Have COX-2 inhibitors influenced the co-prescription of anti-ulcer drugs with NSAIDs?

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Aims

To quantify usage of COX-2 inhibitors compared with nonselective NSAIDs and to determine their impact (including financial) on the co-prescription of anti-peptic ulcer (anti-PU) drugs.

Methods

The Irish General Medical Services prescription database (covering 1.2 million people) was examined for NSAID prescriptions during December 1999–November 2001. NSAID users were excluded during the first 6 months. During the next 12 months (study period) patients on NSAIDs (≥ 3 prescriptions) were identified. The study period and final 6 months provided data on co-prescription of anti-PU drugs. Age, gender, number of concomitant prescriptions, co-prescribing of anti-PU drugs and monthly cost were evaluated for 8 NSAIDs ($n = 4$ non-selective NSAIDs and $n = 4$ COX-2 inhibitors) and odds ratios (OR) calculated using logistic regression.

Results

COX-2 inhibitors were prescribed more frequently in older, female patients and those receiving multiple medications. After adjustment for age, gender and polypharmacy, anti-PU drugs were prescribed more frequently with COX-2 inhibitors (OR = 1.31 (1.23, 1.40)). COX-2 inhibitors were up to 10-fold more expensive, median monthly costs (including anti-PU drugs) ranging from €34.61 (COX-2 inhibitors) to €3.26 (nonselective NSAIDs).

Conclusions

Since COX-2 inhibitors are associated with increased rates of co-prescription of anti-PU drugs and are more expensive than non-selective NSAIDs, these results suggest that the expected cost-savings with COX-2 inhibitors may not be occurring in practice.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medicines in the world. They have a wide variety of indications for use ranging from treatment of acute pain to more chronic conditions such as rheumatoid arthritis. These agents exert their effect by inhibiting activity of the enzyme cyclooxygenase, with a resultant reduction in prostaglandin synthesis and an alleviation of the inflammatory response [1]. Their association with gastrointestinal (GI)

toxicity – dyspepsia, ulcers, bleeds – is well known [2]. The demonstration of 2 unique isoforms of cyclooxygenase (designated COX-1 and COX-2) has led to a greater understanding of the mechanisms of action of NSAIDs and also pointed to an explanation of their toxicity [1]. Selective COX-2 inhibitors have been developed with the aim of minimizing GI toxicity, while maintaining anti-inflammatory activity [3]. These agents (hereafter referred to as COX-2 inhibitors) may be up to 10-fold more expensive than some conventional nonse-

lective NSAIDs. It has been suggested that COX-2 inhibitors may be more cost-effective because of their improved GI tolerability, which should result in a reduction in GI adverse events and a reduction in concomitant prescription of antiulcer agents, both of which place a heavy economic burden on healthcare systems [4–6]. However, a recent review has questioned this financial benefit [7].

Several COX-2 inhibitors are currently on the market in Ireland. Celecoxib and rofecoxib, so called first generation COX-2 inhibitors, were launched on the market in Ireland in June and October 2000, respectively. In addition, meloxicam and nimesulide, which also show some selective COX-2 inhibition in certain in-vitro assays [8] have been on the market since the mid 1990s; in particular nimesulide, although not licensed as a selective COX-2 inhibitor in Ireland [9] is marketed as such and therefore may be prescribed as a COX-2 inhibitor by many physicians. There is a lack of information available evaluating the impact of COX-2 inhibitors on NSAID prescribing patterns. The aims of the current study are to quantify the usage of these newer agents, including their use in specific subgroups of patients, in comparison with nonspecific NSAIDs and to determine the impact (including financial) of COX-2 inhibitors on the co-prescription of anti-peptic ulcer drugs with NSAIDs.

Methods

The General Medical Services (GMS) prescription database was used to identify the study population. The GMS scheme provides free health services to approximately 31% of the Irish population, including provision of medicines without charge [10]. Eligibility for this service is means tested and therefore such groups as children, the elderly and the socially disadvantaged are over represented with respect to the general population. However the GMS covers 1.24 million people and previous reports have estimated that it accounts for up to 70% of all medicines prescribed in primary care in Ireland [11]. In 2001, this amounted to a cost of €434 million [10]. The GMS database records basic demographic information on the patients (such as age and sex) and full details on all items dispensed in the scheme, including ingredient costs and pharmacist dispensing fees per item dispensed. Medicines are coded using the WHO ATC classification system [12]. It does not record data on diagnosis.

