“Most new drug concepts are launched with fanfare, and it takes many years on the market for their appropriate role in practice to be established. An excellent example is the concept of cyclooxygenase-2 (COX-2) selective NSAIDs, which was launched in Canada in early 1999 with celecoxib (Celebrex). The launch of the COX-2 selective NSAIDs was based on 2 hypotheses. The first hypothesis is that the major adverse effects limiting the usefulness of nonselective NSAIDs are gastrointestinal symptoms, ulcers, ulcer complications and ulcer complications leading to death. The second hypothesis is that COX-2 selective NSAIDs are associated with less gastrointestinal toxicity than nonselective NSAIDs. At the time of the launch of COX-2 selective NSAIDs neither of these hypotheses had been proven and, as documented in this review, both remain uncertain. However, skilful marketing of these hypotheses without any published complete trial reports by the fall of 1999 resulted in celecoxib’s achieving a record for the most sales in the shortest period of time. Worldwide sales of celecoxib exceeded $3.1 billion in 2001. In 2000, 2 large randomized controlled trials testing the second hypothesis were published. In the Celecoxib Long-term Arthritis Safety Study (CLASS) and the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, celecoxib and rofecoxib respectively were compared with nonselective NSAIDs. These well-designed trials claimed to prove the safety of these agents, but the results became controversial when more complete data from the trials became available from the US Food and Drug Administration (FDA).”

“NSAIDs act by inhibiting cyclooxygenase, an enzyme involved in the formation of various prostanoids with a wide variety of pharmacologic actions. The COX-2 selective NSAIDs resulted from the discovery that cyclooxygenases represent at least 2 different isoenzymes, designated COX-1 and COX-2. COX-1 is mostly constitutive and is involved in such actions as platelet activation, gastrointestinal protection and kidney function. COX-2 is primarily produced in response to tissue damage and is involved in inflammatory responses to injury. The discovery of the different COX enzymes has allowed grading of the more than 20 available NSAIDs based on their ability to selectively inhibit the 2 COX enzymes. The best attempt to grade the available NSAIDs used standardized in vitro human assay systems. This demonstrated that ketorolac inhibits COX-1 300 times more than COX-2 at one extreme, and rofecoxib inhibits COX-2 80 times more than COX-1 at the other extreme. Four drugs marketed in Canada are claimed to be COX-2 selective. The selectivity of these drugs as well as of some nonselective NSAIDs is shown in Table 1.”

“Benefits of NSAIDs

To properly put the harms of NSAIDs into perspective, it is necessary to appreciate the magnitude of the benefit derived from taking NSAIDs. The benefit of NSAIDs, based on short-term placebo-controlled trials, is a reduction in the severity of musculoskeletal pain, stiffness and swelling. Several systematic reviews of the efficacy of NSAIDs have been performed, but the reviewers have judged it impossible to systematically quantitate the magnitude of the benefit of NSAIDs because of incomplete reporting as well as biased analysis and presentation of the trial results. This is a remarkable observation for a class of drugs that is so widely used today.”

“Two placebo-controlled trials illustrate the magnitude of the benefit of NSAIDs as compared to placebo. In these trials the investigators used reduction in pain, as assessed with a 10-cm visual analogue scale (with 0 indicating no pain and 10 indicating maximum pain), as one of the
The double-edged sword of COX-2 selective NSAIDs

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benefit outcomes. In one trial, after 12 weeks, patients with osteoarthritis of the knee (baseline pain rating 6) had an average reduction in pain of 0.9 with 2 NSAIDs (celecoxib [100 or 200 mg twice daily] and naproxen [500 mg twice daily]) compared to placebo. In the second trial, rofecoxib therapy (25 mg/d for 8 weeks) in patients with rheumatoid arthritis led to a reduction in pain of 0.7 compared to placebo. With another outcome measure, swollen and tender joint counts (American College of Rheumatology 20% response proportion [ACR 20]), rofecoxib caused an absolute increase in ACR 20 responders of 12.2% compared to placebo. This means that 8 patients would have to be treated for 8 weeks with rofecoxib for 1 patient to benefit by achieving a 20% or greater reduction in tender and swollen joint counts. These modest short-term benefits in osteoarthritis and rheumatoid arthritis must be balanced against the potential harms of these drugs.

"Harms of NSAIDs

Inflammation is a component of the normal healing process. All NSAIDs inhibit inflammation and have the potential to interfere with this healing process. Impairment of joint healing can lead to joint deterioration in the various forms of arthritis. Evidence demonstrating this potential adverse effect comes from a trial of 812 patients with osteoarthritis randomly assigned to receive indomethacin (25 mg 3 times daily), tiaprofenic acid (300 mg twice daily) or placebo. Patients taking either drug did not have any reduction in symptoms in comparison to placebo. Furthermore, over 1 to 2 years, those who received indomethacin and, to a lesser extent, those who received tiaprofenic acid had increased radiologic joint deterioration compared to those who received placebo. Although duplication of this trial with other NSAIDs has not been attempted, it is possible that all NSAIDs may have diminishing symptomatic benefit over time as a result of or independent of an effect leading to accelerated joint deterioration. How this potential manifests in the clinical setting may depend on NSAID potency, COX selectivity, pharmacokinetics, dosage and duration of use. Recent evidence of impaired fracture healing in rats supports the concept of impaired joint healing with NSAIDs and suggests that this may be worse with the COX-2 selective drugs."

