Quality use of medicines: The elderly patients with Osteoarthritis

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Osteoarthritis (OA) is an exceedingly common diagnosis in family practice, particularly in the elderly population. It is certainly the most common of the arthritides, but differs substantially in that inflammation, if present, is usually mild and restricted to the affected joint(s). The causes are as yet not completely understood and there is no known cure. Taken together, this means that a large proportion of elderly patients, in whom concurrent morbidities are common and who are at increased risk of receiving multiple, potentially inappropriate medicines, will most probably require pain relief of some sort. It is probable that many of these patients contribute to the high use of analgesic agents in South Africa, and in particular of combination agents containing meprobamate.[1,2] In contrast, a more recent US survey has shown that the use of pharmacotherapy for OA has decreased over time, and that while use of the non-steroidal anti-inflammatory drugs (NSAIDs) has decreased, use of paracetamol has increased somewhat.[3] Like in many areas of medicine use, the evidence for and against various options in OA is continually changing. This paper will attempt to review some of the efficacy and safety concerns, paying less attention to the other relevant issues - suitability and cost. The goals of therapy should include the control of pain and other symptoms, while maintaining maximal joint mobility and minimising functional impairment, but at the same time avoiding, if possible, the toxic effects of the treatment used. *(SA Fam Pract 2003;45(7):54-57)*

PARACETAMOL

As with so many chronic ailments, non-pharmacological measures are indicated as the first resort in management. These include weight loss (if appropriate), physical and occupational therapy as well as patient education on a variety of topics. However, many patients will require pharmacotherapy. The first real change in decades of reliance on the NSAIDs came in 1995, with the publication of the American College of Rheumatology (ACR) guidelines.[4,5] These stated quite baldly "The non-prescription, non-opioid analgesic acetaminophen, at doses up to 4,000 mg/day is the recommended initial drug of choice". Acetaminophen is the American term for paracetamol. This was based on expert opinion and common usage, not on evidence from randomised, controlled trials (RCTs). Many might accept that paracetamol is an appropriate starting point, but might protest that (1) it is seldom sufficient, and (2) it is not devoid of adverse effects.

Subsequent review articles, some by members of the ACR guideline team, argued that there was evidence both of efficacy and of an acceptable safety profile. Shamoon and Hochberg concluded that paracetamol, at full doses (4g/day), "has comparable efficacy to ibuprofen in the management of patients with osteoarthritis at the knee who have mild to moderate pain".[6] The same authors reviewed the efficacy and safety literature, focussing on comparative trials of paracetamol and NSAIDs in OA, and concluded that paracetamol "merits a trial as initial therapy, based on cost-effectiveness and safety profile".[7] In September 2002, an update to the relevant Cochrane review combined the data from 6 RCTs, involving 1689 patients.[8] Only 1 RCT (involving 25 patients), compared paracetamol to placebo, whereas all the rest used NSAIDs as the comparator. It concluded that, while paracetamol was effective, it was less effective than NSAIDs in terms of pain reduction and global assessments of efficacy (whether performed by the patient or the investigator), but as effective in terms of functional improvement.

Interestingly, the Cochrane review did not show NSAID-associated adverse effects to be worse, but this has to be viewed with caution, as the RCTs reviewed were generally of short duration (ranging from 6 days to 2 years). At high dose, paracetamol is also capable of causing gastrointestinal (GI) side effects. There was no difference in the number of GI adverse events when NSAIDs (traditional as well as coxib-type) were compared with paracetamol (RR 1.43, 95% CI 0.97-2.10), as well as when the supposedly advantageous

coxib-type were compared with paracetamol (RR 0.96, 95% CI 0.57-1.61). However, the relative risk of withdrawal from treatment was higher with traditional NSAIDs than paracetamol (RR 2.15, 95% CI 1.05-4.42), and more adverse events were recorded (RR 2.24, 95% CI 1.23-4.08). That leaves the clinician with an uncomfortable choice – while the initial medicine might well be paracetamol, what should be used when, as can be predicted, some patients fail to respond to the highest recommended dose (4g/day)?

NSAIDS – OLD AND NEW

The ACR guidelines were updated in 2000, and retained the recommendation that paracetamol be the first choice: "For many patients with OA, the relief of mild-to-moderate joint pain afforded by the simple analgesic acetaminophen, is comparable to that achieved with an NSAID".[9] It re-iterated that paracetamol is safe, at doses up to 4g/day, but cautioned that this might not be true for those with pre-existing liver disease or chronic alcohol abuse. However, it was considered safe in patients with impaired renal function. The real challenge was to find an appropriate choice in those non-responsive to paracetamol, taking into account the patient's risk for serious upper GI and renal toxicity. Those at higher risk of upper GI bleeding were identified as:

- patients aged 65 years or older;
- those with a history of peptic ulcer disease or previous upper GI bleeding;
- those using oral steroids or anticoagulants;
- those with co-morbid conditions; and
- possibly, those who smoked cigarettes or consumed alcohol.