For the purpose of this study the GMS prescription database was used to identify a cohort of patients, aged 16 years of age and older, who had been prescribed NSAIDs and to investigate their concomitant use of

anti-peptic ulcer drugs. The study took place over a 2-year period (from December 1999–November 2001). The first 6 months provided a lead-in phase, whereby those on any NSAIDs were excluded. The next 12 months provided the study period, where patients were classified as being new to NSAID treatment (defined as 3 or more prescriptions during the period) or receiving no NSAID treatment (controls). The final 6 months (follow-up period) and study period were used to provide data on the co-prescription of anti-peptic ulcer drugs, prescribed at the same time as or subsequent to NSAID initiation.

The following WHO ATC codes were used to identify NSAIDs and anti-peptic ulcer drugs for inclusion in the study – M01A (anti-inflammatory and anti-rheumatic products, nonsteroids) and A02B (drugs for treatment of peptic ulcers). ATC codes N02BA01, N02BA51 and N02BE01, N02BE51 (aspirin-containing compounds and paracetamol-containing compounds, respectively) were excluded. Where appropriate, adjustments were made for age, gender and number of prescriptions. Adjusted odds ratios and 95% CIs were calculated using logistic regression. All cost analyses of NSAIDs and anti-PU drugs were based on ingredient costs only and did not include pharmacists' dispensing fees. All analyses were performed using the SAS package (SAS Institute Inc.). The analysis was performed in two ways, one on the individual NSAIDs, using diclofenac (the market leader) as the reference and the other on all COX-2 inhibitors using all nonselective NSAIDs as the reference category. Significance at $p < 0.05$ is assumed throughout.

Results

Figure 1 shows the prescription pattern of the four COX-2 inhibitors, compared with the pattern of the four most commonly prescribed nonselective NSAIDs. Overall, diclofenac was the most commonly prescribed NSAID during the study period, followed by mefenamic acid. Nimesulide was the most commonly prescribed COX-2 inhibitor. Patients receiving COX-2 inhibitors were significantly more likely to be older (mean age 64.3 years) than those receiving nonselective NSAIDs (mean age 52.8 years $p < 0.001$) and to have a higher rate of polypharmacy (mean of 31.9 vs 22.7 prescriptions over a 12-month period, respectively, $p < 0.001$) – Table 1. The majority of patients were female in each group. The overall odds of being prescribed a COX-2 inhibitor were significantly greater in those aged 65 years and older (OR 2.78 [2.64,2.93]) and in females (OR 1.10 [1.04,1.16]) although the absolute effect of gender was much less. These findings are

Figure 1

Distribution of chronic NSAID prescribing in Ireland during the study

maintained when each drug is evaluated separately (Table 1).

When age and gender were adjusted for in the analyses, results showed that co-prescribing of anti-peptic ulcer drugs was significantly more likely to occur with any COX-2 inhibitor than with any nonselective NSAID (OR = 1.31 [1.23,1.40]). Considering each drug individually and using diclofenac (the market leader) as the reference, co-prescription of anti-peptic ulcer drugs was significantly more likely to occur with nimesulide (Table 2), whereas rofecoxib, celecoxib and meloxicam showed no difference in coprescription rates. In contrast mefanamic acid and ibuprofen showed significantly less co-prescription of anti-peptic ulcer drugs and naproxen showed similar results compared with diclofenac. When the number of prescriptions was additionally adjusted for, the overall results remained

Table 1

Baseline characteristic of patients in the study by usage of NSAIDs

NSAID	Mean age (s.d.)	% Females	Mean prescriptions over 12 months, other than NSAIDs (s.d.)
Diclofenac	54.81 (18.0)	55.8	22.3 (23.9)
Mefanamic acid	46.01 (19.3)	75.2	22.8 (23.9)
Ibuprofen	56.83 (19.3)	61.4	23.44 (24.48)
Naproxen	59.26 (18.0)	60.6	25.84 (27.4)
Nimesulide	61.91 (17.7)	63.3	29.82 (29.06)
Meloxicam	65.81 (15.9)	64.6	32.28 (27.98)
Rofecoxib	67.72 (15.0)	65.7	36.86 (32.12)
Celecoxib	67.42 (14.7)	68.3	33.5 (30.2)
Any COX-2 inhibitor	64.3 (16.8)		31.9 (29.7)
Any nonselective NSAID	52.8 (19.09)		22.7 (24.1)

