Clinical Pharmacology of Novel Selective COX-2 Inhibitors

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Abstract: Novel coxibs (i.e. etoricoxib, valdecoxib, parecoxib and lumiracoxib) with enhanced biochemical cyclooxygenase (COX)-2 selectivity over that of rofecoxib and celecoxib have been recently developed. They have the potential advantage to spare COX-1 activity, thus reducing gastrointestinal toxicity, even when administered at high doses to improve efficacy. They are characterized by different pharmacodynamic and pharmacokinetics features. The higher biochemical selectivity of valdecoxib than celecoxib, evidenced *in vitro*, may be clinically relevant leading to an improved gastrointestinal safety. Interestingly, parecoxib, a pro-drug of valdecoxib, is the only injectable coxib. Etoricoxib shows only a slightly improved COX-2 selectivity than rofecoxib, a highly selective COX-2 inhibitor that has been reported to halve the incidence of serious gastrointestinal toxicity compared to nonselective nonsteroidal antiinflammatory drugs (NSAIDs). Lumiracoxib, the most selective COX-2 inhibitor *in vitro*, is the only acidic coxib. The hypothesis that this chemical property may lead to an increased and persistent drug accumulation in inflammatory sites and consequently to an improved clinical efficacy, however, remains to be verified. Several randomized clinical studies suggest that the novel coxibs have comparable efficacy to nonselective NSAIDs in the treatment of osteoarthritis, rheumatoid arthritis and acute pain, but they share similar renal side-effects. The apparent dose-dependence of renal toxicity may limit the use of higher doses of the novel coxibs for improved efficacy. Large-size randomized clinical trials are ongoing to define the gastrointestinal and cardiovascular safety of the novel coxibs.

Key Words: Valdecoxib, parecoxib, etoricoxib, lumiracoxib, cyclooxygenase-2, coxibs.

MECHANISM OF ACTION OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

Aspirin and related nonsteroidal antiinflammatory drugs (NSAIDs) are a heterogeneous group of compounds that share therapeutic-effects (antipyretic, analgesic, and antiinflammatory actions) and unwanted side-effects [primarily gastrointestinal (GI) and renal toxicity], largely dependent on the inhibition of prostanoid biosynthesis [1-3].

Prostanoids are ubiquitous lipid mediators that coordinate a wide variety of physiologic and pathologic processes through the interaction with specific cell-membrane receptors that belong to the G-protein-coupled rhodopsin-type family [4] (Fig. (**1**)). Under physiologic conditions, prostanoids play an important role in the cytoprotection of the gastric mucosa, hemostasis and renal hemodynamics. The biosynthesis of prostanoids is induced in pathologic condition, such as inflammation and cancer [2, 3, 5-7]. The enzyme cyclooxygenase (COX) catalizes the rate-limiting step in the formation of prostanoids from arachidonic acid (AA) [7-11] (Fig. (**1**)). Two isoforms of the COX enzyme have been cloned and characterized: COX-1 and COX-2 [12]. The expression of the two COX isozymes is differently regulated [6-8]. COX-1 displays the characteristics of a "housekeeping gene" and is constitutively expressed in virtually all tissues. It is mainly utilized in the immediate biosynthesis of prostanoids, which occurs within several minutes after stimulation with Ca^{2+} mobilizers [4]. Differently, the inducible COX-2 is an absolute requirement for delayed prostanoid biosynthesis, which lasts for several hours following proinflammatory stimuli [4]. However, this simplified paradigm of constitutive COX-1 and inducible COX-2 has many exceptions: COX-1 can be regulated during development [7, 13], whereas COX-2 is constitutively expressed in the brain [14], reproductive tissues [15] and kidney [16-18].

The two COX-isozymes are membrane-anchored proteins with remarkable structural similarity. The substrate, AA, gains access to the active site *via* a hydrophobic channel (COX channel) and NSAIDs block the biosynthesis of prostanoids as they occupy the COX channel of COX-1 and COX-2 [19-21]. COX-2, but not COX-1, is characterized by an accessible side pocket that is an extension to the hydrophobic channel [20, 21].

The inhibition of COX-2 is thought to mediate the therapeutic actions of NSAIDs, while the inhibition of COX-1 results in unwanted side-effects, particularly at the GI tract [1-3] (Fig. (**2**)). In fact, COX-1 is the major COX isoform expressed in platelets and gastric mucosa of normal humans [22, 23]. NSAIDs toxicity in the GI mucosa leading to ulceration, bleeding, perforation and obstruction, is the result of inhibition of COX-1 activity in platelets, that increases the tendency of bleeding, and in gastric mucosa, where

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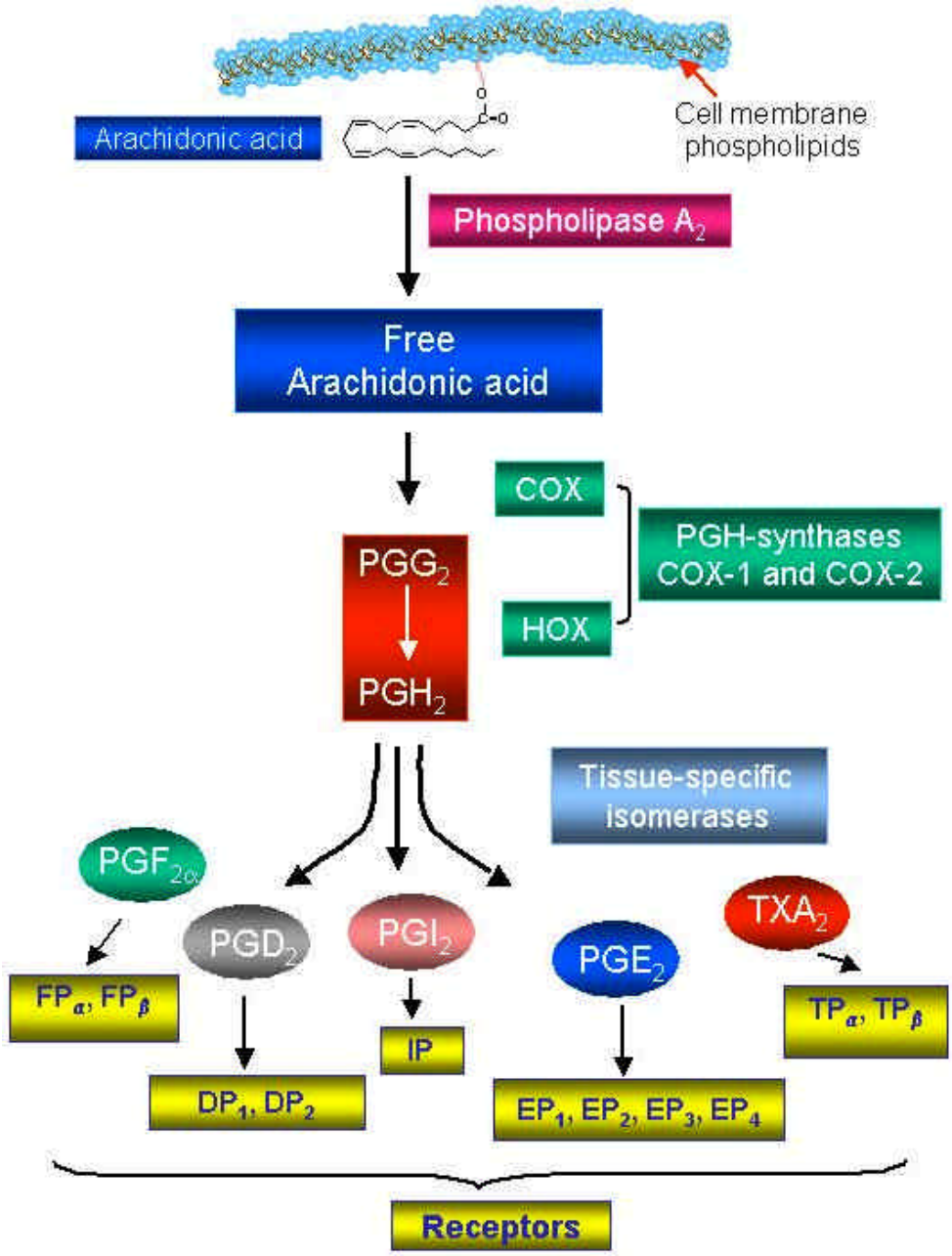

