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Benefit-Risk Assessment of Rofecoxib in the Treatment of Osteoarthritis

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Abstract

NSAIDs are widely used to treat pain and inflammation in osteoarthritis. Their use in this indication is generally intermittent and fluctuates with the intensity of the disease. Nonetheless, success of the therapy is frequently limited by injury to the gastrointestinal mucosa and complications such as bleeding, ulceration and perforation. A careful and detailed evaluation of these aspects in regard to the newly introduced NSAIDs is of considerable clinical importance.

This review focuses on the NSAID rofecoxib, one of the selective cyclo-oxygenase (COX)-2 inhibitors, which are claimed to be as effective as nonselective NSAIDs with better gastrointestinal tolerability. Indeed, phase II, phase III and epidemiological studies have revealed that the efficacy of rofecoxib is comparable to that of conventional NSAIDs but with lower gastrointestinal toxicity, although this advantage may not be demonstrable in every patient.

In patients treated with low-dose aspirin (acetylsalicylic acid) for cardiovascular prophylaxis, celecoxib (another selective COX-2 inhibitor) seems to have no obvious advantages over conventional NSAIDs, and similar conclusions may be applied to rofecoxib. A comparison of NSAID therapy ± concomitant low-dose aspirin was not a primary outcome in this trial with celecoxib and there is thus a need for further studies which compare the gastrointestinal risk of a selective COX-2 inhibitor plus aspirin versus a conventional NSAID.

Recent debate has emerged regarding the cardiovascular safety of rofecoxib. Although there is evidence both for and against higher cardiovascular risk with rofecoxib, a retrospective cohort study recently published suggested that there is no increased risk of acute myocardial infarction in the short-term when compared with non-selective NSAIDs.

The renal toxicity of rofecoxib has been thoroughly investigated. Clinical studies revealed renal effects of rofecoxib similar to those of conventional NSAIDs. Since adverse effects increase with the degree of renal impairment, monitoring of renal function should be carried out in patients at risk.

Although there are still insufficient data concerning certain important adverse effects of rofecoxib, this drug is becoming an important alternative in the therapy of osteoarthritis, especially in high-risk patients. Clinicians need to weigh up the benefits and risks of rofecoxib on a case-by-base basis.

1. Osteoarthritis

1.1 Disease Characteristics

Osteoarthritis is a chronic disease with symptoms characterised by joint pain, stiffness and loss of physical function. It is the most common joint disorder in the world affecting between 15–30 million people in the US alone.[1] Its onset is usually seen in patients aged between 50–60 years.[1] Abnormal joint morphology, prior joint injury and obesity can increase the risk of developing osteoarthritis, especially in weight-bearing joints such as hips and knees. Patients with osteoarthritis usually require long-term treatment and, in particular, when joint pain and stiffness are present.[1]

1.2 Treatment Strategies and the Problem of Adverse Drug Reactions

NSAIDs are widely used to treat pain and inflammation in osteoarthritis. Their use in this indication is generally quite intermittent and fluctuates with intensity of the disease. However, their therapeutic value can be limited by injury to the gastric mucosa and complications such as bleeding, ulceration and perforation. Estimates of the magnitude of NSAID-related gastrointestinal adverse events vary, but demonstrate clearly the seriousness of the problem. In the US 16 500 patients/year die as a consequence of conventional NSAID-related gastrointestinal adverse events.[2] Furthermore, approximately 1 in 1200 patients taking NSAIDs for ≥2 months die as a result of these adverse events.[3] Patients administering NSAIDs are >5 times more likely to be hospitalised for treatment-related gastrointestinal problems than non-users, and mortality among patients hospitalised for gastrointestinal bleeding is 5–10%.[2,3]

2. Selectivity of Cyclo-Oxygenase (COX)-1/COX-2 Inhibition and Toxicity of NSAIDs

2.1 Molecular Mechanisms

The basic mechanism of action of NSAIDs is the inhibition of prostaglandin H synthase, more commonly referred to as cyclo-oxygenase (COX), which converts arachidonic acid to prostaglandin (PG) H_2.[4] This enzyme exists in two distinct isoforms, COX-1 and COX-2. COX-1 is expressed mainly constitutively in a large number of tissues and is involved in the synthesis of prostanoids that regulate physiological functions including gastric cytopro-

tection, platelet aggregation, vascular homeostasis and renal sodium and water balance. In contrast, COX-2 is a predominantly inducible enzyme, which is upregulated at sites of inflammation and pain in diseases such as osteoarthritis. However, COX-2 is also constitutively expressed in a variety of tissues (brain, kidney, spinal cord, sexual organs) where it has a physiological role. Conventional NSAIDs at therapeutically relevant doses inhibit both COX-1 and COX-2. Thus the same mechanism of action, COX inhibition, may result in successful treatment of pain and inflammation but may also cause adverse events such as injury to the (upper) gastrointestinal (GI) tract. This finding has led to the introduction of drugs which show selectivity for the COX-2 isoform (see section 3.1).

