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Paracetamol in the Treatment of Osteoarthritis Pain

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Abstract

Osteoarthritis (OA) is the most common joint disease and OA of the knee, in particular, is the major cause of chronic disability among people >65 years. Because nonsteroidal anti-inflammatory drugs (NSAIDs) improve symptoms in many patients with OA, it is widely considered that OA pain is due to synovial inflammation. However, OA pain may arise also from subchondral bone, the joint capsule, ligaments, tendons, entheses and periarticular muscle spasm. In many patients, the relief of OA pain and overall satisfaction with therapy may be as great with paracetamol (acetaminophen [APAP]) as with an NSAID. Cyclo-oxygenase (COX)-1-sparing NSAIDs (coxibs) are no more effective in the treatment of OA pain than non-selective NSAIDs and, although they may significantly decrease the risk of serious adverse effects related to gastrointestinal ulcers (GI) and ulcer complications, their gastroprotective effect may be reduced by concomitant administration of low-dose aspirin. Also, they may increase the risk of myocardial infarction in predisposed individuals. Because coxibs do not inhibit platelet aggregation, if prophylaxis against thromboembolic disease is required in patients being treated with a selective COX-2 inhibitor, low-dose aspirin should be used in conjunction with the coxib. Furthermore, nonselective NSAIDs and coxibs may have adverse effects on the kidney, fracture healing and salt and water homeostasis. This paper discusses the relative positioning of APAP, NSAIDs and coxibs in the management of OA, on the basis of considerations of tolerability, efficacy and costs.

1. Introduction

In any consideration of pharmacological treatment for osteoarthritis (OA) it is important to recognize that the *keystone* of management of the patient with OA is based, not on drugs, but on non-pharmacological measures. Analgesics and anti-inflammatory drugs are adjuncts, not alternatives, to non-medicinal measures in treatment of the patient with OA.

2. Efficacy of NSAIDs and APAP in OA

Physicians prescribe NSAIDs abundantly for symptomatic treatment of OA. Given the significant morbidity and mortality associated with NSAID use and the difference in cost between paracetamol (acetaminophen [APAP]) and branded NSAIDs, including coxibs, what is the evidence that an NSAID is more effective than APAP in treatment of OA pain? Until publication of the landmark study by Bradley et al.,[1] no direct comparison of these two classes of drugs for treatment of OA was available. The *new* information that emerged from that study was that the efficacy of an anti-inflammatory dose of APAP was essentially no greater than that of paracetamol (table I). These results could have been predicted:

Table I. Efficacy: comparison of paracetamol with analgesic and anti-inflammatory doses of NSAID. (Reproduced with permission from Bradley JD, et al.[1])

Variable	Acetaminophen 4 000 mg/day (n = 60)[a]	Ibuprofen		p
		1 200 mg/day (n = 61)[a]	2 400 mg/day (n = 61)	
HAQ pain score[b]	0.33	0.30	0.35	0.93[c]
Walking pain score[b]	0.13	0.31	0.45	0.10[c]
Rest pain score[b]	0.06	0.33	0.40	0.05[c]
Walking distance score[a]	0.06	0.01	0.09	0.77[c]
Time to walk 15.25m (min)	0.50	0.50	0.70	0.93[c]
HAQ disability score[b]	0.08	0.08	0.11	0.91[c]
Improvement according to physician (% of group)	37	44	38	0.73[d]

a One patient did not return for follow-up assessment.

b Range of possible scores: 0–3.

c One-way ANOVA among the three groups.

d χ^2 test.

HAQ = Health Assessment Questionnaire

several previous trials had shown that a low (i.e. analgesic) dose of ibuprofen was as effective as an anti-inflammatory dose of other NSAIDs in providing symptomatic relief for patients with knee OA.

For these reasons and, particularly, because of concern about serious side effects of NSAIDs (see below), recent American College of Rheumatology (ACR) guidelines for management of OA[2-4] have recommended APAP, up to 4 000 mg/day, as the initial drug of choice for symptomatic treatment of OA. Similarly, European League Against Rheumatism (EULAR) guidelines for management of knee OA state: "paracetamol is the oral analgesic to try first and, if successful, is the preferred long-term oral analgesic"[5] and guidelines of the American Geriatric Society (AGS) for management of chronic pain in older persons, conclude: "For most patients with mild to moderate pain from degenerative joint disease (i.e., OA), acetaminophen provides satisfactory pain relief with a much lower risk of side effects than with NSAID drugs."[6]

2.1 How Effective are NSAIDs in Treatment of OA Pain?

Non-selective cyclo-oxygenase (COX) inhibitors, COX-1-sparing NSAIDs (coxibs) and APAP are only *modestly* effective in OA; in studies documenting superiority of an NSAID over placebo, the improvement is typically only about 20%, relative to baseline, and the difference between NSAID and placebo about 15–20%,[7-9] although some studies have shown improvement of somewhat greater magnitude.[10-12]

