

## **Title. Valdecoxib: The rise and fall of a COX-2 inhibitor**

### **Abstract**

Introduction: Valdecoxib is a cyclooxygenase 2 (COX-2) selective anti-inflammatory drug. It is associated with a reduced incidence of gastrointestinal complications and is potentially useful for patients with rheumatological diseases requiring longer term anti-inflammatory treatment.

Areas covered: Due to a perceived increased risk of thrombotic events, particularly cardiovascular hazards and reports of unpredictable, potentially life threatening skin reactions, valdecoxib has been voluntarily withdrawn from the market since 2005. This review manuscript examines the therapeutic potential and the adverse events of valdecoxib utilising a pubmed and web of sciences search to select literature on this subject.

Expert opinion: Whilst valdecoxib did have reduced incidence of gastrointestinal complications due to a perceived increased risk of thrombotic events it was withdrawn. The limitations of the research supporting the withdrawal of this potential are discussed.

### **Keywords**

Valdecoxib, COX-2 inhibitor, osteoarthritis, rheumatoid arthritis, cardiovascular side effects

## 1. Overview of the market

The COX-2 inhibitors were developed with the promise of improved gastro-intestinal safety in comparison with non-selective anti-inflammatory agents. These drugs were perceived to be of particular use in the treatment of rheumatological diseases where long term anti-inflammatory drug use, with the combination of other disease modifying drugs, is still the norm. Unfortunately, these agents have been associated with a small but measurable increased risk of cardiovascular events which originally lead to the voluntary withdrawal of rofecoxib (Vioxx) in 2004 and then valdecoxib in 2005. One coxib, celecoxib (Celebrex) remains on the market despite similar findings.

## 2. Introduction to compound

Inflammation is a prominent component of most local and multisystem musculoskeletal diseases. Though therapies modifying the disease course of autoimmune rheumatological diseases are the mainstay of treatment, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX-2) inhibitors continue to be of value in disease management. These drugs provide pain relief, reduce joint swelling, and moreover are effective in reducing pain and regional inflammation in acute sprains, fractures and soft tissue rheumatic disorders. The main mediators of inflammation are eicosanoids (prostaglandin, prostacyclin [PGI<sub>2</sub>], thromboxane A<sub>2</sub>, and leukotrienes) produced from arachidonic acid derived from membrane phospholipids (figure 1). NSAIDs inhibit the fatty acid cyclo-oxygenase (COX) enzyme; prostaglandin G/H synthase; resulting in reduced prostaglandin and thromboxane production [1]. There are two isoforms of this enzyme: COX-1 is generally believed to be a constitutive, housekeeping enzyme present in most tissues; whilst COX-2 is induced by pathological processes [2][3]. The inhibition of COX-1 and COX-2 pathways results not only in reduced inflammation and anti-pyresis but also in reduced platelet aggregation, a propensity to cause gastrointestinal ulceration and perforations, and fluid and sodium retention, especially when taken on a chronic basis [4-6] The selective COX-2 inhibitors such as valdecoxib were developed with the aim of reducing the untoward side effects of NSAIDs whilst preserving its useful anti-inflammatory function.

