Inhibitors of cyclooxygenases (COXs) are the most widely used drugs. They reduce discomfort and fever, inhibit peri-operative and inflammatory pain. These effects are largely mediated by inhibition of cyclooxygenase-1 and -2 (COX-1 and COX-2)–enzymes found throughout the body producing prostaglandins, which are important mediators of pain and fever, but also adaptive and protective reactions in many organs. A first step to reduce the overall toxicity and to increase the anti-inflammatory activity of these drugs was achieved with the development of acidic ‘non-selective’ (traditional) non-steroidal anti-inflammatory drugs (tNSAIDs). These agents distribute unequally throughout the body, reaching effective concentrations in inflamed tissue (effect compartment) for prolonged time periods. They can also reach effective concentrations in the bloodstream, kidney and gastrointestinal (GI) mucosa, where they can cause unwanted effects, such as GI toxicity, kidney dysfunction and cardiovascular impairment. All these effects are particularly prominent with compounds which are eliminated slowly [half-life ($T_{1/2}$) $>$12 h] and thus also block prostaglandin production permanently outside the effect compartment. A second step towards improving safety was achieved with selective COX-2 inhibitors. These agents reduce the incidence of GI toxicity, pseudo-asthmatic reactions and blood loss following surgical interventions. However, they may be more toxic to the cardiovascular and renal systems than some tNSAIDs, possibly because they distribute homogeneously throughout the body and inhibit COX-2 in the endothelial layer of the vessels and the kidney permanently due to their slow elimination. Another step towards improvement in safety appears possible by combining both enzyme specificity and tissue selectivity, to achieve a further reduction of unwanted drug effects while maintaining the anti-inflammatory/analgesic efficacy.

Inhibition of prostaglandin (PG) production: good, but sometimes bad

PGs are ubiquitous mediators. Among their many functions, they are involved in tissue protection [e.g. in the gastrointestinal (GI) tract], they can increase the osmotic resistance of kidney tubular cells, and they regulate blood coagulation and fertility [1]. In addition, they are key mediators in the development of defence reactions, including pain and inflammation [2].

The rate-limiting enzymes of PG production are the cyclooxygenases (COXs). There are two isoforms of COX (COX-1; COX-2) in humans, and the absence of both enzymes appears to be incompatible with life [3–5]. Temporary blockade of both enzymes goes along with serious unwanted drug effects. Nevertheless, inhibition of PG production is the prevailing intervention to reduce inflammation and pain. Two approaches have been used to reduce unwanted effects, such as GI toxicity, renal damage and bleeds; these are:

(i) Sequestering the COX inhibitor in the effect compartment(s), i.e. at the site of inflammation.
(ii) Limiting enzyme inhibition to the COX-2 isoform, which is the producer of the pro-inflammatory pain-mediating PGs.

Both approaches have led to compounds with improved effect/side-effect ratios [6].

In 1974, it was proposed by one of us that COX inhibitors with distinct physicochemical characteristics (lipophilic/hydrophilic polarity, acids, pKa-values between 3 and 5, and $>$98% protein binding) would accumulate in certain body compartments and cause a localized blockade of the otherwise ubiquitous PG production [7]. Many widely used acidic, highly protein-bound, non-selective inhibitors, such as diclofenac, ibuprofen and indomethacin, fulfill these criteria (for review see [8]). Autoradiography of rats given radiolabelled propyphenazone (non-acidic control) or phenylbutazone (acidic, non-selective COX inhibitor) demonstrates that tissue selectivity is achieved by certain (acidic) COX inhibitors (e.g. phenylbutazone) while others (e.g. propyphenazone) distribute equally throughout the body (Fig. 1) [9–12]. Similar observations have been noted with selective COX-2 inhibitors. Indeed, radiolabelled celecoxib, a non-acidic compound, has been shown to distribute homogeneously in inflamed and non-inflamed tissue whereas lumiracoxib, which is acidic, was observed at higher concentrations in inflamed tissue compared with non-inflamed tissue [13].

