

Do the COX-2 inhibitors still have a role to play?

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Introduction

The 30th September 2004 saw the withdrawal from the worldwide market of Vioxx because of the risk of adverse cardiovascular thrombotic events (acute myocardial infarction; thrombotic stroke; sudden cardiac death). This constituted the largest drug withdrawal in history. By the end of its 5 year reign, rofecoxib had been used by 80 million American patients; had 10 million scripts filled per month and had achieved sales in excess of \$ 2.5 billion in the USA (\$ 10 billion worldwide for all coxibs). The withdrawal led to enormous distress to patients, physicians, regulatory bodies and pharmaceutical companies – all for different reasons. It was probably entirely avoidable, had due process applied.

The saga continued in April of 2005 with the withdrawal of valdecoxib (Bextra) from the North American market on 8 April and from the South African shelves on 14 April. At this stage, only celecoxib (Celebrex) and parecoxib (Rayzon) remain available in this country. Of note is that parecoxib is the pro drug of valdecoxib and should share all of its pharmacological effects.

The history of COX-2 inhibitors

The use, particularly the chronic use of conventional or non-selective non-steroidal anti-inflammatory agents ((NSNSAIDs) mainly for arthritis, has been associated with an often unacceptably high rate of upper GIT irritation, erosion, ulceration and bleeding; surgical bleeding; bronchospasm and renal dysfunction, oedema and hypertension. From the identification of cyclooxygenase (COX) in 1971 until the discovery of its 2 isoforms in the early '90s, the precise mechanism of the complications was unclear. The concept then began to arise that COX-1 was the "housekeeping enzyme" generating prostaglandins (PGs) that were responsible for homeostasis in most organs, whereas COX-2 was expressed ("induced") by cells involved in painful and inflammatory states, and its prostaglandins (PGs) mediated and amplified these states. This was also the era of the discovery that many disease states, from Alzheimer's to atherosclerosis, were typified by an inflammatory process and the production of toxic oxygen free radicals, which were either the cause or the marker of cellular damage. The obvious conclusion was that COX-1 inhibition caused these deleterious side effects and that COX-2 inhibition was responsible for the anti-inflammatory, analgesic, antipyretic and, possibly, disease-

controlling effects. The search was therefore on for a COX-2 selective drug and the pot of gold that would accompany it.

Celecoxib, a weakly COX-2 selective agent, was released in 1998 following trials lasting 3 – 6 months. Rofecoxib ("Vioxx"), the first highly COX-2 selective agent, was approved for release on 21 May 1999. Its release was based on studies of 6 months' duration showing anti-inflammatory and analgesic efficacy and improved GIT safety compared with NSNSAIDs. The studies had yet to be completed or published in peer-reviewed journals and contained limited, preliminary cardiovascular (CVS) safety data. The VIGOR trial (on which registration was based), was eventually published in late 2000. It contained > 8 000 patients and showed unequivocally that rofecoxib produced less gastrointestinal (GIT) toxicity than naproxen (4% vs. 2%). CVS data was incomplete or not sought. However, it was apparent, even from the incomplete data, that the rate of acute myocardial infarction (AMI) in the rofecoxib group was 5 times higher than that in the naproxen group. This was attributed to a protective effect of naproxen. The CLASS study of celecoxib (once aspirin users were excluded) showed a small GIT benefit and a numerical but not statistically significant increase in cardiovascular morbidity.

The FDA met in February 2001 to discuss the apparent cardiovascular risk of these agents. They concluded that there was cause for concern and recommended trials of CVS safety because of:

- The high likelihood of arthritis and cardiovascular risk co-existing and that coxibs would be used in these patients
- Hopes that coxibs would be shown to be beneficial in the arterial inflammation and endothelial dysfunction that underlies coronary and cerebro-vascular disease.