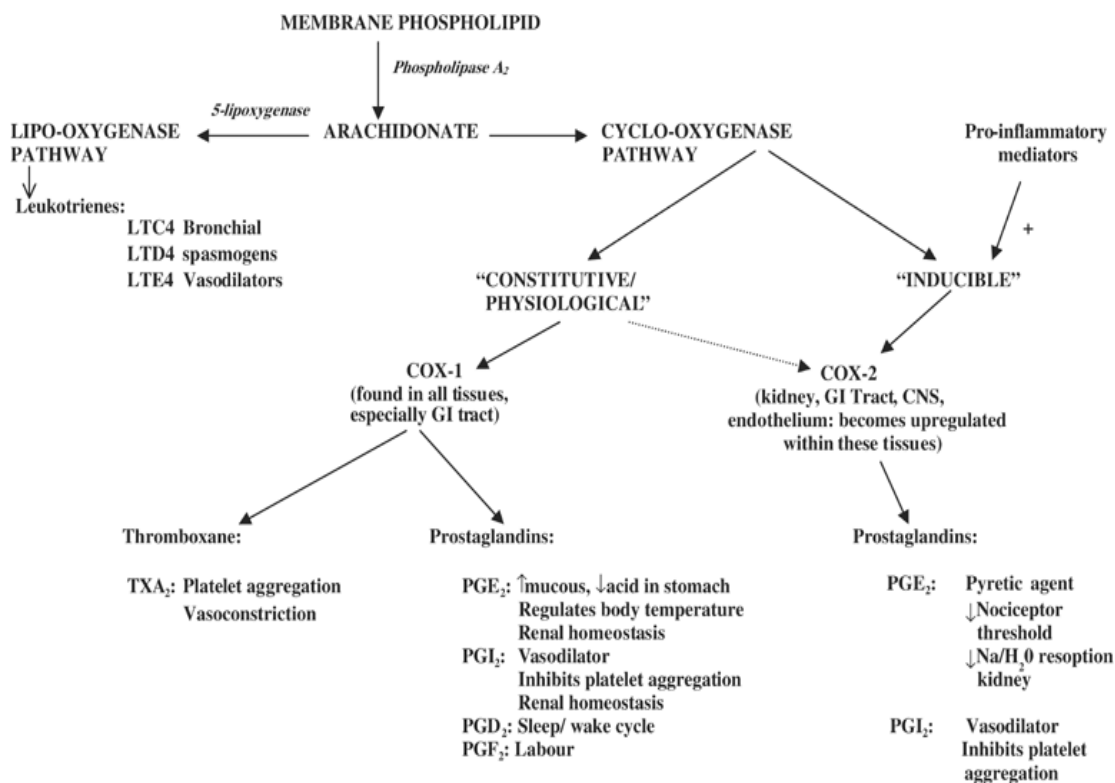
## 2.1. Chemistry

The mechanism of action of valdecoxib is best understood by comprehending the intricacies of the prostanoid (PG) and thromboxane synthesis. The first committed step in this process is the metabolism of arachidonic acid to prostaglandin H by the enzyme prostaglandin H<sub>2</sub> synthetase, also known as cyclo-oxygenase (COX). The first step, the dioxygenase step, incorporates two molecules of oxygen into the arachidonic chain at C11 and C15 positions resulting in the formation of the highly unstable endoperoxidase mediator PGG<sub>2</sub>. As the COX enzymes are bi-functional, these enzymes are capable of peroxidation of this end product. The result is the conversion of PGG<sub>2</sub> to PGH<sub>2</sub>, where the PGG<sub>2</sub> hydroperoxidase group in C15 is transformed to a hydroxy-group PGH<sub>2</sub>. Thereafter, PGG<sub>2</sub> is subject to other isomerases, reductases or synthetases which transforms it to other prostanoids [7].

Both COX-1 and COX-2 are homodimers in the intracellular membrane. Both of these similar isoforms contain a hydrophobic channel into which arachidonic acid or other fatty acid substrates can dock in order for oxygenation to occur. COX 2 contains a bulky side pocket which is not present in COX-1 and therefore drugs such as valdecoxib, which contain a bulky groups or moieties bind only to COX-2. These COX2 inhibitors then enter the hydrophobic channel in these enzymes blocking the entry of the fatty acid substrates.

Valdecoxib is a diaryl substituted isoxazole, structurally similar to celecoxib, the first COX2 inhibitor (Figure 3). Hydroxylamine hydrochloride in the presence of sodium acetate was used to convert deoxybenzamin to its corresponding oxime [8]. The oxime was deprotonated using 2 equivalents of butyllithium followed by condensation with ethyl acetate. The result, isoxazoline was treated with chlorosulfonic acid [9]. This was followed by the reaction of sulfonyl chloride with aqueous ammonia yielding valdecoxib [10].

**FIGURE 1: THE CYCLO-OXYGENASE AND LIPOOXYGENASE PATHWAY**



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## 2.2. Pharmacokinetics and metabolism

In healthy young subjects, valdecoxib is well absorbed on an empty stomach and achieves maximum plasma concentrations in about 3 hours (Tmax). Approximately 83% of the drug reaches the systemic circulation and peak plasma concentration (Cmax) and concentration time curves (AUC) remain little affected by meals or concomitant antacid use (Pharmacia corporation 2002). The Cmax and AUC show proportional increases with doses up to a maximum of 400mg with steady state concentrations being achieved after four days of treatment [11].

