A clinical audit of the prescribing of celecoxib and rofecoxib in Australian rural general practice

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Aims The new cyclooxygenase-2 (COX-2) selective inhibitors, celecoxib (Celebrex®) and rofecoxib (Vioxx®), have been widely prescribed since their launch. No reviews currently appear in the literature of prescribing patterns in Australia. This paper describes a self-audit of the clinical use of selective COX-2 inhibitor therapy undertaken with rural general practitioners (GPs) in Australia.

Methods A structured audit form was developed and distributed to interested GPs. The form was self-administered and focused on issues about COX-2 inhibitors and the types of patients who were receiving them, e.g. indications, patient demographics, risk factors and drug interactions.

Results A total of 627 patients were recruited (569 celecoxib and 58 rofecoxib). A range of doses was prescribed. Osteoarthritis was the most common indication (68.1%). Risk factors known for the nonselective nonsteroidal anti-inflammatory drugs were identified in 65.1% of patients, with the most common being advanced age, hypertension and previous peptic ulcer disease. Potential drug interactions were common. A variety of reasons for initiation of therapy was identified; these included perceived increased efficacy, safety and failure of other treatment.

Conclusions These results show that COX-2 inhibitors are being prescribed for patients with multiple risk factors that may place the patient at increased risk of adverse drug reactions to a COX-2 inhibitor. The perception of improved safety and efficacy was common and is of concern. Limitations of the study include the reliance on self-reporting.

Keywords: audit, celecoxib, COX-2 inhibitor, NSAID, prescribing, rofecoxib

Introduction

The new cyclooxygenase-2 (COX-2) selective inhibitors, celecoxib (Celebrex®) and rofecoxib (Vioxx®), have been widely prescribed since their launch in 1998 and 2000, respectively. Celecoxib is currently registered in Australia for the symptomatic treatment of osteoarthritis and rheumatoid arthritis and rofecoxib for the symptomatic treatment of osteoarthritis. Australian expenditure on all COX-2 inhibitor therapy was almost $174 million in the first 10 months after Pharmaceutical Benefits Scheme (PBS) listing [1]. This class of drugs attributes its mechanism of action to selective inhibition of COX-2 and therefore is proposed to provide a 'safer' alternative with respect to gastrointestinal (GI) effects compared with the nonselective nonsteroidal anti-inflammatory drug (NSAID) therapy [2]. The risks of nonselective NSAID therapy such as GI ulceration, aggravation of hypertension and heart failure, renal impairment and hypersensitivity reactions are well established [3–10].

Celecoxib and rofecoxib have been demonstrated to have similar efficacy to the nonselective NSAID in rheumatoid arthritis and osteoarthritis [11–13]. Improved gastrointestinal tract (GIT) side-effects have been reported and highly promoted [11–15]. The difficulties of establishing the safety of COX-2 medications with respect to serious gastrointestinal complications have been discussed in recent publications [16, 17]. The two major safety trials, CLASS [14] and VIGOR [15] showed a lower relative risk of serious gastrointestinal complications but the absolute benefits were small. CLASS and VIGOR estimated the annual incidence of serious GIT complications from NSAID at 1.4%, while COX-2 medications in these trials reduced the relative risk of such events by

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50% (i.e. down to 0.6%–0.8% or number needed to treat = 125–130) [15–17]. Furthermore, subsequent analysis of the CLASS study (comparing celecoxib with either diclofenac or ibuprofen), highlighted by the Food and Drug Administration, found that the benefits shown in the 6 month analysis were not continued to the prespecified 12 month endpoint of the study, placing doubt on the clinical significance of any gastrointestinal safety benefits from the chronic use of celecoxib over traditional NSAIDs [18].

Since the introduction of celecoxib to Australia, the Australian Drug Reactions Advisory Committee (ADRAC) had received 2218 reports of suspected adverse drug reactions as of February 2001 [19, 20]. In the first 6 months of use in Australia the most common reports to ADRAC involved GIT upset (predominately nausea, abdominal pain and dyspepsia with relatively small numbers of severe upper or lower GIT events) and skin reactions (though again, few reports of serious reactions), other notable reports include allergy, approximately 5%, including face or tongue oedema and angioedema, and cardiovascular events such as hypertension and peripheral oedema [14, 21]. Published case reports include serious GI bleeds, sodium retention possibly leading to aggravation of heart failure, deterioration of renal function, dyspnoea and hypersensitivity reactions [21–26].