Acidic traditional non-steroidal anti-inflammatory drugs (tNSAIDs) show both analgesic and anti-inflammatory properties [14]. Their tissue selectivity may explain why they are the preferred drugs in inflammatory pain and why they are believed to exert superior anti-inflammatory properties compared with non-acidic analgesic drugs, such as phenazone derivates and acetaminophen [15]. These acidic compounds reach high concentrations in inflamed tissue leading to long-lasting, intensive inhibition of PG synthesis at the desired site of action, but not throughout the body (Fig. 1). However, these tNSAIDs can cause serious side effects in the GI tract, the kidney, the blood and in blood-bathed organs, such as the liver. These effects occur because tNSAIDs can reach concentrations in organs that are as high as those seen in inflamed tissue [8], although some remain for longer in inflamed tissue than, for example, in the blood [14].

Limiting the presence of COX inhibitors in these ‘side effect’ compartments should reduce unwanted drug effects. This would explain why tNSAIDs exhibiting a short elimination half-life ($T_{1/2}$), such as ibuprofen or diclofenac at low doses,
areas, agents were developed that were eliminated slowly from the body. Moreover, slow elimination had the added advantage of allowing once-daily administration.

Recent evidence, however, indicates that the basis for these assumptions was incorrect. It has been shown that COX-2 is constitutively expressed in several organ systems, including the kidney, the central nervous system (CNS) and the vascular wall (Fig. 2A) [1, 6, 24–26]. In addition, repair and adaptive processes throughout the body are associated with increased expression of COX-2 (in animal and in vitro systems) [21]. Consequently, the first generation of COX-2 inhibitors may be burdened with cardiovascular (CV) and renal toxicity, reduced adaptive capacity of the kidney and questionably impaired healing of the GI mucosa—similar to that of non-COX-2 selective tNSAIDs [1, 20, 21, 25, 26]. On the other hand, these drugs appear advantageous because, unlike NSAIDs, they do not inhibit the production of COX-1-derived GI- and lung-protective PGs. Neither do they interfere with blood coagulation [20]. However, this latter characteristic may contribute to adverse vascular, i.e. atherothrombotic, drug events [23] of first-generation selective COX-2 inhibitors. Moreover, when these drugs are given daily for prolonged periods of time, as in recent outcome studies [27], the slow plasma elimination results in a constant exposure of endothelial cells to active drug concentrations [28]. Consequently, it appears that an additional step towards less harmful but equally efficacious COX inhibitors is possible by combining both enzyme specificity and tissue selectivity [29]. Luminacoxib (Table 1), an agent with such features, is presently being introduced in several countries. We will therefore refer to this compound later on to demonstrate our deliberations.

COX inhibitors block peripheral and central hyperalgesia

There is little to choose between any non-selective COX inhibitor in relation to analgesia when doses are comparable. They all reduce pain by inhibiting hyperalgesia and they have a limited effect when allodynia (neuropathic pain) develops. Selective inhibition does not appear to provide an advantage with respect to efficacy [5].

The main therapeutic effect of all COX inhibitors is a reduction in PG production and thereby relief from hyperalgesia caused by tissue damage (inflammation, trauma, edema) [6]. Hyperalgesia, an increased sensitivity to pain, occurs following tissue damage
and is independent of the cause of the injury. Immunological reactions, infection or trauma (surgical as well as accidental) are all equally able to initiate hyperalgesia. Hyperalgesia is mediated by PGs and results from a change in excitability of non-nociceptors (Figs 2B and C) [6]. In addition, following peripheral inflammation, PG production is upregulated in the CNS [30]. This further facilitates the recognition of painful (nociceptive) peripheral inputs (central hyperalgesia) (Fig. 2B). Inhibition of COX-2 and, consequently, PGE2 production in inflamed tissue and in the dorsal horn of the spinal cord downregulates hyperalgesia and reduces pain [31]. It is now accepted that reducing the production of PGE2 by COX-2 is a key event explaining the analgesic or, more accurately, the anti-hyperalgesic effects of selective and non-selective COX inhibitors [6]. Indeed, it has been shown that PGs produced by COX-2 mediate hyperalgesia in inflamed tissue by increasing the activity of transient receptor potential vanilloid 1 (TRPV1) receptors (Fig. 2B) and in the dorsal horn of the spinal cord by inactivating specific glycine receptors [Gly3α] (Fig. 2C) [31–33]. Peripheral and central hyperalgesia contribute to post-traumatic, rheumatic (RA) and osteoarthritic (OA) pain. In order to achieve suppression of peripheral hyperalgesia and other signs of inflammation, complete and long-lasting COX-2 blockade in inflamed, oedematous tissue appears to be important [34].