2.2 Role of COX-1/COX-2 Inhibition in the Gastrointestinal (GI) Effects of NSAIDs

Since the launch of aspirin (acetylsalicylic acid) about 100 years ago, gastric damage and related complications have not only been the most frequently observed adverse effects of NSAIDs but also the most frequent reasons for termination of anti-inflammatory therapy.[2] In order to assess GI toxicity, the mechanism through which NSAIDs cause injury to the gastric mucosa needs to be clarified. Phase III clinical trials reveal that selective inhibition of COX-2 using one of the newly introduced selective NSAIDs spares gastric PG synthesis and is associated with a reduced incidence of gastric damage compared with treatment with conventional NSAIDs. This has led to the hypothesis that inhibition of gastric COX-1 is the key mechanism responsible for mucosal damage. On the other hand however, mice in which the gene for COX-1 is disrupted exhibit greatly reduced PG synthesis in the stomach, but show no gastric lesions.[5]

This apparent discrepancy led Wallace et al.[6] to hypothesise that suppression of both COX-1 and COX-2 is necessary for NSAID-induced damage. They investigated the effects of the selective COX-1 inhibitor SC-560 and the selective COX-2 inhibitor celecoxib on GI toxicity in rats. Parameters measured included inhibition of gastric PGE_2 synthesis, gastric blood flow and leucocyte adherence to the vascular endothelium. Both gastric blood flow and leucocyte adherence are thought to contribute to the pathogenesis of NSAID-induced gastric damage.[7] Neither the COX-1 inhibitor nor the COX-2 inhibitor caused macroscopically or histologically detectable gastric damage. However, administration of both inhibitors or of the nonselective inhibitor indomethacin invariably resulted in the development of gastric lesions (figure 1). The conclusion that suppression of both COX-1 and COX-2 is necessary for NSAID-induced gastric damage is consistent with the previous observation that mice in which the gene for COX-1 is disrupted develop erosions only when indomethacin is given. Although it is not known whether these findings can be extrapolated to humans they provide a plausible explanation for the apparent discrepancy mentioned above.

3. Pharmacology and Efficacy of Rofecoxib in Osteoarthritis

3.1 General Characteristics

Lipsky et al.[8] classified NSAIDs with COX inhibitory activity into four categories: COX-1 selective, COX nonselective, COX-2 preferential, and COX-2 selective.

- COX-1 selective inhibitors (category 1) target COX-1 but have no measurable effect on COX-2 activity (e.g. low-dose aspirin).
- COX nonselective inhibitors (category 2) show no biological or clinically relevant difference in the inhibition of COX-1 and COX-2. These agents usually exhibit only minimal differences

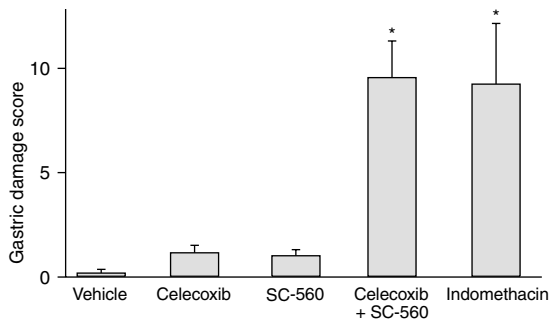

Fig. 1. Effects of SC-560 (selective cyclo-oxygenase [COX]-1 inhibitor, 40 mg/kg) and celecoxib (selective COX-2 inhibitor, 15 mg/kg) on the integrity of the gastric mucosa in rats. Significant increases in gastric damage were observed only in the group treated with celecoxib plus SC-560 and in the group treated with indomethacin (5 mg/kg). n = 5–10/group.[6] * $p < 0.05$ vs vehicle-treated group.

in the dose-response curves for inhibition of recombinant COX-1 and COX-2 *in vitro* (e.g. flurbiprofen, indomethacin).[9]

- COX-2 preferential agents (category 3) possess some anti-inflammatory or analgesic activity at doses that inhibit COX-2 but which show no significant effect on COX-1. At higher doses these agents do inhibit COX-1 (e.g. meloxicam, diclofenac).[9]
- COX-2 selective inhibitors (category 4) show no clinically significant inhibition of COX-1 even at maximal therapeutic doses. Agents in this category show a >100-fold difference in the concentration required to inhibit recombinant COX-2 compared with COX-1 *in vitro* or in the whole blood assay.[10]

Rofecoxib (category 4) is selective for the COX-2 isoform over its clinical dose range and was the second selective COX-2 inhibitor to become commercially available after celecoxib.