No such trial was undertaken. Instead, Merck embarked on a barrage of marketing, which included:

- Press releases titled "Favourable CVS safety of Vioxx."
- The sponsorship of several papers in peer-reviewed journals on the same topic and the protective effects of naproxen.
- The launch of a blitz of educational symposia for physicians on the inert effect of Vioxx on the CVS and the protective effects of naproxen.
- Spending in excess of \$ 100 million per year on the outlawed practice of direct to consumer advertising. This is 10 times more than such a trial would have cost.

Meanwhile, evidence continued to mount of potential CVS toxicity. In a period of 5 years, more than 1.4 million patients were

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enrolled in trials involving rofecoxib. Increased CVS complications became a recurring theme. On each occasion, Merck dismissed the problem, stating that only a prospective randomised controlled trial (RCT) could satisfactorily address this issue. Yet between Merck and the FDA, no such trial was instituted.

Finally, in September 2004, the APPROVe trial on use of rofecoxib for long-term prevention of colonic polyps after colonic malignancy, was terminated 2 months early on instruction of the external safety-monitoring board. This was as a result of an excess of 16 adverse CVS events per thousand patients per year versus placebo (rofecoxib caused an approximate doubling of risk). The drug was immediately withdrawn from the market. The study was published in 2005.

Several questioned remained unanswered:

1. Are the problems isolated to rofecoxib or are we looking at a group effect?
2. Does the risk apply only with long term use and in high risk patients?
3. Do other benefits outweigh the CVS risks?
4. Are NSNSAIDs free of these risks?

I shall attempt to deal with these by reviewing the current notions about COX physiology and a barrage of recent papers assessing the CVS safety of both NSNSAIDs and coxibs.

What do we know about COX-2 physiology and pathophysiology? The evidence

COX-2 physiology has moved on substantially since the early '90s. It is now clear that the isoform has constitutive or house-keeping functions in many organs and tissues. It should be made clear from the outset that NSNSAIDs are all also COX-2 inhibitors to a greater or lesser extent. They will therefore share many of the advantages and disadvantages of COX-2 inhibitors, while adding the risks and benefits of COX-1 inhibition.

COX-2 and pain perception

- Inflammation increases COX-2 synthesis and results in peripheral nociceptor sensitisation
- COX-2 is expressed constitutively (normally) in the dorsal horn and undergoes short-term up-regulation in pain and trauma states. This enhances pain transmission.
- COX-2 inhibitors (coxibs and NSNSAIDs) suppress cerebrospinal (CSF) prostaglandin (PG) levels and reduce immediate mechanical hyperalgesia
- Delayed hyperalgesia or persistent acute pain appears to be mediated to a degree by inducible COX-1 in the glial cell network and is more effectively inhibited by NSNSAIDs

COX-2 and alzheimers disease

- The neurodestructive process in Alzheimer's appears to be inflammatory in nature
- Evidence of up-regulation of COX-2 in the hippocampus and memory associated areas in these patients
- COX-2 derived PGs appear to potentiate glutamate excitotoxicity, which is also thought to contribute to the pathogenesis
- There is epidemiological evidence that NSAIDs, especially coxibs, may control or limit the inflammatory degradative process. These patients will, of course, be subject to all the complications of long-term therapy.

COX-2 and the eye

- There is loss of COX-2 expression in the eyes of glaucoma patients
- Coxibs may induce glaucoma in susceptible patients e.g. those on steroids
- Contra-indicated in patients with steroid-induced or open-angle glaucoma

COX-2 and cancer

- Most work has been done on colonic adenocarcinoma
- Both COX-2 and COX-1 have been implicated in enhanced tumour angiogenesis, leading to accelerated tumour growth
- COX-2 over-expression in the colonic endothelium leads to resistance to apoptosis with consequent dysregulation of growth and of normal cell death
- Increased COX-2 levels have been seen in other tumours (lung, breast, stomach and pancreas) and coxibs may have an adjuvant chemotherapeutic and tumour preventative effect.