For the first generation of COX-2 inhibitors, clear-cut anti-inflammatory effects have been claimed. Although they distribute homogeneously throughout the body [Table 1: volume of distribution (Vd) ~11kg], they do not cause the necessary (complete) local enzyme inhibition [35]. They do, however, cross the blood–brain barrier and interfere with central PG production [36, 37]. Lumiracoxib, a member of the second generation of specific COX-2 inhibitors [22], reaches high concentrations in peripheral tissue for prolonged periods of time (like acidic tNSAIDs) [29], thereby producing lasting local enzyme inhibition as well as COX-2 blockade in the CNS, demonstrating specificity (for COX-2) and a degree of selectivity (retention in inflamed tissue).

**Tissue selectivity of COX inhibitors: when does it matter?**

Most drugs do not reach the same concentrations throughout the body. They often achieve high concentrations in one compartment and low concentrations in another (Fig. 1). High concentrations in a compartment may be associated with efficacy or toxicity therein. Indeed, high concentrations in critical compartments, such as the neuromuscular endplate (Fig. 1B) or the synovial lining cells in RA, may be quite important to therapeutic activity. Of course, tissue selectivity is of minor importance provided that the drug targets (receptors) are limited to certain cells or compartments of the body. In these cases, a drug need only reach the targets in sufficient concentrations and it does not matter if it achieves even higher concentrations in areas where receptors are lacking. Morphone, for example, attains only relatively low concentrations in the CNS. Still, analgesia and euphoria are mediated in the CNS when administered parenterally, blocks neuromuscular transmission for a short period of time by occupying nicotinic receptors at the endplate (Fig. 1B). The same receptors are present in the CNS but are not blocked because the polar drug does not cross the blood–brain barrier. On the other hand, chloroquine, an anti-malaria drug still used in RA, accumulates not only in the malaria parasite, but also in cells containing the pigment melanin (Fig. 1A). Thus, in addition to elimination of plasmodia, chloroquine can produce unwanted effects, such as damage to the uvea and bleaching of skin and hair, which are related to localized high concentrations in pigmented cells.

The \( V_{d_{\text{ss}}} \) hints at tissue selectivity or homogeneity of distribution. It is calculated by dividing the amount of drug in the body (at steady state) by the concentration in the blood. The \( V_{d_{\text{ss}}} \) of chloroquine is about 1001kg, indicating that chloroquine is sequestered into compartments outside the blood, i.e. uvea, hair follicles, etc. Some \( V_{d} \) values for NSAIDs are given in Table 1. Clearly, there are two types: acidic with small \( V_{d} \) values and non-acidic with large \( V_{d} \) values (Table 1). \( V_{d} \) values below 11kg.
COX inhibitors: acidic drugs accumulate in the effect compartment

Acidic NSAIDs are, in terms of physio-chemical characteristics, a unique group of drugs. They are weak acids, amphiphilic and highly bound to plasma proteins [8]. Due to these characteristics they distribute unequally. Their small $V_d$ (~0.13 l/kg; Table 1) indicates that the central compartments (blood), liver and kidney show higher concentrations than most other tissues (Fig. 1). In addition, these drugs reach high concentrations in inflamed tissue (Figs 1 and 3A). This phenomenon results from the extremely high degree of binding to plasma proteins (>99%) and the acidity of these compounds (pKa ~4–5). The high degree of plasma binding together with the acidity, which results in a negative charge (polarity) of the drug molecules at the neutral pH of blood, limits the exit of the drug from the plasma into most tissues (Fig. 3) [11, 38]. The situation is different in organs, such as the liver and kidney, where the endothelial layer separating tissue cells from the bloodstream is open (fenestrated, discontinuous) (Fig. 3B).