In various phase III clinical trials, it has been shown that rofecoxib has an improved GI safety profile compared with conventional NSAIDs and that this agent has no effect on platelet aggregation.

3.2 Pharmacokinetics

The mean oral bioavailability of rofecoxib is approximately 93% at doses (12.5–25mg) recommended in the treatment of osteoarthritis. Maximal plasma concentrations of approximately 200 μg/L are reached 2–4 hours with individual values varying between 2–9 hours after the oral administration of rofecoxib 25mg. Human plasma protein binding is approximately 85%. Metabolism of rofecoxib primarily involves reduction mediated by cytochrome P450-independent cytosolic enzymes. About 72% of a single radiolabelled dose of rofecoxib 125mg is excreted in urine as metabolites, and 14% in faeces as unchanged drug. The terminal elimination half-life (based on steady-state levels) is approximately 17 hours and the plasma clearances after 12.5 and 25mg doses are approximately 140 and 120 mL/min, respectively.[11,12]

3.3 Dosage and Efficacy

The recommended starting dose of rofecoxib in the treatment of osteoarthritis is 12.5mg once daily. Some patients may receive additional benefit by increasing the dose to the maximum recommended daily dose of 25mg.

At doses of 12.5 and 25mg, the efficacy of rofecoxib was comparable to ibuprofen 800mg three times daily,[1,13] diclofenac 50mg three times daily[1,14] and naproxen 500mg twice daily.[15] In one study, rofecoxib 25mg daily was more effective than paracetamol (acetaminophen) 1000mg four times daily, celecoxib 200mg daily and rofecoxib 12.5mg daily in treating osteoarthritis of the knee.[16] In a recent study, rofecoxib 25mg daily significantly improved the quality of life in patients with osteoarthritis of the hip or knee.[17] However, in a short-term study of 7 days, nimesulide 100mg daily when compared with rofecoxib 25mg daily was significantly more effective in providing symptomatic relief for patients with osteoarthritis of the knee.[18]

In a 6-month prospective study (phase 2 of the VICOXX study) 562 osteoarthritis patients were continued on established conventional NSAID therapy for the first 3 months and then switched to rofecoxib (12.5mg or 25mg daily). In this study, use of rofecoxib when compared with conventional NSAIDs was associated with marked improvements in several indices of treatment effectiveness and tolerability.[19] The results of a Spanish observational study suggested that rofecoxib 25mg daily may be more effective in some patients with osteoarthritis who do not respond well to celecoxib 200mg daily.[20] A postmarketing surveillance study which enrolled 80 371 patients assessed the efficacy and tolerability of rofecoxib in the treatment of osteoarthritis. Most of those responding to the questionnaire considered rofecoxib to be an effective, easy to use and well tolerated treatment for osteoarthritis.[21] A nationwide survey among 74 192 patients with osteoarthritis in Belgium evaluated satisfaction with rofecoxib 12.5mg or 25mg, given once daily for an average of 30 days. The results of this large survey demonstrated a clear preference for rofecoxib over conventional NSAIDs in a substantial majority of osteoarthritis patients.[22,23]

It should be noted that rofecoxib is most effective in the chronic treatment of inflammation rather than for the management of acute pain since the time to reach maximum plasma concentrations is approximately 3 hours.

4. Safety of Rofecoxib

4.1 General Aspects

All phase III clinical trials demonstrate that rofecoxib, when compared with conventional NSAIDs, has a lower incidence of gastric damage involving the upper GI tract. The therapeutic significance of this finding must be assessed with caution. Up until now, only short-term phase III clinical trials with a duration of a few weeks to a few months have been performed under controlled conditions, although it is known that NSAIDs are taken for several years, and in some cases for life. Elderly subjects have an increased GI risk when receiving NSAIDs, due to the physiological changes associated with increased age,[24] and when they are taking aspirin for cardiovascular prophylaxis. Other risk factors including a history of ulcers or GI events, dyspepsia, concomitant medication (anticoagulants, corticosteroids) and comorbidities also limit the use of NSAIDs in the therapy of osteoarthritis.[25]

The efficacy and associated risk of damage to the upper GI tract using rofecoxib and celecoxib have been compared with conventional NSAIDs in two large trials, the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial[26] and the Celecoxib Long-Term Arthritis Safety Study (CLASS) trial,[27] respectively.

