The effect of the withdrawal of rofecoxib on prescribing patterns of COX-2 inhibitors in Scotland

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Background

Concerns have been raised regarding the cardiovascular safety of the COX-2 inhibitors. In September 2004, rofecoxib was withdrawn from the market as a result of concerns regarding its cardiovascular safety.

Aims & Methods

We set out to examine the effect of the withdrawal of rofecoxib on the prescription of other COX-2 inhibitors and nonselective nonsteroidal anti-inflammatory drugs (nsNSAIDs) in Scotland, using a national prescription database.

Results

The withdrawal of rofecoxib led to an initial increase in the prescription of celecoxib as prescribers presumably switched to this alternative agent. However, this rise was short-lived, presumably as a result of concerns that the safety concerning rofecoxib may be a class effect. A parallel increase in the prescription of diclofenac and ibuprofen was also noted, suggesting that prescribers were prescribing these medications as alternatives to COX-2 inhibitors.

Conclusions

While prescribers and their patients may have initially interpreted safety concerns regarding rofecoxib to be drug specific, prescribers appear to have interpreted this effect to be class specific.

Introduction

There have been increasing concerns regarding the cardiovascular safety of COX-2 inhibitors, a group of non-steroidal anti-inflammatory drug (NSAID), originally developed to reduce gastrointestinal toxicity but maintain anti-inflammatory activity [1]. In September 2004, rofecoxib was withdrawn from the market following the adenomatous polyp prevention trial, which demonstrated an increase in cardiovascular events in patients with a history of colorectal adenomas who were randomized to receive rofecoxib, compared with those in the placebo

group [2]. This represented one of the largest withdrawals of a prescription drug with estimated world-wide sales of US\$2.5 billion in 2004. Further concerns have been raised regarding the cardiovascular safety of celecoxib and valdecoxib [3, 4], although a recent case-control study has suggested that celecoxib was not associated with any increased risk of cardiac events when compared with remote NSAID use [5]. We wished to examine the effect of the withdrawal of rofecoxib on the prescription of other COX-2 inhibitors and nonselective nonsteroidal anti-inflammatory drugs (nsNSAIDs) in Scotland.

Methods

Information Statistics Division (ISD) Scotland maintains a detailed database of all National Health Service prescriptions dispensed in the community in Scotland [6]. The majority of these prescriptions are dispensed by community pharmacies, or dispensing doctors. They also include prescriptions written in hospitals that are dispensed in the community, but exclude drugs dispensed within hospitals themselves. A limitation of the data is that as they are not linked to individual patients or prescribers, it is therefore not possible to determine the length of individual prescriptions. Dispensed data for Scotland for the period April 2004 to March 2005 were obtained for all COX-2 inhibitors (celecoxib, etoricoxib, rofecoxib, valdecoxib) and the most commonly prescribed nsNSAIDs (ibuprofen, diclofenac). This period was selected in order that it would include the period during which rofecoxib was withdrawn. We also examined the prescription of NSAIDs which demonstrate a significant COX-2 inhibitory effect *in vitro*, including meloxicam and etodolac [7].

Results

Prescribing trends for the COX-2 inhibitors and principle nsNSAIDs in Scotland are shown in Figure 1. The withdrawal of rofecoxib led to an initial increase in the prescription of celecoxib as prescribers presumably switched to this alternative agent. However, this rise was

Figure 1

Prescription of COX-2 inhibitors in Scotland between April 2004 and March 2005. Celecoxib (—■—), Diclofenac (—▲—), Etodolac (—▼—), Etoricoxib (—◆—), Ibuprofen (—●—), Meloxicam (—□—), Naproxen (—△—), Rofecoxib (—▽—), Valdecoxib (—◇—).

short-lived, presumably as a result of concerns that safety issues concerning rofecoxib might be a class effect. The prescription of celecoxib has since shown a significant further decline coincident with safety concerns concerning this agent [3]. A parallel increase in the prescription of diclofenac and ibuprofen was also noted, suggesting that prescribers were prescribing these medications as alternatives to COX-2 inhibitors. The prescription of meloxicam and etodolac, which also have COX-2 inhibitory properties, increased by 95% and 123%, respectively, over the 12-month period.