Table 2

Adjusted Odds ratios (OR) and 95% CIs for co-prescription of anti-peptic ulcer drugs with NSAIDs

NSAID	Adjusted for age and gender only	Adjusted for age, gender and no of prescriptions
Diclofenac	1.0	1.0
Mefanamic acid	0.86 (0.78,0.94)*	0.82 (0.75,0.89)*
Ibuprofen	0.68 (0.61,0.75)*	0.67 (0.60,0.74)*
Naproxen	0.97 (0.79,1.19)	0.95 (0.78,1.17)
Nimesulide	1.26 (1.16,1.38)*	1.20 (1.10,1.31)*
Meloxicam	1.0 (0.87,1.15)	0.93 (0.81,1.07)
Rofecoxib	1.11 (0.97,1.28)	1.01 (0.88,1.17)
Celecoxib	1.15 (0.98,1.36)	1.09 (0.92,1.28)
Any COX-2 inhibitor vs nonselective NSAID	1.31 (1.23,1.40)*	1.25 (1.17,1.34)*

* $p < 0.001$.

Table 3

Anti-peptic ulcer (PU) drug usage (and percentage) by NSAIDs included in the study

NSAID	No Anti-PU drugs	H ₂ antagonist	PPI	Prostaglandins	Others
Diclofenac	7273 (78.1)	487 (5.2)	1542 (16.6)	5 (0.05)	8 (0.09)
Mefenamic acid	4155 (82.2)	228 (4.5)	666 (13.2)	7 (0.1)	1 (0)
Ibuprofen	2613 (84.0)	150 (4.8)	344 (11.1)	2 (0.06)	2 (0.06)
Naproxen	456 (78.1)	35 (6.0)	92 (15.8)	1 (0.2)	0 (0)
Nimesulide	3032 (73.1)	200 (4.8)	912 (22.0)	4 (0.1)	2 (0.05)
Meloxicam	1057 (77.0)	63 (4.6)	251 (18.3)	2 (0.2)	0 (0)
Rofecoxib	968 (74.8)	56 (4.3)	269 (20.8)	2 (0.2)	0 (0)
Celecoxib	646 (74.2)	39 (4.5)	185 (21.2)	1 (0.1)	0 (0)

the same, but the magnitude of the effect was less (Table 2).

The degree and type of anti-peptic ulcer drug co-prescribed was examined for each NSAID included in the study and the results are shown in Table 3. Nimesulide had the highest level of co-prescription within the COX-2 inhibitors group at 26.9% and meloxicam the lowest at 23.0%. These figures compare with lower rates of co-prescription of anti-peptic ulcer drugs for all of the nonselective NSAIDs studied – results ranged from co-prescription rates of 16.0% recorded for ibuprofen to 21.9% for diclofenac and naproxen. Proton pump inhibitors accounted for approximately 75% for all anti-peptic ulcer drug prescriptions in each group (Table 3).

The average monthly costs of prescribing individual NSAIDs and anti-peptic ulcer drugs were calculated and the results are shown in Table 4. The COX-2 inhibitors were the most expensive NSAIDs, with over a 10-fold difference noted between the average monthly cost of rofecoxib (median €34.61) and that of mefenamic acid (median €3.26). When the average monthly cost of the co-prescribed anti-peptic ulcer drugs was calculated, the costs were generally greater for each of the COX-2 inhibitors (ranging from a median of €37.32 for celecoxib to a median of €25.56 for ibuprofen) but the differences were much less marked. The main reason for the differences in cost associated with anti-peptic ulcer drug use between the groups related to the proportion of prescribed proton pump inhibitors, which was generally higher in the COX-2 inhibitor group – greater than 80% for both celecoxib and rofecoxib compared with 69.1% in the ibuprofen group.

The type of co-prescribed anti-peptic ulcer drug according to age is recorded in Figure 2. The linear trend for age is statistically significant ($p < 0.001$). Proton pump inhibitors accounted for 75.18% of the anti-ulcer drugs co-prescribed and H₂ antagonists accounted for

Figure 2

Prescribing pattern of anti-peptic ulcer drugs in those receiving NSAIDs, according to age from the GMS database. PPI (◆), H₂ antagonists (■)

24.22% in men compared with 75.62% and 23.71%, respectively, in women ($p = 0.027$). A similar age trend was noted in the overall pattern of prescription of anti-peptic ulcer drugs in the GMS database during the period of study (linear trend $p < 0.0001$).