Since epidemiological studies suggest that NSAIDs also increase the risk of developing lower GI events,[28,29] the protocol of the VIGOR trial also included an analysis of bleeding from sites beyond the duodenum that resulted in hospitalisation, discontinuation of treatment, or a decrease in the haemoglobin level of at least 2 g/dL (Laine et al.,[30] section 4.2.1).

4.2 GI Toxicity

4.2.1 The Vioxx Gastrointestinal Outcomes Research Trial (VIGOR)

The VIGOR trial[26] involved 8076 patients with rheumatoid arthritis who were randomised in a double-blind fashion to receive rofecoxib 50mg daily, twice the upper limit of dose recommended for osteoarthritis, or naproxen 500mg twice daily for an average of 9 months.

The incidence of confirmed GI events involving the upper GI tract per 100 patient-years for rofecoxib versus naproxen was 2.1 versus 4.5, respectively (figure 2), resulting in a number-needed-to-treat (NNT) of 41. Thus, 41 patients must be treated for 1 year with rofecoxib instead of naproxen in order to prevent one GI event involving the upper GI tract. The GI advantage of rofecoxib versus naproxen is reduced by about a factor of three when comparing GI events involving the upper GI tract with severe GI events. The respective rates of severe upper GI events were 0.6 versus 1.4 per 100 patient-years (NNT 125). Thus, 125 patients would need to be treated for 1 year with rofecoxib rather than naproxen to avert one severe GI event. Aspirin for cardiovascular prophylaxis was not permitted in this trial.

Laine and coworkers[30] assessed serious events involving the lower GI tract in a *post hoc* analysis of the VIGOR trial. The term lower GI tract refers to the small intestine (beyond the duodenum) and the colon, and serious lower GI events were defined as bleeding with a 2 g/dL drop in haemoglobin or hospitalisation for bleeding, or hospitalisation for perforation, obstruction, ulceration, or diverticulitis. The rate of serious lower GI events per 100 patient-years was 0.41 for rofecoxib and 0.89 for naproxen resulting in an NNT of 208 (figure 3). The serious lower GI events accounted for 39.4% of all serious upper and lower GI events among patients receiving naproxen and 42.7% among patients receiving rofecoxib. These data suggest that serious events

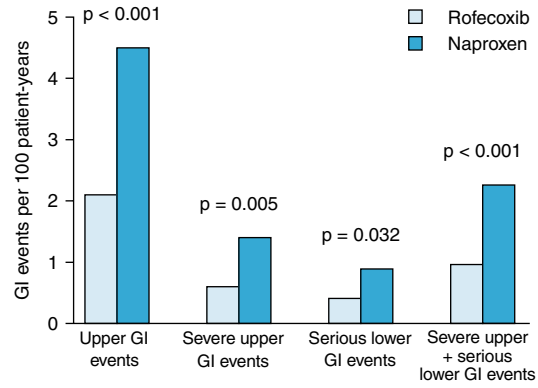

Fig. 2. Upper gastrointestinal (GI) events, severe upper GI events and serious lower GI events per 100 patient-years in the rofecoxib- and naproxen-treated groups of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial.[26]

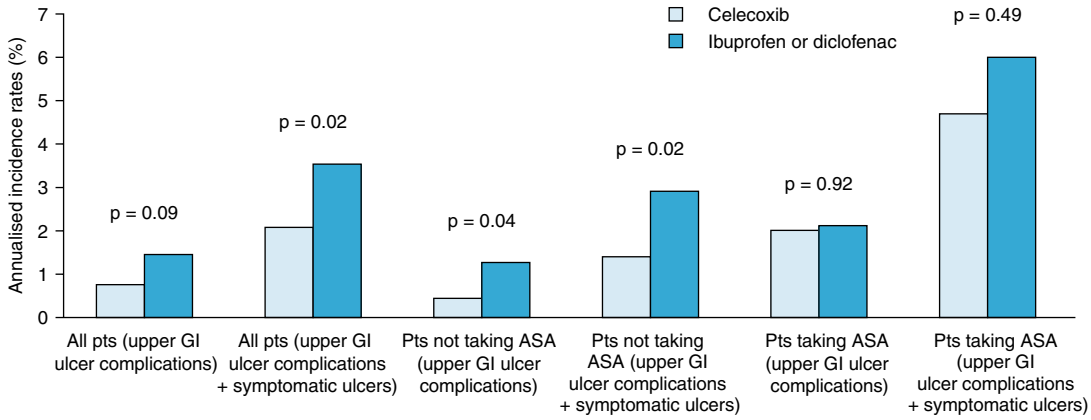

Fig. 3. Annual incidence of upper gastrointestinal (GI) ulcer complications alone and combined with symptomatic ulcers for celecoxib versus ibuprofen or diclofenac in the Celecoxib Long-Term Arthritis Safety Study (CLASS)[27] trial. Aspirin (acetylsalicylic acid; ASA) use for cardiovascular prophylaxis (≤325mg daily) was permitted.

involving the lower GI tract account for a large proportion of GI complications and that, when compared with naproxen, therapy with rofecoxib is associated with a significant reduction of about 50% in serious lower GI events. By way of comparison, the rates of all severe upper and serious lower GI events were 0.96 for rofecoxib and 2.26 per 100 patient-years for naproxen corresponding to an NNT of 77.

