

Emerging Evidence in NSAID Pharmacology: Important Considerations for Product Selection

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of drugs widely used in managing a spectrum of conditions, including musculoskeletal conditions caused by inflammatory and degenerative joint diseases, low back pain, discomfort associated with minor injuries, and headache.^{1,2} As the overall US population increases in size and age, the number of individuals receiving prescription NSAIDs is likely to increase. Because a large number of NSAIDs are commercially available, it is important to consider several factors that contribute to the diversity of this drug class when choosing the most appropriate NSAID for a patient.³

As a group, NSAIDs are broadly classified as nonselective (ie, “traditional”) or selective, based on their relative preference for the cyclooxygenase (COX)-2 enzyme inhibition.^{1,4} Beyond this broad categorization of NSAIDs according to COX selectivity, marked variability in clinical differences exists among NSAIDs with similar degrees of COX selectivity.⁴ To achieve a thorough understanding of the differences among NSAIDs, it is necessary to consider the effects of dosing as well as the impact of pharmacokinetics, including absorption and half-life, on efficacy and tolerability.

The purpose of this article is to summarize considerations for informed NSAID selection based on emerging pharmacokinetic and pharmacodynamic data, as well as information from observational studies that highlight the potential impact of immediate versus extended/delayed release formulations of some NSAIDs. These considerations provide a basis for understanding how the risk for gastrointestinal (GI), cardiovascular (CV), and renal events might be mitigated.⁵⁻⁹

Normal COX Physiology

To distinguish among commercially available NSAIDs, it is first necessary to consider their overall

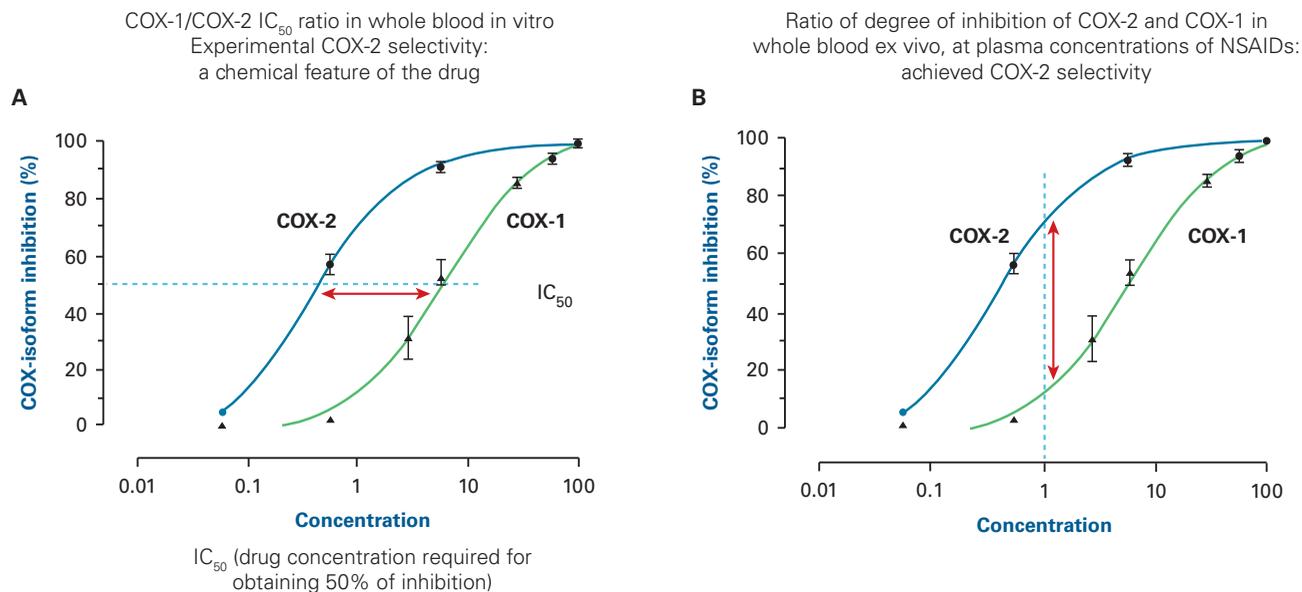
Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of pain and inflammation. Emerging pharmacokinetic and pharmacodynamic evidence in NSAID pharmacology provides important criteria for selecting an appropriate NSAID. The inhibition of COX enzymes by NSAIDs affects physiologic functions in the gastrointestinal, cardiovascular, and renal systems. Of the 2 principal types of COX enzymes, COX-1 and COX-2, the pain-relieving (anti-hyperalgesia) effects of NSAIDs are driven mainly by the inhibition of COX-2. Commonly, NSAIDs are categorized by in vitro selectivity (ie, the ratio of the NSAID concentrations required for inhibition of COX-1 and COX-2) as selective or nonselective. Theoretically, the concept of selectivity is convenient; however, the actual relative inhibition of COX-1 and COX-2 isoenzymes measured in vitro is dose-dependent. As a result, the predicted in vivo reduction of prostanoid-induced hyperalgesia and the expected adverse effects of an NSAID are dose dependent. Individual NSAIDs also differ on pharmacokinetic and pharmacodynamic parameters such as the absorption, time to availability of drug at the site of inflammation, and persistence at the site of inflammation. NSAIDs with longer half-life durations may offer longer durations of analgesia due to continued COX enzyme inhibition, but may provide less opportunity for recovery of COX activity between doses than NSAIDs with shorter half-lives. Understanding these pharmacokinetic and pharmacodynamic factors informs selection of an appropriate NSAID among this heterogeneous class of drugs.

