventions.

Age is a major risk factor for NSAID GI tract complications and renal risk complications. NSAIDs are usually reserved for patients who do not gain adequate pain relief from paracetamol. A double-blind study of 287 arthritis patients with high-risk of gastrointestinal bleeding in Hong Kong found that the 6-month incidence of combined recurrent bleeding and ulcers was 32.3% in patients receiving diclofenac. Renal adverse effects occurred in 30.8% of these patients.

Although COX-2 inhibitors have less risk of side effects than NSAIDs and generally better GI tolerability, 24.1% of arthritis patients in Hong Kong with high-risk of gastrointestinal bleeding had recurrent bleeding and/or ulcers within 6 months of receiving celecoxib. In terms of renal and cardiovascular risk, both first-generation COX-2 inhibitors, celecoxib and rofecoxib, have demonstrated similar effects, such as fluid retention and hypertension. The 6-month incidence of renal adverse effects was 24.3% in patients taking celecoxib. It is important to note that the withdrawal of rofecoxib had possibly been based on changes in blood clotting, leading to myocardial infarction and stroke, which constitute an entirely separate cardiovascular risk factor and is believed not to be associated with traditional NSAIDs and other analgesics. NSAIDs have a different pharmacological action to COX-2 inhibitors, which precludes this particular cardiovascular risk. Whether the cardiovascular concerns that led to the withdrawal of rofecoxib prove to be a class effect remains to be seen. In general, elderly patients have an increased risk of adverse effects. Therefore, a ‘start low, go slow’ approach should be adopted when prescribing for this patient group.

Cost considerations

NSAIDs are one of the most widely prescribed medications used in controlling symptoms associated with osteoarthritis. GI toxic effects induced by NSAIDs are extremely common. As NSAID-induced peptic ulcer disease (PUD) and arthritis are said to have the highest incidence amongst the elderly in Hong Kong and in Hong Kong alone, 1000 cases of peptic ulcer bleeding are being managed per treatment centre every year, about half of them related to NSAID use, OA could be considered a costly disease. Compared with other pharmaceutical agents, paracetamol stands out as a cost-effective option for treating OA. Indeed, low cost, together with efficacy and safety, form the basis of the international recommendation for paracetamol as a first-line analgesic for OA. Cost analyses have shown that both intermittent and long-term paracetamol use is associated with significantly less cost than NSAID use, largely due to the lower economic health burden for treating serious adverse events. It is estimated that a third of the overall cost of treating arthritis is attributed to treatment of adverse GI effects caused by NSAIDs. Accordingly, use of COX-2 inhibitors has been more cost-effective than NSAIDs for patients with a higher risk of GI bleeding.

Taking the opportunity

In conclusion, the withdrawal of rofecoxib has prompted the review of other analgesics indicated for OA. Clinicians must be aware of the potential side effects of chronic drug use and consider the balance between benefit and risk. Re-assessing the use of conventional analgesics such as paracetamol may yet result in patients benefiting from appropriate, effective OA treatment that are cost-effective and well tolerated in long-term use.

References