Using pharmacokinetic principles to optimize pain therapy

Kay Brune, Bertold Renner and Burkhard Hinz

Abstract | Cyclo-oxygenase (COX) inhibitors are widely used to relieve musculoskeletal pain. These agents block the production of prostaglandins (PGs) at sites of inflammation by inhibiting the activity of two COX enzymes necessary for PG production and normal organ homeostasis. Inhibition of PG production at sites unrelated to pain is associated with adverse drug reactions (ADRs). The degree of analgesic efficacy, as well as the incidence and the localization of ADRs, are critically influenced by the pharmacokinetics (absorption, distribution and elimination) of these drugs. Ideally, sufficient and permanent inhibition of COX enzymes should be achieved in target tissues, with minimal ADRs. To minimize underdosing or overdosing, which result in therapeutic failure or ADRs, the COX inhibitor with the most appropriate pharmacokinetic properties should be selected on the basis of a thorough pharmacokinetic–pharmacodynamic analysis. In this Review, the pharmacokinetics of the prevailing COX inhibitors will be discussed and enigmatic aspects of these intensively used drugs will be considered.

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Introduction

Most drugs exert their effects only when they interact with their targets, such as receptors, enzymes or ligand-gated ion channels. This tendency implies that the target–drug interaction is reversible or that targets are replaced within a short time.[1] In general, overdosing does not lead to more than a maximum effect (plateau), but rather increases the propensity for adverse effects. However, some pharmacological agents are known to initiate a cascade of events that continues after the drug has left the circulation.[1,2] An example of such a drug is cortisone, which modulates intracellular transcription processes leading to the activation or suppression of secondary mediators that influence many body functions long after the drug has been eliminated. This phenomenon is often referred to as the 'hit-and-run' effect.[1–3] The pharmacokinetics of 'hit-and-run' drugs will not be discussed here as they are not predictive of the final drug effect.

In this Review, the pharmacokinetics of the prevailing cyclo-oxygenase (COX) inhibitors are discussed. As will be outlined in the following sections, the degree of analgesic efficacy, as well as the incidence and the localization of adverse drugs reactions (ADRs), are influenced by the absorption, distribution and elimination of these drugs. Furthermore, we provide suggestions for the selection of a COX inhibitor on the basis of thorough pharmacokinetic and pharmacodynamic analyses.

Competing interests
The authors have declared associations with the following companies/organizations: Aventis, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, Mundipharma, Novartis and Pfizer. See the article online for full details of the relationships.

COX inhibitors

In the early 1990s, the prostanoid-synthesizing enzyme COX was demonstrated to exist as two distinct isoforms (Figure 1a).[4,5] COX1 is constitutively expressed as a 'housekeeping' enzyme in nearly all tissues, and mediates physiological responses, such as cytoprotection of the stomach and platelet aggregation. By contrast, COX2 is expressed in cells that are involved in inflammation (macrophages, monocytes, synoviocytes, etc.) and has emerged as the isoform that is primarily responsible for the synthesis of the prostanoids involved in pathological processes, such as acute and chronic inflammatory states. COX inhibitors, such as celecoxib, diclofenac, etoricoxib, ibuprofen, naproxen, and piroxicam exert their analgesic effects by blocking the production of prostaglandins (PGs) (Figure 1b).[6–10] The degree and duration of COX2 inhibition (and consequently the production of PGE_2) is the basis for their antihyperalgesic (analgesic) effects,[6–7] but might also effect the degree of cardiovascular ADRs.[8–10]

At present, there is no evidence to suggest that differences in the selectivity of these agents towards one COX isoenzyme is of importance with respect to analgesia, as currently all drugs used for analgesia are COX2 inhibitors. The selectivity of a compound towards COX1 or COX2 *in vivo* differs considerably from the *in vitro* selectivity and must therefore be considered with respect to pharmacokinetics (Table 1). Accordingly, substances with preferential COX2 inhibitory activity can lose their selectivity at higher doses.[10]

Aspirin seems to be an exception to most other COX inhibitors as it mediates analgesic effects by its major breakdown product salicylic acid, a weak inhibitor of PGE_2 production.[11] However, aspirin initiates a

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Key points

- Cyclo-oxygenase (COX) inhibitors comprise substances with a broad spectrum of pharmacokinetic characteristics
- Rapid onset of analgesia requires administration of COX inhibitors with fast absorption, such as solutions or uncoated tablets with salts of the respective compound
- Among the COX inhibitors, only acidic compounds are currently considered to accumulate in the inflamed joint (deep compartment) and to confer long-term inhibition of COX2 when given at therapeutic doses
- To achieve acute analgesic effects and to avoid toxic drug accumulation following long-term use, administration of a suitable initial loading dose followed by a smaller maintenance dose should be considered
- Only >95% COX1 inhibition in platelets confers a clinically relevant inhibition of platelet aggregation; moreover, correlation analyses suggest that 80% COX2 inhibition is necessary for pain relief
- Overdosing increases the incidence of adverse effects, but does not enhance analgesia

'hit-and-run' effect on COX1 in platelets, where the enzyme is permanently acetylated and not replaced owing to a lack of *de novo* protein synthesis in platelets (Figure 1b).[8] Hence, although aspirin exemplifies both analgesic and 'hit-and-run' effects, the pharmacokinetic characteristics of this drug define the analgesic effect, but not the cardioprotective action. This dual effect limits its value as an everyday analgesic; aspirin at a dose of 1 g will increase the risk of bleeding for days,[12] but can alleviate pain for only a few hours. Moreover, the antiaggregatory effect of aspirin follows a nonlinear relationship. Accordingly, only >95% COX1 inhibition in platelets confers a clinically relevant inhibition of platelet aggregation (Figure 2a).[8,9] This categorical effect explains why moderate inhibition of COX1 production in platelets is not accompanied by anticoagulative effects.

Inhibition of PGE_2 and PGI_2 (prostacyclin) production leads to graded effects. The less these tissue-protective PGs are produced, the more likely it is that organ-specific ADRs will emerge, such as gastrointestinal ulcerations and kidney dysfunction. In addition, the analgesic therapeutic plasma concentration of a COX inhibitor has been shown to directly correlate with the inhibitory concentration $(IC)_{80}$ (the concentration that leads to 80% inhibition) of the substance on COX2 in a human whole blood assay,[13] implying that approximately 80% inhibition of COX2 results in analgesia (Figure 2b).

Pharmacodynamics of COX inhibitors

The selective and nonselective COX2 inhibitors comprise compounds with variable rates of absorption, distribution and elimination (Table 1). The onset of action (conferred by both absorption and distribution) and the speed of elimination (which determines the duration of pain relief) are of major importance for analgesics. Importantly, an effect greater than complete inhibition of COX enzymes cannot be achieved. Therefore, overdosing, or combining two COX inhibitors, increases the incidence of adverse effects, but is not expected to enhance analgesia. In the following section, a pharmacodynamic interaction of COX inhibitors is highlighted that is critically influenced by a particular pharmacokinetic characteristic (the short half-life of low-dose aspirin).