4.2.2 The Celecoxib Long-Term Arthritis Safety Study Trial (CLASS)

The CLASS trial involved 8059 patients with osteoarthritis or rheumatoid arthritis randomised in a double-blind fashion to receive celecoxib 400mg twice daily, ibuprofen 800mg three times daily or diclofenac 75mg twice daily for 6 months.[27]

In the CLASS trial the annual rate of ulcer complications (excluding symptomatic ulcers) of the upper GI tract for celecoxib versus ibuprofen or diclofenac was 0.76% versus 1.45%, respectively, resulting in an NNT of 144 (figure 3). When symptomatic ulcers were included, the respective NNT was 68. In the CLASS trial, aspirin (≤325mg daily) was permitted for cardiovascular prophylaxis. In the case of patients not taking aspirin, the respective NNTs were 120 (ulcer complications only) and 66 (ulcer complications combined with symptomatic ulcers). In the case of patients taking aspirin, the respective NNTs were 909 (ulcer complications only) and 76 (ulcer complications combined with symptomatic ulcers). In conclusion, about 900 patients taking aspirin must receive celecoxib instead of conventional NSAIDs for 1 year in order to avert one ulcer complication.

In the CLASS trial, the subgroups (A) all patients, (B) all patients not taking aspirin and (C) all patients taking aspirin, were analysed. Comparison of the NNT for ulcer complications combined with symptomatic ulcers showed only small differences between the three groups (NNT range 66–76). However, on comparison of NNT values for ulcer complications only, the results were quite different. Subgroup C showed an approximately 7-fold higher NNT compared with subgroups A and B, where the values were almost identical. The risk of ulcer complications in patients of both cohorts treated with the selective COX-2 inhibitor and patients taking NSAIDs in combination with aspirin are therefore almost identical.

An analysis of events involving the lower GI tract was not reported in the CLASS trial.

4.2.3 Overall Conclusions from VIGOR and CLASS Trials

Analysis of these data show that therapy with a selective COX-2 inhibitor compared with conventional NSAIDs is associated with an approximate 50% reduction in upper GI events. However, the longer-term data from the CLASS trial have raised concern because Silverstein et al.[27] presented only

data for the first 6 months. On reviewing the complete data, the US FDA concluded that there is no GI safety advantage for celecoxib over ibuprofen or diclofenac, but they acknowledged that the use of aspirin may have confounded some of the findings.[31] This issue therefore is still a subject of intensive discussion.[32-34] The finding that differences exist between subgroups in upper GI toxicity indicates that the GI advantage of celecoxib and other selective COX-2 inhibitors may be lost in patients taking aspirin for cardiovascular prophylaxis. However, since a comparison of NSAID therapy ± concomitant low-dose aspirin was not a primary outcome in the CLASS trial, further studies are needed to assess the GI risk of a selective COX-2 inhibitor plus aspirin versus a conventional NSAID.

The following recommendations, which take into account pharmacoeconomic issues, can be made.

- Conventional NSAIDs, especially when used in short-term treatment of pain, are suitable for younger patients with no known risk of ulceration.
- Younger patients with a known risk of ulceration, elderly patients and patients with multi-morbidity not receiving cardiovascular prophylaxis should receive a selective COX-2 inhibitor.
- The use of both selective COX-2 inhibitors and conventional NSAIDs is contraindicated in patients with an existing ulcer, but selective COX-2 inhibitors may be used after the ulcer has healed.

Selective COX-2 inhibitors seem to have no advantage over conventional NSAIDs in patients taking aspirin for cardiovascular prophylaxis. Further trials with large numbers of patients from all age groups and with diverse types of concomitant illnesses are necessary in order to confirm these recommendations.

In 2001, the National Institute for Clinical Excellence (NICE) in the UK published guidelines for the use of selective COX-2 inhibitors in osteoarthritis and rheumatoid arthritis.[35] In addition, in a recent Canadian Technology Report the cost-effectiveness of rofecoxib and celecoxib in osteoarthritis and rheumatoid arthritis were assessed on the basis of the clinical outcome seen in the VIGOR and CLASS trials.[31] The report drew the following conclusions.