Valdecoxib is heavily protein bound with >98% of drug being bound to plasma proteins at plasma concentrations in the range of 21-2384 ug/L. The drug undergoes hepatic metabolism, metabolized by both the nonP450 and P450 cytochrome pathways (Figure 2). The P450 system is predominant with hydroxylation and aryl hydroxylation resulting in the formation of a carboxylic acid derivative via the CYP3A4, CYP2C9, and P450 enzyme systems. In contrast, the non P450 pathway glucuronidates the sulphonamide group. The metabolites of valdecoxib are excreted in the urine with less than 5% of the drug being excreted unchanged in the urine [12].

The elimination half-life of valdecoxib is approximately 8-11 hours. Plasma concentrations of valdecoxib were increased by 130% in patients with mild to moderate hepatic impairment (Child Pugh Class B). It is recommended that patients with hepatic impairment be monitored and commenced on smaller doses of treatment. However, the indication for using this drug in this vulnerable population must be re-examined and alternative options employed whenever possible. There are no studies of the use of valdecoxib in end-stage liver disease, but due to its pathways of metabolism valdecoxib is best avoided in severe liver disease[12].

## FIGURE 2. METABOLISM OF VALDECOXIB

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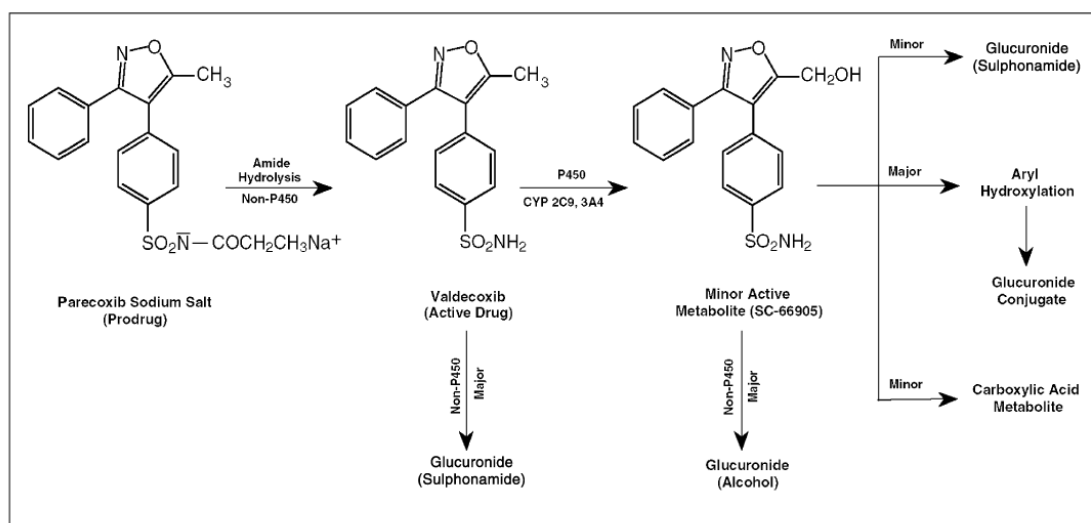


Figure 1. Metabolic pathway of valdecoxib in the human. Valdecoxib is extensively metabolized via non-P-450-mediated (glucuronidation of the sulphonamide group) and P-450-mediated (hydroxylation of the methyl group) pathways. The minor hydroxylated metabolite of valdecoxib (SC-66905) also has cyclo-oxygenase-2 (COX-2) inhibitory activity and undergoes extensive further metabolism via aryl hydroxylation, glucuronidation and the formation of carboxylic acid metabolites. Valdecoxib and SC-66905 are active moieties of the new parenteral COX-2 inhibitor, parecoxib sodium. (Adapted from Karim *et al.*<sup>18</sup>, reprinted by permission of Sage Publications, Inc.).

Elderly persons have higher concentrations of valdecoxib in the circulation, attributed to the decline in hepatic and renal function as well as reduced volumes of distribution. It is therefore recommended that the valdecoxib dose be reduced in the elderly, especially those with reduced body weight <50kg [12].