2.2 Does Greater Severity of OA Pain Predict a Better Response to an NSAID than to Paracetamol?

In a retrospective analysis by Bradley et al.,[13] severity of joint pain at baseline did not predict a better response to an NSAID than to paracetamol. However, a *post-hoc* analysis of the results of a clinical trial comparing APAP with a diclofenac/misoprostol formulation suggested that, although the difference in efficacy between the NSAID and APAP was negligible in patients with mild symptoms, in those with more severe OA pain the NSAID was more efficacious than APAP.[14] Felson[15] has suggested that the failure of the earlier trials to demonstrate a difference in efficacy between APAP and NSAID may have been attributable, in part, to relatively small sample

sizes and the modest effect of the treatments. He concluded that the above study[14] and a multicentre clinical trial with similar findings[16] supported the view that an NSAID merits consideration as first-line treatment in patients with more severe OA pain. The latter study, however, which has been presented only as an abstract, was a 6-day trial in which an *analgesic* dose of ibuprofen (1 200 mg/day) was statistically superior to APAP 4 000 mg/day, in individuals with knee OA who had moderately severe or severe knee pain at baseline, but not in those with mild or moderate pain. The brief duration of this study, however, imbues it with features of an acute pain model, in which pharmacodynamic and pharmacokinetic differences between analgesics may be accentuated. The relevance of the results to management of the chronic pain of OA is questionable. There is a need for prospective data from clinical trials in which patients are stratified at the outset on the basis of pain severity and randomized to treatment with an NSAID or APAP.

2.3 Do Clinical Signs of Inflammation Predict a Better Response to an NSAID than to APAP?

What is the evidence to support the view that an NSAID should be considered as the initial drug of choice in patients with OA who have signs of joint inflammation? There are essentially *no data* to support that view. Neither joint swelling, effusion or synovial tenderness[17] (i.e. clinical signs of joint inflammation) nor the severity of inflammation in a synovial biopsy[18] predict a better response to an anti-inflammatory dose of NSAID than to APAP. However, no prospective randomised controlled trial has been performed in patients stratified at the outset on the basis of severity of inflammation of the OA joint. Such information would be very helpful in ascertaining whether synovitis predicts a better response to an NSAID than to a simple analgesic; given the differences between APAP and NSAIDs with respect to safety and cost, the question is important. Clearly, some patients with OA pain find an NSAID more efficacious than APAP. It is impossible to predict, however, *which* patient with OA will do better with an NSAID than with APAP.

2.4 Additive Effects of APAP and NSAIDs

In many clinical trials of NSAIDs, patients are permitted to take a supplementary analgesic, most often APAP, but the benefit is seldom evaluated. In a small crossover study in patients with OA of the hip, naproxen plus APAP was more effective than the same dose of naproxen alone,[19] and the effect of naproxen 500 mg/day plus APAP 4 g/day was similar to that of 1 000 mg/day of naproxen alone. Thus APAP may be used to treat residual pain in patients with OA who remain symptomatic while receiving NSAID treatment, and for its NSAID-sparing effect in patients whose OA pain is well controlled with an NSAID.

2.5 Patient Satisfaction with NSAIDs Compared with APAP

When patients who had been exposed to APAP and to NSAID(s) for treatment of OA of the hip or knee were asked to compare the effectiveness of, and their overall satisfaction with, these treatments, although the majority favoured NSAIDs, the margin was slim. Nearly 50% felt APAP was about the same as, better than or much better than, their NSAID[20] (table II). Similarly, although the findings of a trial in which a diclofenac/misoprostol formulation was compared with APAP[21] indicated greater improvement in joint pain, function and quality of life with the NSAID, when patients and investigators (both of whom were blinded to the treatments) were asked which treatment they preferred, nearly 50% indicated preference for APAP (table III). Thus, *statistical* significance does not necessarily imply *clinical* significance. Patient preference for one treatment over another may be based, not only on differences in efficacy, but on adverse effects, cost and a variety of unknown factors.

As further evidence that the level of satisfaction with NSAID treatment for OA among patients or physicians is not great, on average only about 20%

Table II. Patient preference: comparative effectiveness of, and overall satisfaction with, paracetamol and NSAIDs reported by patients with hip or knee osteoarthritis. (Modified with permission from Wolfe F, et al.[20])

	Patients' judgement of paracetamol relative to their NSAID(s)		Total (%)
	Much less Somewhat less	Same/More/ Much more	
Effectiveness	56	45	101[a]
Satisfaction	52	48	100

a Total exceeds 100% because of rounding off

of patients with hip or knee OA in whom NSAID treatment is initiated are still taking the same NSAID 12 months later.[22] This attrition is chiefly the result of lack of efficacy or non-specific gastrointestinal (GI) complaints. No studies have been published to indicate that the durability of treatment with a coxib is substantially greater than that with non-selective NSAIDs.

3. Adverse Effects of APAP: What are the Data?

3.1 APAP and Alcohol

Retrospective reports linking therapeutic doses of APAP to hepatic necrosis, liver failure and death in individuals who abuse alcohol have led some physicians to avoid the use of APAP in patients who drink alcohol or to decrease the dose of the drug when APAP is used as an analgesic in such patients. However, most reports of hepatic injury associated with a therapeutic dose of APAP in alcohol abusers are confounded by the presence of serum APAP concentrations much greater than those which would be consistent with a therapeutic dose, liver histopathology inconsistent with paracetamol toxicity, and/or evidence of co-administration of other hepatotoxins. The retrospective nature of such studies and frequently conflicting data make it impossible to be certain of causation.