Fig. (1). Pathway of prostanoid biosynthesis and their specific receptors. Arachidonc acid (AA), a 20-carbon fatty acid containing four double bonds, is released from the *sn2* position in membrane phospholipids by phospholipases and is metabolized enzymatically into the prostanoids, i.e. prostaglandin(PG)E_2, $PGF_{2\alpha}$, PGD_2, prostacyclin (PGI_2) and thromboxane(TX)A_2. The coordinate activity of 3 consecutive enzymatic steps are involved in prostanoid biosynthesis: 1) the release of AA from membrane phospholipids carried out by phospholipase A_2, 2) the transformation of AA to the unstable endoperoxide PGH_2 by PGH-synthases (COX-1 and COX-2), and 3) its metabolization to the different prostanoids by isomerases which have different structures and exhibit a cell- and tissue-specific distribution. The different prostanoids activate specific cell-membrane receptors that belong to the G-protein-coupled rhodopsin-type family.

prostanoids play an important role in protecting the stomach from erosion and ulceration [1-3].

DEVELOPMENT OF SELECTIVE COX-2 INHIBITORS

The discovery of COX-2 [12, 21, 24] has provided the rationale for the development of a new class of NSAIDs, the selective COX-2 inhibitors (denominated coxibs), with the aim of reducing the GI toxicity associated with the administration of nonselective NSAIDs, by virtue of COX-1 sparing [1- 3] (Fig. (**2**)).

Rofecoxib and celecoxib are the first selective COX-2 inhibitors approved by FDA and EMEA for the treatment of rheumatoid arthritis (RA), osteoarthritis (OA) and for relief

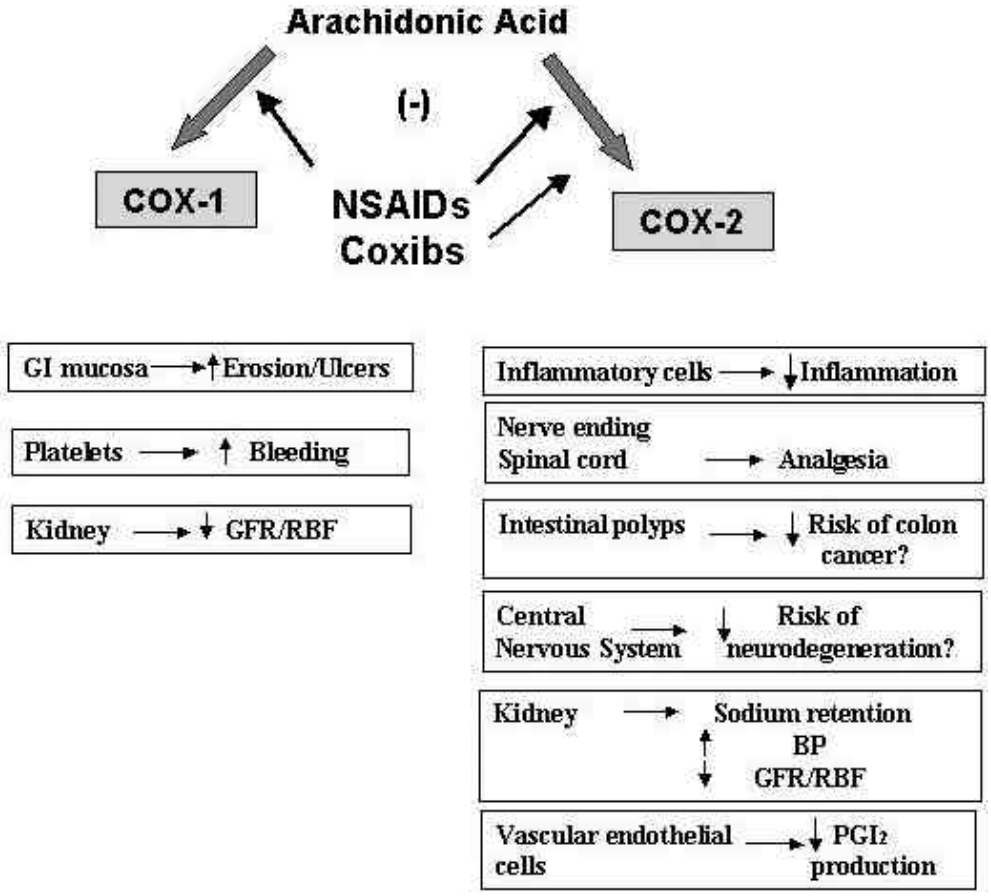

Fig. (2). Pharmacological effects of COX-1 and COX-2 inhibition by nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors (coxibs). GI, Gastrointestinal; GFR, Glomerular Filtration Rate; RBF, Renal Blood Flow; BP, Blood Pressure; PGI_2, Prostaglandin I_2.