COX-2 and the GIT

- COX-1 derived PGs are by far the major cytoprotective factors in the upper GIT
- COX-2 derived PGs appear to be important in the angiogenesis required for ulcer healing and coxibs have been shown to retard ulcer healing
- There is a significantly lower incidence of dyspepsia, GIT bleeds and perforations with some coxibs (rofecoxib in particular) than with NSNSAIDs
- Helicobacter pylori infection markedly increases COX-2 expression. This process is reversed by eradication of the bacterium.

COX-2 and the kidney

- COX-2 derived PGs are critical in the macula densa control of renin secretion and are thus critical in sodium balance
- Coxibs reduce sodium excretion and predispose to hypertension and oedema. They are contra-indicated in moderate or severe hypertension, oedematous states and cardiac failure
- COX-1 plays a role in sodium excretion at tubular level and its inhibition also leads to sodium retention, although perhaps on a lesser scale
- COX-2 is also involved in renal microvascular tone and preservation of glomerular blood (via prostacyclin) and its inhibition (by coxibs or NSNSAIDs) reduces urine output and renal function further.

COX-2 and the CVS

- COX-2 derived prostacyclin (PGI₂) appears vasoprotective and anti-atherogenic, producing:
 - i. Decreased platelet aggregation
 - ii. Decreased leucocyte aggregation and adhesion
 - iii. Decreased cholesterol accumulation
 - iv. Decreased smooth muscle ingrowth into the intima
- Endothelial COX-2 is up-regulated by laminar shear stress and the presence of atherogenic lipoproteins and produces prostacyclin in an attempt to counteract these processes
- COX-2 inhibition produces an exaggerated thrombotic response to plaque rupture
- COX-2 inhibition causes up-regulation of the atherogenic 5-LOX pathway and the COX-1 pathway with diversion of more of the arachidonic acid pool to this pathway

- COX-1 is responsible for the production of the locally vasoconstrictive and pro-aggregant PG thromboxane A2
- Inhibition of both isoforms produces an essentially vaso-neutral state, whereas isolated COX-2 inhibition leads to a vasoconstrictive and pro-atherogenic state
- COX-2 inhibitors share the above pathophysiology as a CLASS EFFECT
- However, differences exist between the coxibs in terms of the degree to which they produce oxidative damage to LDL and membrane phospholipids. This process is far more prominent with sulphone agents (e.g. rofecoxib and etoricoxib) than with sulphonamide drugs (e.g. celecoxib and valdecoxib). This may account for the substantial difference noted in CVS risk between rofecoxib and celecoxib. Celecoxib is also substantially less COX-2 selective than rofecoxib.
- CVS risk is accentuated in patients with anatomical coronary artery disease or multiple risk factors

Answering the questions about the COX-2's

Is it only rofecoxib or is it a group effect?

There is a surfeit of data, opinions and prejudices on the subject of the coxibs and cardiovascular risk. From the above physiological evidence, the following is apparent:

- Hypertension and fluid retention with the risk of cardiac failure are common to NSAIDs of all types although the extent may vary
- Thrombotic risk is predominantly a feature of coxibs (at least mechanistically) although the precise risk may vary within the group.

In Table I, I shall attempt to summarise the findings of several critical studies addressing the CVS risk of coxibs. Studies have been slow to materialise and the zeal shown for proving GIT safety has hardly been matched in assessing CVS risk. Trials were often held on file by pharmaceutical companies for prolonged periods before publication; published without their CVS data; did not seek CVS end points actively; excluded high risk patients; allowed aspirin co-administration or were of short duration. In addition, the vast majority were pharmaceutical industry-sponsored, and CVS data was a by-product of the actual purpose of the trial (GIT effects; Alzheimer's; colonic polyp prevention etc.) and had to be extracted by subsequent meta-analysis. Randomised controlled studies (RCTs) specifically investigating CVS risk of different drugs, doses, durations and patient risk groups have never (and probably will never be done).