Discussion

Adverse drug reactions are an important cause of morbidity and mortality. Benoxaprofen (Opren) was the first NSAID, initially marketed on the basis of a unique mode of action, to be withdrawn from the market as a result of adverse events associated with its use [8]. Following concerns regarding the safety of COX-2 inhibitors, it has been suggested that such drugs could remain a rational choice for patients at a low cardiovascular risk who have had serious gastrointestinal events especially whilst taking traditional NSAIDs [9]. However, a subsequent reanalysis of the CLASS data suggests no added gastroprotective effect of celecoxib [9, 10]. In April 2005, the sales and marketing of valdecoxib were voluntarily suspended as a precautionary measure, due to concerns regarding serious skin reactions in addition to a possible cardiovascular class effect [11] and the remaining COX-2 inhibitors are now contraindicated in patients with a history of cardiovascular or cerebrovascular disease.

Our results suggest that while the withdrawal of rofecoxib led to an initial increase in the prescription of celecoxib, this rise was short-lived, presumably as a result of concerns that the safety issue concerning rofecoxib may be a class effect. The prescription of celecoxib has since shown a significant further decline coincident with safety concerns concerning this agent [3]. A parallel increase in the prescription of diclofenac and ibuprofen was noted, suggesting that prescribers were prescribing these medications as alternatives to COX-2 inhibitors. The prescription of meloxicam and etodolac, which demonstrate a significant inhibitory effect on the COX-2 isoenzyme [7], also increased following the withdrawal of rofecoxib.

Premarketing clinical trials are limited by their ability to detect uncommon but important adverse drug reactions, which may affect a significant number of patients in routine clinical practice. Pharmacovigilance involves the process of identifying and responding to safety issues regarding marketed medicines. A clear need

exists for longer-term studies which are dedicated to examining the safety of newly marketed drugs. Whereas spontaneous reporting systems make it possible to detect an increased incidence of rare events following the introduction of a new drug, the detection of an increased incidence of a common event is much more difficult. The COX-2 inhibitor story has brought into focus important issues related to both the drug approval and surveillance processes for newly approved drugs. It has been suggested that for all new drugs under review, a minimum number of patient-years of safety experience be obtained before approval is granted [7].

Patients may be informed of the potential risk of drug toxicity individually by their physicians, by pharmacists, by patient information leaflets or as a group by the media, including the internet. Evidence exists to support the concept that alarming medical news can influence the general public, either positively or negatively [12]. It is likely that the adverse media attention regarding the COX-2 inhibitor group of drugs had a significant influence on their subsequent prescribing patterns. Communicating information regarding drug safety can be quite complex and is fraught with vested interests such as the pharmaceutical industry, government legislators, health-care professionals and consumer groups. A systematic and united approach to urgent issues regarding drug safety ensures that prescribers can advise patients appropriately. Such information should be communicated in a systematic fashion to avoid undue public concern.

Whilst no randomized, controlled studies have been carried out to address the primary question of cardiovascular toxicity, the debate on whether the cardiovascular adverse effects of COX-2 inhibitors are a class effect will continue. It has been suggested that the cardiovascular toxicity of such drugs may be the result of their inherent COX-2 selectivity by reducing the production of the antithrombotic agent, prostacyclin, without changing the production of the prothrombotic agent, thromboxane [1, 13]. This raises concerns regarding the safety of drugs that also exhibit a significant inhibitory effect on the COX-2 isoenzyme and concerns have been raised regarding the lack of long-term safety of meloxicam [14]. The division of NSAIDs into two groups based on COX selectivity may be an oversimplification and it may be the balance between COX-1/2 inhibition which determines the adverse effect profile of these drugs. Furthermore, the European Commission has recently asked the European Medicines Agency to investigate the safety of conventional NSAIDs [11]. Our results suggest that whilst prescribers and their patients may have initially interpreted safety concerns regarding

rofecoxib to be drug specific, prescribers have appeared to interpret this effect to be class specific.

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