"Prostanoids produced by COX enzymes in the kidney are essential for the regulation of renal blood flow and other physiologic actions. Inhibition of these functions by NSAIDs has been shown in a meta-analysis to increase blood pressure by an average of 5 mm Hg (95% confidence interval [CI] 1.2-8.7 mm Hg). With short-term use this is probably inconsequential, but with long-term daily use the estimated risk of adverse cardiovascular events based on epidemiologic data is substantial. This action of NSAIDs can manifest acutely with salt and water retention and renal impairment in patients with compromised renal function or congestive heart failure."

"Potential advantages of COX-2 selective NSAIDs

It has never been claimed that COX-2 selective NSAIDs are more beneficial in reducing the symptoms of arthritis than nonselective NSAIDs. In the CLASS and VIGOR trials, there was no significant difference in efficacy measures in the longer term between nonselective NSAIDs and COX-2 inhibitors based on the FDA data. The main potential advantage of COX-2 inhibitors is that they may have fewer toxic effects on the gastrointestinal tract as a result of having less
inhibitory effect on the gastroprotective prostanoids produced by COX-1 enzymes in the gastrointestinal tract. This advantage of COX-2 selective NSAIDs has been tested in short-term trials measuring gastroduodenal ulcers and erosions by endoscopy. COX-2 selective NSAIDs were associated with substantially fewer endoscopically visualized ulcers (defined as a mucosal break 3 mm or more in diameter with unequivocal depth) (Table 2). However, it is not known whether such small endoscopically defined ulcers and erosions are an accurate predictor of ulcer complications, the most common presentation being gastrointestinal bleeding. Another potential advantage of COX-2 selective NSAIDs is that they may reduce the risk of gastrointestinal bleeding by not interfering with platelet aggregation, a COX-1 effect.”

“Potential disadvantages of COX-2 selective NSAIDs

An understanding of the physiologic features of COX isoenzymes has led to the appreciation that drugs that preferentially inhibit COX-2 may lead theoretically to problems in thrombosis, salt and water balance, and healing. The well-known reduction of thrombotic events with low-dose ASA therapy is based on selective irreversible inhibition of COX-1-mediated platelet thromboxane production. In contrast, the selective inhibition of prostacyclin formation by COX-2 selective NSAIDs interferes with prostacyclin’s effect of inhibiting thrombosis and permits the unopposed action of platelet thromboxane. In susceptible people this could tip the delicate balance and lead to adverse thrombotic events. Inhibiting both COX-1 and COX-2 likely retains the balance. Prostanoids (regulated by both COX-1 and COX-2) are also involved in salt, water and blood pressure regulation in the kidney via poorly understood mechanisms. Creating an imbalance of prostanoids in the kidney by selectively inhibiting the COX-2 isoenzyme may result in a greater potential for salt and water retention, hypertension and exacerbation of congestive heart failure. Furthermore, the COX-2 isoenzyme plays a critical role in fracture healing, and blocking this enzyme may inhibit healing. A study in rats showed that NSAIDs can markedly interfere with fracture healing; this effect was greater with the COX-2 selective NSAIDs rofecoxib and celecoxib than with the nonselective NSAID indomethacin.”

“Benefits and harms of COX-2 selective NSAIDs from large randomized controlled trials

The CLASS and VIGOR trials were designed to test whether the potential advantages of COX-2 selective NSAIDs on the gastrointestinal tract and platelets would result in a reduced incidence of ulcer complications. The published versions of these studies focused on gastrointestinal events and provide an incomplete picture of the overall benefit and harm of celecoxib and rofecoxib (summarized recently by Wooltorton). One striking finding from these trials is that despite the large size and duration (average 8 to 9 months), there was no decrease in the incidence of death due to gastrointestinal complications. There were no gastrointestinal-related deaths in the CLASS, and there were 4 such deaths in the VIGOR study (3 patients receiving rofecoxib and 1 receiving naproxen). Cardiovascular events were the main cause of death in both trials (69% of 36 deaths in the CLASS and 46% of 37 deaths in the VIGOR trial).”

“Conclusions and suggested future trials

All NSAIDs, both COX-2 selective and nonselective, provide only a modest symptomatic benefit over placebo, and this benefit has been proven only in short-term trials. With long-term
therapy, it is not known whether the benefits of this class of drugs exceed the harms. In fact, there is evidence to suggest that the opposite is true. Meta-analysis of FDA data from the CLASS and VIGOR trials shows, first, that COX-2 selective NSAIDs do not necessarily reduce the incidence of complicated ulcers. Second, the meta-analysis demonstrates that, rather than proving safer, COX-2 selective NSAIDs cause more morbidity (total SAEs) than nonselective NSAIDs. This increase is partly explained by increased thrombotic and cardiac adverse events, but full audit and disclosure of all data are needed to identify other causative mechanisms. Access to this information is necessary to establish whether COX-2 selective NSAIDs could have a role in the long-term treatment of patients with arthritis and to assist in designing future trials.”