The last thing that emerges from these figures is clarity.

<i>TRIAL / AUTHOR</i>	<i>Active drug/s</i>	<i>Comparator/s</i>	<i>Industry-sponsored</i>	<i>Findings</i>
VIGOR	Rofecoxib	Naproxen	Yes	Major GIT complications 2% vs. 4% Acute MI 0.5% vs. 0.1% (attributed to naproxen protective effect)
CLASS	Celecoxib	Ibuprofen Diclofenac	Yes	Aspirin a confounding factor. Without it, AMI 0.2% vs. 0.1% and little GIT protection for celecoxib
TARGET	Lumiracoxib	Naproxen Ibuprofen	Yes	Good GIT protection 47% increase in CVS events Underpowered for real CVS assessment
APPROVe (trial discontinued because of CVS safety data)	Rofecoxib	Placebo	Yes	Relative risk increase for rofecoxib 1.92 overall. RRI for CCF and cardiac failure 4.61 RRI of 6–9 with risk factors
APC (trial discontinued because of CVS safety data)	Celecoxib	Placebo	Yes	RRI 2.3 – 3.4 for celecoxib Dose dependent
Kaiser Permanente	Celecoxib Rofecoxib	Placebo Ibuprofen	No	RRI for high dose rofecoxib 3.15 All NSAIDs confer small increased risk No increased risk with celecoxib
CVS events in valdecoxib arthritis trials – White et al	Valdecoxib	Ibuprofen Naproxen Diclofenac	Yes	Low risk patients Equivalent complication rates for valdecoxib and NSNSAIDs Aspirin conferred increased risk!!!!
Juni et al. Swiss National Science Foundation. Meta-analysis	Rofecoxib	NSNSAIDs Placebo	No	RRI for rofecoxib 2.3 No impact of identity of comparator or trial duration
Mandani et al CCF outcomes	Rofecoxib Celecoxib NSNSAIDs	Placebo	No	RRI for rofecoxib 1.8 RRI for NSNSAIDs 1.4 Celecoxib no risk
Nussmeier et al (highest risk patients excluded)	Valdecoxib (Parecoxib)	Placebo	Yes	High risk post CABG patients RRI 3.7 All patients received aspirin
Fitzgerald et al (in press). Meta-analysis	Valdecoxib	Placebo	No	RRI for valdecoxib 2.19

Why do some studies show no negative impact for celecoxib and others rate it worse than rofecoxib? This must relate to the risk profile of the study populations. Why has the FDA licensed valdecoxib but not parecoxib (which is, after all, its prodrug)? Again, the study population seems crucial. It is the editorial opinion of both the NEJM and the Lancet, inter alia, that coxib related CVS thrombotic complications (AMI, CVA and sudden cardiac death) reflect primarily a class effect and that the onus of proof to the contrary now lies with the pharmaceutical industry. It is unlikely that new coxibs will emerge onto the market given the current climate.

Is risk only with chronic use in high risk patients?

This question remains unanswered as it has simply not been addressed. There seems little doubt that risk increases with dose and with duration of treatment. However, the patient risk profile needs to be factored in as it appears to accelerate as well as exacerbate cardiovascular toxicity. It is estimated that 40% of patients requiring chronic NSAID therapy are also at high cardiovascular risk because of the substantial rate of concurrence of arthritis and cardiovascular disease. Many more are at moderate risk. It appears that hypertension and fluid retention occur early (weeks to months) with all NSAIDs (selective or non). Merck maintained that the thrombotic risk with rofecoxib only became evident at or after 18 months of therapy. However, the Juni meta-analysis and Kaiser Permanente study confirmed that it reached statistical significance versus placebo at 2 – 3 months. The same appears true for other drugs in the class. A study of valdecoxib in post-CABG patients showed increased thrombotic risk within 10 days and prompted a NEJM editorial to brand this agent a “drug of last resort”.