## 2.2 Pharmacodynamics

Valdecoxib binds tightly in a relatively stable fashion to COX-2 thereby inhibiting its function. In vitro studies have demonstrated that valdecoxib potently inhibits prostaglandin E2 production (50% inhibition of COX2 ( $IC_{50}$ ) = 0.0005  $\mu$ M/L compared to COX -1 ( $IC_{50}$ ) = 140  $\mu$ M) [12][13]. Similar results have been obtained in ex-vivo studies, in human whole blood, where the corresponding COX2 ( $IC_{50}$ ) and COX1 (Similar results have been obtained in ex-vivo studies, in human whole blood, where the corresponding COX2 ( $IC_{50}$ ) were 0.89  $\mu$ M and 25.4  $\mu$ M/L respectively.

The COX1/COX2 inhibition ratios are much higher for valdecoxib when compared to celecoxib [10] and the non-selective NSAIDs [14]. The primary metabolites of valdecoxib do not contribute significantly to the mechanism of action of valdecoxib. Valdecoxib is also the active moiety of the parenteral COX2 selective inhibitor parecoxib sodium [15].

The analgesic effects of valdecoxib were studied in rat models of inflammation. The dose of valdecoxib that caused a 50% reduction in inflammation was 0.05, 0.032 and 10.2 mg/kg in the carrageenan air pouch, adjuvant arthritis and carrageenan hind-paw models[10]. The analgesic effect on humans is described below in the clinical efficacy section.

The traditional non-steroidal anti-inflammatory drugs (tNSAIDs) inhibit platelet function. Double blind randomised control studies of the effect of valdecoxib 40mg twice daily on platelet function in healthy adults and elderly demonstrated that this drug does not affect platelet function or bleeding times [16, 17].

### **3. Clinical efficacy**

The clinical efficacy of valdecoxib has been assessed in the treatment of osteoarthritis (OA) of knees, hips [18-20], rheumatoid arthritis [20], analgesia in dysmenorrhoea [21] and post-operative analgesia after hip arthroplasty [22], orthopaedic foot and oral surgery [23][24]. A total of 4000 patients were evaluated in these studies. This review will focus on the patients with knee and hip osteoarthritis and rheumatoid arthritis.

Valdecoxib has been more efficacious than placebo in treating osteoarthritis of the knee. At higher doses (5mg b.i.d and 10mg once or b.i.d.), it was equally efficacious as naproxen 500mg/bd. Assessment at week 1, 2 and 6 revealed an improvement in the patient assessment of pain, patient global assessment of arthritis (using visual analogue scores and the Western Ontario and Mc Masters Universities OA index) from baseline [25]. A double-blind study of patients with moderate to severe knee OA revealed that valdecoxib 5mg b.i.d or 10mg b.i.d was equally efficacious as naproxen with fewer endoscopically proven gastroduodenal ulcers at week 12 (3 vs 10% p<0.05) [18]. Valdecoxib has been similarly efficacious

in patients with hip OA, where the majority of studies compared valdecoxib with naproxen[19].

Valdecoxib 10mg, 20mg and 40mg q.d. has been compared with naproxen in the symptomatic treatment of patients with a flare of rheumatoid arthritis. The studies revealed that valdecoxib was well tolerated and as equally effective as naproxen 500mg b.i.d at doses of 20mg or 40mg q.d.[26, 27]. Similar results were shown when valdecoxib was compared to diclofenac [28] .However, it was noted that valdecoxib had superior gastrointestinal tolerability when compared to slow release diclofenac and ibuprofen [29]. The favourable gastrointestinal tolerance of valdecoxib has been further proven in a meta-analysis [30], where there was decrease in dyspepsia and improved drug tolerance in patients taking valdecoxib even at supra-therapeutic doses.

Similar trends have been reported in the management of acute and chronic low back pain [31].

#### **4. Safety and tolerability**

The gastrointestinal safety of valdecoxib has been proven in the studies discussed above. It is clear that valdecoxib inhibits COX-2 enzyme to reduce prostaglandins E2 and I2 in inflamed joints without affecting the COX-1 mediated, prostaglandin E2, I2 effected gastric mucosal protection [32].