In a placebo-controlled trial in which therapeutic doses of APAP were given to chronic abusers of alcohol for 2 days immediately after they had ceased drinking (i.e. when they would have been most vulnerable to the effects of APAP on the liver), the drug was not found to be associated with

Table III. Treatment of osteoarthritis with an NSAID or paracetamol (APAP). Patients' ratings and physicians' ratings of better treatment in a crossover clinical trial of diclofenac/misoprostol (D/M) compared with APAP. (Reproduced with permission from Pincus T, et al.[21])

	Group I[a]	Group II[b]	Total
Patients' ratings			
D/M better or much better	52 (58)	48 (57)	100 (57)
APAP better or much better, or no difference	38 (42)	36 (43)	74 (42)
Physicians' ratings			
D/M better	54 (59)	49 (56)	103 (58)
APAP better, or no difference	37 (40)	38 (44)	75 (42)

Values given are number (%) of patients.

a Group I received D/M first, followed by APAP.

b Group II received APAP first, followed by D/M.

evidence of hepatic injury.[23] Data are lacking, however, with respect to the effects, if any, of chronic dosing of APAP in those who abuse alcohol or in individuals with hepatic disease. Furthermore, it should not be assumed that supratherapeutic doses of APAP (more than 4 g/day), would not be harmful to alcohol abusers or individuals with aspartate transaminase or alanine transaminase concentrations greater than 120 U/L (table IV). This lack of evidence of a causal relationship is important – if APAP use is proscribed, the alternative over-the-counter (OTC) analgesics that such patients will seek are likely to be NSAIDs, use of which in patients who abuse alcohol may be hazardous and even fatal.

3.2 APAP in Patients with Liver Disease

Whether patients with non-alcoholic chronic liver disease are at risk for APAP hepatotoxicity is unknown. Administration of APAP 4 g/day, to patients with a variety of chronic liver diseases, increased the mean half-life of the drug, but did not result in an increase in liver damage.[24] However, because those observations were limited to only 20 individuals, who were studied for less than 2 weeks, they must be interpreted with caution. Prospective studies examining the risk of hepatotoxicity with *chronic* administration of therapeutic doses of APAP have not been performed in patients with underlying liver disease.

3.3 APAP and Renal Disease

Few reports exist of APAP-induced renal disease. Acute APAP nephrotoxicity has been documented only with overdoses, when it is most often secondary to acute hepatic failure. Although it has been suggested that chronic ingestion of APAP increases the risk of chronic renal disease,[25,26] no evidence was presented that exposure to APAP *preceded* end-stage renal disease in those studies. Obviously, analgesic drugs may be taken to relieve symptoms caused by, rather than resulting from, the conditions leading to renal failure. APAP use has not been established as a significant cause of chronic renal disease.

In addition to APAP, a variety of OTC analgesics, including aspirin, ibuprofen and naproxen, are available. Physicians commonly advise patients with renal insufficiency to avoid aspirin and other NSAIDs because of the risks of bleeding and changes in renal haemodynamics caused by inhibition of prostaglandin synthesis. Use of APAP as an analgesic, therefore, is far greater than that of NSAIDs in patients with renal insufficiency, and some association between APAP use and end-stage renal disease is to be expected. Ingestion of large

Table IV. Hepatic aminotransferase concentrations after administration of paracetamol to alcohol abusers. (Modified with permission from Kuffner EK, et al.[23])

Variable	Paracetamol group (n = 102)	Placebo group (n = 99)	p
Developed AST level greater than baseline value	41 (40.2)	42 (42.4)	0.77
Developed ALT level greater than baseline value	52 (51.0)	62 (62.6)	0.12
Developed AST or ALT level >120 U/L	4 (3.9)	5 (5.1)	0.75
Developed AST or ALT level >1 000 U/L	0 (0)	1 (1.0)	0.49
Day 2			
AST level (U/L)	33.3 ± 21.4	38.0 ± 24.7	–
ALT level (U/L)	33.1 ± 22.0	37.3 ± 23.9	–
Day 4			
AST level (U/L)	38.0 ± 26.7	37.5 ± 27.6	–
ALT level (U/L)	40.1 ± 30.9	41.9 ± 33.9	–

Values are number (%) of individuals or mean ± SD.

AST = aspartate aminotransferase; **ALT** = alanine aminotransferase.

quantities of APAP should be discouraged, but caution is required in restricting modest doses because this might induce habitual APAP users to change to other medications, such as NSAIDs, the safety of which is more questionable than that of APAP. Indeed, APAP is the OTC analgesic of choice for patients with renal disease. A National Kidney Foundation (NKF) position paper[27] stated that APAP "...remains the non-narcotic analgesic of choice for episodic use in patients with underlying renal disease...but habitual consumption of APAP should be discouraged [and if] indicated medically, long-term use of this drug should be supervised by a physician." With respect to NSAIDs, the NKF recommended that "there should be an *explicit* label warning... of the potential renal risk of consuming OTC NSAIDs...[and] prolonged regular use of NSAIDs should be discouraged; if such use is necessary, renal function should be monitored...".

3.4 APAP and Asthma

Shaheen et al.[28] called attention to an association between APAP use and asthma and speculated that, by depleting glutathione (GSH) in the airways, APAP enhanced inflammation and increased bronchial hyper-responsiveness. Evidence for an association between APAP use and asthma in the above study was not compelling, however. Mudge[29] suggested that British Thoracic Society guidelines for management of asthma, which specifically mention avoidance of aspirin, might have influenced the above findings; that is, if patients with asthma were advised to use APAP in preference to aspirin, an association between APAP and asthma might have been iatrogenic. With respect to the postulated mechanism, namely depletion of lung GSH, animal studies have used enormous doses of APAP that, in a 70-kg human, would have been equivalent to a dose exceeding the LD_{50}. Asthma is not a feature of APAP overdose in humans. Therapeutic doses of APAP are unlikely to decrease pulmonary GSH to a greater extent than they depress hepatic GSH, the decrease in which has been shown to be less than 10%. Despite the presence of rare anecdotal reports, which do not permit establishment of causality (see below), there is no convincing evidence that the risk of adverse events with therapeutic doses of APAP is increased in patients with clinical conditions in which low concentrations of GSH have been observed – for example, infection with human imunodeficiency virus or hepatitis C, malnutrition and cirrhosis.[30] Given the usefulness of APAP in treatment of patients with OA, a strong case can be made that it should not be withheld categorically from patients with asthma, but should be discontinued if its use results in deterioration in asthma control. In summary, reports of an association between APAP use and asthma – like those of an *association* between APAP use and renal or hepatic disease – do not provide evidence of a *causal* relationship, but may represent the bias that arises as a result of confounding by indication.[31]