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For author information and disclosures, see end of text.

■ **Figure 1.** The Assessment of COX Selectivity In Vitro (A) and Ex Vivo (B) in Whole Blood Assays⁵



NSAIDs are normally characterized based on their in vitro COX selectivity.

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mechanism of action and the physiologic systems affected by modulation of COX enzymes.¹⁰ COX enzymes are key mediators in the biosynthesis of prostanoids central to numerous biological processes, including inflammatory reactions (eg, modulation of prostaglandin D_2 production by mast cells and thromboxane A_2 by macrophages), protection of the gastrointestinal mucosa, hemostasis (platelet function), and maintenance of endothelial function.^{10,11} Two main isoforms of COX enzymes have been identified, and are referred to as COX-1 and COX-2.^{10,12} Although both COX enzymes are targets of NSAID therapy, notable differences include the location at which they are expressed in the body, and outcomes associated with their inhibition. COX-1 is expressed constitutively in most tissues, such as gastric mucosa and platelets, and performs protective functions in various organ systems.¹³ In contrast, COX-2 is induced in various cell types, such as those in the vascular endothelium and joints, during tissue damage and inflammation. The pain-relieving effects of NSAIDs due to their effects on hyperalgesia are primarily a function of COX-2 inhibition.⁵ However, it should be noted that agents with a higher degree of COX-2 selectivity have been associated with an increased rate of dose-related CV adverse events (AEs). In contrast, agents with a higher degree of COX-1 inhibition are principally responsible for serious gastrointestinal AEs.¹⁴

COX Inhibition of NSAIDs

Structurally, NSAIDs differ in their intrinsic ability to inhibit COX-1 and COX-2, with individual NSAIDs tending to be more selective for one COX enzyme than the other.¹¹ Therefore, NSAIDs are normally characterized based on their in vitro COX selectivity, which has been described as the ratio of concentrations required to inhibit the activity of COX-1 or COX-2 by 50% (inhibitory concentration $[IC]_{50}$ for COX-1 divided by the IC_{50} for COX-2) (Figure 1).⁵ When the ratio is close to 1.0, the NSAID is deemed a nonselective COX inhibitor; in contrast, NSAIDs with selectivity ratios <1 are considered more selective for COX-1. NSAIDs with COX selectivity ratios >1 are considered more potent in inhibiting COX-2.⁵ A comparison of the ratios of IC_{50} for COX-1 and COX-2 among several popular NSAIDs demonstrates that diclofenac and celecoxib have a similar degree of selectivity for COX-2 (Table 1).^{5,11,15-20}