Nonselective COX inhibitors and aspirin

Ibuprofen or naproxen (at higher than nonprescription doses) can interfere with the antiplatelet activity of low-dose aspirin when they are coadministered.[14,15] The underlying mechanism for this effect is thought to be a competitive inhibition at the acetylation site of platelet COX1—ibuprofen and aspirin target sites on COX1 that are in close proximity. Importantly, when these agents are coadministered, COX1 activity will not be suppressed following dissociation of ibuprofen from the binding site because aspirin will already have been metabolized or eliminated. Although the clinical implication of this interaction remains to be further clarified, the cardioprotective effect of aspirin might be decreased or discontinued if other competitive COX1 inhibitors are coadministered. Indeed, patients who were discharged after first admission for cardiovascular disease and who were prescribed low-dose aspirin plus ibuprofen had an increased risk of all-cause mortality and cardiovascular mortality when compared with patients who used aspirin alone.[16] Therefore, the FDA advise patients to use immediate-release aspirin and take a single dose of 400 mg ibuprofen at least 30 min after aspirin ingestion, or more than 8 h before aspirin ingestion.[17]

Selective/preferential COX2 inhibitors and aspirin

With respect to COX2 inhibitors, trials assessing *ex vivo* platelet aggregation did not report alterations in the antiplatelet activity of aspirin by celecoxib,[18,19] rofecoxib,[15,20] or etoricoxib.[21] However, the aspirin dosages used in these trials were not comparable as doses of 81 mg were used in the rofecoxib and etoricoxib studies, whereas fourfold higher aspirin doses were administered in the celecoxib trial. Apart from these *ex vivo* analyses, all COX2 inhibitors have been shown to antagonize the irreversible COX1 inactivation by aspirin *in vitro* with a rank order of potencies (ibuprofen > celecoxib > valdecoxib > rofecoxib > etoricoxib) paralleling that obtained for platelet COX1 inhibition.[22] Thus, it appears that a low affinity for COX1 and a high degree of COX2 selectivity confers a low potential to block the ability of aspirin to inhibit platelet COX1. This topic has gained increased attention lately in view of a detailed *in vitro* study showing that binding of celecoxib to COX1 at pharmacologically relevant concentrations interferes with the inactivation of COX1 by aspirin.[23] The authors presumed that celecoxib binds to the COX active site of one monomer of COX1, thereby altering the binding of aspirin to the partner COX1 monomer. In the same study, administration of celecoxib to dogs was shown to interfere with the antiplatelet action of aspirin which was given at a dose equivalent to low-dose aspirin (81 mg) administered to humans.[23] Although an uncritical transmission of this data to humans is unjustified, we feel that it is timely to assess the impact of celecoxib on the antiaggregatory action of low-dose aspirin in humans.

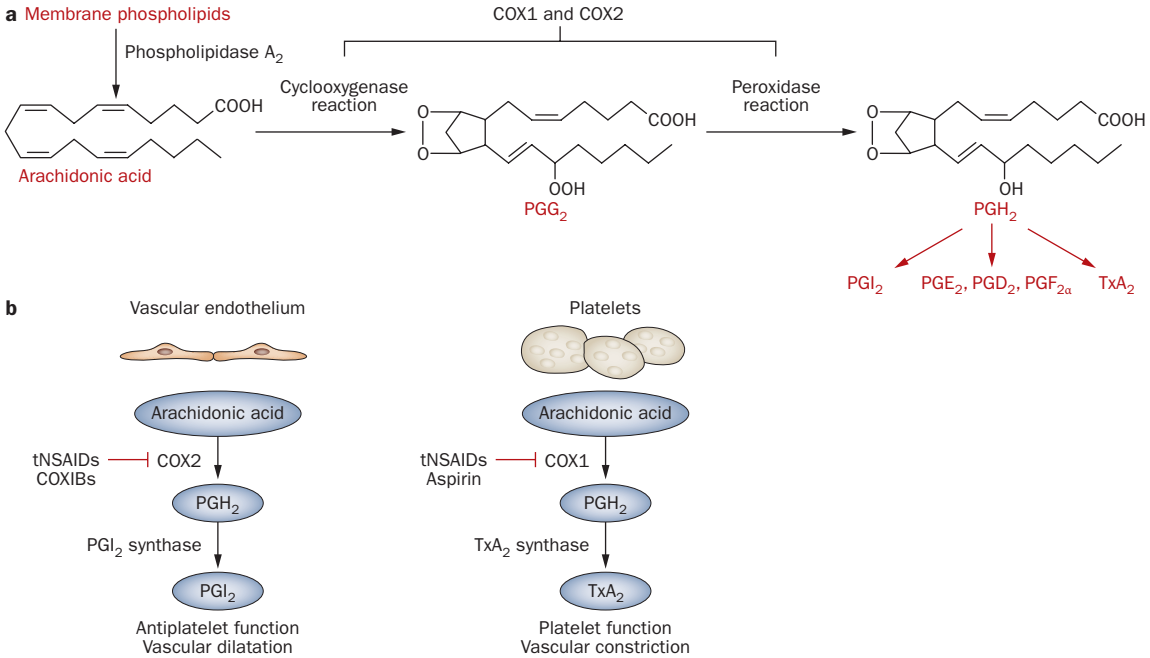

Figure 1 | The pathway of prostanoid synthesis and the role of the COX enzymes. **a** | Arachidonic acid is released from membrane phospholipids by phospholipase A_2. COX1 and COX2 both catalyze the conversion of arachidonic acid into PGH_2 via PGG_2. PGH_2 is the common substrate for tissue specific prostanoid synthases, which catalyze the conversion of PGH_2 to PGI_2 (vessels), prostaglandins (kidney, stomach, vascular, neuronal tissue) or TxA_2 (platelets). **b** | Inhibition of COX enzymes by both nonselective tNSAIDs and COXIBs and the role of aspirin on platelet activity. PGI_2 and PGE_2 are the major prostanoids in the vascular endothelium that prevent platelet aggregation and blood coagulation. TxA_2 is synthesized in platelets and causes vascular muscle constriction and activation of further platelets. The nonselective tNSAIDs inhibit COX2 and COX1 in vascular endothelium and platelets without any obvious tissue preference. The selective COXIBs should not directly interfere with platelet function, since COX2 is not expressed in platelets. Aspirin is able to inhibit the platelet COX1 irreversibly ('hit and run' effect), although the inhibitory effect is blocked when ibuprofen is present at the COX1 binding site. Abbreviations: COX, cyclo-oxygenase; COXIB, COX2-selective inhibitor; PGD_2, prostaglandin D_2; PGE_2, prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PGG_2, prostaglandin G_2; PGH_2, prostaglandin H_2; PGI_2, prostacyclin; tNSAID, traditional nonsteroidal anti-inflammatory drug; TxA_2, thromboxane A_2. Figure 1b reproduced with permission from the American Society for Clinical Investigation © Marnett, L. J. *Annu. Rev. Pharmacol. Toxicol.* **49**, 265–290 (2009).

Pharmacokinetics of COX inhibitors

Among the nonselective COX2 inhibitors, a broad spectrum of pharmacokinetic characteristics exists (Table 1).[24,25] This might contribute to both the intended pharmacological effects as well as to the ADRs. These differences are important for selecting the optimal drug, the right dose and the best galenic formulation.

Absorption

The onset and speed of absorption is of major importance for analgesics, in particular when treating acute pain. COX inhibitors, with a rapid absorption rate, rapidly reach their sites of action, such as the dorsal horn of the spinal cord or inflamed, traumatized or damaged tissue, and are therefore preferred as a therapeutic option by many patients.[26] Several nonselective COX inhibitors marketed as analgesics, such as diflunisal, did not achieve commercial success owing to their slow absorption rate and, consequently, the associated slow onset of pain relief.[27] Celecoxib also displays a slow absorption rate, in addition to variable bioavailability, and is not, therefore, deemed to be an appropriate agent to treat acute pain (Table 1).[28]

Ibuprofen

When ibuprofen was approved for over-the-counter (OTC) sale in 1989, many patients complained about a lack of pain relief following consumption of the drug. At that time, the standard galenic formulations did not allow for fast dissolution and absorption of the low OTC doses (200–400 mg). We previously investigated the pharmacokinetics of ibuprofen and observed that peak concentrations were achieved only several hours after administration.[26] By contrast, the fast absorption of a water-soluble salt of ibuprofen was associated with satisfying pain relief even at low doses.[26] In agreement with this finding, Laska *et al.*[29] observed a direct correlation between ibuprofen plasma concentrations and the onset of pain relief. A further consideration is that low-dose ibuprofen (up to 3 doses of 400 mg per day) is regarded as relatively nontoxic, but higher doses (1.8–3.2 g per day) are relatively toxic. For example, the relatively high incidence of cardiovascular events associated with ibuprofen use in the TARGET study[30] is likely to be due to the high dose administered (800 mg three times daily). Despite the fast elimination of ibuprofen, this dosing regimen is expected to have inhibited COX2