As COX-2 enzyme contributes to renal vasodilatory function by promoting prostacyclin generation in endothelial cells the renal safety of valdecoxib has been a cause for concern. The renal safety of valdecoxib has been explored in cohorts of patients with rheumatoid arthritis and osteoarthritis. The incidence of common renal side effects; albuminuria, peripheral oedema and hypertension following COX2 inhibition is higher than placebo (0.9%, 2.3% and 2.8% compared to 0.2%, 0.7% and 0.6% ) but is not significantly different to conventional NSAIDS (0.5%, 2.2%, and 1.5%) in pooled studies [33, 34][24, 25]. Studies of patients with severe renal dysfunction and those with end stage renal dysfunction on haemodialysis resulted in a 23% reduction of mean plasma clearance when compared with

healthy subjects. But, this is not of clinical significance to warrant a dosage reduction in renal insufficiency. However, the use of valdecoxib in patients with advanced renal disease is strongly discouraged. The majority of renal effects are dose dependent and attributed to the occurrence of oedema and rise in blood pressure. Therefore valdecoxib use in subjects dependent on the renin-angiotensin system haemodynamics; e.g cirrhotics, patients with congestive heart disease; must be accompanied by monitoring of renal function.

Drug interactions between valdecoxib and many other drugs have been extensively studied [35, 36]. Of particular interest is the fact that valdecoxib does not significantly affect the action of methotrexate. Short courses of low dose valdecoxib (10mg b.d.) had no effect on the pharmacokinetics of oral methotrexate. Similar changes have been described with intramuscular methotrexate (unpublished reports). However, there is little data on interactions between valdecoxib and other disease modifying drugs.

## **5. Regulatory affairs**

In 2005 the Food and Drug Administration agency of the United States Department of Health and Human Services (FDA) and the European Medicines Agency (EMA) requested that the manufacturer voluntarily withdraw valdecoxib from the market due to its potential side effect profile. The lack of adequate data on the long-term safety of the drug, increased risk of adverse cardiovascular events in short term coronary artery bypass graft trials, reports of serious skin reactions coupled with the lack of any significant advantage over NSAIDS were cited as reasons for this withdrawal request.

The increase in cardiovascular events has been attributed to its potent inhibition of COX-2 and consequent reduction of prostacyclin biosynthesis. This fact is supported by in vivo studies which have demonstrated that NSAIDS (both the COX-2 inhibitors and some tNSAIDS) reduce systemic biosynthesis of prostacyclins in healthy humans by >60% [37].

In the vascular system, prostacyclin formation in the endothelium is induced in response to platelet vessel wall interactions and haemodynamic stress [38-40]. There is evidence that prostacyclin binding to its receptor activates membrane bound adenylyl-cyclase leading to

formation of cyclic AMP[41]. cAMP initiates inhibition of platelet aggregation, vascular smooth muscle constriction and induction of thrombomodulin which inhibits coagulation, with resultant reduction of vascular occlusion. In addition, studies on rodent models have confirmed that prostacyclin helps prevent hypertension and cardiac hypertrophy [42, 43]. Moreover, clinical trials of COX2 inhibitors used for other indications have demonstrated a trend that CV hazard is dose dependent [44, 45]. It is interesting that the magnitude of concomitant COX-1 inhibition mitigates the cardiovascular risk [46]. One explanation for this is believed to be the result of inhibition of thromboxane A2 (TXA2), another pro-aggregatory agent [47]. It is noteworthy that cardiovascular risk is only minimized in these cases and is not completely abrogated.

Another possible contributory factor to the cardiovascular risk is the occurrence of hypertension. This adverse effect is attributed to the inhibition of COX2 in the kidneys. In susceptible individuals, inhibition of vasodilatory renal prostacyclin leads to sodium retention, oedema and hypertension [48]. This is a feature of COX-2 inhibitors and certain tNSAIDs [49, 50], but is greater in COX-2 inhibitors [51] at high dose, as shown in the MEDAL (Multinational Etoricoxib vs Diclofenac Arthritis Long-term Program) and EDGE studies [52, 53]. These study results suggest that thrombosis rather than hypertension is the main mechanism of cardiovascular risk.