- Rofecoxib and celecoxib are not cost effective in patients at average risk of upper GI events or in a population with a typical mix of average- and high-risk patients.
- Rofecoxib and celecoxib are cost effective in patients who are at high risk because they have a history of upper GI events.
- Rofecoxib and celecoxib become less cost effective in high-risk patients as the rate of co-prescription of proton pump inhibitors increases.
- Rofecoxib and celecoxib become cost-effective in patients over the age of 76 years (for rofecoxib) or 81 years (for celecoxib) who have no additional risk factors.

These guidelines, as well as the recommendations above, serve as a basis for further discussion on the therapeutic use of rofecoxib.

4.2.4 Epidemiological Studies

Since the VIGOR and CLASS trials only compared selective and non-selective NSAIDs, the extent to which selective COX-2 inhibitors increase GI risk relative to that in untreated patients is unclear. Furthermore, the extent to which GI safety varies among selective COX-2 inhibitors is also uncertain because these agents have not been directly compared in a single large study.

In order to address these topics, Mamdani et al.[36] compared the extent of upper GI haemorrhage in elderly patients (aged ≥66 years) given rofecoxib (n = 14 583), celecoxib (n = 18 908), non-selective NSAIDs (n = 5391), diclofenac plus misoprostol (n = 5087) and in patients receiving none of these drugs (n = 100 000) in an observational cohort study. They found, in agreement with the VIGOR and CLASS trials, that the extent of upper GI haemorrhage with selective COX-2 inhibitors was lower than with conventional NSAIDs, but the risk with rofecoxib was significantly higher than that with celecoxib. In fact, the risk of GI haemorrhage with celecoxib was similar to that in controls not receiving NSAIDs.

In a postmarketing prescription-event monitoring study, the GI safety of rofecoxib was monitored in 15 268 patients (mean age 62 years, 67% female) for 9 months. The major indication specified was osteoarthritis (24%). The vast majority of adverse events reported were minor GI events (e.g. dyspepsia and nausea were reported most frequently), the incidences of which were related to factors such as

history of dyspeptic or upper GI conditions, use of concomitant medication (anticoagulants, gastroprotective drugs) and age. However, serious upper and lower GI events, thromboembolic events and renal failure also occurred (e.g. 110 serious GI events, 101 thromboembolic events and three reports of acute renal failure).[37]

In another postmarketing surveillance study, the efficacy and tolerability of rofecoxib in the treatment of osteoarthritis was assessed in 80 371 patients. Tolerability of rofecoxib was comparable to that seen previously in controlled trials with an incidence rate for serious GI adverse events of approximately 1 per 1000 patient-years.[21]

Patient satisfaction with rofecoxib, according to a survey involving a large population of osteoarthritis patients (74 192), was consistently high and this led the authors to conclude that rofecoxib has substantially better GI tolerability in the great majority of osteoarthritis patients.[22,23]

4.3 Cardiovascular Actions

4.3.1 Effect on Cardiovascular Risk

In the VIGOR trial the incidence of myocardial infarction (MI) was lower among patients taking naproxen than among those taking rofecoxib (0.1% vs 0.4%).[26] In the CLASS trial there was no significant difference in cardiovascular events between celecoxib and ibuprofen/diclofenac.[27] However, aspirin (≤325mg daily) was permitted only in the CLASS trial and thus only this trial contained patients (approximately 20%) under thrombosis prophylaxis.

The difference in cardiovascular events between rofecoxib and celecoxib could lead to the conclusion that rofecoxib causes more cardiovascular events than celecoxib. However, a differential analysis using subgroups is necessary in order to reach valid conclusions.

COX-1 is constitutively expressed in platelets and mediates the formation of the potent platelet activator and aggregator thromboxane A_2. COX-2 is not expressed in platelets but catalyses the formation of prostacyclin (PGI_2) in endothelial cells, a PG with potent vasodilatory and anti-aggregatory properties. Thus, it is clear that nonselective NSAIDs would inhibit both the formation of platelet thromboxane and endothelial prostacyclin. In contrast, selective COX-2 inhibitors have no antithrombotic properties but inhibit the formation of prostacyclin and have the potential to interfere with the natural balance between prothrombotic and antithrombotic eicosanoids in favour of the prothrombotic platelet thromboxane. Thus, therapy with selective COX-2 inhibitors may lead to increased cardiovascular thrombotic events. In general, this increased cardiovascular risk would be expected to be small because of other endothelial-derived protective mechanisms such as nitric oxide production.[38] Nevertheless, this would be a drug class-specific effect, and should be present in both the VIGOR and CLASS trials. The reason why a difference in cardiovascular toxicity between celecoxib and ibuprofen or diclofenac was not seen in the CLASS trial may be due to differences in study population, the nature of the nonselective NSAIDs, or the use of aspirin.