Table 1 | Pharmacokinetic characteristics of oral COX inhibitors

Selectivity	Agent	$t_{50\%}$ (h)	t_{max} (h)	F_0 (%)	V_d (l/kg)
Acidic COX inhibitors					
Nonselective	Ibuprofen	2	0.5–2.0	100	~0.15
	Ketoprofen	2–4	1–2	90	~0.15
	Lornoxicam	4–10	0.5–2.0	100	~0.15
	Naproxen*	12–15	2–4	90–100	~0.15
	Piroxicam*	30–60	3–5	100	~0.15
Preferential‡	Meloxicam	20	5–6	~90	~0.15
	Diclofenac	1–2	0.5–12.0§	~60	~0.15
Selective‖	Lumiracoxib	2–6	1–3	74	~0.15
Nonacidic COX inhibitors					
Nonselective	Propyphenazone	1.0–2.5	0.5–1.5	~100	2
	Dipyrone¶	2–4	1–2	~100	~1
Preferential‡	Acetaminophen	1.5–2.5	0.5–1.5	70–100	~1
	Celecoxib#	6–12	2–4	20–60	4
Selective‖	Rofecoxib	15–18	2–4	93	1.5
	Etoricoxib	20–26	1	100	~2

*Enterohepatic circulation. ‡Preferential for COX2. §Depending on the galenic formulation. ‖Selective for COX2. ¶Active metabolite is 4-methylaminophenazone. #Depending on *CYP2C9* status. Abbreviations: COX, cyclo-oxygenase; $t_{50\%}$, plasma elimination half-life; t_{max}, time to maximal plasma concentration; F_0, oral bioavailability; V_d, volume of distribution.

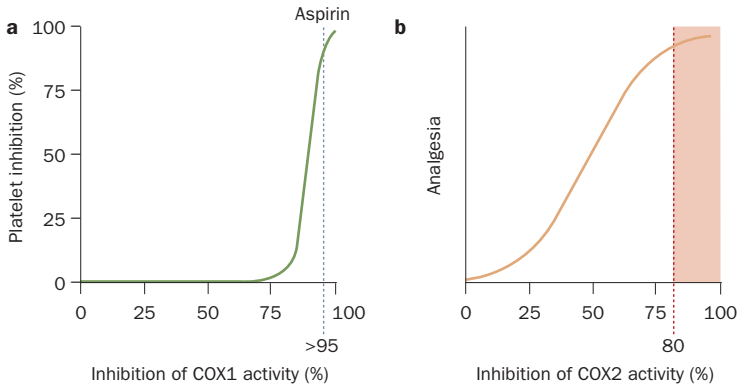

Figure 2 | Discordant dose-response relationships between aspirin and the inhibition of platelet COX1 or analgesia related to COX2 inhibition. **a** | The platelet effect is categorical in that >95% suppression of COX1 enzyme activity is necessary to confer inhibition of platelet aggregation. **b** | The analgesic therapeutic plasma concentration of a COX inhibitor is directly correlated with the IC_{80}, implying that 80% COX2 inhibition is necessary for pain relief. Abbreviations: COX, cyclo-oxygenase; IC_{80}, inhibitory concentration leading to 80% inhibition. Reproduced with permission from the American Society for Clinical Investigation © Grosser, T. *et al. J. Clin. Invest.* **116**, 4–15 (2006).

activity in the vascular wall throughout the body. We hypothesize that ibuprofen, when given at OTC doses, would impair COX2 activity in the vascular wall for only several hours per day, thus allowing for recovery.

Diclofenac

Similarly to ibuprofen, diclofenac does not cause fast pain relief in many patients.[31,32] This monolithic, large, acid-resistant, film-coated tablet can be retained in the stomach for hours before being passed into the small intestine for subsequent dissolution and absorption. Consequently, in one study several patients felt that the drug did not work in a reliable manner and instead they preferred to use solutions or uncoated tablets, including diclofenac potassium salts or resinate formulations, which have a fast onset of action, or a protracted absorption rate, or both.[31]

Rofecoxib

Rofecoxib was launched at a dose of 50 mg for the treatment of acute pain in 2001. As this drug is considered to have a relatively slow absorption rate, and does not provide rapid pain relief when given at low doses as a tablet or solution (time-to-peak of about 3 h with 12.5–25 mg),[24] it was administered in high doses to reduce the time taken to achieve pharmacologically active concentrations. Obviously, such a high dose (50 mg) led to considerable inhibition of COX2 within one hour of administration. The high, sustained plasma concentrations of rofecoxib are typical of drugs that are eliminated slowly ($t_{50\%}$ of approximately 15 h) and used for a prolonged period of time. It is not surprising, therefore, that in several studies that addressed the cardiovascular risk of rofecoxib, long-term use of rofecoxib at 50 mg was revealed to be particularly dangerous in terms of cardiovascular toxicity.[33,34]

Etoricoxib

Although the slow absorption of previous ibuprofen or diclofenac preparations can be remedied by improved galenic formulations (solutions, fast-dissolving tablets or soluble salts), the slow absorption of rofecoxib seems to be a substance-specific problem that cannot be improved by galenic manipulations. The producer of rofecoxib eventually discovered that the alternative COX inhibitor, etoricoxib, displays pharmacokinetic characteristics more suited to the treatment of acute pain relief than rofecoxib (Table 1). The absorption of etoricoxib is much faster than that of rofecoxib, and peak plasma concentrations are reached within 1 h of administration in both healthy volunteers and patients who had undergone hip surgery.[35] In another study addressing the analgesic effect of single oral doses of etoricoxib in the treatment of pain after dental surgery, the median time to onset of analgesia was 24 min for etoricoxib 120 mg, 180 mg, and 240 mg, and 30 min for etoricoxib 60 mg.[36]

Distribution

COX inhibitors have therapeutic targets in both traumatized tissue and the central nervous system;[7] however, they can interfere with the activity of COX enzymes throughout the body.[37] The therapeutic goal, therefore, is to concentrate and maintain the active drug at strategic sites and to keep the concentrations in other body compartments as low as possible.[38] Indeed, it has been shown that acidic, highly protein-bound, amphiphilic compounds, including diclofenac, ibuprofen, ketoprofen, but also the selective COX2 inhibitor lumiracoxib, accumulate and persist in inflamed tissue, such as in the synovial fluid of inflamed joints.[38–40]

There are a number of reasons for this distribution phenomenon. First, the local acidic microenvironment caused by inflammation might promote uptake and retention of the drug by causing a shift of acidic compounds into cell membranes and intracellular space (a process termed ion trapping).[41] Second, during inflammation the concentrations of albumin in inflamed tissue and synovial fluid are greatly augmented leading to increased concentrations of acidic COX inhibitors in

