The rise and fall of the COX-2 inhibitors

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Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely prescribed groups of medicines in clinical practice, their anti-inflammatory, analgesic and anti-pyretic properties making them central to the management of osteoarthritis and rheumatoid arthritis. Gastro-intestinal toxicity represents some of the most-serious adverse drug reactions of this class of drugs. In an attempt to minimize these side-effects, selective cyclo-oxygenase-2 (COX-2) inhibitors were developed. In light of increasing concerns regarding their safety, two COX-2 inhibitors – rofecoxib and valdecoxib were withdrawn from the market in September 2004 and April 2005 respectively. Various restrictions have been also imposed on all the other selective COX-2 Inhibitors.

COX-2 inhibitors were marketed aggressively and rapidly gained wide popularity among prescribing physicians based on the propagated belief that they had a better ADR profile; especially with regards to gastrointestinal side-effects when compared to traditional NSAIDs.

Two independent studies, the VIGOR-study (rofecoxib vs naproxen) and the CLASS-study (celecoxib vs ibuprofen or diclofenac) concluded that the intake of both rofecoxib and celecoxib was associated with a decrease in upper gastrointestinal toxicity when compared to other NSAIDs.[12,13] Both studies were extensively criticized regarding data analysis, publishing policy and study design.[14,15] From the beginning it was obvious that at least rofecoxib was associated with an increased risk of cardiovascular events and that the gastrointestinal benefits of COX-2 inhibitors were at best marginal and completely lost if the patient has to take aspirin.[12,16,17] The VIGOR trial in fact noted a five-fold higher incidence of myocardial infarction in the rofecoxib group compared with the naproxen group.[12,18] Naproxen inhibits the production of thromboxane and platelet aggregation, and the difference in cardiovascular risk was attributed to a cardioprotective effect of naproxen, rather than a cardiotoxic effect of rofecoxib.[12] This interpretation was reiterated in a 2001 meta-analysis of randomised trials of rofecoxib and three case-control studies of naproxen and myocardial infarction published in 2002. [19-22]

Regulatory action

The first global signal of a problem with COX-2-selective inhibitors came in October 2000 – six months after the launch of rofecoxib where evidence for high reporting odds ratio for cardiovascular ADRs with some fatalities and which occurred early in treatment with rofecoxib were presented for the first time at a WHO International Drug Monitoring Programme meeting in Tunis.[23,24] A cumulative meta-analysis of randomised controlled trials in 2001 indicated that an increased risk of myocardial infarction was evident from 2000 onwards; at the end of 2000, the effect was both substantial and unlikely to be a chance finding.[25] Concerns were shared with various regulatory authorities who implemented various labeling changes in 2002, which had as expected no impact on the prescription patterns of selective COX-2 inhibitors.

Data from a placebo-controlled trial with rofecoxib (25mg daily) for the prevention of adenomatous polyps (APPROVe study) proved unequivocally in September 2004 that (as indicated by VIGOR) there was a significant increase in the incidence of serious thromboembolic adverse events for patients taking rofecoxib for more than 18 months.[26] The trial was stopped and rofecoxib (available in Malta

Overview of NSAID Pharmacology

NSAIDs are a chemically diverse group of agents (although most of them are organic acids), that share similar pharmacological properties and adverse-drug-reactions. They are widely-used for the control of pain and inflammation but prospective studies have shown a significant risk of serious gastrointestinal complications and mortality associated with NSAID use.[1-5]

It is well known that both the therapeutic and toxic effects of NSAIDs are mediated by the inhibition of cyclooxygenase (COX) (of which there are three forms[6,7]) and consequent inhibition of prostanoids (a term which encompasses prostacyclins and thromboxanes). Prostanoids are released in the inflammatory process; predominantly PGE_2 but also PGI_2; both generated by local tissues and blood vessels; and PGD_2 released by mast cells.[6] PGE_2, PGI_2 and PGD_2 are powerful vasodilators and synergise with other inflammatory vasodilators such as histamine and bradykinin to dilate precapillary arterioles to contribute to the increased blood flow characteristic of acute inflammation.[6] They also potentiate the effect of bradykinin by sensitising afferent C fibres and thus produce pain.[6] The anti-inflammatory effects of NSAIDs thus result largely from the prevention of these actions of prostaglandins.

Prostaglandins have also a gastro-protective action. PGE_2 when acting on EP_3 receptors inhibits gastric acid secretion and increses gastric mucus secretion. Through COX inhibition there is also an inhibition of PGE_2, which explains why adverse gastrointestinal events are the commonenst unwanted effects of NSAIDs.[6]