Patients with rheumatoid arthritis (VIGOR trial) may have an increased risk of thrombotic events in contrast to patients with osteoarthritis (majority of patients in CLASS trial).[39,40]

An almost complete inhibition of platelet thromboxane is necessary in order to achieve a significant vascular protective effect.[41] Whereas naproxen and aspirin (≤325mg daily permitted in the CLASS trial) inhibit platelet aggregation nearly completely (93% and 92%, respectively), ibuprofen and diclofenac have significantly lower platelet anti-aggregatory potencies (approximately 80% and 40%, respectively)[42] which may be insufficient for a significant cardioprotective effect. Furthermore, Catella-Lawson et al. showed that prior administration of ibuprofen antagonises the platelet anti-aggregatory effect of aspirin.[43] van Hecken et al. demonstrated that diclofenac inhibits COX-2 almost completely (94% in contrast to naproxen which produces only 71% inhibition of COX-2) and thus, diclofenac exhibits some selectivity for COX-2 (potency against COX-2 and reduced potency at COX-1) which may result in a pro-thrombotic effect.[44]

The lower platelet anti-aggregatory effect and presence of pro-thrombotic effects in the case of ibuprofen and diclofenac on the one hand, and the use of low-dose aspirin for cardiovascular prophylaxis on the other, may have masked a higher cardio-

vascular risk with celecoxib or led to an underestimation of the cardiovascular risk in the CLASS trial. In this context it should be noted that Ray et al.[45] suggest that naproxen and other non-aspirin NSAIDs should not be used for cardioprotection because of the absence of a protective effect whereas Cleland, in a reply to the article of Ray et al., stated that chronic ingestion of NSAIDs, including aspirin, may not protect against acute atherothrombotic vascular events and could even be deleterious.[46] Furthermore, Howes and Krum suggested that rofecoxib may be associated with a greater risk of MI than celecoxib and certain nonselective NSAIDs due to a greater tendency to increase blood pressure[47] rather than a pro-thrombotic effect.[48] However, another study found that selective COX-2 inhibitors improved cardiac function after MI.[49]

The above data have been intensively discussed by Mukherjee et al., who obtained evidence for a significantly higher cardiovascular risk for rofecoxib and celecoxib compared with placebo,[42] but the validity of the analysis used by Mukherjee et al. has been questioned.[48,50] Konstam et al. and others[51] found no difference in the incidence of cardiovascular events between rofecoxib and placebo or between rofecoxib and nonselective NSAIDs (with the exception of naproxen).[52]

Since the effect of rofecoxib on cardiovascular events in the VIGOR trial was not included in the protocol as an adjudicated end point and a placebo was not given, much larger trials are needed to adequately assess the cardiovascular toxicity of COX-2 inhibitors.

4.3.2 Epidemiological Studies

Mamdani et al. compared the rates of acute MI among elderly patients (aged ≥66 years) treated with rofecoxib (n = 12 156), celecoxib (n = 15 271), naproxen (n = 5669), non-naproxen nonselective NSAIDs (n = 33 868) or none of these drugs (n = 100 000) in a population-based retrospective cohort study.[53] They found no increase in the short-term risk of acute MI for all drugs.

In a postmarketing prescription event monitoring study, the thromboembolic safety of rofecoxib was monitored in 15 268 patients. In the 9 months after starting therapy, 21 (0.14%), 74 (0.48%) and 6 (0.05%) cardiovascular thromboembolic, cerebrovascular thromboembolic and peripheral venous thrombotic events, respectively, were reported for rofecoxib, resulting in a low overall incidence of <0.5%.[54]

4.3.3 Possible Atheroprotective Action

COX-2 is expressed by monocytes/macrophages in human atherosclerotic lesions but not in normal arteries,[55,56] suggesting the possible role of COX-2 in the inflammatory processes of atherogenesis. The possibility that COX-2 inhibition is anti-atherogenic was investigated by Linton and Fazio in low-density lipoprotein (LDL) receptor-deficient mice and LDL receptor-deficient mice devoid of macrophage COX-2.[57] Treatment with both rofecoxib and indomethacin resulted in a significant reduction in atherosclerosis as compared with control mice. On the other hand, the LDL receptor-deficient mice devoid of macrophage COX-2 developed significantly less atherosclerosis than control mice, providing genetic evidence for a pro-atherogenic role of macrophage COX-2 expression. These results would suggest that anti-inflammatory therapy with rofecoxib prevents atherosclerosis. However, these findings need to be verified in large clinical trials.