The increased risk of cardiovascular adverse events for valdecoxib was highlighted in two short-term multi centre, randomized, double blind, placebo controlled trials assessing the safety of the drug in coronary bypass grafting (CABG) patients. In these trials valdecoxib (or its prodrug parecoxib) were used in post-operative analgesia. COX-2 inhibitors such as valdecoxib are ideal candidates to provide for post-operative pain relief: these agents give pain relief without increasing bleeding (compared to tNSAIDs). This is particularly true for valdecoxib, where the pro-drug parecoxib is intravenously administered, and is therefore eminently useful in the early post-operative period.

In the first study in 2003 [54], 1671 CABG patients were randomly allocated to receive intravenous parecoxib for a maximum of three days followed by oral valdecoxib till postoperative day 10, or intravenous placebo and oral valdecoxib or intravenous and oral placebo throughout the trial period of 14 days (151 patients in the valdecoxib (40mg

bid)/parecoxib sodium (40mg bid) group with 151 in the placebo/placebo group). The primary end-points were adverse events, including cardiovascular events, renal dysfunction, poor wound healing and peptic ulceration. The groups given valdecoxib with parecoxib or valdecoxib with placebo had significantly higher adverse events. This was particularly true for cardiovascular events including myocardial infarction, cardiac arrest, stroke and pulmonary embolism. These events were more frequent in the treatment group when compared to placebo with a risk ratio of 3.7 (95 %CI, 1.0 to 13.5; P=0.03).

However, the drug doses used in this short-term trial designed for pain relief, were different to the conventional doses of valdecoxib recommended for standard rheumatological practice. The doses of valdecoxib, and particularly that of parecoxib were supra therapeutic, leading to profound suppression of COX-2 activity. It is invariable that such profound prostacyclin suppression in a cohort of patients at high coronary risk caused a rapid increase in vascular and thrombotic events.

The second multicenter, phase III, placebo-controlled, double-blind, randomized, parallel-group trial CABG study assessed the risk of cardio-vascular events, renal dysfunction, peptic ulceration and wound infection in 462 patients [55]. Patients were allocated at a ratio of 2:1 to parecoxib/valdecoxib or standard care (control) groups, respectively. Intravenous study drug (parecoxib) (40 mg) was administered within 30 minutes of extubation and at a dose of 20mg IV b.i.d for a minimum of 3 days. Thereafter, oral treatment of valdecoxib 40 mg b.i.d. was initiated and continued for a total of 14 days. Clinical adverse events were assessed from the time of the first dose through the 30-day post-dosing period. Though the parecoxib/valdecoxib groups had better pain relief than the control group during the study time points, serious adverse events were twice as frequent in the valdecoxib-parecoxib group, particular cardiovascular events. The incidences of other individual serious adverse events, including cerebrovascular complications and renal dysfunction, were proportionally greater, though not significantly different, between the groups. However, despite the lower doses of valdecoxib and the shorter treatment duration compared to the first study, parecoxib was used at a dose of 20mg b.i.d., which is still a supra-therapeutic dose completely suppressing COX-2 activity.

Similar findings were obtained from a meta-analysis of the coronary and cerebrovascular

adverse events in these two CABG and other placebo controlled trials of valdecoxib in patients with arthritis demonstrated a threefold higher cardiovascular risk in valdecoxib compared to placebo (RR=3.08; 95%CI = 1.20-7.87) [56]

However, this finding was not corroborated in a similar unpublished study on 1050 patients undergoing major general or orthopaedic surgery. These patients were given an initial dose of parecoxib 40mg i.v. followed by 20mg i.v. b.i.d for three days, followed by oral valdecoxib (20 mg b.i.d) (525 patients) or placebo (525 patients) for the 10 day treatment period or a placebo intravenous infusion followed by oral placebo (525 patients). No significant differences were detected in the overall safety profile [57].

These findings suggest that the CV effects of valdecoxib are most marked in patients with severe haemostatic activation. There are a multitude of potential contributors for this increased thrombotic risk. Patients who are subject to CABG have inherently increased risk of CV complications affecting the cardiovascular, cerebrovascular, renal and intestinal systems. In addition, platelet activation occurs early in the post-CABG patients [58] and may not be counteracted by aspirin. Moreover, valdecoxib potentially interferes with the COX-2 mediated cardiac ischaemia protective effect of anaesthetics [59].