of acute pain associated with dental surgery and primary dysmenorrhea. They are diaryleterocyclic derivatives containing a phenylsulphone and a phenylsulphonamide moiety, respectively (Fig. (**3**)) that interact with COX-2 side-pocket, through slow, tight-binding kinetics [25]. This interaction represents an important determinant for COX-2 selectivity, however, the two drugs display different COX-1/COX-2 IC_{50} ratios in the whole blood assays *in vitro* [26, 27], i.e. 272 and 30, respectively [28]. The COX-1/COX-2 IC_{50} ratio of rofecoxib detected *in vitro* translates into a specific inhibition of COX-2 when the drug is administered at therapeutic doses and above [29, 30]. In fact, rofecoxib almost completely inhibits monocyte COX-2 activity without affecting COX-1 activity up to 1000 mg [29], that is 80-fold higher than the initial dose recommended for clinical use in OA [2]. Moreover, 50 mg, that is 2-fold higher than the therapeutic dose of the drug in RA, does not affect gastric prostaglandin $(PG)E_2$ biosynthesis *ex vivo* [30]. Thus, rofecoxib represents an appropriate tool to test the hypothesis that the antiinflammatory and analgesic effects of NSAIDs are dependent on the inhibition of COX-2, while their typical side-effects are due to the inhibition of COX-1. A large randomized, double-blind GI outcomes study has been performed to assess the risk of clinically important upper GI (UGI) events associated with rofecoxib *vs* the nonselective NSAID naproxen: the Vioxx Gastointestinal Outcomes Research (VIGOR) study [31]. Rofecoxib and naproxen showed similar efficacy against RA, and the incidence of GI perforation, GI haemorrhage, or symptomatic peptic ulcer was significantly (P<0.001) lower in patients with RA treated with rofecoxib *vs* naproxen [31]. The concurrence of biochemical and clinical selectivity of rofecoxib strongly support a cytoprotective role of COX-1. In contrast, detectable inhibition of COX-1 by celecoxib at 800 mg daily [32] (that is 2-fold higher than the maximal chronic dose recommended in OA) may have contributed, at least in part, to its failure in reducing significantly the incidence of ulcer perforation, gastric-outlet obstraction or UGI bleeding *vs* ibuprofen or diclofenac in the Celecoxib Long-term Arthritis Safety Study (CLASS) [33, 34]. The CLASS trial was a combined analysis of two separate studies: in one celecoxib was compared with diclofenac, a drug with a similar COX-2 selectivity to celecoxib (COX-1/COX-2 IC_{50} ratio: 29 *vs* 30, respectively), in the other study celecoxib was compared with ibuprofen (COX-1/COX-2 IC_{50} ratio: 0.5). The different COX-2 selectivity of the two comparators may have contributed to the apparent heterogeneity of the results found in the two studies, i.e. celecoxib was comparable to diclofenac while it was superior to ibuprofen [2, 28].

A NEW WAVE OF COXIBS

Novel COX-2 inhibitors with improved biochemical selectivity over that of commercially available coxibs, have been recently developed, i.e. etoricoxib [35], valdecoxib [36], parecoxib [37] and lumiracoxib [38] (Fig. (**3**) and Table **1**). Etoricoxib, valdecoxib and parecoxib contain a cys-stilbene moiety with a 4-methylsulphonil or sulphonamide substituent, while lumiracoxib is a phenyl acetic acid derivative of diclofenac. Thus, differently from the other coxibs, lumiracoxib is an acidic compound. It has been suggested that this chemical feature might lead to an increased and persistent drug concentrations in inflamed tissues [39] and therefore to an improved clinical efficacy. However, this hypothesis remains to be verified.

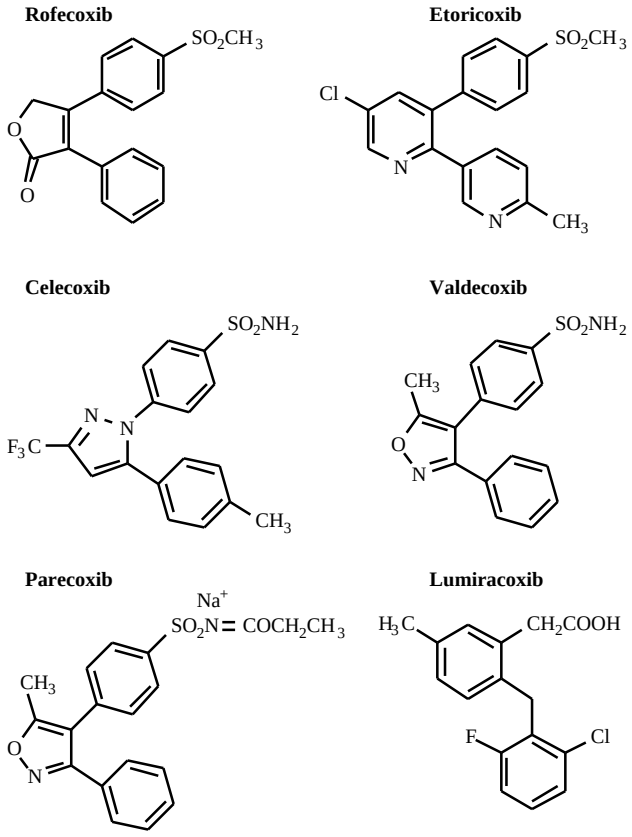

Fig. (3). Chemical structures of selective COX-2 inhibitors.