Identifying patients **not** at risk would seem to be a challenge in many family practice settings. While topical treatments (e.g. methylsalicylate or capsaicin, but not topical NSAIDs) were shown to be effective in some patients, a choice of an NSAID or alternative systemic treatment would still have to be made in many patients at potential risk.

Two options were offered – the COX-2-specific inhibitors or co-administration of a gastro-protective agent (misoprostol or a proton pump inhibitor) with a traditional non-specific NSAID. Other alternatives are beyond the scope of this review, and are perhaps best restricted to specialist use – these include intra-artricular injections of hyaluron or glucocorticosteroids in the case of OA of the knee. Despite the absence of data from large-scale RCTs showing a difference in efficacy and safety of the new COX-2-specific inhibitors (at that stage celecoxib and rofecoxib – hence sometimes referred to as the "coxibs") and traditional NSAIDs, the guideline seemed to favour the former. This choice is perhaps justifiable in comparison to co-administration of another agent, which would incur both cost and potential adverse event consequences. Misoprostol is known to cause diarrhoea and flatulence, which limit its usefulness. However, the comfortable distinctions drawn in 2000 are today far less clear.

Going back, though, it must first be pointed out that evidence for a difference between the older, traditional NSAIDs was already considered to be lacking. A 1997 update on a Cochrane review of NSAIDs in OA of the hip showed that there was then insufficient evidence to make clear recommendations on which particular agent was best.[10] No head-to-head comparisons showed any significant differences in efficacy, including those that evaluated certain combinations (e.g. paracetamol *vs* paracetamol plus codeine; dihydrocodeine *vs* dextropropoxyphene plus paracetamol). Only the combination of naproxen and paracetamol proved more effective than naproxen alone. All of these comparisons were however bedevilled by differences in case definitions, medicine doses and outcome assessment methodologies.

The 2000 ACR guidelines were based on the notion that the new COX-2-specific inhibitors were fundamentally different from their antecedents, and safer. This clear dichotomy is increasingly being challenged. Firstly, it would appear that there is a continuum of selectivity, from the COX-2-specific inhibitors through those that are dual COX-1 and COX-2 inhibitors to those that are more COX-1-specific.[11] Agents such as meloxicam, which were not specifically designed as COX-2-specific, have been shown to have considerable specificity for this enzyme. A hierarchy of the ability to induce GI side effects does exist, and has been stated as "rofecoxib = celecoxib < ibuprofen < meloxicam < diclofenac sodium < naproxen < piroxicam < indometacin < ketoprofen, in increasing order of activity".[12] However, the position of ibuprofen is perhaps incorrect, as this is based on studies in which low, analgesic-only doses were used. In all cases, though, GI effects are dose-dependent and combinations are associated with greater risks.[13]

The real "stink" though, has been created by the release of two large RCTs designed to demonstrate the safety of the new COX-2-specific inhibitors, celecoxib (the CLASS study) and rofecoxib (the VIGOR study).[14,15] The latter appeared to provide more clear-cut results – rofecoxib was better than naproxen, in that fewer GI side effects were noted. However, when all adverse events were recorded (as was shown in a remarkable presentation on the FDA web site of its review of the data), naproxen was shown to be safer. While 9.3% of patients on rofecoxib experienced a serious adverse event, this occurred in only 7.8% of those on naproxen (RR 0.81, 95%CI 0.62-0.97). An even more serious charge has been levelled at the CLASS investigators – who also claimed a benefit for celecoxib. This has been well summarised by Jüni, Rutjes and Dieppe and also in the Therapeutics Initiative newsletter.[16,17] In essence, while the CLASS trial was initially intended to be two longer comparison of celecoxib vs ibuprofen (12 months) and celecoxib vs diclofenac (15 months), only combined data from the six-month analysis was published. It was alleged that the protocols for the two trials differed markedly from that presented in the JAMA paper. A confounding feature was that patients were allowed to take low-dose aspirin. Only in those who did not take aspirin was there a significant difference in the incidence of predefined serious GI events (symptomatic ulcers and ulcer complications – bleeding, perforation and obstruction) between those on celecoxib compared to

ibuprofen, but not diclofenac. However, the full data set was presented to the FDA in February 2001, and a different conclusion was drawn. For both coxibs, the American authorities mandated the usual labelling regarding the risk of gastrointestinal side effects.