There has also been controversy over a study published recently analysing the possible pro-thrombotic risks of COX-2 therapy [27]. The bulk of the data in this meta-analysis have come from the VIGOR study [15]. VIGOR excluded patients on aspirin and showed (perhaps as a result) an increased risk of myocardial infarctions in the group receiving rofecoxib over naproxen [15]. Conversely, the CLASS study permitted patients taking aspirin, and in this subgroup no benefits of celecoxib on serious GIT complications could be shown but no differences in the rate of myocardial infarctions was evident [14]. Thus there appears to be a trade-off between the cardioprotection of aspirin (and perhaps some traditional NSAIDs) and the apparent gastroprotective effect of COX-2 medications [28]. It is still a matter of some controversy whether the apparent increased rates of myocardial infarction shown in the meta-analysis are the result of thrombosis caused by COX-2 inhibitor therapy or the absence of COX-1 induced platelet aggregation inhibition.

The popularity of these drugs raises important questions regarding the clinical situations in which they are prescribed. The Australian COX-2-Specific Inhibitor (CSI) Prescribing Group reminds prescribers that COX-2 drugs are symptomatic modifying drugs and do not alter the course of musculoskeletal disease, so benefits to patients must outweigh the risks.

At present, no reviews appear in the literature of prescribing patterns in Australia. This paper will describe a self-audit of the clinical use of selective COX-2 inhibitor therapy undertaken with general practitioners in rural areas of Queensland, Australia. Self-audit is established as an effective method of continuing medical education for general practitioners [29–31].

The aim of the clinical self-audit was to improve the prescribing of NSAID and COX-2 inhibitors medications in rural general practice using a self-audit educational tool. In particular, the audit was designed to assist GPs to reflect on their prescribing practices in light of identifiable risk of NSAID/COX-2 prescribing in an individual patient.

Methods

An audit form was developed from literature elucidating the indications and risks of NSAID therapy including COX-2 inhibitors [1–27]. The audit form gathered information on patient demographics and the presence of risk factors, and prompted information retrieval for data on monitoring parameters. The participants were required to refer to key references such as the Australian Medicines Handbook and published papers [7] in order to complete the audit. The audit form was approved after a limited pilot exercise and discussion with a range of experts in NSAID/COX-2 inhibitor therapy and clinical audit techniques. Ethics approval was not sought since identifiable data were not requested from participants.

Doctors interested in the audit responded to a brochure faxed out to 250 rural medical practices (approximately 800 medical practitioners). Those indicating interest were then sent out an information pack, complete with audit forms and current literature on NSAID therapy. The doctors were instructed to self-audit 20 patients using the audit form. Patients included in the audit were selected at the discretion of the doctor and could reflect retrospective or prospective prescribing.

Results were collated and analysed on SPSS® statistical software. A pro-forma was developed to feedback results to individual general practitioners with information on their responses, complete with peer group comparison. This information was returned with a set of reflection questions to assess whether the practitioner valued the audit process.

Results

A total of 72 doctors provided data on 1417 patients of whom 627 were taking a COX-2 inhibitor (569 celecoxib and 58 rofecoxib). The other 790 patients were identified as receiving standard NSAID therapy and these patients will not be discussed further in this paper [32].

Table 1 Indications for COX-2 inhibitor therapy.

Indication for NSAID therapy	*Number of patients (%) (n = 627)**
Osteoarthritis	428 (68.1%)
Rheumatoid arthritis	51 (8.1%)
Chronic pain including neuralgia	88 (14.0%)
Non-specific back pain	124 (19.7%)
Strains/Sports injury	41 (6.7%)
Gout	16 (2.6%)
Miscellaneous	21 (3.3%)

*More than one indication for the COX-2 inhibitor therapy may have been recorded for an individual patient.

Patients within a wide range of ages were receiving COX-2 inhibitor therapy (15–98 years). Patients over the age of 70 years comprised 36.8% of the total group. Almost 20% of celecoxib patients were taking doses greater than 200 mg daily. The prescribers noted that approximately half the group was using a COX-2 inhibitor regularly with the remainder using them irregularly (on an 'as required' basis).

Osteoarthritis was the most common reported indication for COX-2 therapy (68% of patients). Other indications identified are listed in Table 1. A minority of patients were using a COX-2 inhibitor for rheumatoid arthritis (RA), reflective of the prevalence of the RA. Many patients were taking other concomitant pain relief therapies including irregular paracetamol (63.5%), regular paracetamol at 1 g four times a day (13.6%) and opioids (8.1%).

Potential risk factors for nonselective NSAID therapy were identified in a significant majority of patients (65.1%, Table 2). Advanced age was the most common risk factor but a high percentage of patients were hypertensive (37.2%) or had previous peptic ulcer disease (17.4%). Potential drug interactions were noted in 329 patients (52.5%). Sulphonamide allergy was recorded in 5.1% of patients.