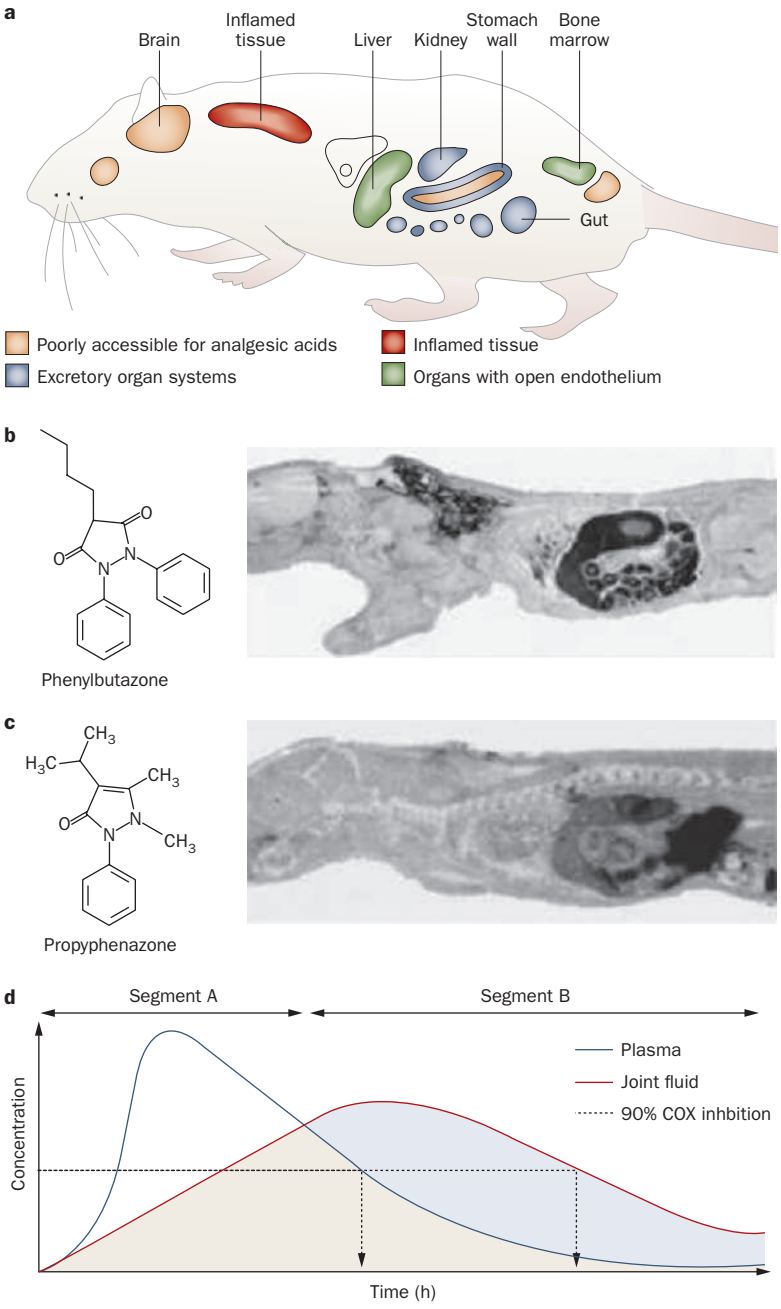

Figure 3 | Distribution of acidic and nonacidic COX inhibitors. **a** | The anatomy of the rat following subcutaneous injection of carrageenan into the neck region to induce inflammation. The differential distribution of **b** | (^{14}C) phenylbutazone (acidic COX inhibitor) and **c** | (^{14}C) propyphenazone (nonacidic COX inhibitor) is indicated as determined by autoradiographic localization.[38] Following 5 h phenylbutazone treatment, high radioactivity (black) is observed in the neck, the stomach wall, the liver, kidney and in the blood. Homogeneous radioactivity distribution is evident following propyphenazone treatment, with high concentrations of metabolites in the kidney and bladder. **d** | In humans, drug accumulation of ibuprofen was measured in an 'effect compartment' (synovial fluid and surrounding tissue cell layers).[39] Initially, plasma concentration exceeds the drug concentration measured in synovial fluid (segment A), whereas the opposite is observed as time progresses (segment B). Moreover, the concentration of ibuprofen required for 90% COX inhibition in the synovial fluid lasted longer compared to plasma, and persistent short half-life drug concentrations are observed in the effect compartment. Similar compartmental kinetics are reported for other acidic short half-life drugs, as diclofenac[76] and ketoprofen.[77] Abbreviation: COX, cyclooxygenase. Panels a–c reproduced with permission from Taylor & Francis Group http://www.informaworld.com © Brune, K. Persistence of NSAIDs at effect sites and rapid disappearance from side-effect compartments contributes to tolerability. *Curr. Med. Res. Opin.* **23**, 2985–2995 (2007). Panel d reproduced with permission from Oxford University Press © Brune, K. & Furst, D. E. Combining enzyme specificity and tissue selectivity of cyclooxygenase inhibitors: towards better tolerability? *Rheumatology (Oxford)* **46**, 911–919 (2007).

the synovial fluid. Furthermore, the acidic environment of the inflamed tissue inhibits the binding of proteins to acidic COX inhibitors, allowing for increased diffusion of the drug into the intracellular space where the therapeutic effect takes place.[42] Finally, changes in the hemodynamics of tissue during inflammation, including increased localized blood flow and capillary 'leakiness', also contribute to increased concentrations of acidic COX inhibitors in the synovial fluid.[43]

In addition to data from several animal models[41,44,45] confirming that acidic COX inhibitors accumulate and persist in inflamed tissue, there is also evidence for a comparable distribution of these compounds in humans.[46,47] Scott *et al.*[47] evaluated the steady-state pharmacokinetics of lumiracoxib, an acidic, selective COX2 inhibitor, in the plasma and the synovial fluid of patients with rheumatoid arthritis (RA). They demonstrated that at 5–28 h following drug administration, concentrations of lumiracoxib were higher in the synovial fluid than in the plasma, with peak drug concentration in the synovial fluid occurring 3–4 h later than the peak plasma concentration. These findings suggest that the distribution kinetics of lumiracoxib in the synovial fluid are likely to prolong the therapeutic action of the drug beyond that expected from analysis of plasma pharmacokinetics.

Short half-life acidic compounds

The pivotal role of the distribution of COX inhibitors in the relationship between pharmacological effects and adverse effects is highlighted by short half-life, acidic compounds. In addition to their enrichment in the inflamed tissue, these drugs also achieve high concentrations in the stomach wall, the blood and the kidney (Figure 3a–c). This seems to be a contributing factor to the typical organ toxicity elicited by these compounds. In particular, they interfere with gastrointestinal, renal and vascular endothelial function.[48,49] By contrast, when administered at low doses and with a dosing interval of up to 8 h, these short half-life, acidic compounds rapidly leave the central compartment (the blood and the vascular endothelial layer), allowing for the recovery of COX2 activity (Figure 3d). Consequently, such a dosing regimen allows for the production of vasoprotective COX2-dependent prostacyclin at the end of each dosing interval, while hyperalgesia resulting from PGE_2 production in the

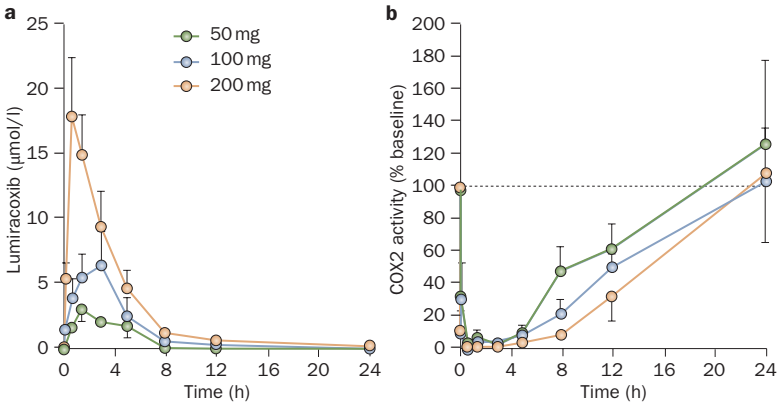

Figure 4 | Doubling the dose of a COX2 inhibitor already eliciting full COX2 inhibition does not produce additional pharmacological effects but rather enhances dose-related ADRs. **a** | Oral administration of lumiracoxib to human volunteers at 50 mg, 100 mg and 200 mg produces peak plasma concentrations 29-fold, 65-fold and 131-fold higher than the concentration that caused half maximal COX2 inhibition *ex vivo*. **b** | Despite a lower plasma concentration, administration of 50 mg lumiracoxib to human volunteers inhibits COX2 to a comparable degree as 100 mg or 200 mg *ex vivo*. Abbreviations: ADRs, adverse drug reactions; COX, cyclo-oxygenase. Reproduced from Hinz, B. *et al.* Lumiracoxib inhibits cyclo-oxygenase 2 completely at the 50 mg dose: is liver toxicity avoidable by adequate dosing? *Ann. Rheum. Dis.* **68**, 289–291 (2009) with permission from BMJ Publishing Group Ltd.

inflamed tissue can be continuously inhibited. In addition, it is hypothesized that these compounds might exert a lower overall toxicity compared with drugs that distribute equally throughout the body, including in organs such as the heart, the brain and the endocrine glands.