3.5 APAP–Warfarin Interaction

Because it does not inhibit platelet function or increase the risk of gastric mucosal damage, APAP is generally preferred to an NSAID for analgesia in patients taking warfarin. Although the anticoagulant effect of warfarin may be potentiated by APAP in a dose-dependent fashion,[32] reports of clinically important bleeding with prolongation of the international normalised ratio (INR) related to the use of APAP in patients taking coumadin are rare. In contrast, it is well established that use of aspirin, other non-selective NSAIDs or coxibs by patients taking warfarin may be associated with serious bleeding. Indeed, package inserts for both celecoxib and rofecoxib caution against their use in patients taking warfarin.

Physicians should counsel patients who take warfarin as to the use of APAP. INR levels should be monitored closely in such patients if they require sustained therapeutic doses of APAP. However, the risk of bleeding appears to be much lower than that in patients taking a non-selective NSAID or coxib, making APAP the non-opioid analgesic of choice in such cases.

3.6 APAP and Upper Gastrointestinal Ulcers

A recent report of the results of a nested case-control study, using United Kingdom General Research Database entries from April 1993 to October 1998, concluded that use of APAP in doses in excess of 2 g/day was associated with an adjusted risk of 3.6 for an upper GI complication (95% CI 2.6 to 5.1) – a risk similar to that for anti-inflammatory doses of NSAIDs.[33] Furthermore, when the analysis was restricted to individuals who had not previously received a prescription for NSAIDs and had no recorded history of upper GI disorders, including dyspepsia, the corresponding relative risk (RR) for use of APAP in quantities greater than 2 g/day was 5.7 (95% CI 2.0 to 16.4). Notably, these results contrast with those of previous epidemiological studies[34-38] that provided estimates of the RR of upper GI complications associated with use of APAP in any dose, in which estimates ranged from 0.2 to 1.9 (mean 1.4, 95% CI 1.0 to 2.0); only one of these studies reported an increased risk of upper GI complications with APAP doses greater than 1 g/day (RR 2.6).[37] The authors recognized the inevitability of confounding by indication in observational studies such as the above – that is, that use of APAP was a surrogate for greater risk of upper GI complications from NSAID use, and acknowledged that their effort to control for known risk factors for upper GI complications would not have eliminated such bias. Furthermore, they recognised that their use of a computerised prescription database may have resulted in underascertainment of OTC drug use. Wilcox et al.[39] emphasised that upper GI bleeding may be as common, or more common, with OTC use of aspirin as with prescription doses.

4. Serious Adverse Effects of Non-Selective NSAIDs

4.1 The Gastrointestinal Tract

Although the greatest concern relative to NSAID toxicity has been directed toward the risk of symptomatic ulcers and ulcer complications, these occur in only 2–4% of patients treated with an NSAID for a year. Non-specific GI complaints are much more frequent. In clinical trials of NSAIDs, 25–50% of individuals report epigastric pain, dyspepsia, nausea, vomiting or diarrhoea. Even though these are not life-threatening, they affect adherence to the prescribed dosing regimen, result in frequent switching from one NSAID to another, generate additional costs for treatment of the gastric complaints, and lead to expensive radiological or endoscopic studies, or both, to rule out underlying peptic ulcer disease or neoplasm. NSAIDs are also associated with adverse effects on the intestine, such as inflammation, with loss of blood and protein, stricture, ulceration, perforation and diarrhoea.

The serious GI adverse events associated with the use of NSAIDs are dose-dependent and occur even within the recommended therapeutic range. This is important, because there is no evidence that a greater (i.e. anti-inflammatory) dose of NSAID is more effective in relieving OA pain than a lower (i.e. analgesic) one. As noted above, concomitant administration of APAP may permit a reduction in NSAID dose without compromising pain relief. Similarly, implementation of non-pharmacologic measures will often permit reduction in NSAID dose, decreasing the risk of a serious adverse event.

Not all patients taking an NSAID are at identical risk for a serious NSAID-related GI event. A number of risk factors have been identified (table V). In deciding whether to institute NSAID treatment in a patient with OA, *the risks must be weighed against the benefits*.

4.2 Cardiovascular/Renal Effects of NSAIDs

In contrast to APAP, NSAIDs may cause sodium and water retention and blunt the response to diuretics. NSAID-induced inhibition of prostaglandin synthesis may cause renal insufficiency, oedema, hypertension, hyperkalaemia and hyponatraemia (figure 1).[40] Patients with underlying renal disease, congestive heart failure (CHF), diabetes mellitus, cirrhosis, hypertension or depletion of the circulating blood volume (as a result of,

for example, the use of diuretics, haemorrhage, diarrhoea or profuse sweating) are particularly vulnerable to development of NSAID-induced renal disease. Even a dose of NSAID so low that it has minimal anti-inflammatory effects may cause renal insufficiency.