The Relationship Between COX Selectivity and NSAID Dose

NSAID COX selectivity is not limited to the structural properties of the compound; COX-1/COX-2 selectivity is also markedly affected by the dose of NSAIDs.^{5,14} Therefore, although in vitro selectivity described by the IC_{50} may be useful as a starting point to characterize NSAID selectivity, the selective inhibition of either

COX-1 or COX-2 may be better characterized based on in vivo measures of COX inhibition with dose as a continuous variable, a phenomenon referred to as *achieved* selectivity. In other words, in contrast to the in vitro measures of selectivity, the achieved selectivity varies according to the administered dose.^{5,11}

Both in vitro and achieved COX isoenzyme selectivity may be determined using a human whole blood assay.^{5,17,21} The in vitro human whole blood assay quantitatively determines an NSAID's ability to inhibit COX-2 activity (as indicated by prostaglandin E₂ [PGE₂] levels). The procedure involves (1) obtaining whole blood samples from healthy individuals, (2) eliminating any contribution of COX-1 enzyme activity to PGE₂ production by incubating the blood sample in the presence of aspirin for 24 hours, and (3) adding lipopolysaccharide (LPS) to the blood sample, which stimulates COX-2 enzymes to produce PGE₂ in the presence of various concentrations of NSAIDs in vitro.^{17,22} The degree of COX-2 inhibition is then analyzed to estimate the concentration of an NSAID at which production of the COX-2 activity marker PGE₂ is reduced by half—the in vitro 50% inhibitory concentration, or IC₅₀.¹⁷ A similar procedure can be used to determine the inhibitory effect of a given NSAID on COX-1 at several different concentrations by monitoring levels of the COX-1 enzyme activity marker thromboxane B₂. In this instance, neither aspirin nor LPS are added to the whole blood samples.^{17,22} With these data, the in vitro IC₅₀ value for COX-1 inhibition in human whole blood for a given NSAID can be estimated.¹⁷ Comparing the COX-2 and COX-1 IC₅₀ values as a ratio provides an estimate of an NSAID's selectivity but does not indicate the actual ratio of inhibition of COX-2 to COX-1 achieved in vivo at commonly prescribed NSAID doses. However, the whole blood assay can be used to determine the degree of COX-1/COX-2 inhibition (the *achieved selectivity*) in vivo at NSAID concentrations equivalent to in vivo blood levels in humans administered commonly prescribed NSAID doses (Figure 1B).⁵ Thus, in vivo measures of COX-1/COX-2 inhibition may provide a more clinically relevant view of the relationship between NSAID dose and selectivity.^{5,23}

Achieved selectivity for various NSAIDs can be found in a number of pharmacologic studies where the COX-inhibitory effects of NSAIDs are assessed by administering commonly prescribed NSAIDs to healthy human volunteers. In these studies, diclofenac was associated with a greater percentage of inhibition of COX-2 compared with therapeutic doses of other traditional

■ **Table 1.** Ratio of COX-1 to COX-2 Selectivity of Commonly Used NSAIDs Based on IC₅₀ Values¹⁵⁻²⁰

Biochemical selectivity of currently available COX-2 inhibitors, as measured in vitro with human whole blood assays of COX-isozyme activity	
Inhibitor	COX-1/COX-2 IC₅₀ ratio
Ibuprofen	0.5
Naproxen	0.7
Indomethacin	1.9
Meloxicam	18
Diclofenac	29
Celecoxib	30
Rofecoxib	267