In contrast, there are several large prospective studies in low risk patients with celecoxib and valdecoxib, that show little or no increased cardiovascular thrombotic risk compared with NSNSAIDs. So, what is a low risk patient? Is there such a thing as a low risk patient in the thrombogenic peri-operative period? The valdecoxib post-CABG is the only one I can locate looking specifically at CVS risk in the post-operative period and its findings are scarcely encouraging! Subsequent

to this study, Pfizer Canada released a public health advisory relating to the peri-operative use of valdecoxib. They stated that “Bextra is NOT approved for use after surgery in any setting. Specifically, Bextra should NOT be used after CABG surgery” (The capital letters are theirs, not mine). Studies of young healthy patients undergoing relatively non-invasive surgery may tell a completely different story but we cannot extrapolate from non-surgical patients so we do not know.

There is a school of thought that advocates the addition of low-dose, enteric-coated aspirin to chronic coxib therapy to reduce CVS risk while preserving some benefit in terms of CVS tolerability. The valdecoxib CABG study showed that this does not eliminate (or possibly even reduce) the CVS risk in high-risk patients. The GIT tolerability is lower than with the coxib alone.

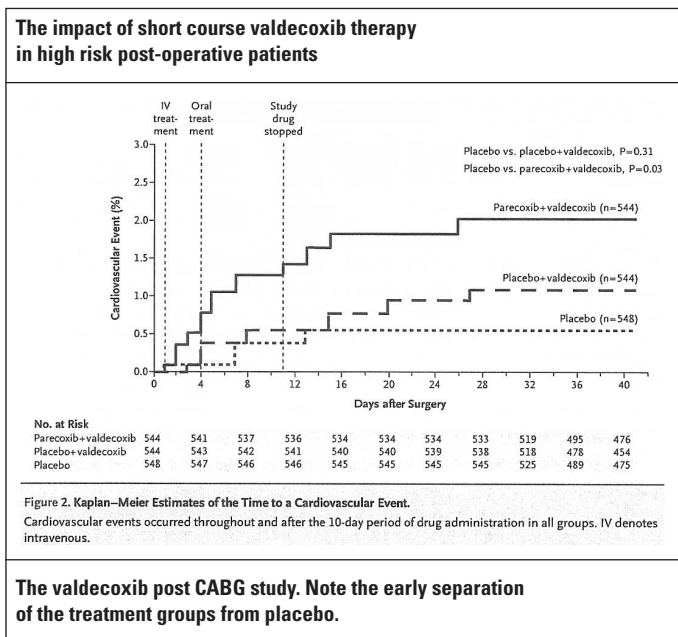
At this stage, it may be prudent to limit the duration of post-operative coxib therapy to 3 to 5 days. In addition, they are probably contra-indicated for cardiac and vascular surgery, cancer surgery and surgery on patients with more than one cardiovascular risk factor (previous MI; unstable angina; hypercholesterolaemia; diabetes mellitus; symptomatic cerebrovascular disease; previous cardiac failure; moderate to severe hypertension; smoking; family history of IHD). This may seem excessively restrictive but one needs to be able to justify oneself medico-legally in view of recent editorial comments (some of which would see the class disappear forever).

Do the benefits of coxibs outweigh the risks?

There is no advantage for coxibs over NSNSAIDs in terms of efficacy as anti-inflammatories or post-operative analgesics. NSNSAIDs may be more complete analgesics mechanistically as both COX-1 and COX-2 are involved in the spinal processing of pain at different phases after the surgical injury. It is unclear whether this necessarily translates into a meaningful clinical advantage for NSNSAIDs in acute pain (although we all know the legendary status of the Voltaren suppository!).