Nonacidic compounds

As mentioned previously, only acidic drugs are considered to show accumulation in the inflamed joint when given at therapeutic doses. Due to their lack of acidic structure, other COX inhibitors, such as phenazone, propyphenazone and acetaminophen (paracetamol), distribute homogenously throughout the body (Table 1 and Figure 3c).[50] We hypothesize a comparable pattern of distribution for the nonacidic COX2 inhibitors rofecoxib, celecoxib and etoricoxib, although experimental evidence is currently lacking in this respect. Interestingly, however, Biachi *et al.*[51] compared the impact of a 2-week treatment with the acidic COX inhibitor nimesulide and the nonacidic celecoxib in patients with osteoarthritis (OA), and they observed a considerable reduction of substance P concentrations in the synovial fluid following nimesulide treatment only, consistent with a faster analgesic action of this compound in comparison with celecoxib. However, more experimental and clinical data are necessary to confirm this finding. In the case of celecoxib, a sequestration into fat tissue by virtue of its extreme lipophilicity[28] has been suggested to further delay its analgesic effect. The question of whether the accumulation of celecoxib in human cells might explain the ability of the drug to interact with non-COX2 targets *in vivo*, despite comparatively low plasma concentrations, has been raised[52] and needs to be investigated in future studies.

At therapeutic doses, nonacidic drugs seem to achieve only analgesic effects, but no anti-inflammatory effects. Indeed, for decades, it was believed that acetaminophen and dipyrone were pure analgesics, and not that they operate via inhibition of peripheral COX enzymes. In comparison to acidic COX inhibitors, dipyrone, produces a less pronounced anti-inflammatory action in different animal models.[53,54] However, both drugs block COX2 sufficiently (>80%) at therapeutic doses to achieve analgesic effects.[55,56]

Acetaminophen deserves special discussion. Notwithstanding its low concentration in inflamed tissues, the lack of an anti-inflammatory effect of acetaminophen in patients with RA[57,58] might also be explained by the high extracellular concentrations of arachidonic acid and peroxide at the sites of inflammation; both substances diminish the redox-sensitive inhibitory effect of acetaminophen on PG synthesis.[59,60] By contrast, acetaminophen has been shown to considerably suppress COX2-dependent PG synthesis in human whole blood,[56] which might be explained by the various enzymatic and nonenzymatic antioxidant components present in plasma. Acetaminophen at 1 g single oral doses does not inhibit platelet function.[15,61] However, sufficiently high concentrations for blocking >95% COX1 activity can be achieved at higher doses. Accordingly, clinical trials that reported inhibition of platelet function by acetaminophen used high parenteral doses of the drug.[62,63]

As both acetaminophen and dipyrone are effective COX2 inhibitors, combining them with other COX inhibitors is not expected to increase the effect, since a plateau is reached by sufficient doses of either drug. Combining different COX inhibitors will simply increase the propensity for ADRs.[64,65]

Elimination

COX inhibitors are associated with a range of different elimination half-lives (Table 1). For all four groups of COX inhibitors (acidic, nonacidic, selective and nonselective), drugs with fast or slow elimination rates are currently in clinical use.

Short half-life compounds

Diclofenac, ibuprofen, ketoprofen, and acetaminophen have an elimination half-life of approximately 1–4 h. However, prolonging the active concentration of short half-life drugs in the blood by either high doses or retardation takes away the advantage of the short half-life. In order to allow for a single daily administration, lumiracoxib, a short half-life compound, was introduced with a 400 mg dose to treat acute pain.

To stimulate more research on the use of lumiracoxib at relevant doses for pain therapy, we conducted a comparative analysis in 2009 on the pharmacokinetics, dose-dependence and duration of COX2 inhibition in volunteers following oral administration of lumiracoxib at single doses of 50 mg, 100 mg or 200 mg.[66] The peak plasma concentrations of lumiracoxib were 29-fold (50 mg), 65-fold (100 mg) and 131-fold (200 mg) higher than the concentration that caused half maximal COX2 inhibition *ex vivo* (Figure 4a). Despite the disparate peak plasma concentrations, 50 mg lumiracoxib inhibited

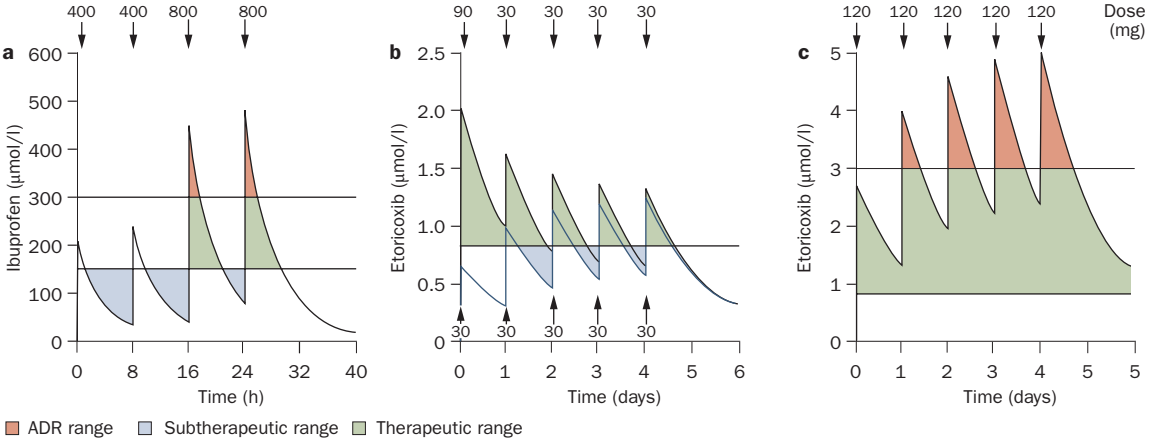

Figure 5 | Simulation of the pharmacokinetic profile of a short half-life (ibuprofen, t_{50}: 2 h) and long half-life (etoricoxib, t_{50}: 24 h) COX-inhibitor. **a** | A sufficient dose (400 mg ibuprofen) hits the analgesic window (therapeutic range) after the first and second dose. Low doses, given repeatedly, allow for putative recovery phases (such as in the endothelium of the vasculature) as the plasma concentration falls below substantial COX2 inhibition. This might be associated with a loss of analgesic activity, which can be compensated for by increasing the dose to 800 mg ibuprofen. However, prolonged effect time might be associated with more ADRs (when the concentrations exceed the therapeutic range) and the disappearance of the recovery phases. **b** | Slow accumulation of a long half-life drug. When a maintenance dose of 30 mg etoricoxib is given once daily (blue line), it takes 2–3 days to reach the therapeutic window. However, using a loading dose of 90 mg etoricoxib at day one will ensure immediate onset of action and speed up the time to reach steady state conditions (black line). **c** | Plasma concentrations of etoricoxib were simulated for a case when high maintenance doses of etoricoxib (120 mg) are used. The simulation indicates fast onset of action, the development of critically high concentrations and the lack of recovery phases. Simulation was performed using a two compartment model with 1st order input and 1st order elimination rate (WinNonlin® Vers. 3.3, Pharsight Corp., USA). Pharmacokinetics data for ibuprofen simulation were derived with t_{50} = 2 h.[78] Pharmacodynamic data for therapeutic range (ibuprofen) were taken from Laska *et al.*[29] Data for etoricoxib were adopted from Dallob *et al.*[21] Abbreviations: ADRs, adverse drug reactions; COX, cyclo-oxygenase.