Blood vessels in normal connective tissue show a closed endothelial layer (Fig. 3B). However, this changes in inflamed tissue (Fig. 3C). Inflamed tissue becomes permeable to macromolecules and drugs (open triangle) bound to them [11, 38]. Figure 3A: Reprinted from Pharmacol Ther, Vol 5, Brune et al., Autoradiographic methods for the evaluation of ulcerogenic effects of anti-inflammatory drugs, 199–207, Copyright 1979, with permission from Elsevier.

Fig. 3. (A) Autoradiograph of a rat treated with $^{14}$C-salicylic acid. Carrageenan was injected subcutaneously into the back of the neck and then $^{14}$C-salicylic acid administered by a stomach tube. After 3 h, the rat was exsanguinated, deep frozen and prepared for autoradiography (100 μm slices). The autoradiographs show high activity in the glandular (GS) and non-glandular (NS) stomach and kidney (K) and the inflamed tissue (IT) of the neck [11]. (B) Schematic representation of capillaries in different regions of the body. Direct contact between tissue specific cells and plasma exists only in the liver, spleen, lymph nodes and bone marrow [38]. Figure 3B: Reprinted from Pharmacol Ther, Vol 5, Brune et al., Autoradiographic methods for the evaluation of ulcerogenic effects of anti-inflammatory drugs, 199–207, Copyright 1979, with permission from Elsevier.

In addition, these drugs reach high concentrations in inflamed tissue (Figs 1 and 3A). This phenomenon results from the extremely high degree of binding to plasma proteins (>99%) and the acidity of these compounds (pKa ~4–5). The high degree of plasma binding together with the acidity, which results in a negative charge (polarity) of the drug molecules at the neutral pH of blood, limits the exit of the drug from the plasma into most tissues (Fig. 3) [11, 38]. The situation is different in organs, such as the liver and kidney, where the endothelial layer separating tissue cells from the bloodstream is open (fenestrated, discontinuous) (Fig. 3B).

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Fig. 4. (A) Influence of extracellular pH on the intracellular concentration of phenylbutazone. It is assumed that the cell membrane is impermeable for phenylbutazone ions ($\text{\textcircled{I}}$). Hence, the concentration in the intracellular space is a function of the concentration of non-ionized phenylbutazone (O) in the interstitial fluid and consequently of the pH in the intercellular space. The figure shows that ion trapping, i.e. increased concentration of ionized drug, occurs in cells when the extracellular pH decreases [38]. (B) Autoradiograph of an area of the glandular stomach of a rat treated with radiolabelled salicylic acid [11]. The specimens were obtained 1 min (a, b) and 5 min (c) after drug administration. In (a) the drug accumulated in a line of parietal cells below the mucus layer. Higher magnification of these cells (b) shows the location of activity in individual parietal cells. Such areas were found in serial sections of the glandular stomach of all rats killed 1 min after drug administration and in two out of three rats killed 5 min after drug administration (c). The stomachs of all three rats investigated 15 min after drug administration showed no localized drug accumulation. Figure 4B: Reprinted from Pharmacol Ther, Vol 5, Brune et al., Autoradiographic methods for the evaluation of ulcerogenic effects of anti-inflammatory drugs, 199–207, Copyright 1979, with permission from Elsevier.
inflammation (Fig. 3C); the endothelium becomes porous, allowing oedema to form and protein-bound and unbound drugs to escape into the tissue (Fig. 3C). Moreover, in inflamed tissue the mildly acidic extracellular pH reduces plasma binding and increases the free fraction of the drug. The low extracellular pH facilitates non-ionic diffusion into the cell interior and consequently increases intracellular drug concentrations due to ion trapping (Fig. 4A). This, in turn, increases the concentration of the drug intra-cellularly. Assuming the standard receptor binding model, this increases receptor binding at the target enzyme and decreases inflammation [39]. Ion trapping occurs in all regions where an acidic extracellular pH surrounds cells with a neutral (pH ~7) intracellular pH, i.e. the gastric and duodenal mucosa, the (distal) kidney tubules and inflamed tissue. The existence of ion trapping in cells bordering an acidic extracellular space has been shown in parietal cells of the glandular stomach in rats fed radioactively labelled salicylic acid (Figs 3A and 4B). The cells retain the trapped drug, which prolongs its effect. Ion trapping is one reason for the gastrointestinal toxicity of acidic tNSAIDs, their effect on the kidney and their anti-hyperalgesic properties. Ion trapping with selective COX-2 inhibitors may be an important mechanism in inflamed tissue and renal tissue, where COX-2 is of functional importance, but not in the GI tract, which is largely devoid of COX-2 [36].