The two major benefits and marketing weapons of coxibs are advantages in terms of GIT tolerability and platelet-related bleeding. A subsidiary advantage is the fact that the drugs can be used safely in aspirin-sensitive asthmatics (although there have been isolated case reports of cross reactivity). They have added a group of new complications to the NSAID arsenal, namely the problem of contra-indication in sulphonamide allergy (celecoxib, valdecoxib, parecoxib) and life-threatening toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (all, but especially valdecoxib). There are also significant concerns related to bone, soft tissue and wound healing.

There is little doubt that coxibs produce less upper GIT problems than NSNSAIDs in clinical reality. Strong statistical evidence exists for rofecoxib, while there is a trend towards fewer symptoms and complications for other coxibs. Chronic use of NSNSAIDs results in some form of upper GIT symptomatology in 70% of patients, whereas this occurs in only 25 – 30% of coxib users. The rate of significant complications such as bleeding with a fall in haemoglobin, confirmed ulcers or perforation of an ulcer is 2% vs. 4% with NSNSAIDs. Rates with acute post-operative use are also high and endoscopic changes are seen in 10 – 70% of NSNSAID users and half of this rate for coxibs. Combining a NSNSAID with a proton pump inhibitor (PPI) produces the same rate of symptoms and complications as coxibs at about 25 – 30%. This remains high and



chronic coxib use has not solved the problem of gastric intolerance.

Patients at a high risk of upper GIT pathology (age > 65; concurrent steroid therapy; anti-coagulant therapy; previous ulcers) who cannot manage without anti-inflammatories should receive coxibs, provided their cardiovascular risk is not high. If they are at high risk for CVS complications, then a COX-2 favouring NSNSAID, such as meloxicam, can be combined with a PPI and the patient monitored carefully for the development of GIT morbidity. Patients at moderate risk for GIT complications can receive either a coxib or NSNSAID plus PPI, with the CVS risk determining the choice. The choice of NSAID for those at low risk for GIT complications is based entirely on which agent is most efficacious for them and on their CVS risk profile.

From their mechanism of action, it should be apparent that coxibs do not contribute to platelet-related bleeding. In fact, they appear to divert an above normal amount of the arachidonic acid pool to the thromboxane pathway and thus be pro-aggregant. This, added to their vasoconstrictive effect, results in a net pro-coagulant effect. This produces the CVS thrombotic risk, but makes them ideal agents for post-operative use in patients with a low CVS risk but a high bleeding potential.

Allergy is a problem, particularly with the sulphonamide COX-2 inhibitors. The rate of allergic reactions with celecoxib or valdecoxib is 80% greater than with the sulphone drugs like rofecoxib. There is, however, a relatively low rate of cross reactivity in patients with known sulphonamide allergy. In addition, the rate of severe allergic reactions in patients with cross reactivity is low. Coxibs very rarely trigger asthma in aspirin sensitive asthmatics.

Pfizer Canada recently issued a public advisory warning about serious skin reactions in response to valdecoxib. Some cases of TEN and Stevens Johnson syndrome have been fatal. They appear to occur independently of sulphonamide allergy and within the first 2 weeks of therapy. Development of any skin rash, mucosal lesions or other allergic manifestation mandates immediate cessation of therapy and emergency medical attention.

The same health warning alluded to problems with wound healing. Other studies have identified retarded bone healing and delay in healing of ruptured Achilles tendon. The mechanism of wound healing requires PG mediated hyperaemia and angiogenesis and this is produced by COX-2 derived PGs. COX-2 inhibition interferes with this process.

So what is the outcome of the risk-benefit analysis? At this point, COX-2 inhibitors still appear appropriate for short-term peri-operative use in patients at low CVS risk but high GIT or bleeding risk, in whom an NSAID is considered necessary. In the chronic setting, the drugs should be used at the lowest possible dose for the shortest possible time in patients not at increased CVS risk who do not respond to NSNSAIDs or have a high risk of GIT complications.

Are NSNSAID's free of these risks?