The improved biochemical COX-1/COX-2 selectivity of the novel COX-2 inhibitors (Table **1**) should translate into a lower proportion of exposed patients to a clinically meaningful inhibition of COX-1 activity in the presence of a profound suppression of COX-2 [2, 3]. This may lead to COX-1 sparing even in patients characterized by an enhanced biochemical response to the drug. In fact, intersubject variability in the inhibition of platelet COX-1 and monocyte COX-2 *ex vivo* by COX inhibitors has been detected and it has been proposed to involve both pharmacokinetics and pharmacodynamic variability [32, 40]. Thus, the expression of variant forms of the cytochrome P450 2C9 (CYP2C9), the major pathway of metabolism of some coxibs (Table **1**) [41, 42], with slower drug metabolism could be responsible for detectable inhibition of platelet COX-1 after the administration of a therapeutic coxib dose. It has been recently shown that CYP2C9*3 allelic variant of CYP2C9 (whose frequency ranges 3-8.5% in Caucasians) is associated with markedly slower metabolism of celecoxib [43]. Studies are ongoing to verify whether the expression of variant forms of COX-1 with enhanced sensitivity to coxibs may be involved in their detected pharmacodynamic variability. Thus, theoretically, a highly selective COX-2 inhibitor has the advantage to spare COX-1 even in subjects with slower drug metabolism and/or enhanced enzyme sensitivity. Another advantage of the development of COX-2 inhibitors with improved biochemical selectivity over that of commercially available coxibs could be that of using higher coxib doses for improved efficacy. Several studies suggest that the second generation of COX-2 inhibitors is efficacious as nonselective NSAIDs in the treatment of OA, RA and acute pain [38, 44-47]. Only one clinical study by Matsumoto *et al.* showed that etoricoxib is more efficacious than naproxen in the treatment of RA [48]. However, it should be pointed out that these trials were designed to detect equivalence of efficacy between coxibs and NSAIDs, but not difference between the treatments. Moreover, the clinical end-points used in these trials are largely inadequate to detect small differences in efficacy that might reflect the participation of COX-1-derived prostanoids in inflammation [49]. However, an important limitation to the use of higher coxib doses for improved efficacy could be the dose-dependence of mechanism-based renal effects associated with these agents [50].

Pharmacodynamic

Using the human whole blood assays, we have characterized the biochemical selectivity of novel COX-2 inhibitors *in vitro* [28].

Valdecoxib inhibited platelet COX-1 and monocyte COX-2 activities with IC_{50} values of 40±3.90 μM (mean±SEM) and 0.65±0.06 μM, respectively (COX-1/COX-2 IC_{50} ratio: 61.50±8.30), that are 2.5-fold higher (P<0.01) and similar (P=0.299) to that of celecoxib (16±12.5 and 0.54±0.07μM, respectively) [28]. The 2-fold higher COX-1/COX-2 selectivity of valdecoxib *vs* celecoxib demonstrated *in vitro* may be adequate to reduce the chance of a patient to have detectable COX-1 inhibition at therapeutic plasma levels as compared with the parent compound. It has been reported that, at steady-state, valdecoxib (40 mg b.i.d., a 8-fold higher dose than that recommended in OA) administered to healthy adult [51] and healthy elderly volunteers [52] did not affect platelet aggregation, bleeding time or serum TXB_2 production, an index of platelet COX-1 activity.

Parecoxib is the water-soluble inactive prodrug of valdecoxib [37]. It is rapidly converted by hepatic enzymatic hydrolysis to the active COX-2 inhibitor, valdecoxib, thus sharing the same pharmacodynamic properties [37].

In the human whole blood assays, etoricoxib showed a COX-1/COX-2 IC_{50} ratio of 344±48 [28]. In particular, etoricoxib reduces platelet COX-1 and monocyte COX-2 activities with IC_{50} values of 162±12 (mean±SEM) and

Table 1. Pharmacodynamic and Pharmacokinetics Characteristic of Coxibs

	Celecoxib	**Rofecoxib**	**Etoricoxib**	**Valdecoxib**	**Parecoxib**	**Lumiracoxib**
Chemistry	Sulphonamide-derivative	Sulphonyl-derivative	Sulphonyl-derivative	Sulphonamide-derivative	Ester amide of valdecoxib	Phenil-acetic derivative
COX-1/COX-2 IC_{50} ratio in vitro	30[a]	276[a]	344[a]	61[a]		400[b]
Pharmacokinetics						
Oral bioavailability (%)	22-40	92-93	100	83		74
Time to maximal plasma concentration (h)	2-4	2-3	1	2.3	0.5 i.v./1.5i.m.[c]	2-3
Maximal plasma concentration (ng/ml)[d]	705*	320**	788****	161***	1681[&&]	6740±2060[&]
Half-life (h)	11	10-17	22	8-11	0.87	3-6
Vol. Dist. (liters)	455	86-91	120	86		9±1.7
Bound in plasma (%)	97	87	92	98		>98
Metabolism						
Main pathway of liver metabolism	Oxydation by cytochrome P-450 (2C9, 3A4)	Cytosolic reduction	Oxydation by cytochrome P-450 (3A4)	Oxydation by cytochrome P-450 (2C9, 3A4)	Oxydation by cytochrome P-450 (2C9, 3A4)	Oxydation by cytochrome P-450 (2C9)
Urinary excretion (%)	29	72	60	70		54
Approved daily doses (mg)						
For Osteoarthritis	200	12.5-25	60	10		Phase III of clinical development
For Rheumatoid Arthritis	200-400	25	90	10		
For Acute Gouty Arthritis	Not approved	Not approved	120	Not approved		
For Acute Pain and primary dysmenorrhea	up to 400	up to 50	up to 120	up to 40	20-40	
Chronic Low-Back Pain	Not approved	25	up to 90	Not approved		
Familial Adenomatous Polyposis	800	Not approved	Not approved	Not approved		

[a] [ref. 28]
[b] unpublished results
[c] T max of valdecoxib after parecoxib (i.v./ i.m.)
[d] After the administration of 200*, 25**, 40****, 40[&&] and 400[&] mg, respectively.

0.47±0.06 μM, that are 2.6- and 3.3-fold higher than those of rofecoxib (49±6 and 0.18±0.03 μM, respectively, COX-1/COX-2 IC_{50} ratio: 272±35) [28]. Dallob *et al.* [53] have reported that the administration of etoricoxib, as single doses (5-500 mg) to healthy subjects, was associated with a dose- and time- dependent inhibition of whole blood COX-2 activity *ex vivo* without significantly affecting platelet COX-1 activity. At steady state, etoricoxib caused a dose-dependent inhibition of monocyte COX-2, but not platelet COX-1 [53]. At 4 hr after the last administration of 100 and 150 mg, monocyte COX-2 activity was reduced by 82 and 93%, respectively, and then recovered slowly. In fact, a profound inhibition was still present at 24 hr, i.e. 60 and 80%, respectively. These results support a once-daily dosing regimen of etoricoxib. The effects of etoricoxib (120 mg once daily) and naproxen (500 mg b.i.d.), administered for 4 consecutive days, on PGE_2 synthesis in gastric biopsies of healthy subjects, presumably COX-1-dependent, was studied [53]. Naproxen, but not etoricoxib, significantly inhibited gastric PGE_2 synthesis.

Lumiracoxib is a highly selective COX-2 inhibitor *in vitro*. In fact, using the whole blood assays, we have found a COX-1/COX-2 IC_{50} ratio of 400 (unpublished results). The available data on the clinical pharmacology of lumiracoxib are only published in abstract form and have been recently reviewed [38]. It has been reported that at the antiinflam-

matory dose of 200 mg b.i.d. administered for a week, and at a single dose of 800 mg, lumiracoxib did not affect platelet aggregation and COX-1 activity *ex vivo* [38].