monocyte COX2 activity to a comparable degree as 100 mg or 200 mg lumiracoxib for at least 5 h (Figure 4b). On the basis of these findings, 50 mg or 100 mg is probably a sufficient dose for this drug; indeed, the 400 mg dose causes hepatic toxicity.[67]

Medium half-life compounds

The use of naproxen, which is representative of medium half-life compounds, has been associated with a potential cardioprotective effect. Indeed, evidence suggests that continuous and regular administration of naproxen (500 mg administered twice daily) can affect platelet COX1 activity and subsequent platelet aggregation throughout the dosing interval in some, but not all, patients.[68] In line with this notion, a meta-analysis of 138 (published and unpublished) randomized trials[69] concluded that the incidence of serious vascular events was similar between a COX2 inhibitor and any non-naproxen COX inhibitor and that the risk of naproxen was in the placebo range. A similar tendency was reported in the TARGET study where lumiracoxib and naproxen elicited myocardial infarction, stroke or cardiovascular death in 40 out of 67 patients.[30] Naproxen also enhances the risk of ulcer bleeds at therapeutic doses, similar to low-dose aspirin in combination with selective COX2 inhibitors. Ulcer bleeds are seen more frequently with naproxen than with ibuprofen, which does not cause lasting platelet inhibition.[70] Indeed, the risk of peptic ulcers in high-risk patients taking a COX inhibitor can be significantly reduced by concomitant administration of proton-pump inhibitors.[71,72] This combination, however, does not provide protection against damage caused by COX inhibitors in the lower gastrointestinal tract. Accordingly, a double-blind, placebo-controlled trial using capsule endoscopy revealed celecoxib to be associated with considerably fewer small bowel mucosal breaks than naproxen plus omeprazole.[73]

Long half-life compounds

Other COX inhibitors, including piroxicam, tenoxicam and phenylbutazone, have elimination half-lives of up to 6 days. In order to achieve acute analgesic effects and to allow long-term use of these long half-life drugs, it is assumed that a suitable initial loading dose, followed by a smaller maintenance dose would be a useful approach to avoid toxic drug accumulation.

Advantages and disadvantages of drug half-life

As is usual in pharmacology, both fast and slow elimination rates can have advantages and disadvantages, depending on the individual patient and the disease. Although drugs with fast elimination rates generally achieve the required concentration range with the first dose, the effect can vanish rapidly (Figure 5a). In cases where a prolonged duration of action of short half-life drugs is desired, two possibilities can be considered: galenic retardation or an increase of dose. However, under these conditions, the associated advantages of recovery phases and the production of vasoprotective prostacyclin will be lost. In fact, an association study between the frequency, the dose and the

duration of COX2 inhibition by several analgesics and the risk of myocardial infarctions revealed a relative risk of 1.60 for those drugs that suppress COX2 by >90%.[74] Moreover, the same study concluded that myocardial infarctions are more likely to be caused by COX2 inhibitors when given as sustained release products as opposed to normal tablets.[74]

In contrast to drugs with fast elimination rates, slow elimination allows for the maintenance of stable, effective, plasma drug concentrations. This seems to be particularly important for patients suffering from persistent pain. If a maintenance dose is given without a loading dose, the first (or second) dose might not be sufficient to reach the necessary therapeutic concentration (Figure 5b), and the patient might complain about a lack of pain relief. However, if a patient is treated with a dose that causes fast pain relief, the continued administration of this dose will increase the risk of toxicity (Figure 5c) given that long-term administration of a drug can result in drug accumulation and steady-state plasma levels after four or five elimination half-lives. A drug such as phenylbutazone (including the active metabolite oxyphenbutazone), which in some patients has an overall elimination half-life of up to 5 days will reach the plateau only after several weeks. Thus, in order to compensate for this delay, these drugs can be administered with a high concentration loading dose followed by low concentration maintenance doses (Figure 5b).

The sustained administration of high doses of long half-life COX inhibitors is both unnecessary and dangerous. For the same reason, benoxaprofen, isoxicam, oxyphenbutazone, phenylbutazone, and tenoxicam were all removed from the market or are restricted in use due to apparent high toxicity. Piroxicam is still on the market, but is suspected to be particularly dangerous, and in 2007 the European Medicines Agency issued recommendations to further limit the use of this drug.[75] As a general rule with respect to long half-life drugs, a dose that is effective on the first day will be dangerous if taken continuously for more than five half-lives.[75]

Conclusions

COX inhibitors remain important agents in pain therapy. Among this group of compounds, a broad spectrum of pharmacokinetic characteristics exists that contributes to the intended pharmacological effects, as well as to the ADRs. According to clinical and experimental evidence, pharmacokinetic differences are critical for selecting the optimum drug, the right dose and the best galenic formulation. To gain fast pain relief, for instance, the administration of COX inhibitors with fast absorption (such as solutions or uncoated tablets with salts of the respective compound) should be preferred. A particularly beneficial property of the acidic COX inhibitors is their tendency to accumulate in the inflamed joint, which confers long-term inhibition of COX2 in this deep compartment. In addition, high concentrations of acidic COX inhibitors are also achieved in the stomach wall, the blood and the kidney—a characteristic that appears to contribute to the typical organ toxicity elicited by these compounds. Importantly, however, acidic COX inhibitors with a short half-life administered at low doses, and with a dosing interval of up to 8 h, show a fast clearance from the central compartment (blood, vascular wall, heart and kidney), thus allowing for the recovery of COX2 activity in this adverse effect compartment. However, this advantage is lost when the active concentration of these drugs in the blood is prolonged by either high doses or retardation.

Administration of COX inhibitors with a slow elimination rate allows for the maintenance of stable effective plasma drug concentrations in patients experiencing 'breakthrough' pain, but is unavoidably associated with drug accumulation following long-term use. To achieve acute analgesic effects and to avoid toxic drug accumulation following long-term use, a suitable initial loading dose followed by a smaller maintenance dose should be administered.

With respect to the relationship between extent of inhibition of COX enzymes and pharmacodynamic output, the evidence indicates that only >95% COX1 inhibition in platelets confers a clinically relevant inhibition of platelet aggregation. In addition, correlation analyses suggest an 80% inhibition of COX2 as necessary for pain relief, and so overdosing or combining two COX inhibitors (including acetaminophen) increases the incidence of adverse effects, but is not expected to enhance analgesia. This becomes increasingly important in view of studies suggesting that the nonacidic analgesic acetaminophen is a member of the family of COX inhibitors. Collectively, COX inhibitors for diverse indications should be selected on the basis of thorough pharmacokinetic and pharmacodynamic analyses.

Review criteria

Published articles for inclusion in this Review were identified form the authors' extensive records of papers on data on COX inhibitors based on their long-standing interest in this area.