Table 3 shows the aggregate number of risk factors and drug interactions within the total group of patients. Two or more risk factors were identified in almost 35% of patients and over 20% were taking two or more potentially interacting drugs.

The reasons given by the participants for initiating or changing to COX-2 inhibitor therapy are listed in Table 4. The most common reason for change in therapy was noted to be side-effects from previous nonselective NSAID therapy (30.6%). A perception that COX-2 inhibitor therapy was safer constituted 23.8% of cases. A proportion of patients (149, 23.8%) were noted to be NSAID naive.

Table 2 Risk factors identified in patients taking COX-2 inhibitor therapy.

Risk factor	*Number of patients (%)* (n = 627)*
Age greater than 70 years	230 (36.8%)
Renal impairment	37 (5.9%)
Heart failure	53 (8.5%)
Hypertension	233 (37.2%)
Aspirin allergy	11 (1.8%)
Previous peptic ulcer disease	109 (17.4%)
Self purchase of NSAID therapy (oral or topical)	10 (10.6%)
Sulphonamide allergy	32 (5.1%)
Taking low dose aspirin	145 (23.1%)
Taking an ACE inhibitor	131 (20.9%)
Taking warfarin	13 (2.1%)
Taking diuretics	105 (16.7%)
Taking a corticosteroids	51 (8.1%)

*Patients may have been noted to have more than one risk factor or drug interaction.

Table 3 Levels of concurrent risk factors in patients receiving COX-2 inhibitors.

Cumulative number of risk factors or drug interactions identified in patients	*Number of patients with concurrent risk factors (%)*	*Number of patients with concurrent drug interactions (%)*
0	219 (34.9%)	298 (47.5%)
1	191 (30.5%)	201 (32.1%)
2	154 (24.6%)	90 (14.4%)
3	47 (7.5%)	38 (6.1%)
4	14 (2.2%)	0
5	2 (0.3%)	0

Concurrent gastroprotective drugs were being taken in 33% of patients. These included 22 (3.5%) taking antacids, 121 (19.4%) taking H_2-receptor antagonists and 65 (10.4%) taking proton pump inhibitors. No patients were receiving misoprostol.

Discussion

This intervention was designed as an educational activity rather than a research tool. The key methodological problem in drawing conclusions from these data in a broader context is the issue of self-selection. The data have been gained from doctors who self-selected, and they chose their own patients to audit, either prospectively or retrospectively, so there is a clear potential for confounding factors when considering the general conclusions which may be drawn from these data. All doctors were practising in rural areas which may also limit the

Table 4 Themes of the reasons given by GPs for prescribing of COX-2 inhibitors.

Reason	*Number of patients (%) (n = 627)**
GI side-effect from conventional NSAID	192 (30.6%)
Non-GI side-effects of conventional NSAID	12 (1.9%)
COX-2 inhibitor perceived to be more effective	149 (23.8%)
COX-2 inhibitor perceived as being safer	8 (1.3%)
Conventional NSAID not effective	54 (8.6%)
Conventional NSAID not suitable	2 (0.4%)
Patient request for COX-2 inhibitor	7 (1.1%)
Trial of new agent needed	13 (2.1%)
Specialist advice	2 (0.4%)
No reason stated on the audit form	188 (30%)

*467 (74.5%) patients had previously taken conventional NSAIDs, 149 (23.8%) patients had not taken any NSAID previously and was unknown in 10 (1.7%) cases.

generalizability of the results. Data are available, however, demonstrating no significant differences in the prescribing of NSAID therapy or in the incidence of musculoskeletal problems encountered by general practitioners between rural and urban areas [33]. Despite these limitations, the results described in this paper highlight certain key issues surrounding COX-2 prescribing.

The arrival of the new COX-2 inhibitor medications was heralded as a significant advance in the treatment of pain and inflammation due to the reduction in the risk of gastrointestinal adverse effects in comparison to nonselective NSAIDs. As a result of this suggested benefit it is easy to understand why these drugs have been prescribed so widely. Yet the proposed benefits of these medications need to be tempered against the real risk of adverse effects in the very population for whom the proposed benefits would be greatest, i.e. those of advanced age with multiple pathology. It is in this group of patients that the benefits of COX-2 therapy are in most doubt and that are at the most risk of non-GI related adverse effects of COX-2/NSAIDs. Unfortunately, the majority of clinical trials have excluded these patients [14].