Many antihypertensive drugs exert their therapeutic effect, in part, through prostaglandin-mediated mechanisms. Although NSAIDs generally have little or no effect on blood pressure in normotensive individuals, they may increase blood pressure in hypertensive patients who are receiving treatment.[41] Although the increase may be only 4–5 mmHg, over a few years an increase in diastolic blood pressure as small as 5–6 mmHg may increase the risk of a cerebrovascular accident by 67% and of coronary artery disease by 15%. In contrast, reductions in increased diastolic blood pressure may decrease the incidence of stroke and congestive heart failure by nearly 40% and 25%, respectively.[42]

While acute effects on renal blood flow in NSAID users are much more common than chronic renal changes, NSAIDs *can* cause chronic renal disease; indeed, they are much more likely to do so than APAP. An excellent review of the renal effects of NSAIDs and analgesics has recently been published.[43]

Table V. Risk factors for serious upper gastrointestinal adverse events in NSAID users

Increasing age
Co-morbidity (poor or fair general health)
Oral glucocorticoids
History of peptic ulcer disease
History of upper gastrointestinal bleeding
Anticoagulation
Combination NSAID therapy
Increasing NSAID dose
Smoking (?)
Alcohol (?)
Helicobacter pylori infection (?)

4.3 NSAIDs and Congestive Heart Failure

The changes in salt and water metabolism associated with the effects of NSAIDs on the kidney may precipitate CHF. Among patients with a prior history of heart disease, use of an NSAID strikingly increases the risk of CHF (figure 2).[44] It has been suggested that NSAID use is responsible for nearly 20% of admissions to hospital with CHF, and that the burden of illness resulting from

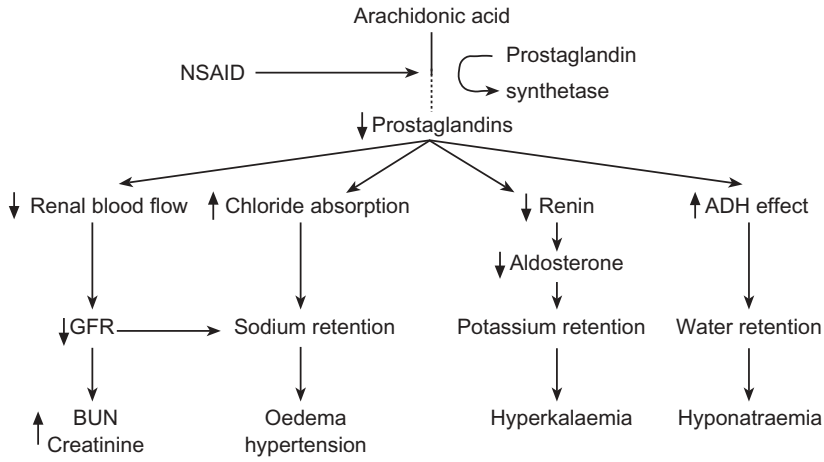

Fig. 1. Renal effects associated with NSAID-induced prostaglandin inhibition. **ADH** = antidiuretic hormone; **BUN** = blood urea nitrogen; **GFR** = glomerular filtration rate. (Reproduced with permission from Aronoff GR.[40])

NSAID-related CHF may exceed that resulting from damage to the GI tract.[45]

4.4 Inhibition of the Antiplatelet Effect of Aspirin by Ibuprofen

It has recently been shown that the non-selective NSAID, ibuprofen, may *inhibit* the antiplatelet effect of aspirin.[46] Maximal inhibition of serum thromboxane B_2 concentrations (an index of COX-1 activity in the platelet) and platelet aggregation produced by a low dose of aspirin were blocked by a single daily dose of ibuprofen (400 mg) administered 2 hours before the dose of aspirin. Similar results were obtained with doses of ibuprofen 400 mg three times daily (as commonly used in treatment of OA pain). In contrast, concomitant administration of single doses of rofecoxib, a slow release formulation of diclofenac or APAP 1 000 mg, had no effect on aspirin pharmacodynamics. The inhibitory effects of multiple daily doses of ibuprofen were apparent even when patients received aspirin before their morning dose of ibuprofen. The effects of multiple daily doses of APAP, as might be used in treatment of OA pain, or of other NSAIDs, were not tested. Although the clinical implications of these results have not been demonstrated, these data suggest that APAP, rather than ibuprofen, is the agent of choice in patients taking low-dose aspirin who require an OTC analgesic.

5. Should COX-1 Sparing NSAIDS Replace APAP as Initial Therapy for OA?

5.1 Efficacy of Coxibs in OA

Despite claims that the coxibs were 'super-aspirins,' they are no more efficacious in OA than non-selective NSAIDs which, as described above, often result in only modest improvement.[47-51] There is no evidence that the ratio of COX-2 to COX-1 inhibition is related to differences in efficacy among NSAIDs. Celecoxib 200 mg/day and rofecoxib 12.5 or 25 mg/day were recently found to have greater efficacy than APAP 4 000 mg/day in patients with knee OA,[52] assessed on the basis of improvement in some of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, but most of the differences were not statistically significant.[53] Brune[54] noted that those results stood in contrast