Pharmacokinetics

The novel coxibs display different pharmacokinetic characteristics that are reported in Table **1**. Etoricoxib has the longest half-life, supporting a once-daily dosing regimen. In contrast, lumiracoxib has a short half-life (3-6 hr), but its long-lasting clinical efficacy has suggested a once-daily dosing regimen [38].

Differently from rofecoxib, that is extensively metabolized by the liver *via* reductive pathways, the other coxibs are metabolized by CYP 3A4 and 2C9 enzymes [44-47, 54-58]. The CYP reaction phenotype of etoricoxib (of which the CYP3A4 seems to account for the majority of the activity) differs from that of other COX inhibitors, such as celecoxib, valdecoxib, meloxicam, ibuprofen, flurbiprofen and indomethacin, that are primarily (≥80%) metabolized by CYP2C9 [41, 42].

Parecoxib, the prodrug of valdecoxib, is the first injectable COX-2 inhibitor. Following intravenous (i.v.) administration in healthy volunteers, parecoxib sodium (50 mg every 12 hr), was rapidly converted to valdecoxib (elimination $t_{1/2}$: 0.69 hr) with peak plasma levels reached 30 min after dosing [59].

Interactions with other Drugs

The potential interactions of novel coxibs with other drugs, that might be utilized concomitantly in the intended target population and that might have clinical consequences if their pharmacokinetics were substantively altered, have been studied, but most of the results have not been published yet. The administration of selective COX-2 inhibitors with drugs that are known to inhibit CYP3A4 and CYP2C9 (e.g. fluconazole and ketoconazole) can result in their increased plasma concentrations [54-58]. The pharmacokinetics of warfarin are altered by valdecoxib and etoricoxib leading to slightly increased anticoagulant effects. As NSAID treatment may potentially increase the nephrotoxic effects of cyclosporin or tacrolimus and lithium plasma levels, renal function and blood lithium should be monitored when coxibs and either of these drugs are used in combination. No relevant interactions with methotrexate, propofol, glyburide or midazolam have been observed following the administration of valdecoxib [54-57]. In contrast, etoricoxib induced no changes in the plasma pharmacokinetics of prednisone/ prednisolone [45, 46], ketoconazole and antiacids, while it may influence the plasma pharmacokinetics of oral contraceptives, digoxin, methotrexate and oral anticoagulants. Moreover, similarly to nonselective NSAIDs and selective COX-2 inhibitors (celecoxib and rofecoxib), etoricoxib and valdecoxib may cause a slight attenuation of the effects of several classes of antihypertensive drugs, including angiotensin converting enzyme inhibitors and furosemide.

Parecoxib shows the same drug-interactions of its metabolite, valdecoxib [55-57, 59, 60]. About lumiracoxib, no information are available.

Clinical Efficacy

The results of clinical trials demonstrate that the novel coxibs have similar clinical efficacy compared with nonselective NSAIDs and that they are superior to placebo in the treatment of OA, RA and acute pain (i.e. primary dysmenorrhea and post-operative dental pain) (Tables **2-5**) [48, 61-81]. Differently from other coxibs, etoricoxib has been approved also for the treatment of chronic low-back pain and acute gouty arthritis [77, 78].

The use of COX inhibitors in preemptive analgesia has been suggested to induce a better control of post-surgical pain, thus reducing the opioid use. In this regard, coxibs, that do not alter hemostasis, offer an important advantage over the nonselective NSAIDs [82]. Recently, it has been shown that the use of single dose of rofecoxib or celecoxib before orthopedic surgery reduced both post-operative pain and post-surgical morphine use. Similarly, Desjardins *et al.* have shown the efficacy of parecoxib before oral surgery [73].

Safety and Tolerability of Novel Coxibs

The GI safety data of the novel coxibs have been extrapolated from clinical efficacy trials. Data on long-term (up to 12 weeks) administration of valdecoxib at doses of 5-40 mg, pooled from 3 multi-center studies with a total of 1480 patients with OA of the hip and knee and with RA, confirm that the drug is safe when used in chronic treatment [61-69]. The most common adverse effects were GI symptoms (i.e. abdominal pain, diarrhoea, dyspepsia and nausea), headache and infection of the upper respiratory tract that however have an incidence of only ~5% during the 12-week treatment period. The incidence of gastroduodenal ulcers evaluated in the study of Sikes *et al.* [83] was comparable in patients receiving valdecoxib 10 or 20 mg, or placebo over 12-weeks, and was significantly higher in patients receiving ibuprofen and diclofenac ($P<0.05$ *vs* placebo). A minority of patients in each treatment group (9-18%) received concomitant low-dose aspirin (≤325 mg/day) during the trial. Users of low-dose aspirin receiving valdecoxib 10 mg daily, ibuprofen 2400 mg daily or diclofenac 150 mg daily were at significantly higher risk of developing gastroduodenal ulcers than patients not taking low-dose aspirin. Despite the higher overall incidence of gastroduodenal ulcers in patients taking low-dose aspirin, compared with non-users, patients taking valdecoxib 10 mg or 20 mg once daily with low-dose aspirin had a significantly lower incidence of ulceration compared with patients taking ibuprofen 2400 mg or diclofenac 150 mg daily, with low-dose aspirin ($P<0.014$) [83].

The GI safety of parecoxib has been evaluated *vs* ketorolac, a nonselective NSAID widely used as a preoperative analgesic. The incidence of gastroduodenal and gastric ulcers or erosions was significantly increased in the group receiving ketorolac as compared to parecoxib sodium and placebo groups ($P<0.05$) [84]. However, this study is limited by the the small sample size (92 patients) and the short duration of treatment (up to 7 days).