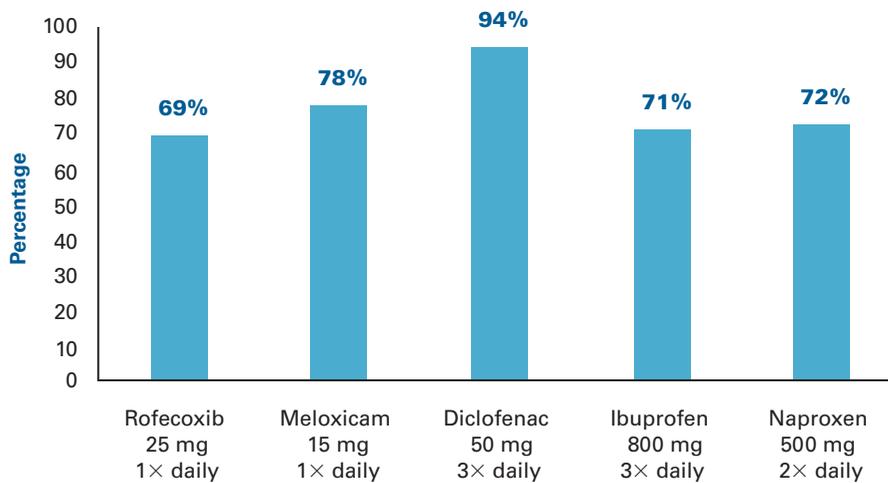
IC₅₀ values for the inhibition of platelet COX-1 and monocyte COX-2 were obtained as described.^{16,17} A substantially similar rank order of selectivity has been reported by other investigators using the same methodology.^{18,20} Republished with permission of American Society for Clinical Investigation from Patrono C, Patrignani P, García Rodríguez LA. Cyclooxygenase-selective inhibition of prostanoid formation: transducing biochemical selectivity into clinical read-outs. *J Clin Invest.* 2001;108(1);7-13; conveyed through Copyright Clearance Center, Inc.

NSAIDs and celecoxib.^{6,7} The mean percent inhibition of COX-2 was 93.9% for diclofenac (50 mg 3 times daily), 77.5% for meloxicam (15 mg daily), 71.5% for naproxen (500 mg twice daily), and 71.4% for ibuprofen (800 mg 3 times daily) (Figure 2).⁶ At these same doses, naproxen and ibuprofen demonstrated higher percentages of COX-1 inhibition compared with diclofenac and meloxicam. Mean COX-1 inhibition was 95% for naproxen, 89% for ibuprofen, 53% for meloxicam, and 50% for diclofenac.⁶ A more recent study used similar methodology for determining COX-1 and COX-2 inhibition—ie, whole blood samples for LPS-induced PGE₂ formation as a measure of COX-2 inhibition and serum thromboxane B₂ generation in clotting whole blood for determining COX-1 activity. This study compared the COX inhibition of diclofenac (75 mg twice daily) with celecoxib (200 mg twice daily) and etoricoxib (90 mg daily) and found that, at anti-arthritic doses, diclofenac demonstrated significantly ($P < .001$) greater maximal COX-2 inhibition than etoricoxib and celecoxib.²⁴ Diclofenac and celecoxib demonstrate virtually superimposable dose-response relationships for COX-2 and COX-1, suggesting that they have similar COX selectivity profiles, yet different potencies (Figure 3).^{16,25-27} These data suggest the importance of understanding achieved selectivity when deciding on the appropriate dose.