**Acetaminophen-like (non-acidic) drugs distribute homogeneously throughout the body**

In contrast to the acidic aspirin-like drugs, non-acidic tNSAIDs (phenozene, prophyphenazone, acetaminophen and, more recently, proquazone, indoxol, rofecoxib, etoricoxib and many others) distribute equally throughout the body. They are neutral or weak bases with moderate (propyphenazone) to high (etoricoxib) binding to plasma proteins and a V_dss of about 11/l/kg. In principle, celecoxib belongs to this group as it has a high V_dss (exact data are still missing) that appears to derive from its high degree of lipophilicity. It is assumed that this may cause sequestration of celecoxib into fat tissue, a process that takes time due to the low blood perfusion of fat tissue. Indeed, celecoxib does not accumulate specifically in inflamed paw tissue [13] and clinical evidence lends further support to this contention [40].

Taken together, this group of non-acidic compounds does not show accumulation in effect compartments and, therefore, is unlikely to take advantage of tissue selectivity. Indeed, high doses of these agents for long periods of time may be associated with greater risks. The analgesic effect of acetaminophen is limited at therapeutic doses [34].

**Tissue selectivity: therapeutic advantages?**

The lack of a direct correlation between plasma drug concentrations and therapeutic response has been observed for many tNSAIDs, particularly those with a short elimination T1/2, such as diclofenac and ibuprofen. It has been noted that their therapeutic effect often far outlasts their pharmacokinetic T1/2. Since it is known that these compounds exert part of their therapeutic effect by blocking PG production at the site of the tissue damage, local persistence in the effect compartment was examined to see whether this could explain their protracted effect.

Studies of the pharmacokinetics of acidic tNSAIDs (T1/2 <12 h) have noted that the concentration in the synovial fluid of arthritic joints always outlasts that in plasma. This difference was most obvious for tNSAIDs with a short plasma T1/2, such as ibuprofen [15, 41], diclofenac [42, 43] and lumiracoxib (Figs 5A, B, C and 6A) [29]. This persistence in the effect compartment was not observed with tenoxicam (T1/2 ~60 h) (Fig. 5D).

The more sustained exposure of synovial fluid lining cells to high concentrations of tNSAIDs (as shown for diclofenac and ibuprofen; Figs 5B and C) results in a long-lasting inhibition of COX-2. Given the right dose, twice-daily application will inhibit PG production constantly despite an elimination T1/2 of 2 h [41]. Therefore, inhibition of PGE2-mediated peripheral hyperalgesia will persist as long as dosing is continued and the drug stays in the effect compartment (Figs 5C and E). Consequently, the dosing interval for a tNSAID with a short T1/2, such as diclofenac and lumiracoxib, may be much greater than that predicted from its plasma T1/2. This prolonged exposure of cells in the effect compartment (inflamed tissue) is likely to contribute to the therapeutic effect of diclofenac, ibuprofen and lumiracoxib [29].

Non-selective tNSAIDs with long elimination T1/2, for example, tenoxicam (Fig. 5D), lack this pharmacokinetic advantage. At no point in time is there COX inhibition in inflamed tissue without blockade of PG production in blood, kidney and other critical organs.