It is believed that the contact between blood and synthetic surfaces in the extra-corporeal circuit activates platelets, endothelial cells and leucocytes with resultant thrombotic tendency [60][61]. Furthermore, the cardiopulmonary bypass increases prostacyclin and thromboxane levels [62, 63] In addition, cross clamping may contribute to ischaemic-reperfusion insults to the myocardium [64]. The combination of these factors, which may be exponential, explain why CABG patients are more susceptible to the CV complications of valdecoxib. The near total suppression of COX-2 inhibition, and subsequent thrombosis could not be mitigated by low dose aspirin. The rapid suppression of vascular prostacyclin by intravenous parecoxib could not be countered by the orally administered aspirin, which requires at least an hour to suppress platelet COX-1. In addition, a high number of CABG patients are not-responsive to aspirin in the immediate post surgical period [65, 66]. This may be a consequence of the intense inflammatory cascade activation due to reperfusion of vital organs. This may induce thromboxane synthesis through COX-2 induction in platelet-leucocyte aggregates reducing the ability of aspirin to suppress thromboxane [67].

Furthermore, there may be de-novo synthesis of COX-1 in the platelets activated by pro-aggregatory stimuli which counteracts aspirin inhibition of platelet thromboxane biosynthesis [68].

There are no large scale RCTs performed which assess the safety of valdecoxib in OA or RA. There are unpublished data of 10 RCT in OA and RA where 4531 patients in total received valdecoxib. The doses ranged from 10-80mg with a wide treatment duration of 6-52 weeks. It is noteworthy that the majority of these patients received valdecoxib for <12 weeks. The incidence of serious CV events in patients of valdecoxib, or placebo (n=1142) or tNSAID (n=2261) were compared. There was no significant difference between the exposure adjusted incidence of adverse events of or CV events when the three groups were compared. However, as most of the studies were of short duration, and were inadequately powered to detect cardiovascular events in a lower CV risk group, the validity of this information is questionable [57].

Systematic review and meta-analyses have been performed to estimate the risk of MI associated with COX-2 inhibitors compared with placebo. Chen *et al* used a fixed- effect model to analyse 55 RCTs of 99,087 patients to estimate the odds ratio of MI associated with COX-2 inhibitors when compared to placebo, tNSAIDS and other COX-2 inhibitors. The overall odds ratio for MI risk for COX-2 inhibitors was 1.46 (95% CI=1.02, 2.09). Celecoxib, Rofecoxib, Etoricoxib, Valdecoxib and Lumiracoxib were associated with higher MI risks compared to placebo though subgroup comparisons failed to achieve conventional levels of significance. The pooled OR for any COX-2 inhibitor compared to other tNSAIDS was 1.45 ( 95% CI=1.09, 1.93). Interestingly, valdecoxib had a lower MI risk than diclofenac (OR=0.14; 95% CI=0.03, 0.73), though diclofenac continues to be used extensively. The available head-to-head comparisons of COX-2 inhibitors failed to identify any difference in risk of MI between the different COX-2 inhibitors [69].

Similar results were yielded by the meta-analysis done by Kearney et al, with some significant new developments [70]. Data from 138 randomized trials involving 145,373 participants were evaluated in this meta-analysis. Trials for this meta-analysis were selected if they had at least 4 weeks scheduled treatment and included a comparison of a COX-2 inhibitor versus placebo or versus a tNSAID. This meta-analysis explored the following pre-