Discussion

This study showed that COX-2 inhibitors were more likely to be prescribed for chronic use in older patients who were receiving several other medications and that overall, users were more likely to be co-prescribed anti-peptic ulcer drugs. The development of NSAIDs, which preferentially inhibited the COX-2 enzyme, was heralded as a breakthrough because it was felt that such drugs should cause less GI toxicity compared with non-selective NSAIDs [4, 13]. Our findings are in keeping with this concept as they suggest that prescribers used COX-2 inhibitors preferentially in those patients judged

Table 4

Descriptive statistics of average monthly costs (€) per patient of NSAIDs and anti-peptic ulcer (PU) drugs

		Diclofenac	Mefenamic acid	Ibuprofen	Naproxen	Nimesulide	Meloxicam	Rofecoxib	Celecoxib
Average monthly cost NSAID	Median	9.43	3.26	3.59	10.26	16.14	12.70	34.61	31.36
	(IQR)	(5.98, 18.30)	(2.17, 5.02)	(2.25, 5.49)	(6.71, 16.15)	(11.28, 22.00)	(11.03, 16.65)	(33.37, 37.08)	(23.98, 34.05)
Average monthly cost anti-PU drugs (where co-prescribed)	Mean	10.34	4.02	4.32	11.47	16.16	13.51	35.63	31.66
	Median	28.59	29.27	25.56	31.21	32.42	30.70	32.42	37.32
Average total monthly cost (NSAID +/- anti-PU drugs)	(IQR)	(16.53, 42.70)	(14.36, 42.71)	(13.02, 41.17)	(18.95, 43.39)	(20.29, 45.75)	(20.19, 42.70)	(21.26, 45.75)	(23.87, 47.16)
	Mean	30.57	30.32	28.90	31.58	33.15	31.03	33.27	35.91
	Median	11.28	3.74	4.14	12.51	20.01	14.62	36.26	31.59
	(IQR)	(6.55, 19.02)	(2.36, 7.65)	(2.45, 7.41)	(7.79, 20.19)	(12.38, 29.20)	(11.85, 22.58)	(34.61, 53.43)	(34.61, 53.43)
	Mean	15.11	9.45	9.01	18.44	25.89	20.66	44.09	41.00

to be at higher risk of GI toxicity from NSAIDs [14]. However in our study physicians still co-prescribed anti-peptic ulcer drugs more often with these agents, compared with the nonselective NSAIDs, even after age and polypharmacy were taken into account in the analysis. This suggests that prescribers still had concerns about the gastro-protective efficacy of COX-2 inhibitors. This pattern of prescribing of high cost COX-2 inhibitors, with the associated increased use of costly proton pump inhibitors means that use of COX-2 inhibitors may not necessarily be a more cost-effective treatment regimen.

During the time period of our study (December 1999–November 2001) celecoxib and rofecoxib were new to the market. Their relatively low prescribing rates probably reflected prescriber unfamiliarity with these drugs – limited information about their long-term effects (both in terms of efficacy and side-effects) was available at this time. However, nimesulide, which has been available in Ireland since 1995, was seen to have a major share of the NSAID market during the study period. This may be due to the fact that it is available in 2 dosage formulations (tablets and granules), which may provide prescribers with a better choice for their patients. It may also be due to the persistent advertising campaign by the brand leader company, regarding its selective COX-2 inhibitor properties [15] although it is not licensed as such by the Irish regulatory authorities. Nimesulide showed the highest rate of co-prescribing of anti-peptic ulcer drugs – it was the only one of the COX-2 inhibitor class, which showed statistically significantly increased rates of co-prescription, when adjustments were made for age and number of prescriptions. This may reflect concerns about GI toxicity with use of nimesulide [9]. Although meloxicam has also been available in Ireland since the mid 1990s, its usage was low during this study and it showed a pattern of co-prescription of anti-peptic ulcer drugs most like that of the nonselective NSAIDs.