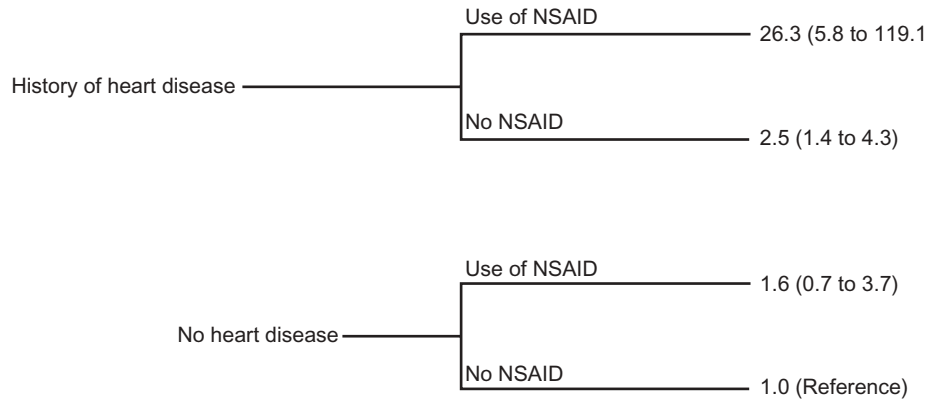

Fig. 2. Relationship between consumption of NSAIDs and history of heart disease in patients presenting with their first episode of congestive heart failure (CHF). Odds ratios (95% CI) for development of an initial episode of CHF in individuals taking an NSAID (other than low-dose aspirin) within the previous week. (Reproduced with permission from Page J, et al.[44])

to those of other 'head-on' comparative studies, in which COX-2 inhibitors have not proved superior to APAP. Furthermore, it should be recognized that exclusion of patients with significant co-morbidity limits the generalisability of such studies, as does the requirement for a flare after withdrawal of prestudy analgesics/NSAIDs, as is typically required in such trials.[55] Even if rofecoxib holds some advantage of efficacy over APAP, routine recommendation of a coxib (or non-selective NSAID) would put patients at risk for cardiovascular and renal adverse effects that are not issues with APAP.

5.2 The CLASS and VIGOR Gastrointestinal Safety Trials

Two major, large GI safety studies, conducted by the manufacturers of celecoxib and rofecoxib, have been published – the Celecoxib Long-Term Arthritis Safety Study (CLASS)[56] and the Vioxx Gastrointestinal Outcomes Research (VIGOR).[57] Both of these studies were designed to ascertain whether treatment with a coxib results in a lower incidence of clinically important NSAID-associated ulcers and ulcer complications than is seen with non-selective NSAIDs. It should be noted that the experimental designs of the CLASS and VIGOR studies differed in some important respects (table VI).

In the VIGOR trial, a clear reduction in the incidence of upper GI events was apparent in the rofecoxib treatment arm, in comparison with the naproxen arm. The risk of all clinical upper GI events was reduced by some 54% ($p < 0.01$), that of complicated upper GI events by 57% ($p = 0.005$) and that of any GI bleeding by 62% ($p < 0.01$).

In the CLASS study, the difference between the annualised incidence rates of upper GI ulcer complications (the primary outcome measure) with celecoxib and comparator non-selective NSAIDs was not statistically significant. For ulcer complications combined with symptomatic ulcers, however, the difference was significant (2.08% compared with 3.54%, respectively; $p = 0.02$). Among those who were not aspirin users, results over the first 6 months showed a significant reduction in ulcer complications with celecoxib – mimicking the results obtained with rofecoxib in the VIGOR trial (figure 3). However, use of low-dose aspirin appeared to mitigate the gastroprotective effect: among aspirin users, celecoxib treatment did not result in a statistically significant decrease in the incidence of ulcer complications in comparison with that in patients treated with non-selective NSAIDs. (Furthermore, although only 22% of individuals in the CLASS study were taking low-dose aspirin, in the author's practice as many as 60% of patients with OA who are older than 60 years are doing so.)

It must be noted that, although the major publication describing the results of the CLASS trial[56] presented the data for only the first 6 months of treatment, results were available for longer periods. In those who were not aspirin users, no significant difference between treatment groups was apparent with respect to the incidence of ulcer complications in patients treated for 12 months – that is, the superiority of celecoxib over the comparator NSAIDs observed during the first 6 months of treatment was not apparent in those who continued to receive treatment thereafter (figure 4).

In addition, although the publication of the CLASS study reported the comparative incidence rates of two main outcome measures – upper GI ulcer complications and symptomatic ulcers – during the first 6 months of treatment in a three-arm trial comparing celecoxib with ibuprofen and diclofenac, the paper actually referred to a combined analysis of the results of the first 6 months of *two separate and longer trials*, the protocols of which differed from those in the published paper with respect to design, outcomes, duration of follow-up and analysis. Specifically, two comparisons were originally planned: celecoxib versus ibuprofen and celecoxib versus diclofenac and, because the US FDA was concerned that coxibs might interfere with ulcer healing, leading to a long-term increase in ulcer-related complications, the prespecified primary outcome measure was

Table VI. Comparison of study designs for rofecoxib (VIGOR) and celecoxib (CLASS) gastrointestinal (GI) outcomes trials

Parameter	Trial	
	VIGOR[57]	CLASS[56]
Number of participants	8076	7982
Mean age (years)	~58	~60; ~38% older than 65
Underlying disease	Rheumatoid arthritis	Osteoarthritis 73% Rheumatoid arthritis 27%
Duration of follow-up	Median 9 months Maximum 13 months	Median 9 months Maximum 13 months
Type of analysis	Intention to treat (includes events within 14 days of last dose of study drug)	Excludes events on days 0–2 and after 6 months
Dose of coxib	Rofecoxib 50 mg/day	Celecoxib 800 mg/day
Comparator NSAID	Naproxen 1 000 mg/day	Ibuprofen 2 400 mg/day or diclofenac 150 mg/day
Low-dose aspirin	Not permitted	22%
Concurrent steroid use	56%	30%
Primary endpoint	Clinical upper GI events	Complicated ulcers
Secondary endpoint	Complicated upper GI events	Symptomatic + complicated ulcers