specified outcomes: a serious vascular event, fatal/non-fatal myocardial infarction, fatal/non-fatal stroke or vascular death. Due to the hypothesis that naproxen has aspirin-like antiplatelet effects the analysis of COX-2 inhibitor versus tNSAIDs were subdivided to naproxen and non-naproxen like NSAIDs. In placebo comparisons, the use of a selective COX-2 inhibitor was associated with a 42% increased incidence of serious vascular events (1.2% per year vs 0.9% per year; rate ratio 1.42 95% relative increase in the incidence of serious vascular events 1.13-1.78: P=0.0003.) This was chiefly attributed to increased incidence of myocardial infarction (0.6% yearly versus 0.3% year; 1.86, 1.33 to 2.59; P=0.0003). There was no significant heterogeneity amongst the different types of COX-2 inhibitors, though the data was inadequately powered to detect a real difference. High dose regimens of some tNSAIDs, i.e. ibuprofen and diclofenac had a similar risk of serious vascular events to COX-2 inhibitors (0.9% yearly versus 1% yearly, rate ratio 1.16, 0.97 to 1.38; P=0.1). A marked difference in heterogeneity was detected when COX-2 inhibitors were compared with naproxen and non-naproxen tNSAIDs. The explanation for these results is the profound inhibitory effect both tNSAIDs and COX-2 inhibitors on prostacyclin is unopposed by platelet COX-1 inhibition. High dose naproxen inhibits both COX-1 in platelets and COX-2 in inflammatory tissues reducing the possibility of increased CV risk. As indicated before, valdecoxib and fellow COX-2 inhibitors suffer from only inhibiting COX-2 mediated prostacyclin synthesis. The platelet COX-1 remains functional with a propensity for thrombosis leading to thrombotic risk. [71].

Another cause for concern in the use of Valdecoxib is the risk of serious skin infections. Despite lacking the aromatic amine portion of sulphonamide usually implicated in toxic epidermal necrolysis (TEN), post-marketing surveillance of Valdecoxib demonstrated an increase of TEN, Steven Johnson Syndrome and Erythema multiforme [72, 73]. The arbitrary nature of Valdecoxib skin-reactions are of particular concern: they occur in patients with and without previous sulphonamide allergy and after short or long term use [72][73]. The skin reactions reported in valdecoxib ranged from widespread erythema to target lesions and TEN. However, a more recent retrospective analysis of some of the reported skin reactions revealed that cutaneous effects of valdecoxib are distinctly different to TEN [74].

## 6. Expert Opinion

Valdecoxib is an efficacious drug. It, like other COX-2 inhibitors, is particularly useful in rheumatological practice, due to its superior gastrointestinal tolerability. Gastroprotection is especially important as most patients with rheumatological disease are on multiple drugs, including disease modifying drugs, which cause gastrointestinal adverse effects. In addition, most patients require anti-inflammatory medication frequently, and occasionally as a long term therapeutic option. The presence of an injectable pro-drug, extends the usefulness of valdecoxib. There is potential for use in rheumatology patients with disease flares in the immediate post-operative period .

It is unfortunate that this main advantage of valdecoxib, the presence of a parenterally administered pro-drug, led to its trials on a group of patients at particularly high risk of cardiovascular events. In addition, the subjects for these trials were patients immediately after post coronary bypass graft surgery: circumstances with exaggerated propensity for thrombosis and vascular occlusion. Moreover, valdecoxib was used in supra-therapeutic doses, with the use of its parenteral drug, parecoxib. The doses used in both these trials are much higher than those used in rheumatological practice, or those trialled in the rheumatology treatment trials. This dosage results in profound suppression of COX-2 pathways. The results obtained are therefore of little surprise. However, it is possible, though it will never be formally proven, that the cardiovascular risk will be attenuated in patients in whom valdecoxib would have been used in clinical practice, at the customary dosage.

Similar findings have been highlighted for celecoxib (75). Despite its increased cardiovascular risk highlighted in patients with colorectal continues to be used extensively in clinical practice. The attenuated cardiovascular risk may be attributed the circumstances under which the drug was used (43).

In our opinion, these trials have questioned the long-term safety not only of valdecoxib, but also of other COX-2 inhibitors, which should by virtue of mechanism of action result in a higher thrombotic risk. The fact that only rofecoxib and valdecoxib were selected for withdrawal warrants further discussion. The fate of valdecoxib, in particular, was sealed by

reports of potentially life threatening skin reactions, the validity of these findings have been subsequently questioned (74). It is clear that valdecoxib, apart from having an injectable prodrug, has no other advantages over the other COX-2 inhibitors. Therefore, there is currently little justification for the continued use of the drug. However, there are lessons to be learned from the processes that lead to the withdrawal of the drug. The need for caution in extrapolating the findings of trials to different patient subpopulations is highlighted from the unfortunate plight of valdecoxib.

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