Etoricoxib was generally well tolerated in the randomized clinical trials performed to evaluate the clinical efficacy of the drug in patients with OA, RA, acute dental

Table 2. Clinical Efficacy of Valdecoxib

Model of acute pain	Author	Primary end-points	Treatments	Results
Ostearthritis	Makarowski *et al.* [61] Kivitz *et al.* [62]	Patients'assessment of arthritis pain –VAS, patients global assessement of arthritis and WOMAC index	Valdecoxib 5-20 mg daily *vs* naproxen 500 mg b.i.d.or placebo	For all primary end-points, valdecoxib showed dose-dependent efficacy significantly superior to placebo. Valdecoxib 10-20 mg provided similar efficacy to naproxen
Rheumatoid arthritis	Bensen *et al.* [63]	American College of rheumatology 20% improvement (ACR20%) index	Valdecoxib 10, 20 or 40 mg b.i.d *vs* naproxen 500 mg b.i.d.	Valdecoxib was superior to placebo and similar to naproxen. No significant differences in efficacy between the three dosages of valdecoxib have been found.
Primary dysmenorrhea	Daniels *et al.* [64]	Total pain relief over 8 and 12hr Sum of pain intensity difference 8 and 12 hr	Valdecoxib 20 and 40 mg b.i.d as needed *vs* placebo and naproxen sodium 550 mg b.i.d as needed	For all primary end-points, valdexob 20 and 40 mg b.i.d. were significantly superior to placebo and comparable to naproxen sodium.
Oral surgery	Daniels *et al.* [65] Fricke *et al.* [66]	TOTPAR 24 hr SPID 24 hr Duration of analgesia Onset of analgesia	Valdecoxib (20 or 40 mg) *vs* a combination of oxycodone 10 mg/acetaminophen 1000 mg *vs* placebo 40 mg valdecoxib *vs* 50 mg rofecoxib *vs* placebo	Valdecoxib 40 mg caused pain relief comparable to oxycodone/acetaminophen. Both valdecoxib doses had a significantly longer duration of analgesic effect than oxycodone/acetaminophen. Valdecoxib was superior than rofecoxib and placebo.
Orthopaedic surgery: hip arthroplasty knee replacement	Camu *et al.* [67] Reynolds *et al.* [68]	Total amount of morphine administered Pain intensity	Valdecoxib 40 or 80 mg daily *vs* placebo in patients receiving morphine	For all primary end-points, valdecoxib 40 and 80 mg were superior than placebo
Orthopaedic surgery: bunionectomy	Desjardin *et al.* [69]	Time to rescue medication Pain intensity Patient's global evaluation	Valdecoxib 20, 40 or 80 mg *vs* placebo	For all primary end-points, all doses of valdecoxib were superior to placebo. A dose-dependent effect was observed up to 40 mg of valdecoxib.

pain and chronic low-back pain [48, 74-79]. A prospectively defined combined analysis of 10 clinical trials of etoricoxib (3142 patients) suggests that etoricoxib halves both investigator-reported perforations, ulcers and bleeds (PUBs) and confirmed PUBs compared with nonselective NSAIDs [45, 46]. In addition, the results of another combined analysis suggests that the treatment with etoricoxib significantly reduced the need for gastroprotective agents and for GI co-medications by approximately 40% compared with nonselective NSAIDs (P<0.001). Moreover, the treatment with NSAIDs significantly increased the need for gastroprotective agents and GI co-medication treatment, compared with placebo (P<0.001), whereas treatment with etoricoxib did not (P=0.22) [45, 46]. It has also been demonstrated that etoricoxib reduced by over 40% the number of discontinuations due to adverse GI effects [45, 46]. To assess the GI safety of etoricoxib *vs* non selective NSAIDs, Hunt *et al.* [85] have performed two randomized, double-blind, placebo- and active-controlled studies. Daily faecal red blood cell loss was measured in 62 healthy subjects receiving etoricoxib (120 mg once daily), ibuprofen (2400 mg daily) or placebo for 28 days, and the incidence of endoscopically detectable gastric/duodenal ulcers was determined in 742 OA or RA patients receiving etoricoxib (120 mg once daily), naproxen (500 mg b.i.d) or placebo over 12 weeks. In the first study, the between-treatment ratio of faecal blood loss for etoricoxib *vs* placebo (1.06) was not significantly different from unity while that for ibuprofen *vs* placebo (3.26) and etoricoxib (3.08) were significantly greater than unity (P<0.001). In the second study, the incidence of ulcers of ≥ 3 mm with naproxen (25.3%) was significantly higher than that with etoricoxib (7.4%) or placebo (1.4%, P<0.001); the results were similar for ulcers of ≥5 mm.

Regarding luminacoxib, only two studies have been performed to evaluate the GI safety and have been published as abstracts and reviewed by Stichtenoth and Frolich [38]. The small bowel toxicity of lumiracoxib was compared with that of naproxen or placebo in a randomized, three period, cross-over, double-blind, double-dummy, placebo-controlled study. Twenty-five healthy subjects were randomized to receive lumiracoxib 800 mg once daily, naproxen 500 mg b.i.d or placebo, for 9 days. The intestinal permeability has

Table 3. Clinical Efficacy of Parecoxib

	Author	Primary end-points	Treatments	Results
Oral surgery	Daniels *et al*. [70]	Pain intensity difference, time to onset analgesia and time to use of rescue medication	Parecoxib sodium 20 mg i.m, 20 mg i.v., 40 mg i.m. or 40 mg i.v. *vs* ketorolac tromethamine 60 mg i.m. or placebo	Parecoxib sodium 20 and 40 mg i.m. or i.v. and ketorolac 60 mg i.m. were significantly superior to placebo for all primary end-points. The 40 mg dose was comparable to ketorolac 60 mg on most measures of analgesia but had a longer duration of action.
Postsurgical orthopedic pain	Barton *et al.* [71]	Onset, level and duration of analgesia	Single i.v. doses of parecoxib sodium 20 or 40 mg, *vs* morphine 4 mg, ketorolac 30 mg or placebo	Onset of analgesia was similarly rapid with i.v. parecoxib sodium 40 mg, morphine and ketorolac. Level and duration of analgesia were significantly superior with parecoxib sodium than with morphine, and were similar for parecoxib sodium and ketorolac.
Post-operative hip arthroplasty	Malan *et al.* [72]	Cumulative morphine use	Single i.v. dose of parecoxib sodium (20 or 40 mg) or placebo together with i.v. morphine 4 mg	Parecoxib sodium-treated patients used significantly less morphine over 24 and 36 hr, compared to placebo.
Preoperative oral surgery	Desjardins *et al.* [73]	Time to rscue medication, proportion of patients requiring rescue medication, patients global assessment and pain intensity	Single i.v. doses of parecoxib sodium (20, 40, and 80 mg) *vs* placebo	For all primary end-points, all doses of parecoxib sodium were significantly superior to placebo. There were no significant differences between the parecoxib sodium 40 and 80 mg groups.