A subsequent meta-analysis of celecoxib trials had however shown the agent to be as effective as other NSAIDs in arthritis, but with "significantly improved gastrointestinal safety and tolerability".[18] However, another concern raised was the possibility that use of the COX-2-specific inhibitors was associated with increased cardiovascular thrombotic events. Patients in the VIGOR trial were not allowed to take aspirin, and those on rofecoxib showed a greater risk of cardiac events, particularly not-fatal myocardial infarction. This was not the case in CLASS, but aspirin use was allowed. A review in 2001, combining the VIGOR and CLASS data with two smaller trials, failed to rule out this possibility, and urged caution in those patients in whom prophylactic aspirin was indicated.[19] Such events would be captured in what are referred to as "serious adverse events" in clinical trials, emphasising why these should be reported as well as the specific effects targeted by the trial design. Despite such concerns, there is still support for the use of COX-2-specific inhibitors, together with low-dose aspirin where indicated, and claims that the FDA labelling requirements are unwarranted.[20,21] Others have pointed to the need for continued vigilance, and for phase IV data obtained under "real world" settings.[22] In those at risk of GI problems, the choice remains difficult. While it has been stated confidently that "when economically feasible, a coxib alone is preferable to a conventional NSAID plus a GPA" (a 'gastro-protective' agent), the same authors were of the opinion that "patients at high risk require a GPA in addition to a coxib".[23]

An aspect not covered in depth in this debate has been the known effect of NSAIDs on blood pressure control. This has been well summarised by Chawla and Kochar, who noted that NSAIDs may increase mean blood pressure by a clinically significant 5mmHg, interfering with the actions of diuretics, ACE-inhibitors, beta-blockers and alpha-blockers.[24] The effects of the different COX-2-specific inhibitors remain to be elucidated, although a lesser effect with celecoxib is claimed.[25,26]

OTHER ANALGESICS

A range of other analgesics has been investigated in OA patients. These include controlled release codeine (effective), tramadol (effective) and propoxyphene (possibly no more effective than paracetamol).[27,28] Addition of a tramadol-paracetamol combination to existing NSAID therapy (traditional or coxib) has also been shown to help in the management of OA flare pain.[29]

INDIVIDUALISING THERAPY

As much as guidelines like the ACR's, or review articles like that published in the BMJ in 2000, help to direct practitioners, individual care choices remain difficult.[9,30] Even intuitive approaches seem not to work – Bradley *et al* have shown that the severity of knee pain did not predict whether the patient would respond better to ibuprofen or paracetamol.[31] Hungin and Kean have claimed that the sheer volume of side effects noted in the US (where 75 million NSAID prescriptions are issued each year) points to overuse of these drugs, yet also argue that "more patients with OA are likely to gain more benefit from NSAIDs".[32] Patient preference is also difficult to unravel. Pincus *et al* reported on a telephonic survey with 300 patients receiving treatment for OA (of whom 172 had confirmed OA).[33] The percentages of respondents rating medicines as "very helpful" were somewhat different for paracetamol (24%), ibuprofen (31%), naproxen (30%) and diclofenac (56%). However, respondents were less likely to discontinue paracetamol than an NSAID for reasons of toxicity. Nonetheless, of those who did identify a medicine as "most helpful", 80% named an NSAID, but only 20% chose paracetamol. Of those who were taking paracetamol, 30% also took an NSAID.

In the elderly patient, who would typically present with at least one of the risk factors for developing GI problems, and where cardiovascular effects (and interactions with antihypertensives) would be probable, careful choices need to be made. Paracetamol at least deserves a trial, at an appropriate dose, together with serious application of the proven non-drug measures. Where relief is not obtained, an additional analgesic needs to be considered if an NSAID is not appropriate. Where NSAIDs are used, careful consideration needs to be paid to whether or not an expensive COX-2 selective agent is warranted. Generalising economic analyses is very difficult, but it should be noted that a recent cost utility analysis in the US showed that, for average risk patients, an additional expenditure of $275 809 per year would be necessary to gain one additional quality-adjusted life year (QALY) from the use of a coxib instead of a non-selective NSAID.[34] This was reduced to $55 803 if the analysis was limited to those patients with a history of bleeding ulcers. The degree to which practitioners are bombarded with promotional material for these agents has to be taken into account. In the US it was noted that, despite criticisms directed at the CLASS study publication in JAMA, more than 30 000 reprints of the paper had been ordered, presumably for distribution to practitioners.[16] A critical eye is called for when being presented with the next "miracle" results.

Maximal benefit has been shown when patients are active participants in their own management, and understand the complex interplay of drug and non-drug measures. This demands good communication and counselling skills. It is therefore worthwhile reflecting on an issue highlighted in a BMJ editorial by Andrew Herxheimer.[35] Noting that "uncomprehending adherence is dangerous", he reviewed evidence that patients on NSAIDs are seldom adequately informed about the symptoms of a possible GI complication, such as upper abdominal pain and tarry stools, and that patient information leaflets were also deficient in this regard. The opportunities for review of patients on long-term Schedule 5 analgesic combinations (such as dextropropoxyphene

and meprobamate-containing preparations) created by the 1997 Medicines Amendment Act, now in force, should also be exploited to improve the quality of medicines use in this common condition.❐

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Please refer to the CPD questionnaire on page 71.

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