It is now accepted that noceceptor (hyperalgesia)-related pain is associated with PG production and plasma extravasation [44]. Therefore, it is not surprising that the same lack of correlation between plasma drug concentration and analgesic response that was found for diclofenac, ibuprofen and lumiracoxib in RA (Figs 5C, E, F and 6A) was also noted in an acute post-surgical dental pain model. Indeed, a single dose of lumiracoxib 400 mg has been shown to produce a sustained (24 h) reduction in pain intensity [pain intensity difference (PID) score] (Fig. 6B) [45] even though plasma concentrations with this dose had fallen much earlier in the dose interval due to its short elimination half-life [29].

Further support of an effect compartment comes from a 4-week study in patients with OA, where pharmacokinetics and analgesic response were assessed on day 0 (up to 6 h post first dose) and day 28. A comparison of mean plasma concentration vs mean change in OA pain [visual analogue scale (VAS)] from baseline for the 6th post-dose shows an anticlockwise hysteresis loop [46]. Unlike the data from day 0, the VAS scores on day 28 were relatively constant with respect to time post-dose [46], indicating that there appears to be no direct relationship between plasma concentration and effect. The persistent effect on VAS on day 28 may result from a relatively constant steady-state level of lumiracoxib in the effect compartment.

The most likely reason for this phenomenon is that lumiracoxib elicits part of its effect on pain in a compartment other than the central compartment. If this is true, following the first application of the drug, increasing plasma concentrations would not be paralleled by an increasing effect, as the deep compartment was not sufficiently ‘filled’ (segment A in Fig. 5A). After the crossover point (Figs 5B and C), decreasing drug concentrations would also not influence the drug effect (segment B in Fig. 5A).

Such a phenomenon could result from the formation of an active metabolite. Extensive studies in humans and animals characterizing the biotransformation of diclofenac and lumiracoxib have excluded this possibility [47, 48]. One might also consider the effect of lipophilicity to explain or confound this effect. While lipophilicity would influence single-dose pharmacokinetics/pharmacodynamics (PK/PD), it would not be likely to affect steady-state relationships. Therefore, these data suggest that the long-lasting effects of these drugs are not directly related to plasma concentration, but are instead governed by concentrations of the drug in an effect compartment. An effect compartment model has been proposed in the literature for several tNSAIDs [7]. This contention has been evaluated for diclofenac [42] and lumiracoxib [28]. The pharmacokinetic/pharmacodynamic data would fit well with a two-compartment model with first order input, a lag phase and a maximum effect. The presence of such a theoretical effect compartment may have physiological relevance under more than one clinical condition dominated by peripheral hyperalgesia, i.e. oedema formation and enhanced nociception. The persistence of acidic drugs with a short T1/2 in compartments where ion-trapping takes place is visible in Fig. 3A, where salicylic acid is cleared from all other compartments including blood 3 h after administration.
Tissue selectivity: reducing unwanted drug effects

It is obvious that COX inhibitors that distribute equally throughout the body or concentrate in non-effect compartments, such as fat, lack a localized effect. In order to achieve suppression of peripheral hyperalgesia, an almost complete blockade of PGE2 production would be required, and this would be accompanied by almost complete inhibition of COXs throughout the body. It may be speculated that recent, non-acidic compounds do not achieve such an effect at meaningful doses or toxicity would be expected. In fact, several years ago very potent COX-1/COX-2 inhibitors, such as indoxole or proquazone, were developed but were removed shortly after introduction to the market due to their hepatic toxicity.
As indicated earlier, COXs are ubiquitous enzymes. Almost all cells in the human body are able to produce PGs via COX-1. Mice lacking COX-1 compensate for this deficit with increased expression of COX-2. Similarly, COX-2 knock-out mice (COX-2−/−) often show several deficits that may be compensated, in part, by COX-1. Absence of both enzymes is incompatible with life [36]. Moreover, repeated intensive and long-lasting inhibition of COXs throughout the body appears to be life threatening. Indeed, non-selective COX inhibitors without tissue selectivity (i.e. older compounds, such as phenazone) are lethal at overdose [49].