Table 4.Clinical Efficacy of Etoricoxib

	Author	Primary end-points	Treatments	Results
Ostearthritis of knee or hip	Leung *et al*. [74]	WOMAC pain and physical function subscales 100mm VAS and patient's global assessment of disease status	Etoricoxib 60 mg once daily *vs* placebo *vs* naproxen 500 mg b.i.d for 12-weeks	Etoricoxib and naproxen demonstrated significantly greater improvements in clinical efficacy parameters compared with placebo
Rheumatoid arthritis	Collantes *et al.* [75] Matsumoto *et al.* [48]	Patient global assessment of disease activity, investigator global assessment of disease activity, tender joint count and swollen joint count.	Etoricoxib 90 mg daily *vs* naproxen 500 mg b.i.d. *vs* placebo for 12-weeks	For all primary end-points, etoricoxib and naproxen were statistically superior to placebo In the second study, etoricoxib was significantly superior to naproxen and placebo
Acute gouty arthritis	Schumacher *et al.* [76]	Patients assessment of pain in the study joint	Etoricoxib 120 mg daily *vs* indomethacin 50 mg b.i.d. for 8-days	Both treatment groups experienced comparable pain relief over the entire treatment period.
Chronic low back-pain	Geba *et al*. [77]	Low-back pain intensity scale-VAS	Etoricoxib 60 mg and 90 mg *vs* placebo for 12-weeks	Etoricoxib 60 and 90 mg once daily provided clinical efficacy significantly superior to placebo.
Acute pain: post-operative dental pain	Malmstrom *et al.* [78]	Total pain relief over 8 hr (TOPAR8).	Etoricoxib 60-240 mg, *vs* placebo and ibuprofen 400 mg (study I) Etoricoxib 120 mg *vs* to placebo, naproxen sodium 550 mg, or acetaminophen/codeine 600/60 mg (study II)	Study I: Etoricoxib 120 mg daily provided maximal analgesic effect Study II: Etoricoxib 120 mg had comparable rapid onset of analgesic effect to naproxen and acetaminophen/codeine. The maximal pain relief persisted up to 8 hr after dosing with etoricoxib and naproxen.
Acute pain: primary dysmenorrhea	Malmstrom *et al.* [79]	Total pain relief over 8 hr (TOPAR8).	Etoricoxib 120 mg *vs* naproxen sodium 550 mg *vs* placebo	The TOPAR8 score for etoricoxib and naproxen were significantly greater than that of placebo.

Table 5. Clinical Efficacy of Lumiracoxib

	Author	Primary end-points	Treatments	Results
Osteoarthritis of the knee of hip	Moore *et al.* [80]	Response to treatment defined as 20 % reduction from baseline in overall OA pain intensity assessed by VAS	Lumiracoxib 50-400 mg b.i.d. *vs* diclofenac 75 mg b.i.d, or placebo for 4 weeks.	Lumiracoxib 400 mg was comparable to diclofenac. Lumiracoxib 50, 100 and 200 mg b.i.d. were superior to placebo, but less effective than diclofenac
Osteoarthritis of the knee	Tannenbaum m *et al.* [81]	Overall pain intensity (VAS) in the target joint and patients assessment of disease activity	Lumiracoxib 200 or 400 mg daily *vs* placebo or celecoxib 200 mg daily for 13 weeks	Compared to placebo, lumiracoxib showed significant improvements in all primary end-points. Compared to celecoxib, lumiracoxib 400 mg demonstrated significantly superior efficacy for overall pain intensity up to 8 weeks and comparable efficacy at week 13

been assessed by timed urinary excretion of ^{51}Cr-EDTA over 0 to 5 hr (for small bowel permeability) and 5- to 24-hr periods and lumiracoxib was not different from placebo in this setting. In contrast, treatment with naproxen caused a significant increase in intestinal permeability [38]. In addition, a long-term study performed in 1042 patients with OA receiving lumiracoxib 200, 400 mg once daily, celecoxib 200 mg once daily, or ibuprofen 800 mg t.i.d for 13 weeks, has showed that the cumulative incidence rate of gastroduodenal ulcers was comparable between patients who received lumiracoxib and celecoxib, and was significantly reduced in patients treated with lumiracoxib and celecoxib, compared with patients treated with ibuprofen. Moreover, the mean number of gastroduodenal erosions was significantly higher in the ibuprofen group compared with all other treatment groups [38]. Further studies with lumiracoxib are underway. The ongoing TARGET study (Therapeutic Arthritis Research & Gastrointestinal Event Trial) will evaluate the safety and efficacy of lumiracoxib 400 mg once daily compared with ibuprofen 800 mg t.i.d. and naproxen 500 mg b.i.d. in 18000 patients with OA over 12 months. This trial will evaluate the incidence of complicated GI ulcers as primary end-point.

Although an improved GI safety profile of the novel selective COX-2 inhibitors *vs* nonselective NSAIDs is assumed, it should be confirmed by the results of large size randomized clinical trials with serious UGI events (i.e. gastroduodenal perforation, obstruction and UGI bleeding) as primary end-point.

Renovascular Safety Profile

Several lines of evidence support a critical role for COX-2 in the regulation of renal function. COX-2 is expressed in critical locations within the kidney (i.e. in the renal vasculature, in the macula densa associated cells, in the cortical thick ascending limb and medullary interstitial cells) [2, 50]. By contrast, COX-1 is localized in the vasculature, the conducting ducts and the thin loops of Henle [2, 50]. Recently, Qi *et al.* have demonstrated that COX-2 inhibition enhances and prolonges the vasopressor effects of Angiotensin II (Ang II), while COX-1 inhibition diminishes the pressory effect of Ang II [86]. These findings support the contribution of COX-2 rather than COX-1 inhibition to the development of hypertension, salt retention and edema associated with NSAID use [86]. Moreover, the observation that in normal salt-replete subjects, celecoxib and rofecoxib, but not nonselective NSAIDs, are GFR sparing while the two coxibs affect sodium excretion similarly to nonselective NSAIDs, suggests that the control of GFR may be predominantly COX-1 mediated, whereas COX-2 modulates sodium and water balance [87-90]. Recently, Whelton *et al.* compared the renovascular effects of celecoxib 200 mg daily and rofecoxib 25 mg daily administered for six weeks to elderly patients with systemic hypertension and OA. They found that significantly (P<0.01) more patients in the rofecoxib group (14.9%) compared with the celecoxib group (6.9%) developed increased systolic blood pressure (change >20 mm Hg plus absolute value $\geq$140 mm Hg) [91]. Clinically significant new-onset or worsening edema associated with weight gain developed in a greater percentage of patients in the rofecoxib group (7.7%) compared with the celecoxib group (4.7%) (P<0.05). These results may suggest that the renal toxicity of COX inhibitors is dependent on the extent of COX-1/COX-2 selectivity. However, this important issue cannot be solved by this study because the doses of the two drugs were not comparable. In fact, Geba *et al.* have shown that rofecoxib 25, but not 12.5, mg daily, administered up to 6 weeks to OA patients, was clinically superior to celecoxib 200 mg daily [92]. Dose-dependent hypertensive effects has been reported with rofecoxib but not with celecoxib, however, this question has not been examined in appropiate randomized clinical trials. Thus, based on the current data, there are no clinically significant differences among celecoxib, rofecoxib and nonselective NSAIDs in terms of renal effects.