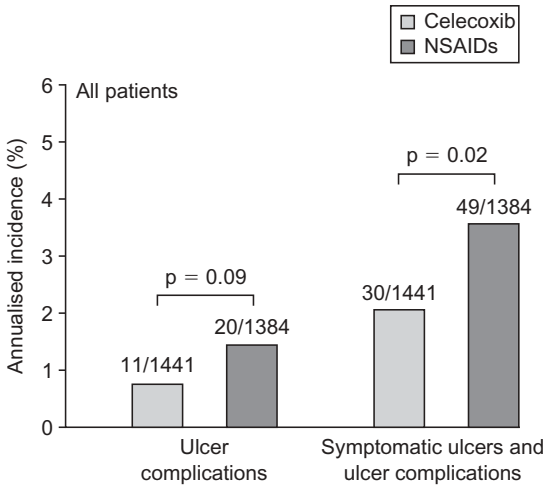

Fig. 3. The CLASS trial. Annualised incidence of upper gastrointestinal tract ulcer complications after 6 months. Numbers above bars indicate events per patient-years of exposure. NSAIDS indicates nonsteroidal anti-inflammatory drugs. (Reproduced with permission from Silverstein FE, et al.[56])

ulcer complications (not symptomatic ulcers) in both of these trials, in which the maximum duration of follow-up was 15 months and 12 months, respectively.

When the results of those studies were analysed, the incidence of ulcer complications in all treatment groups was similar. Almost all the ulcer complications that occurred during the second half of the trial (and were not reported in the publication) occurred in the celecoxib treatment group. These results, which were available when the manuscript was published but were not referred to in the article, contradict the published conclusions.[58]

5.3 Other Adverse Effects of Coxibs

Coxibs are no less likely than non-selective NSAIDs to cause salt and water retention, hypertension, oedema and CHF, or to impair fracture healing. They are also not free of non-specific GI adverse effects, such as epigastric pain, dyspepsia, nausea, vomiting and diarrhoea, the incidence of which appears to be only slightly lower with coxibs than with non-selective COX inhibitors.[59] Although Geba et al.[52] reported recently that non-specific GI adverse effects were as frequent in patients with OA of the knee treated with APAP as with celecoxib or rofecoxib, the significance of

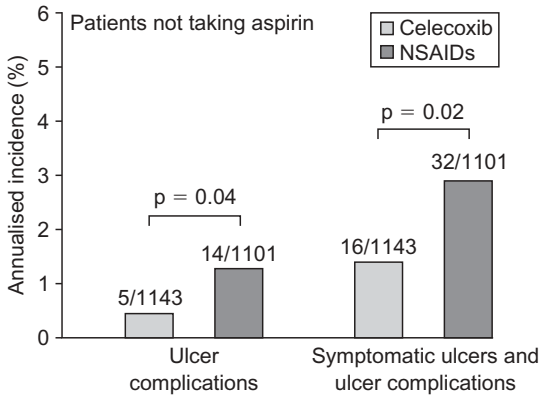

Fig. 4. The CLASS Trial. Ulcer complications and symptomatic ulcers in patients who were not taking aspirin, at 6 months and 12 months. Numbers above bars indicate events per patient-years of exposure. (Reproduced with permission from Silverstein FE, et al.[56])

that observation is uncertain because of the lack of inclusion of a placebo control group.

5.4 Do COX-1-Sparing NSAIDs Increase the Risk of Thrombosis?

Analysis of the data from the VIGOR study revealed an unanticipated result: the incidence of myocardial infarction was four times greater among patients treated with rofecoxib than among those treated with naproxen (table VII). Although the total number of individuals who experienced a myocardial infarction during the trial was low and the study was not powered to detect a significant difference in incidence of myocardial infarction between treatment groups, this observation raised significant concerns about possible detrimental cardiovascular effects of COX-1 sparing NSAIDs.

Because the risk of myocardial infarction is twice as great in rheumatoid arthritis as in OA, it is important to note that the VIGOR trial enrolled only patients with rheumatoid arthritis, and may have provided a more sensitive model for detection of thrombogenic effects of selective COX-2 inhibition than clinical trials of non-selective NSAIDs in patients with OA. However, because no information was provided with respect to the prevalence of risk factors for myocardial infarction (table VIII) in the two treatment groups in the VIGOR trial, it is difficult to interpret the suggestion of an increased risk of thrombosis among patients with arthritis taking a COX-1-sparing NSAID. Also, the doses of coxibs used in the CLASS and VIGOR studies were much greater than those used in treatment of OA, providing yet another basis for uncertainty about the relevance of the findings to treatment of patients in clinical practice. Nonetheless, the US FDA has recently approved revision of the package insert for rofecoxib, which now recommends that caution be exercised when this drug is used in patients with a history of ischaemic heart disease.

5.5 A Rational Approach to Use of Coxibs in OA

Is the patient in an intensive care unit better off if he is there because of a GI bleed rather than a myocardial infarction? The evidence needed to inform the physician as to which patient with OA might benefit most from a coxib or in which patient a coxib might be contraindicated is not available. Are the gastroprotective effects of coxibs negated by concomitant use of low-dose aspirin? Should coxib NSAIDs not be used in patients at risk for coronary thrombosis? Large randomised clinical trials of sufficient duration are required to answer these questions.

