A regional audit of the use of COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) in rheumatology clinics in the West Midlands, in relation to NICE guidelines

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Objectives. Whilst all non-steroidal anti-inflammatory drugs (NSAIDs) can cause adverse gastrointestinal events, COX-2-selective inhibitors (COX-2) may have improved gastrointestinal safety compared with non-selective NSAIDs (NSNSAIDs). In 2001, the National Institute for Clinical Excellence (NICE) published guidance on the use of the COX-2 agents celecoxib, rofecoxib, meloxicam and etodolac for rheumatoid arthritis (RA) and osteoarthritis (OA). This study aimed to audit the appropriateness of NSAID use in relation to NICE guidance in rheumatology out-patients.

Methods. Questionnaires were completed for all patients attending clinics in 18 rheumatology units in the West Midlands over a 2-week period. Data collected included patient demographics, NSAID type, indications, duration of use (≥3 months was considered prolonged), and concomitant prescription of corticosteroids, warfarin and gastroprotective agents.

Results. Data were collected on 2846 patients; 1164 (41%) were taking NSAIDs (791 NSNSAIDs, 373 COX-2). Of the 1164 NSAID users, 753 (65%) had a diagnosis of RA or OA (483 NSNSAIDs, 270 COX-2). Overall, 37% of NSAID prescriptions were appropriate. Of the NSNSAID users, 92% had at least one risk factor for adverse gastrointestinal events and were therefore inappropriately treated. Prolonged use (in 89%) and age ≥65 yr (in 23%) were the most frequent risk factors identified. Of the COX-2 users, 97% had one or more risk factors and were appropriately treated. Analysis of the RA/OA subgroup revealed similar findings. Thirty-six per cent were taking NSNSAIDs appropriately; 97% of NSNSAID use was inappropriate and 97% of COX-2 use was appropriate treatment. In the whole cohort, gastroprotective agents were used in 26% of NSNSAID users, 56% of gastroprotective agents being proton pump inhibitors.

Conclusions. Ninety-two per cent of patients attending rheumatology clinics who were taking NSNSAIDs should have been prescribed a COX-2-selective agent in relation to NICE guidance. Duration of use and age ≥65 yr emerged numerically as the most important risk factors. Significant numbers of patients taking NSNSAIDs may be at risk from adverse gastrointestinal events and clinicians may wish to review their prescribing patterns. Conversely, 97% of patients taking COX-2 agents were treated appropriately. Although practice overall conformed poorly with NICE guidance, NSAID prescribing also needs to be considered in the context of recent concerns regarding the cardiovascular risks of COX-2 agents.

KEY WORDS: Rheumatoid arthritis, Osteoarthritis, NSAIDs, COX-2 inhibitors, NICE guidelines.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the symptomatic treatment of rheumatic diseases and have become one of the most commonly used classes of drugs in the UK [1]. NSAIDs are, however, associated with serious adverse effects on the gastrointestinal (GI) tract, including perforation, ulceration and bleeding (PUB), impairment of renal function, cardiovascular disease and interaction with other medications [2–6]. Age is one of the most important risk factors for an upper GI tract bleed [7]; this risk is further increased four-fold when using NSAIDs, the full dosage of which may be inappropriate in the elderly long-term [8, 9]. Annually, 0.5–2% of NSAID users have a serious PUB [10], causing an estimated 2000 deaths in the UK [11]; the adverse GI effects of NSAIDs lead to increased health-care expenditure [12–14].

NSAIDs inhibit cyclooxygenase (COX), an enzyme existing in two isoforms. COX-1 inhibition may result in the unwanted GI side-effects of NSAIDs and COX-2 inhibition in anti-inflammatory effects [15, 16]. Many traditional NSAIDs inhibit COX-1 and COX-2 to similar degrees [15]; in recent years, increasing numbers of COX-2-selective drugs have become

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available. Their use may reduce both GI adverse effects and the need for gastroprotective agents (GPAs), often coprescribed with non-selective NSAIDs (NSNSAIDs).

The National Institute for Clinical Excellence (NICE) published guidance on the use of the COX-2 inhibitors celecoxib, rofecoxib, meloxicam and etodolac for rheumatoid arthritis (RA) and osteoarthritis (OA) in July 2001 [17]. It was recommended that only patients with identified risk factors for adverse GI events (Table 1) should be treated with COX-2 in preference to NSNSAIDs. We aimed to audit the use of NSAIDs in all patients attending rheumatology clinics in the West Midlands, in relation to NICE guidance.