This is one of the first studies reporting the clinical use of COX-2 inhibitors in the general Australian population. Data have been presented on the demographics of patients receiving the drugs, indications, risk factors, concomitant drug use and reasons for prescribing. The results show a wide range of use within the community. Celecoxib was more widely prescribed but this is most likely due to the later licensing of rofecoxib.

Celecoxib is currently licensed for treatment of osteoarthritis, rheumatoid arthritis and as an adjunct in familial adenomatous polyposis, whereas rofecoxib is only approved for treatment of osteoarthritis. Table 1 shows a variety of prescribing for nonapproved indications for COX-2 inhibitor drugs which is not surprising considering the wide use of nonselective NSAID therapy for many other indications. It is possible that providing the doctors with a range of preselected indications on the audit form, some of which were outside approved indications for COX-2 therapy (Table 2), may have encouraged the participants to choose some of these off-label indications.

The most common indication for the COX-2 inhibitor drugs was osteoarthritis. For the treatment of osteoarthritis, paracetamol has been shown to be as effective as standard nonselective NSAIDs [34]. No trials have yet shown any superiority of the new COX-2 drugs over the older NSAIDS for osteoarthritis [13, 17]. A perception that COX-2 inhibitor drugs are more effective for osteoarthritis may be misplaced. This was reported by a proportion of the respondents (Table 4).

It is likely that because of heavy promotion of an improved adverse reaction incidence, COX-2 inhibitors would be chosen for patients with multiple pathologies. The identification in the COX-2 inhibitor population of risk factors (65.1%) to the standard NSAID therapy is concerning. The safer profile in gastrointestinal adverse effects has been reported but they are not free from GIT adverse effects [14–16]. Over 17% of patients in this study had a history of GI disease and these will remain at risk, albeit perhaps reduced, from the COX-2 inhibitor agents. It is not known if the use of these COX-2 inhibitors in patients with previous GI disease is actually safer prescribing practice.

No improved safety data have been reported in patients with hypertension, renal impairment or heart failure and it is likely these will be aggravated by COX-2 therapy [19–27]. However, this paper demonstrates a wide use of these agents in patients with such problems. The recent controversy regarding whether COX-2 drugs increase the risk of cardiovascular disease via prothrombotic effects occurred after the completion of the audit, therefore this issue was not included in the audit form or analysis of risk factors [27, 28].

More than a quarter of the patients were identified as having two or more risk factors possibly indicating that prescribers are particularly prescribing COX-2 inhibitors for so called 'high-risk' patients (Table 3). This may not be wise prescribing in the situations where minimal safety data are available. However, it is not clear from current evidence if the risk of an adverse event from a COX-2 inhibitor is greater in patients with multiple risk factors.

A variety of reasons for initiation of the COX-2 inhibitor therapy was identified.

It appeared patient pressure was a minimal cause for initiation, despite a great deal of indirect marketing to consumers of these drugs by media release when they were first introduced. Equally, the perception by prescribers of COX-2 being safer drugs is understandable based on the significant marketing effort.

Limited information and guidance is available about the concurrent use of COX-2 inhibitors and gastrointestinal protective drugs and any potential for increased safety. One third of the study sample was receiving gastroprotective agents. It could be proposed that the use of gastroprotective drugs would be unnecessary considering the 'safer' profile of the COX-2 inhibitor. If patients are still requiring gastroprotective drugs while taking COX-2 inhibitors this may indicate the patient is still experiencing GIT adverse effects. Alternatively, the continuation of gastroprotective medication in patients switched from NSAID therapy may be an oversight, or reflect the paucity of clinical data (and clinical guidelines) on the safety of COX-2 medications in patients at higher risk of serious GIT events. This concomitant use of GIT protective drugs may just reflect the general prescribing to a population of patients with multiple problems.

Conclusions

This study has contributed to the understanding of the prescribing of COX-2 inhibitor drugs. A plethora of information has been published about the role and possible risks of COX-2 inhibitor therapy. It appears that sustained and intense promotion has had an effect on prescribing patterns, based on the high PBS expenditure. The wide use of these agents in patients with possible risk factors should be of concern to all involved in the Quality Use of Medicines, including the pharmaceutical industry. This study has shown that the drugs are used in all populations and many have risk factors associated with standard nonselective NSAID therapy. Importantly, it appears some of these risk factors could equally apply to the COX-2 inhibitors and prescribers need to be alerted to these issues. A recent consensus statement is welcomed as guidance to prescribers but more rigorous study data is essential [16]. A clearer appreciation of any difference in the prescribing patterns of both the selective and nonselective NSAIDs is essential to allow effective targeting of educational strategies.

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