Celecoxib and etoricoxib lack tissue selectivity. Therefore, one would assume that these compounds either lack prominent anti-inflammatory activity or are dosed high enough to inhibit PG production sufficiently in inflamed tissue as well as in other critical organs. This may indeed be one reason for the putatively higher CV risks exerted by these drugs. On the other hand, it is well documented that diclofenac is superior to acetaminophen for pain relief [34]. Although partial inhibition of COX-2 in the CNS appears sufficient for analgesia, almost complete inhibition in inflamed tissue is required for an anti-inflammatory effect. Indeed, Buvanendran et al. [37] found that rofecoxib blocked postoperative PG production in the CNS more effectively than at the surgical site. Moreover, there was a correlation between analgesia and reductions in PG production in the CNS, but not in the plasma. Many years ago, it was shown in an animal model of inflammation that, despite equal potency at the COXs, the dose of (the acid) phenylbutazone required for ~50% inhibition of PG production was only a 10th of that needed with (the non-acidic) propyphenazone [50].

A relationship between analgesic efficacy and the ability of the acidic NSAIDs or COX-2 inhibitors to target inflamed tissue is not readily identifiable from the various clinical study results. For example, comparable efficacy has been reported between celecoxib 200 mg once-daily (o.d.) and lumiracoxib 100 mg o.d. [51] or diclofenac 150 mg/day [52] in OA, and between etoricoxib 90 mg o.d. and naproxen 500 mg twice-daily (b.i.d.) in RA [53]. However, following dental surgery, lumiracoxib 400 mg (acidic) has been shown to be more effective than celecoxib 400 mg (non-acidic) at reducing pain intensity [54], whereas rofecoxib 50 mg (non-acidic) has shown better analgesic efficacy than entericoated diclofenac 50 mg three times-daily (t.i.d.) (acidic) [55]. Thus, in the treatment of acute pain, differences in efficacy between NSAIDs seem to be more readily identified. It seems likely that differences in pharmacokinetic and pharmacodynamic properties (such as rate of absorption, time to maximal concentration, etc.), dose intervals and formulation between the various compounds exert a greater influence on efficacy in short-term studies. A potential explanation for the comparable efficacies of many of these agents in chronic conditions may be that NSAIDs or COX-2 inhibitors are dosed high enough and or often enough that steady-state concentrations are sufficient to inhibit PG production in the CNS and target tissue. The increase in systemic concentrations to obtain efficacy with non-acidic compounds might result in unwanted effects, such as higher rates of side effects and CV events. However, suitable comparative studies are needed to confirm this suggestion.

At therapeutic doses, the first generation of selective COX-2 inhibitors interfere with PG synthesis via COX-2 only to a limited degree, about 60% in the blood compartment [28] or in the CNS [39]. This appears sufficient to reduce hyperalgesia. It remains doubtful if anti-inflammatory (e.g. anti-oedema) effects are achieved at such doses. It is unknown what would happen with complete inhibition of this enzyme throughout the body. Long-term intensive (high-dose) inhibition, such as with rofecoxib (50 mg/day) in the Vioxx® Gastrointestinal Outcomes Research (VIGOR) study, resulted in a small but significant increase in myocardial infarctions (MIs) [27]. Similar effects, although much less definitive, were observed with celecoxib in a meta-analysis [56]. On the other hand, acidic non-selective NSAIDs, such as tenoxicam, with a long elimination T1/2 [16, 17], which allow for recovery phases in the central compartments when given in moderate doses.

These findings suggest that the full benefit of COX inhibition will be manifest for inhibitors with both enzyme and tissue selectivity, and with a short elimination T1/2 [16, 17], which allow for recovery phases in the central compartments when given in moderate doses.