**Methods**

Eighteen rheumatology units participated in the study, including 42 consultants and 15 specialist registrars, covering a mixed urban and rural population of approximately 5 million. Proformas were completed for all patients attending doctor- and nurse-led adult out-patient clinics over a 2-week period during 2002. Information recorded included demographic data, NSAID type and usage, duration and indications for use, concomitant corticosteroid, warfarin and GPA prescriptions, history of PUBs and presence of comorbidities, including diabetes (DM), cardiovascular disease (CVD), hypertension (BP), and renal and hepatic impairment. NICE do not define ‘prolonged use’ of NSAIDs; we used ≥3 months. Additional information collected included smoking history and low-dose aspirin use. This information allowed identification of risk factors for adverse GI events for each patient and assessment of whether their NSAID medication was appropriate, in relation to NICE guidance. Since NICE guidance relates only to RA and OA, results were analysed in relation to all patients and to the RA/OA subgroup.

**Statistics**

Results were analysed using SPSS for MacOS X version 11.0 (SPSS, Chicago, IL, USA). Statistical analysis was performed, where appropriate, using either the Pearson \( \chi^2 \) test or Fisher’s exact test; \( P \) values of less than 0.05 were considered statistically significant.

**Results**

Data was collected from 2846 patients; 96% of forms had sufficient details entered to allow detailed analysis. Diagnoses were: RA, 53%; spondyloarthropathy, 13%; OA, 11%; regional musculoskeletal syndromes, 5%; psoriatic arthritis, 4%; connective tissue diseases, 3%; gout, 2%; other, 4%; and unspecified, 5%.

1164 (41%) patients were taking any NSAID; 791 were taking NSNSAIDs (no patient was taking aspirin at a daily dose of >300 mg for anti-inflammatory effect) and 373 were taking COX-2. Seven hundred and fifty-three NSAID-takers had RA or OA (483 NSNSAID, 270 COX-2). For all NSAID prescriptions, 52% were issued by general practitioners (GPs) and 38% through hospital clinics.

** Appropriateness of treatment**

Overall, 430 (37%) patients taking NSAIDs were receiving appropriate therapy, in accordance with NICE guidance. Of the 791 patients taking NSNSAIDs, only 65 (8%) patients were receiving appropriate treatment, the remaining prescriptions (92%) being inappropriate (Fig. 1). Of the latter, only 191 (26%) were coprescribed GPAs [56% of GPAs were proton pump inhibitors (PPIs)].

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**Table 1. Risk factors for adverse GI events, as identified by NICE**

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<th>Risk Factor</th>
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<tr>
<td>Age of 65 yr or over</td>
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<td>Previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation</td>
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<tr>
<td>Concomitant use of medications that are known to increase upper GI adverse events, e.g. corticosteroids and anticoagulants</td>
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<tr>
<td>Presence of serious comorbidity, such as cardiovascular disease, renal or hepatic impairment, diabetes and hypertension</td>
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<tr>
<td>Requirement for the prolonged use of maximum recommended doses of standard NSAIDs</td>
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**Fig. 1. NSAID usage in relation to appropriateness of prescription, age and duration.**
Conversely, the majority of COX-2 use was appropriate (97%), although 77 patients (21%) were also taking GPAs, which was felt not to be justified in NICE guidance.

Similar results were found in the RA/OA subgroup; 274 (36%) of NSNSAID prescriptions were appropriate. Again, the majority of NSNSAID use was inappropriate (97%), with COX-2 use appropriate (97%). Of the inappropriate NSNSAID treatments, only 128 (27%) were coprescribed GPAs. Further analysis of the RA/OA subgroup revealed no significant differences in comparison with the whole cohort in respect of the risk factors detailed below; separate figures have therefore not been included.

**Risk factor profile in patients taking NSNSAIDs**

**Duration of use.** In 704 patients (89%) use of NSNSAID was prolonged (Fig. 1).

**Age.** One hundred and eighty-five (23%) of NSNSAID takers were aged ≥65 yr (Fig. 1).

**Comorbidities.** Comorbid risk factors occurred in patients as follows: BP, 15%; CVD, 7%; DM, 5%; hepatic, 2%; renal, 1%. One hundred and seventeen (15%) patients taking NSNSAIDs were smokers.