On a basis of the available information, the therapeutic recommendations for a patient with risk factors for myocardial infarction (table VIII) but a paucity of risk factors for an NSAID-associated peptic ulcer (table V) may differ from those for a patient with risk factors for a GI catastrophe who has no, or minimal, risk factors for myocardial infarction.

In any event, the results of the VIGOR trial emphasise the absence of antiplatelet activity of coxibs, because of their high level of COX-2 selectivity. The practical clinical point is this: in the patient with OA who is treated with either a non-selective NSAID or a coxib and who is also at

Table VII. Incidence of myocardial infarction in the VIGOR trial. (From Bombardier C, et al.[57])

	Rofecoxib (%) (n = 4047)	Naproxen (%) (n = 4029)	Difference (%) (95% CI)
All deaths	0.5	0.4	0.1 (−0.15 to 0.49)
Cardiovascular deaths	0.2	0.2	0.0 (−0.21 to 0.212)
Myocardial infarctions	0.4	0.1	0.3 (0.07 to 0.57)
Cerebrovascular accidents	0.2	0.2	0.0 (−0.17 to 0.27)

CI = confidence interval

Table VIII. Risk factors for myocardial infarction

Increasing age
Diabetes mellitus
Hypercholesterolaemia
Prior thrombotic event
Family history
Hypertension
Obesity
Smoking

risk for cardiovascular thrombosis and is a candidate for aspirin treatment, the NSAID will *not* obviate the need for prophylactic treatment with aspirin. In patients taking aspirin for cardiovascular prophylaxis, that treatment should *not* be discontinued if the patient also requires a non-selective NSAID or coxib. (However, as discussed above, in the CLASS study, low-dose aspirin abolished the gastroprotective effect of celecoxib.)

6. Costs of Treatment

6.1 NSAIDs versus APAP

Although safety and efficacy are two important considerations in the selection of a drug for treatment of OA, cost considerations cannot be ignored. As indicated above, in many patients, APAP may be as effective as a non-selective NSAID or coxib in treating OA pain. Although the low cost of APAP may be rivalled by that of a generic OTC NSAID such as ibuprofen or naproxen, if the cost of gastric co-therapy with misoprostol or a proton pump inhibitor for management of non-specific GI complaints or protection against NSAID-induced peptic ulcer disease is added, the cost may increase some 15-fold. In the USA, treatment with a coxib may be 10 times more expensive than treatment with APAP (table IX). Although it is not recommended therapy, a significant number of patients who are receiving coxibs concurrently take a proton pump inhibitor. Smalley et al.[60] reported recently that 52% of coxib users were co-prescribed anti-ulcer treatment, in comparison with 33% of users of traditional NSAIDs ($p < 0.0001$). Proton pump inhibitors were co-prescribed for 4% of users of traditional NSAIDs, but for 17% of coxib users. The prevalent co-prescription of coxibs and gastroprotective drugs appears to run contrary to the expectations that existed when the coxibs were launched. The assumption that coxib use would result in lower overall pharmacy costs has not been borne out, because of the substantial continued use of expensive anti-ulcer medications in patients receiving coxibs.

7. NSAID Withdrawal in Patients with OA

Even though the level of satisfaction of patients and physicians with NSAIDs is, in general, low, patients with OA are typically switched from one NSAID to another because of lack of efficacy or adverse effects. Barring development of a serious adverse event, treatment with NSAIDs is rarely discontinued. However, many patients with OA improve symptomatically – they *get better*.

Table IX. Monthly cost of treatment for osteoarthritis pain in Indianapolis. Values shown are averages for four randomly chosen Indianapolis pharmacies, from which retail prices were obtained at the beginning and end of the 17-month interval shown

Treatment	Average cost (US$)		Change (%) Jan 2000 to May 2001
	Jan 2000	May 2001	
APAP (generic) 4 g/day			
Tablets	11.34	10.38	(−) 8.5
Caplets	11.34	10.38	(−) 8.5
Gel caps	12.64	10.95	(−) 13.4
Celecoxib 200 mg/day	73.26	81.64	(+) 11.4
Rofecoxib			
12.5 mg/day	75.47	81.82	(+) 8.4
25 mg/day	75.47	83.89	(+) 11.1
Naproxen (generic)			
750 mg/day	20.29	20.52	(+) 1.0
1 000 mg/day	23.82	24.87	(+) 4.4
1 000 mg/day + **misoprostol** 800 μg/day	148.43	164.50	(+) 10.8
1 000 mg/day + **omeprazole** 20 mg/day	140.21	151.33	(+) 7.9

Despite the inclination to maintain NSAID treatment in perpetuity for the patient with OA, it is possible – and advisable – to decrease the dose of NSAID or discontinue NSAIDs entirely and thereafter to use APAP or an NSAID only as needed. Because the risks of adverse effects of NSAIDs are dose-dependent, this is highly desirable.

In a study of NSAID withdrawal[61] in elderly patients, NSAIDs were replaced, as needed, by measures such as a simple analgesic, hot or cold packs, massage or a muscle relaxant. Results showed that, in more than 50% of elderly individuals the NSAID could be successfully discontinued without a need for reinstitution of NSAID treatment over the ensuing 6-month period.

8. Conclusion

There is no question that an NSAID may be more effective than a therapeutic dose of APAP in decreasing joint pain and improving function in some patients with OA. However, it is impossible to predict which patient will do better with an NSAID than with APAP. Taking into consideration safety, efficacy and cost, the above data argue powerfully that APAP deserves a prominent place in the management of OA pain and should be viewed as the initial drug of choice for symptomatic treatment of OA.

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