1. Hughes, D. A. & Aronson, J. K. A systematic review and empirical analysis of the relation between dose and duration of drug action. *J. Clin. Pharmacol.* **50**, 17–26 (2010).
2. Greenblatt, D. J. Elimination half-life of drugs: value and limitations. *Annu. Rev. Med.* **36**, 421–427 (1985).
3. Levy, G. & Gibaldi, M. Pharmacokinetics of drug action. *Annu. Rev. Pharmacol.* **12**, 85–98 (1972).
4. Fu, J. Y., Masferrer, J. L., Seibert, K., Raz, A. & Needleman, P. The induction and suppression of prostaglandin H_2 synthase (cyclooxygenase) in human monocytes. *J. Biol. Chem.* **265**, 16737–16740 (1990).
5. Xie, W. L., Chipman, J. G., Robertson, D. L., Erikson, R. L. & Simmons, D. L. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. *Proc. Natl Acad. Sci. USA* **88**, 2692–2696 (1991).
6. Ahmadi, S., Lippross, S., Neuhuber, W. L. & Zeilhofer, H. U. PGE_2 selectively blocks inhibitory glycinergic neurotransmission onto rat superficial dorsal horn neurons. *Nat. Neurosci.* **5**, 34–40 (2002).
7. Zeilhofer, H. U. Prostanoids in nociception and pain. *Biochem. Pharmacol.* **73**, 165–174 (2007).
8. Grosser, T., Fries, S. & FitzGerald, G. A. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J. Clin. Invest.* **116**, 4–15 (2006).

9. Patrono, C. & Baigent, C. Low-dose aspirin, coxibs, and other NSAIDS: a clinical mosaic emerges. *Mol. Interv.* **9**, 31–39 (2009).
10. Hinz, B. & Brune, K. Can drug removals involving cyclooxygenase-2 inhibitors be avoided? A plea for human pharmacology. *Trends Pharmacol. Sci.* **29**, 391–397 (2008).
11. Aronoff, D. M., Boutaud, O., Marnett, L. J. & Oates, J. A. Inhibition of prostaglandin H2 synthases by salicylate is dependent on the oxidative state of the enzymes. *J. Pharmacol. Exp. Ther.* **304**, 589–595 (2003).
12. Palmer, J. D., Sparrow, O. C. & Iannotti, F. Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. *Neurosurgery* **35**, 1061–1064 (1994).
13. Huntjens, D. R., Danhof, M. & Della Pasqua, O. E. Pharmacokinetic-pharmacodynamic correlations and biomarkers in the development of COX-2 inhibitors. *Rheumatology (Oxford)* **44**, 846–859 (2005).
14. Capone, M. L. *et al.* Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. *J. Am. Coll. Cardiol.* **45**, 1295–1301 (2005).
15. Catella-Lawson, F. *et al.* Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N. Engl. J. Med.* **345**, 1809–1817 (2001).
16. MacDonald, T. M. & Wei, L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* **361**, 573–574 (2003).
17. US Department of Health and Human Services *Information for Healthcare Professionals: Concomitant Use of Ibuprofen and Aspirin* [online], http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm (2006).
18. Wilner, K. D. *et al.* Celecoxib does not affect the antiplatelet activity of aspirin in healthy volunteers. *J. Clin. Pharmacol.* **42**, 1027–1030 (2002).
19. Gladding, P. A. *et al.* The antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. *Am. J. Cardiol.* **101**, 1060–1063 (2008).
20. Greenberg, H. E. *et al.* A new cyclooxygenase-2 inhibitor, rofecoxib (VIOXX), did not alter the antiplatelet effects of low-dose aspirin in healthy volunteers. *J. Clin. Pharmacol.* **40**, 1509–1515 (2000).
21. Dallob, A. *et al.* Characterization of etoricoxib, a novel, selective COX-2 inhibitor. *J. Clin. Pharmacol.* **43**, 573–585 (2003).
22. Ouellet, M., Riendeau, D. & Percival, M. D. A high level of cyclooxygenase-2 inhibitor selectivity is associated with a reduced interference of platelet cyclooxygenase-1 inactivation by aspirin. *Proc. Natl Acad. Sci. USA* **98**, 14583–14588 (2001).
23. Rimon, G. *et al.* Coxibs interfere with the action of aspirin by binding tightly to one monomer of cyclooxygenase-1. *Proc. Natl Acad. Sci. USA* **107**, 28–33 (2010).
24. Brune, K. & Hinz, B. Selective cyclooxygenase-2 inhibitors: similarities and differences. *Scand. J. Rheumatol.* **33**, 1–6 (2004).
25. Hinz, B., Renner, B. & Brune, K. Drug insight: cyclo-oxygenase-2 inhibitors—a critical appraisal. *Nat. Clin. Pract. Rheumatol.* **3**, 552–560 (2007).
26. Geisslinger, G., Menzel, S., Wissel, K. & Brune, K. Single dose pharmacokinetics of different formulations of ibuprofen and aspirin. *Drug Invest.* **5**, 238–242 (1993).
27. Fulkerson, J. P. & Folcik, M. A. Analgesia following arthroscopic surgery: comparison of diflunisal and acetaminophen with codeine. *Arthroscopy* **2**, 108–110 (1986).
28. Werner, U. *et al.* Celecoxib inhibits metabolism of cytochrome P450 2D6 substrate metoprolol in humans. *Clin. Pharmacol. Ther.* **74**, 130–137 (2003).
29. Laska, E. M. *et al.* The correlation between blood levels of ibuprofen and clinical analgesic response. *Clin. Pharmacol. Ther.* **40**, 1–7 (1986).
30. Farkouh, M. E. *et al.* Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* **364**, 675–684 (2004).
31. Stüber, W. *et al.* Untersuchungen zur Bioverfügbarkeit von Diclofenac-Natrium aus einer neu entwickelten magensaftresistenten Pellet-Zubereitung. *Pharm. Ztg* **133**, 29–35 (1988).
32. Colombo, G., Giombini, A., Pamich, T., Peruzzi, E. & Pisati, R. Diclofenac dispersible provides superior analgesia with faster onset of action compared to naproxen granular in patients with acute, painful, minor sports injuries. *J. Sports Med. Phys. Fitness* **37**, 228–233 (1997).
33. Griffin, M. R. *et al.* High frequency of use of rofecoxib at greater than recommended doses: cause for concern. *Pharmacoepidemiol. Drug Saf.* **13**, 339–343 (2004).
34. Roumie, C. L., Arbogast, P. G., Mitchel, E. F. Jr & Griffin, M. R. Prescriptions for chronic high-dose cyclooxygenase-2 inhibitors are often inappropriate and potentially dangerous. *J. Gen. Intern. Med.* **20**, 879–883 (2005).
35. Renner, B. *et al.* Absorption and distribution of etoricoxib in plasma, CSF and wound tissue in patients following hip surgery—a pilot study. *Naunyn–Schmiedeberg's Arch. Pharmacol.* **381**, 127–136 (2010).
36. Malmstrom, K. *et al.* Etoricoxib in acute pain associated with dental surgery: a randomized, double-blind, placebo- and active comparator-controlled dose-ranging study. *Clin. Ther.* **26**, 667–679 (2004).
37. Simmons, D. L., Botting, R. M. & Hla, T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. *Pharmacol. Rev.* **56**, 387–437 (2004).
38. Brune, K. Persistence of NSAIDs at effect sites and rapid disappearance from side-effect compartments contributes to tolerability. *Curr. Med. Res. Opin.* **23**, 2985–2995 (2007).
39. Brune, K. & Furst, D. E. Combining enzyme specificity and tissue selectivity of cyclooxygenase inhibitors: towards better tolerability? *Rheumatology (Oxford)* **46**, 911–919 (2007).
40. Day, R. O., McLachlan, A. J., Graham, G. G. & Williams, K. M. Pharmacokinetics of nonsteroidal anti-inflammatory drugs in synovial fluid. *Clin. Pharmacokinet.* **36**, 191–210 (1999).
41. Graf, P., Glatt, M. & Brune, K. Acidic nonsteroid anti-inflammatory drugs accumulating in inflamed tissue. *Experientia* **31**, 951–953 (1975).
42. Dutta, S. K., Basu, S. K. & Sen, K. K. Binding of diclofenac sodium with bovine serum albumin at different tuemperatures, pH and ionic strengths. *Indian J. Exp. Biol.* **44**, 123–127 (2006).
43. Fowler, P. D., Shadforth, M. F., Crook, P. R. & John, V. A. Plasma and synovial fluid concentrations of diclofenac sodium and its major hydroxylated metabolites during long-term treatment of rheumatoid arthritis. *Eur. J. Clin. Pharmacol.* **25**, 389–394 (1983).
44. Doyle, M. J., Eichhold, T. H., Loomans, M. E., Farmer, R. W. & Kelm, G. R. Comparison of tebufelone distribution in rat blood plasma and inflamed and noninflamed tissues following peroral and intravenous administration. *J. Pharm. Sci.* **82**, 847–850 (1993).
45. Schweitzer, A., Hasler-Nguyen, N. & Zijlstra, J. Preferential uptake of the non steroid anti-inflammatory drug diclofenac into inflamed tissues after a single oral dose in rats. *BMC Pharmacol.* **9**, 5 (2009).
46. Elmquist, W. F., Chan, K. K. & Sawchuk, R. J. Transsynovial drug distribution: synovial mean transit time of diclofenac and other nonsteroidal antiinflammatory drugs. *Pharm. Res.* **11**, 1689–1697 (1994).
47. Scott, G. *et al.* Pharmacokinetics of lumiracoxib in plasma and synovial fluid. *Clin. Pharmacokinet.* **43**, 467–478 (2004).
48. Schrör, K., Mehta, P. & Mehta, J. L. Cardiovascular risk of selective cyclooxygenase-2 inhibitors. *J. Cardiovasc. Pharmacol. Ther.* **10**, 95–101 (2005).
49. McAdam, B. F. *et al.* Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc. Natl Acad. Sci. USA* **96**, 272–277 (1999).
50. Brune, K., Rainsford, K. D. & Schweitzer, A. Biodistribution of mild analgesics. *Br. J. Clin. Pharmacol.* **110** (Suppl. 2), 279S–284S (1980).
51. Bianchi, M., Broggini, M., Balzarini, P., Franchi, S. & Sacerdote, P. Effects of nimesulide on pain and on synovial fluid concentrations of substance P, interleukin-6 and interleukin-8 in patients with knee osteoarthritis: comparison with celecoxib. *Int. J. Clin. Pract.* **61**, 1270–1277 (2007).
52. Maier, T. J. *et al.* Cellular membranes function as a storage compartment for celecoxib. *J. Mol. Med.* **87**, 981–993 (2009).
53. Brune, K. & Alpermann, H. Non-acidic pyrazoles: inhibition of prostaglandin production, carrageenan edema and yeast fever. *Agents Actions* **13**, 360–363 (1983).
54. Tatsuo, M. A. *et al.* Analgesic and antiinflammatory effects of dipyrone in rat adjuvant arthritis model. *Inflammation* **18**, 399–405 (1994).
55. Hinz, B., Cheremina, O. & Brune, K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J.* **22**, 383–390 (2008).
56. Hinz, B. *et al.* Dipyrone elicits substantial inhibition of peripheral cyclooxygenases in humans: new insights into the pharmacology of an old analgesic. *FASEB J.* **21**, 2343–2351 (2007).
57. Boardman, P. L. & Hart, F. D. Clinical measurement of the anti-inflammatory effects of salicylates in rheumatoid arthritis. *BMJ* **4**, 264–268 (1967).
58. Ring, E. F., Collins, A. J., Bacon, P. A. & Cosh, J. A. Quantitation of thermography in arthritis using multi-isothermal analysis. II. Effect of nonsteroidal anti-inflammatory therapy on the thermographic index. *Ann. Rheum. Dis.* **33**, 353–356 (1974).
59. Ouellet, M. & Percival, M. D. Mechanism of acetaminophen inhibition of cyclooxygenase isoforms. *Arch. Biochem. Biophys.* **387**, 273–280 (2001).
60. Boutaud, O., Aronoff, D. M., Richardson, J. H., Marnett, L. J. & Oates, J. A. Determinants of the cellular specificity of acetaminophen as an inhibitor of prostaglandin H_2 synthases. *Proc. Natl Acad. Sci. USA* **99**, 7130–7135 (2002).