4.4 Renal Toxicity

The kidneys are the second most frequent organ showing adverse effects during NSAID treatment. The kidney is a site of formation and metabolism of PGs. PGE_2, the most abundant PG in the renal tubules, regulates sodium and chloride transport in the loop of Henle. PGE_2 also influences water transport and renal medullary blood flow. Prostacyclin is the most abundant PG in the renal cortex where it regulates renal vascular tone, glomerular filtration rate (GFR) and renin release. Therapy with NSAIDs leads to a decrease in renal perfusion, decrease in GFR, decrease in sodium and potassium excretion, oedema, and an increase in blood pressure.

COX-2, but not COX-1, is expressed in the region of the cortical macula densa and is involved in renin release.[58,59] The activity of COX-2 in this region is increased in rats chronically deprived of sodium, indicating that COX-2 has a role in the renin-angiotensin system. The selective COX-2 inhibitor NS398 reduces renin content and renin mRNA expression in salt-depleted mice but not in

mice on a normal sodium diet.[60] This suggests that COX-2-derived PGs have a compensatory function in the maintenance of systemic and renal haemodynamic functions. Inhibition of this compensatory role would therefore account for the common renal adverse effects associated with nonselective NSAID therapy.[61] Because selective COX-2 inhibitors inhibit COX-2 in the same manner, differences in renal toxicity between conventional NSAIDs and selective COX-2 inhibitors would not be expected.

Clinical studies on renal toxicity[62,63] show that the renal effects of COX-2 inhibitors are similar to those of conventional NSAIDs.[64] Only Zhao et al.[65] reported an increase in renal toxicity of rofecoxib compared with celecoxib and conventional NSAIDs (ibuprofen and diclofenac).

Although the risk of serious renal toxicity is relatively low, up to 5% of individuals exposed to NSAIDs develop some adverse renal effects.[66] The number of cases can approach 20% in groups of patients at high risk (those with pre-existing renal impairment, heart failure, liver dysfunction, those taking diuretics and/or ACE inhibitors, and the elderly).[67] Therefore, kidney function should be monitored closely for signs of renal impairment soon after initiating treatment with both selective COX-2 inhibitors and conventional NSAIDs. The amount of monitoring or concern should be tailored to the perceived risk, e.g. young healthy individuals would need little if any monitoring.

4.5 Minor Adverse Effects

Minor adverse effects (low severity or rare) including dyspepsia, nausea (vomiting), diarrhoea, pain in the abdomen, oedema, dizziness, intolerance, headache (migraine), unspecified GI events (aside from the GI events previously discussed in section 4.2), malaise (lassitiude), pruritus, rash, dyspnoea, constipation, insomnia, drowsiness (sedation) and other unspecified adverse effects can occur in up to 5% of patients treated with rofecoxib.[37,68]

4.6 COX-Independent Actions

Several studies have demonstrated that both selective and nonselective COX inhibitors have pharmacological effects that are independent of the inhibition of COX and prostanoid synthesis but which are mediated through inhibition of transcription factors such as nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1).[69] Celecoxib in high doses activates NF-κB and NF-κB-dependent gene transcription resulting in complete loss of anti-inflammatory action.[70] Rofecoxib at high doses inhibits NF-κB activation and activates AP-1 and these actions may explain the lack of clear dose dependency seen in some clinical and animal experiments. It should be noted that AP-1 is involved in renal sodium transport and renal sodium channels are regulated through AP-1.[71]

5. Conclusion

The efficacy of rofecoxib in osteoarthritis in various clinical studies is comparable to that of conventional NSAIDs but the incidence of GI adverse events with rofecoxib is significantly lower than with nonselective NSAIDs. However, rofecoxib is likely to have no obvious advantage over conventional NSAIDs in patients receiving low-dose aspirin for cardiovascular prophylaxis, from evidence obtained with celecoxib. The possibility that therapy with rofecoxib is associated with increased cardiovascular toxicity is a topic of ongoing discussion. Furthermore, rofecoxib offers no advantage over conventional NSAIDs with regard to renal toxicity.

On the basis of these data, nonselective NSAIDs and rofecoxib possess a spectrum of biological effects, both favourable and unfavourable. At one end of the spectrum, rofecoxib shows a lower tendency to cause GI toxicity but possibly with a higher thrombotic risk. At the other end of the spectrum, aspirin and naproxen show greater potential for GI toxicity but may have a cardioprotective effect. Other agents occupy intermediate positions within this spectrum. Clinicians would need to consider these patterns of risk and benefit in order to select the most appropriate agent for the individual patient.[42]

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