Very few information are available on the renal effects of novel coxibs. A combined analysis of 8 phase III studies in OA, RA, chronic low-back pain and surveillance endoscopy has shown that the risk of lower extremity edema and hypertension adverse experiences with etoricoxib was low and generally similar to comparator NSAIDs and there was

no evidence of strong dose-related trends [45, 46]. Regarding renal safety of valdecoxib, pooled data obtained from OA and RA trials have demonstrated that the incidence of common renal adverse effects (albuminuria, peripheral edema and hypertension) following valdecoxib treatment (40 mg) is higher than that of placebo, but does not significantly exceed that of traditional NSAIDs [60].

Cardiovascular Safety Profile

Prostacyclin is thought to be part of a homeostatic defence mechanism that limits the consequences of platelet activation *in vivo* [93, 94]. Prostacyclin biosynthesis is largely mediated by COX-2, in fact, similarly to nonselective NSAIDs, coxibs reduced the urinary excretion of prostacyclin metabolites in normal subjects [32, 95], but, in contrast, they did not affect platelet thromboxane (TX) A_2 biosynthesis [29, 32]. The cardiovascular implications of these effects are currently debated, based on the results of the VIGOR trial showing a statistically significant difference in acute myocardial infarction (MI) rates between rofecoxib and naproxen (0.4 *vs*. 0.1%, respectively) [31]. Three possible explanations can be proposed [96]: 1) a cardioprotective effect of naproxen: but, there is both contradictory and supporting evidence that naproxen reduces the risk of MI [97-101], 2) a thrombogenic effect of coxibs: but, the size of the effect is not biologically plausible if due to incomplete inhibition of a single mediator of "thromboresistance", i.e. prostacyclin [32], 3) the play of chance: the apparent difference in VIGOR might represent uneven distribution of a small number of events occurring over a short time frame in a low-risk population, a metaanalysis of all coxib trials might address this possibility.

Very few information are available on the cardiovascular effects of COX-2 inhibition by etoricoxib that are only published as abstract. Fisher *et al.* [102] have performed a combined analysis of the results of several clinical trials in patients with OA, RA or chronic low-back pain. The rates of confirmed cardiovascular thrombotic events (per 100 patients years) were numerically higher in etoricoxib (60 mg/day) *vs* naproxen (1000 mg/day) users but comparable *vs* placebo. However, to evaluate the cardiovascular safety of rofecoxib and etoricoxib, a prospective, randomized, controlled trial on 30.000 patients at risk of developing adverse cardiovascular events will be performed. The cardiovascular safety of valdecoxib was assessed in a combined analysis of 4 randomized, placebo-controlled trials (up to 3 months of duration). The incidence of serious thrombotic events (cardiac, cerebro and peripheral vascular, or arterial thrombotic events) associated with valdecoxib (10-80 mg daily, n=1945) was compared with naproxen (500 mg b.i.d, n=744) and placebo (n=529) in patients with RA. The results of this analysis showed no differences in the incidence of any serious thrombotic events among treatments groups [103], however, it should be pointed out that it is based on a comparison of a very small number of events.

About lumiracoxib, the TARGET trial will also evaluate the incidence of cardiovascular events in patients taking and not taking low-dose aspirin for cardioprotection in combination with lumiracoxib as secondary end-points, thus offering the chance to address the question not only of the long-term incidence of ulcer complications, but also of cardiovascular events.

More information are needed on the cardiovascular effects of selective COX-2 inhibitors. However, patients with arthritis who have had a major cardiovascular event should be treated with low-dose aspirin in combination with a highly selective COX-2 inhibitor. In contrast, the coadministration of a nonselective NSAID with aspirin should be avoided. In fact, the concomitant administration of the nonselective NSAID ibuprofen, but not rofecoxib, has been shown to antagonize the irreversible inhibition of platelet COX-1 activity by low-dose aspirin [104].

On the other hand, it should be mentioned that selective COX-2 inhibition may have potential beneficial effects in addition to low-dose aspirin in the setting of acute coronary syndromes. Thus, COX-2 expressed in inflammatory cells [26, 105, 106] may account for aspirin-resistant TXA_2 biosynthesis in acute coronary syndromes [107, 108]. Enhanced baseline urinary excretion of 11-dehydro-TXB_2 (a major enzymatic metabolite of TXA_2) predicted the future risk of MI or cardiovascular death in a subgroup of high-risk aspirin-treated patients participating in the HOPE trial [109]. However, whether the coadministration of low-dose aspirin with a highly selective COX-2 inhibitor will maintain the advantage of a coxib over a nonselective NSAID with respect to GI side effects remains to be tested.

CONCLUSIONS

Novel selective COX-2 inhibitors with different COX-1/COX-2 selectivity and pharmacokinetics features have been developed. The improved biochemical selectivity of valdecoxib *vs* celecoxib may be clinically relevant leading to an improved GI safety, however this is not sustantiated by the results of appropriate clinical trials. Interestingly, parecoxib, a pro-drug of valdecoxib, is the only injectable coxib. Similarly to rofecoxib, etoricoxib reaches a specific COX-2 inhibition that should translate into a similar GI safety. Lumiracoxib, the most selective COX-2 inhibitor *in vitro*, is the only acidic coxib. It has been hypothesized that this pecular chemical feature may lead to an enhanced concentration in inflammatory sites that may translate into an improved clinical efficacy.

The results of clinical trials have shown that the novel coxibs have a camparable clinical efficacy in OA, RA and acute pain. However, it should be pointed out that is quite difficult to detect differences in efficacy in comparative clinical trials because of the low sensitivity of the clinical end-points utilized. The occurrence of renal side-effects that seem to be dose-dependent limits the use of higher doses. Similarly to the first coxibs, it is imperative to evaluate their renal toxicity in high-risk patients in long-term treatment. More information are needed also on the cardiovascular and GI toxicity of the novel coxibs. Large-size clinical trials have been designed to address these issues and are ongoing.

ACKNOWLEDGEMENTS

Supported by a grant from the Italian Ministry of University and Research (MURST) to the Center of Excellence on Aging, "G. d'Annunzio" University of Chieti.

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