There are three isoforms of COX; COX-1, COX-2 and COX3 which has recently been described.[6,7,8] COX are bifunctional having two distinct activities; the main action which gives PGG_2, and a peroxidase action, which converts PGG_2 to the unstable PGH_2 which is then converted into another prostaglandin.[6] According to the working hypothesis that constitutive COX-1 is responsible for the physiological production of prostanoids and inducible COX-2 for the elevated production of prostanoids at sites of inflammation, selective COX-2-inhibitors have been developed in the hope of a specific anti-inflammatory function and less gastrointestinal side-effects attributable to inhibition of COX-1. Most traditional NSAIDs in current use are inhibitors of both isoenzymes though they vary in their degree of inhibition of each.[9,10] Ketorolac, flurbiprofen, suprofen, ketoprofen, indomethacin, aspirin, naproxen, tolmetyn and fenoprofen are COX-1 selective in vitro.[9,10] Zomepirac, niflumic acid, sodiun salicylate, diflusinal, piroxicam, tomoxiprol, meclofenamate, sulindac and diclofenac have a less than five-fold selectivity to COX-2.[9,10] Nimesulide, celecoxib, meloxicam and etodolac have a five to fifty fold selectivity towards COX-2, whilst still producing full inhibition of COX-1. Rofecoxib has a greater than 50-fold selectivity towards COX-2.[9,10]

Both COX-1 and COX-2 are predominantly located on the lumenal side of the endoplasmic reticulum membrane and the nuclear membrane and each consists of a long, largely hydrophobic, channel with a bend at the end, the channel being wider in COX-2.[11] Arachidonic acid enters and has two oxygens inserted and a free radical extracted, resulting in the 5-carbon ring characteristic of the prostaglandins. The crucial structural difference between COX-1 and COX-2 is at position 523; here COX-1 has a bulky isoleucine whilst COX-2 has the much smaller valine; which leaves a gap which gives access to a side-pocket.[8,11] This side-pocket is believed to be the binding site for COX-2 inhibitors which in general have a rigid side-extension which can reach across the channel and interact with the side-pocket.[8,11] This aspect is the basis of COX-2 inhibitor's selectivity for COX-2; they are in fact too bulky to fit into the COX-1 channel.[8,11]

since October 2001), was voluntarily withdrawn world-wide on 30th September, 2004.[27,28] By the time it was withdrawn, rofecoxib had been taken by an estimated 80 million people and sales had reached US$2.5 billion in 2003.[29]

The rofecoxib withdrawal triggered a debate regarding safety issues; in particular the cardiovascular toxicity of other COX-2 inhibitors such as celecoxib, etoricoxib, lumiracoxib, parecoxib and valdecoxib. In December, 2004 the Adenoma Prevention with Celecoxib (APC) Study was stopped for the same reasons as the APPROVe study: patients on celecoxib (200mg twice daily or 400mg daily) had dose-dependently a 2.5 and 3.4 fold increased risk for cardiovasacular events when compared to placebo.[30] 8 April, 2005 saw the suspension of sales and marketing of valdecoxib in Europe and the US.[31,32] This action followed increasing concerns about the risk of serious skin reactions, including Stevens-Johnson Syndrome and toxic epidermal necrolysis, in addition to established class-evidence of cardiovascular risk, with the selective COX-2 inhibitors as well as evidence from two randomised, placebo-controlled trials in patients who had undergone a coronary-artery bypass grafting which showed that valdecoxib and its prodrug parecoxib increased the risk of servious cardiovascular events almost 3 fold.[33-36]

Several drug regulatory agencies worldwide have undertaken a full review of all selective COX-2-inhibitors. The Australian Therapeutics Goods Administration (TGA), European Medicines Agency (EMeA – of which both Medicines

and Healthcare products Regulatory Agency [MHRA] – UK and Medicines Authority [MA] – Malta are parties to) and the New Zealand Devices Safety Authority (MEDSAFE) have all issued preliminary accelerated reviews of the selective COX-2-inhibitors, and pending a full review, have all announced interim regulatory restrictions on the use of these medicines. Analysis by these agencies suggests a class-effect with an increased risk of cardio-vascular events for all COX-2 inhibitors which risk may increase with dose and duration of exposure.[37-42] As per MHRA guidance this risk was considered unlikely to exceed one extra serious thrombotic event per 100 patient years, over the rate for no treatment.[39]

Various reports concur with EMeA's decision that cardiovascular toxicity represents a group effect of selective COX-2-inhibitors.[43,44] The very similar cardiovascular toxicity can be explained by their common mechanism of action. Both rofecoxib and celecoxib for example suppress the formation of PGI_2, which is mostly produced by COX-2 in endothelium and which inhibits platelet aggregation causing vasodilation and prevents proliferation of vascular smooth-muscle cells. These effects contrast sharply with those of thromboxane (TxA_2), the major COX-1 product of platelets, which causes platelet aggregation, vasoconstriction and vascular proliferation.[14] Selective COX-2-inhibitors tend to cause a metabolic shift towards TxA_2 and consequently predispose patients to thrombotic stroke and myocardial infarction.[14]