61. Mielke, C. H. Jr. Comparative effects of aspirin and acetaminophen on hemostasis. *Arch. Intern. Med.* **141**, 305–310 (1981).
62. Niemi, T. T., Backman, J. T., Syrjälä, M. T., Viinikka, L. U. & Rosenberg, P. H. Platelet dysfunction after intravenous ketorolac or propacetamol. *Acta Anaesthesiol. Scand.* **44**, 69–74 (2000).
63. Munsterhjelm, E. *et al.* Dose-dependent inhibition of platelet function by acetaminophen in healthy volunteers. *Anesthesiology* **103**, 712–717 (2005).
64. Garcia Rodríguez, L. A. & Hernández-Díaz, S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. *Arthritis Res.* **3**, 98–101 (2001).
65. Rahme, E., Barkun, A., Nedjar, H., Gaugris, S. & Watson, D. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. *Am. J. Gastroenterol.* **103**, 872–882 (2008).
66. Hinz, B. *et al.* Lumiracoxib inhibits cyclo-oxygenase 2 completely at the 50 mg dose: is liver toxicity avoidable by adequate dosing? *Ann. Rheum. Dis.* **68**, 289–291 (2009).
67. Hammett, R. Urgent advice regarding management of patients taking lumiracoxib (Prexige). *Australian Government Department of Ageing and Therapeutic Goods Administration* [online], www.tga.gov.au/alerts/prexige.htm (2007).
68. Capone, M. L. *et al.* Clinical pharmacology of platelet, monocyte, and vascular cyclooxygenase inhibition by naproxen and low-dose aspirin in healthy subjects. *Circulation* **109**, 1468–1471 (2004).
69. Kearney, P. M. *et al.* Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* **332**, 1302–1308 (2006).
70. Goldstein, J. L. *et al.* Reduced incidence of upper gastrointestinal ulcer complications with the COX-2 selective inhibitor, valdecoxib. *Aliment. Pharmacol. Ther.* **20**, 527–538 (2004).
71. Chan, F. K. *et al.* Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *N. Engl. J. Med.* **347**, 2104–2110 (2002).
72. Lai, K. C. *et al.* Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications. *Am. J. Med.* **118**, 1271–1278 (2005).
73. Goldstein, J. L. *et al.* Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. *Clin. Gastroenterol. Hepatol.* **3**, 133–141 (2005).
74. Garcia Rodríguez, L. A., Tacconelli, S. & Patrignani, P. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *J. Am. Coll. Cardiol.* **52**, 1628–1636 (2008).
75. European Medicines Agency press release. European Medicines Agency recommends restricted use for piroxicam. *European Medicines Agency* [online], http://www.ema.europa.eu/pdfs/human/press/pr/26514407en.pdf (2007).
76. Benson, M. D., Aldo-Benson, M. & Brandt, K. D. Synovial fluid concentrations of diclofenac in patients with rheumatoid arthritis or osteoarthritis. *Semin. Arthritis Rheum.* **15** (2 Suppl. 1), 65–67 (1985).
77. McCrea, J. D., Telford, A. M., Kaye, C. M. & Boyd, M. W. A comparison of plasma and synovial fluid profiles of standard and controlled-release formulations of ketoprofen in patients with rheumatoid arthritis. *Curr. Med. Res. Opin.* **10**, 73–81 (1986).
78. Wagner, J. G., Albert, K. S., Szpunar, G. J. & Lockwood, G. F. Pharmacokinetics of ibuprofen in man IV: absorption and disposition. *J. Pharmacokinet. Biopharm.* **12**, 381–399 (1984).

Author contributions

K. Brune, B. Renner and B. Hinz researched the data for the article and K. Brune and B. Hinz provided a substantial contribution to discussions of the content. K. Brune and B. Hinz wrote the article and K. Brune, B. Renner and B. Hinz contributed to review and/or editing of the manuscript before submission.