Coxibs would not have been developed and taken off exponentially in the way that they did, if conventional NSNSAIDs were entirely safe and easy to take. It must be remembered that NSNSAIDs are also COX-2 inhibitors to varying extents. There are differences between agents (particularly with respect to GIT tolerability). However, in general, the chronic

use of NSNSAIDs is associated with as much renal dysfunction as coxibs and considerably more GIT irritation, bleeding complications and asthma. We have merely become familiar with the profile of the at-risk patient and tend to avoid, tailor or discontinue use in such patients. Coxibs were released as a panacea for the GIT problems and became used, across the board, in all high and low risk patients. Safety trials involving acute or chronic use in these patients did not exist prior to release. The imperative to reduce GIT complications of NSAIDs overcame natural caution.

The extent of the morbidity associated with the chronic use of NSNSAIDs can be gauged from the estimate that complications of their use are responsible for 100 – 150 thousand hospitalisations and 10 – 20 thousand deaths per year in the USA. To put this into perspective, rofecoxib was responsible for an excess of 16 AMIs per thousand patients in the APPROVe trial. 80 million people worldwide had received rofecoxib before its withdrawal (fortunately the minority of them at the same dose and for the same duration as the trial). Little wonder that Merck elected to withdraw the drug, rather than face the potential tidal wave that seemed likely to follow. Death rates in the APC (celecoxib) trial were 3.4 per 1000 patient years in the placebo group; 7.8 for low dose celecoxib and 11.4 for high dose celecoxib. Properly conducted safety trials prior to the release of the coxibs would probably have meant that we would only be using these agents selectively today (and espousing their virtues!).

Many of the trials of the CVS safety of the coxibs have used NSNSAIDs as comparators. Several observations become apparent from these trials:

- Aspirin produces a 23 – 27% protective effect against cardiovascular thrombotic complications versus placebo
- NSNSAIDs show some intra-group and intra-trial variation but range from a mild protective effect (up to 14% for naproxen) to a moderate detrimental effect (possibly proportional to their degree of COX-2 inhibition)
- The only trials showing a significant protective effect for NSNSAIDs have been for naproxen and sponsored by Merck. A single trial shows a 50% protective effect for ketorolac in hospitalised patients.
- There is little difference in CVS outcome between the 2 classes when patients with CVS risk factors are excluded from the trials
- Coxibs produce a 2 – 10 fold increase in risk vs. placebo in patients at high CVS risk.

Conclusion

The withdrawal of rofecoxib came amidst a media frenzy unlike any before. The subsequent machinations of the regulatory bodies, politicians, lawyers and pharmaceutical companies rivalled any soap opera. Thinly veiled threats and accusations abound to this day about who owns and has bought whom. The state of play at present is that rofecoxib is gone (a commercial decision by Merck); that all pharmaceutical companies marketing coxibs have been hammered on the market and have had to shed parts of their work force; but that the FDA has voted overwhelmingly to keep coxibs on the market and for the return of rofecoxib. It is true that 1/3 of the members of the FDA panel have ties to coxib manufacturers, but I feel that their decision remains a reasonable one given that they carry the appropriate “black box” warning

about CVS and other risks.

Coxibs are good and effective anti-inflammatories and have a role in both the acute and chronic setting (in patients with high GIT and bleeding risks and a low CVS risk profile or those unable to tolerate NSNSAIDs). They are not drugs for the frailest patients with multi-organ disease undergoing major surgery. They are certainly not the only anti-inflammatories available, nor the most efficacious. It is entirely unacceptable to place patients at risk for cardiovascular morbidity or mortality when they could have tolerated drugs largely lacking this side effect. We need to be cognisant of their risks and limitations and use them sensibly – like any other drug including NSNSAIDs. We were failed by the FDA and the pharmaceutical industry in that a class of drugs was released for long term use without any long term safety assessment. It is a warning to us not to embrace new agents too readily and that our primary responsibility is to first do no harm.

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