Unexpectedly the Food and Drug Administration (FDA) – USA came to a different conclusion. FDA declared that despite the limitations of the available data, overall, there is evidence, that selective COX-2-inhibitors are associated with an increased risk of serious adverse cardiovascular (CV) events (e.g., MI, stroke, and death). However FDA unlike EMeA doubted that it is the presence of, or the degree of, COX-2 selectivity that accounts for these observations. In various controlled clinical trials, COX-2 selective drugs have been indistinguishable from non-selective NSAIDs (such as ibuprofen, diclofenac and naproxen) in studies of substantial size and duration.[45] Further, FDA declares that although on theoretical grounds the addition of low-dose aspirin (a COX-1 inhibitor) to a COX-2 selective drug should resolve any increased cardiovascular risk caused by COX-2 selectivity, this effect has not in fact been observed in several studies in which such comparisons are possible. FDA declares that taken together, these observations raise serious questions about the so called "COX-2 hypothesis," which suggests that COX-2 selectivity contributes to increased CV risk and that it remains unclear to what extent the COX-2 selectivity of an individual drug predicts the drug's potential for an increased risk of adverse CV events compared to drugs that are less COX-2 selective. FDA declares that an increased risk for serious (CV) adverse events, represents a class effect of all NSAIDs (excluding aspirin) and not just selective COX-2 inhibitors.[45,46]

Practice Points

- Selective COX-2 inhibitors should not be prescribed to patients with cerebrovascular disease, established ischaemic heart disease, or those with moderate heart failure (NHYA class II-IV).
- For all patients, the balance of gastrointestinal and cardiovascular risk should be considered before prescribing a COX-2 inhibitor, particularly for those with risk factors for heart disease and those taking low dose aspirin, for whom gastrointestinal benefit has not been conclusively demonstrated.
- The lowest effective dose of selective COX-2 inhibitor should be used for the shortest necessary period. Periodic re-evaluation is recommended, especially for osteoarthritis patients who may only require intermittent treatment.
- Gastroprotective agents (such as H_2-receptor antagonists [e.g. ranitidine] or proton-pump inhibitors [e.g. omeprazole]) should be considered for patients switched to non-selective NSAIDs (i.e. traditional NSAIDs).
- Selective COX-2 inhibitors should not be used routinely in the management of patients with rheumatoid arthritis or osteoarthritis.
- Selective COX-2 inhibitors should be used in preference to standard NSAIDs only when specifically indicated (i.e. for patients with a history of gastroduodenal ulcer or perforation or gastrointestinal bleeding or in patients who are at a particularly high risk of developing gastroduodenal ulcer, perforation, or bleeding such as patients aged over 65 years, patients who are taking other medicines which increase the risk of gastrointestinal effects, patients who are debilitated or those receiving long-term treatment with maximal doses of standard NSAIDs) *and always* after an assessment of cardiovascular risk.
- MHRA Guidelines also indicate that etoricoxib may be associated with more frequent and severe effects on blood pressure than some other COX-2 inhibitors and NSAIDs, particularly at high doses. Etoricoxib treatment should therefore not be initiated in patients whose hypertension is not under control. Careful monitoring of blood pressure is advised for patients taking etoricoxib.

Conclusion

The selective COX-2-inhibitors situation should spur us to be more conscious as regards the importance of medicines information and pharmacovigilance. The continuous monitoring of the safe use of medicinal products - one of the main activities in pharmacovigilance - is critical to the protection of public health. European

legislation is in place to ensure that all stakeholders including National Competent Authorities (eg. MA-Malta), marketing authorisation holders, applicants and sponsors of clinical trials in the European Economic Area (EEA) collect, collate and exchange adverse drug reactions. This is essential to ensure that rapid and appropriate responses are made to potential safety issues related to medicinal products.

The various regulatory restriction of the COX-2 inhibitors go to show the extreme importance of post-market surveillance which include Phase 4 studies, epidemiological studies as well as spontaneous reporting by prescribers and other healthcare professionals. Underreporting of suspected ADRs by health professionals is a major obstacle in drug safety monitoring. Locally this can be done through the Medicines Authority, Malta. [48,49]

It is already known that warnings and letters to health care professionals have little or no effect, so it would seem that much more emphasis should be placed on better communication strategies.[50] Medicines Information Centers are essential in providing useful, accurate and unbiased information that can be accessed at an appropriate place and time by everyone with an interest in effective use of medicines be it health-care professionals or the patient.

Addendum

Following the submission of this review two observational studies have been published addressing the issue of cardiovascular safety of COX-2 inhibitors and NSAIDs. A case-control study found a similar risk of myocardial infarction for celecoxib, rofecoxib, ibuprofen and naproxen and a somewhat higher risk with diclofenac; with the authors warranting a reconsideration of the cardiovascualr safety of all NSAIDs.[51] A retrospective cohort study in patients with congestive heart failure found lower mortality in patients treated with celecoxib than with rofecoxib and traditional NSAIDs.[52] These results should be interpreted with caution. For example the two studies contradict each other as regards the similar risk of myocardial infarction for naproxen and rofecoxib. Both studies were also criticised as regards quality of the data.[53]

The Medicines Authority Malta, has reassured patients and health-care professionals regarding the safety of ibuprofen but has advised prescribers and patients alike that the lowest effective dose of NSAIDs should be used for the shortest period of time necessary for treatment.[54]

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