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as diclofenac and ibuprofen, appear to do comparatively less harm, although not completely consistently—indeed, for all of their degree of enzyme specificity—so long as they are not overdosed. This advantage disappears at high doses and short dosing intervals. In the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study, the risk of CV events was not significantly different among etoricoxib 60 or 90 mg o.d. and diclofenac 75 mg b.i.d. [57]. Diclofenac has also been reported to increase CV risk in a recent meta-analysis [58]. These findings would seem to contradict our suggestion that there might be differences in CV risk between an acidic NSAID with a short half-life and a non-acidic selective COX-2 inhibitor with a long half-life. The CV risk associated with selective and non-selective should be similar provided they produce the same degree of COX-2 inhibition in the circulation and endothelium. However, the dose of diclofenac used in MEDAL was high (maximum daily dose). This is likely to cause permanent, almost complete inhibition of COX-2 in the vasculature [28] offset any benefit of tissue selectivity and short half-life. Indeed, this dosing regimen for diclofenac has been reported to completely inhibit COX-2 in plasma during all of the dose interval [28]. When using short half-life compounds, such as lumiracoxib or diclofenac, low doses and long dosing intervals could allow for daily recovery phases of COXs in the circulation and endothelium. This option may not have been explored sufficiently as yet.

It has been shown that diclofenac 25 mg inhibits COXs in the bloodstream for about 12 h whereas complete inhibition is present for up to 18 h in inflamed tissue (Fig. 5c). Given that lumiracoxib is acidic and displays similar pharmacokinetics to diclofenac [i.e., a similarly short half-life (Table 1) and similar behaviour in targeting inflamed tissue], only marginal inhibition of PG synthesis might be expected via COX-2 in the bloodstream or vessel wall compared with an almost complete inhibition of this enzyme in inflamed tissue during the second half of the dose interval with once-daily dosing of lower doses (100 mg). However, this needs to be confirmed by additional studies.

Lumiracoxib: a step forward?

Lumiracoxib differs from non-COX-2 selective NSAIDs by its selectivity and from the other coxibs by its pharmacokinetics. Its safety profile is similar—possibly superior to other non-acidic selective COX-2 inhibitors. Notably, there was an ~80% reduction in serious ulcer complications with lumiracoxib 400 mg o.d. (four times the recommended daily dose) compared with naproxen 500 mg b.i.d. and ibuprofen 800 mg t.i.d. in patients not receiving aspirin in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) [59]. Interestingly, the CV safety profile of lumiracoxib 400 mg o.d. (four times the recommended daily dose) in TARGET was comparable with that of naproxen (500 mg b.i.d.) and ibuprofen (800 mg t.i.d.) for clinical and silent MIs, stroke and CV death [60]. Unfortunately, all drugs were given in very high doses and this study did not extend beyond 1 y. Therefore, long-term effects which may become statistically significant at lower doses and/or beyond that time could not be ascertained. However, a re-analysis of the Adenomatous Polyp Prevention On Vioxx (APPROVE) trial has indicated that the risk of thrombotic events with rofecoxib compared with placebo could diverge as early as after 4–6 months of treatment [61]. Rofecoxib has been shown to increase and destabilize blood pressure control compared with placebo over 6 weeks [62]. In contrast, administration of lumiracoxib even at 400 mg o.d. for 12 months did not aggravate pre-existing hypertensive conditions relative to naproxen and ibuprofen [60]. In addition, it did not differ from placebo with respect to changes in systolic or diastolic blood pressure [63] or the instances of newly occurring hypertension in other clinical trials [Prexige Summary of Product Characteristics. URL: www.medicines.org.uk (accessed April 26 2006)].

Conclusions: combining enzyme and tissue selectivity, new options for safer therapy

Recent evidence indicates that the first generation of selective COX-2 inhibitors is well suited to reduce the GI toxicity but not renal and CV side effects. This may be due to the long-lasting inhibition of COXs throughout the whole body, including the vascular wall and kidney, where PGs produced by COX-2 exert protective effects. Selective COX-2 inhibitors that are tissue-specific have a low Vdss and a short elimination T1/2 (Vd < 1 l/kg, T1/2 < 6 h), would spare several body compartments from (permanent) effective concentrations and cause only brief effects in others (bloodstream, vascular wall and kidney), making them attractive therapeutic options. Such drugs (at adequate dosing) may profit from both tissue and enzyme selectivity to deliver analgesic efficacy comparable with traditional NSAIDs, but with an improved safety profile. This additional option should be explored in the future.

Rheumatology key messages

- Pharmacokinetics can play an important role in the tolerability of COX inhibitors.
- Acidic COX inhibitors can distribute preferentially into inflamed tissue.

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