In this study the average cost of the individual COX-2 inhibitors was considerably greater than any of the individual nonselective NSAIDs reviewed. This additional cost, combined with the increased rate of co-prescription of anti-peptic ulcer drugs (especially the more expensive proton pump inhibitors) noted with COX-2 inhibitors resulted in a much larger overall cost to the GMS scheme with use of the COX-2 inhibitors compared with nonselective NSAIDs. Early reports suggested that the lower level of GI toxicity seen with COX-2 inhibitors would reduce the burden of NSAID-induced gastropathy [16] and that this would lessen the need for co-prescription of anti-peptic ulcer drugs [17]. However, a recently published cost-utility analysis [7] of use of rofecoxib and celecoxib in the management of chronic

arthritis suggested that the reduction in risk of GI toxicity, seen with these COX-2 inhibitors did not offset their increased costs, compared with nonselective NSAIDs in the management of average-risk patients with chronic arthritis. There have been no published studies which have looked at the effect of the availability of COX-2 inhibitors on physicians' co-prescribing patterns of anti-peptic ulcer drugs with NSAIDs. Our study has shown that use of COX-2 inhibitors was significantly more costly than nonselective NSAIDs in our study population because they were individually more expensive and were associated with more co-prescription of anti-peptic ulcer drugs, particularly the more costly proton pump inhibitors.

The finding of high prescribing levels of proton pump inhibitors compared with other anti-peptic ulcer drugs is in keeping with the general prescribing pattern of these drugs in the GMS population in Ireland which also shows a linear relationship between age and use of proton pump inhibitors. However, even when we adjusted for age in our study, proton pump inhibitors remained the most commonly co-prescribed anti-peptic ulcer drug for all patients receiving a NSAID, although the level of usage varied between NSAIDs. This may be because use of proton pump inhibitors is thought to confer greater protection against NSAID-induced gastric and duodenal ulcers. A recent review [18] concluded that standard doses of proton pump inhibitors were effective at reducing the risk of NSAID-induced endoscopic duodenal and gastric ulcers whereas double dose H₂ antagonists were required to achieve the same effects. It is of interest that the prostaglandin misoprostol was co-prescribed infrequently in this study. Although misoprostol has been shown to be the only anti-peptic ulcer drug that reduces the risk of NSAID-induced ulcer complications (such as perforation, haemorrhage or obstruction) its usage is limited by its poor tolerance [18].

In Ireland in 2001 [8] NSAID prescribing accounted for 3.24% (€14.1million) of the total GMS drug costs (€434 million). COX-2 inhibitors accounted for 25% of NSAID prescriptions at a cost of €7.7 million (over half of the NSAID costs) while expenditure on anti-peptic ulcer drugs (mostly due to proton pump inhibitors) accounted for 8.5% (€36.9 million) of total drug costs. Since proton pump inhibitors were by far the most commonly co-prescribed anti-peptic ulcer drugs in our study, the finding of their increased co-prescription with COX-2 inhibitors, the most expensive NSAIDs, has significant cost implications for the healthcare system in Ireland.

Our prescription database relates to prescriptions dispensed and therefore we cannot be sure that the medi-

cations were taken as prescribed. It does not contain information on patient diagnosis nor do we have information on other potential risk factors such as smoking, alcohol consumption or *helicobacter pylori* infection [14]. However, the database comprises large numbers of patients who can be followed on a longitudinal basis and detailed information is available on all medications at an individual level. Moreover, in this study patients were only included if they had received at least 3 prescriptions of the same NSAID during the study period, to reflect chronic usage of NSAIDs and usage of aspirin and paracetamol, which may have influenced the results was not included. The database cannot account for the use of over-the-counter (OTC) NSAIDs such as aspirin, paracetamol or ibuprofen, in addition to prescribed NSAIDs. Other studies evaluating the pattern of NSAID use have also been unable to accurately determine the level of nonprescription usage of NSAIDs [19, 20]. It is important to note that patients, covered by the GMS free drugs scheme are obliged to pay for nonprescription items. Since there is a strong financial incentive not to co-medicate with OTC NSAIDs, it is likely that such usage is small in comparison to the chronic usage of NSAIDs identified in this study and therefore bias would be minimal.

Conclusions

Our study has shown that COX-2 inhibitors tended to be prescribed to older patients who were receiving more prescriptions, compared with patients prescribed nonselective NSAIDs. This suggests that COX-2 inhibitors are used preferentially in at-risk patients. However, when adjusted for age, gender and number of prescriptions, patients in the COX-2 inhibitor group were still co-prescribed anti-peptic ulcer drugs more frequently than patients prescribed nonselective NSAIDs. Therefore use of COX-2 inhibitors has not reduced the concomitant use of anti-peptic ulcer drugs and despite the promised cost-savings associated with the COX-2 inhibitors these results suggest that such savings may not be made. The potential cost implications for the Irish healthcare system are significant.

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