**Pub.** Thirty-two (4%) NSNSAID takers had a history of PUB; 32 (41%) were coprescribed a GPA (77% of GPAs were PPIs).

**Coprescriptions.** One hundred and three (13%) patients were coprescribed corticosteroids. Twenty-six (3%) patients were coprescribed or were self-administering low-dose aspirin; 81% had risk factors for CVD. Only 13 (50%) of these were taking a GPA. Four (0.5%) patients were coprescribed warfarin; two were taking a GPA.

**Discussion**

Our study demonstrates significant underprescription of COX-2 in RA and OA in relation to NICE guidance, and also suggests underprescription of GPAs. Similar findings from smaller studies [18, 19], and in our patients with other rheumatic diseases, suggest that a large number of rheumatology out-patients in the UK taking NSNSAIDs are at risk of adverse GI events. Evidence from the USA [20] and the Netherlands [21] suggests that the use of strategies to reduce the upper GI complications of NSNSAIDs is also relatively uncommon in other countries.

The risk of adverse GI events and related death increases within the first few weeks of NSNAID treatment [7, 11, 22, 23]. For our study, further definition of ‘prolonged use of maximum recommended doses of standard NSAIDs’ as identified by NICE was required; we elected to use ≥3 months. This was influential in our results as 87% of RA/OA patients prescribed NSNSAIDs had been taking their medication for longer than this period. We did not, however, collect data on NSNSAID dosage. Feedback of audits may be of value when NICE reviews its guidance to facilitate clarification of criteria.

Our study assesses a defined secondary care patient population and may not reflect practice in primary care, although the majority of our patients were commenced on NSNSAIDs in the community. In addition, follow-up clinics for patients with chronic rheumatic diseases will tend to include those requiring long-term therapy.

Although NICE identified age ≥65 as a risk factor, some studies have used age ≥75 [24]. In our study, using age ≥75 would have resulted in only 5.8% RA/OA patients having this risk factor, as opposed to 33% aged ≥65.

In our study, BP was the most commonly occurring comorbid risk factor for adverse GI events. Similar numbers of individuals were smokers, and although smoking was not included by NICE as a risk factor, most of these patients had other risk factors. NSNSAIDs, including COX-2, have a range of negative renal effects. Renal dysfunction has recently been considered a strong predictor of cardiovascular risk [25, 26]. In data not shown we estimated glomerular filtration rate in 389 patients with RA/OA taking NSNSAIDs; 150 (39%) had renal impairment, although only four of these had ‘renal impairment’ indicated on the proforma, suggesting that there may be substantially more patients with renal impairment taking NSNSAIDs than their clinicians recognize.

Although NICE included CVD as a risk factor for GI adverse events, NICE guidance indicated uncertainty over the use of COX-2 in patients with CVD and recommended that they should not be prescribed routinely. NICE also indicated that because of reduced benefit of COX-2 when coprescribed with aspirin, this combination was not justified on current evidence. Although, therefore, we included patients with CVD and those taking aspirin with NSNSAIDs as inappropriate prescriptions, the vast majority (99%) of these patients had other risk factors and will not have affected significantly our overall estimates of inappropriate prescription of NSNSAIDs.

Following completion of our study, increasing concerns about cardiovascular toxicity of COX-2 have emerged; rofecoxib was withdrawn in September 2004 due to an increased risk of cardiovascular events [27] and advice has subsequently been issued to avoid celecoxib or other coxibs in prescriptions in patients with cardiovascular disease [28]. Currently this advice does not extend to the use of meloxicam or etodolac, which are not as highly cardioselective as the coxibs, but further work is required to determine the extent to which this is a class effect [29]. Despite conforming poorly to NICE guidance in respect of COX-2 prescription, our findings may reflect, at least in part, a justifiably cautious approach adopted by rheumatologists when recommending novel NSNSAIDs. It currently appears far from certain that the low prescription rates for COX-2 in our patients has been contrary to their best interests.

Rheumatologists need to reassess the risk/benefit ratio of NSNSAID prescriptions for individual patients in relation both to NICE guidance and to current concerns regarding the safety of COX-2 agents. Perhaps most importantly, in view of the potential toxicity of all NSNSAIDs, the indication for any of these agents needs careful consideration and, if prescribed, the agent should be used at the lowest effective dose for the shortest duration required. The review by NICE of its guidance, due in 2005, will be awaited with interest.

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