NSAID Dose, COX-2 Selectivity, and Anti-Hyperalgesic Effects

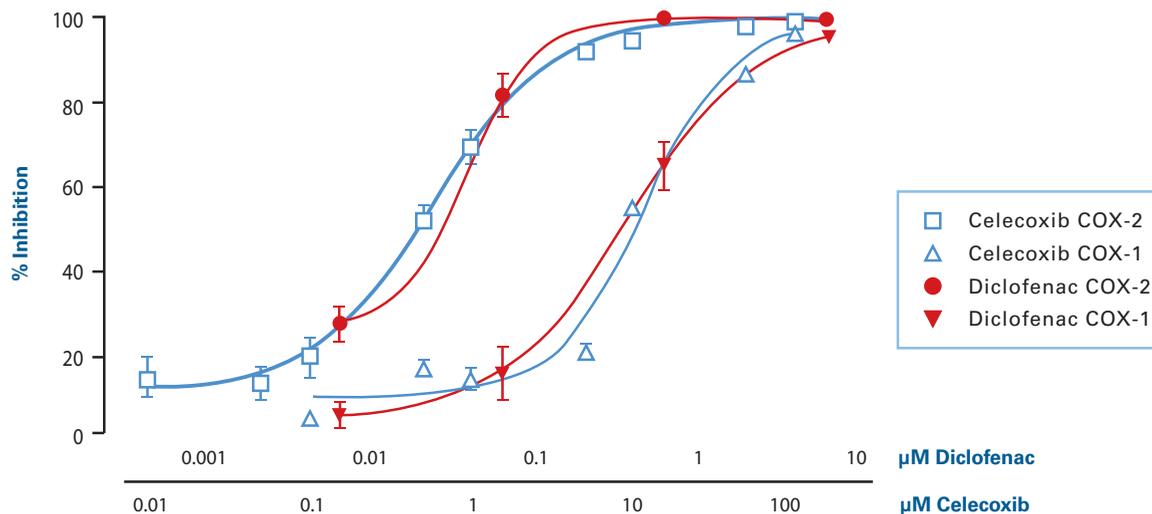
Determining the drug concentration necessary for achieving pain relief is another important consideration

■ **Figure 2.** Comparison of COX-2 Inhibition at Effective Doses of NSAIDs⁶



Mean inhibition of COX-2 for approved doses of frequently prescribed NSAIDs. Adapted from Van Hecken A, et al. *J Clin Pharmacol.* 2000;40:1109-1120.

■ **Figure 3.** COX-2 to COX-1 Inhibition Curves for Diclofenac and Celecoxib^{16,25-27}



Concentration-response curves for inhibition of COX-1 and COX-2 in human whole blood assays by celecoxib and diclofenac in vitro. Diclofenac and celecoxib show the same COX-1/COX-2 biochemical selectivity in vitro (COX-1/COX-2 IC_{50} ratio: 29 and 30, respectively),^{16,26,27} although there is a difference in potency (diclofenac: IC_{50} 0.38 μ M for COX-1 and 0.013 μ M for COX-2; celecoxib: IC_{50} 16 μ M for COX-1 and 0.54 μ M for COX-2), the concentration-response curves of celecoxib and diclofenac are superimposable.

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when selecting the appropriate NSAID, due to their anti-hyperalgesic effects. IC_{80} concentrations of NSAIDs for COX-2 have been found to correlate with analgesia.^{19,28} The ratio of IC_{50} values for COX-1 to COX-2 inhibition for each NSAID provides some indication of the relative inhibitory activity of each NSAID on the COX-1 and COX-2 isoenzymes.^{11,15} The selectivity of diclofenac for COX-2 over COX-1 inhibition in

vitro is lower than that of celecoxib, but diclofenac provides greater COX-2 selectivity than meloxicam, etodolac, ibuprofen, and naproxen.¹¹ Specifically, the concentration of diclofenac necessary to reduce the activity of COX-1 by 50% is 29 times the concentration of diclofenac needed to reduce the activity of COX-2 by 50%; the same ratio for celecoxib is slightly higher at 30.^{11,15} In contrast with the selectivity of celecoxib and

diclofenac, the IC₅₀ selectivity ratio for meloxicam is 18 (Table 1).¹⁵⁻²⁰

The Effect of NSAID Dosing on Adverse Events

The risks of GI and CV AEs are related to the same mechanisms associated with NSAID benefits—namely, inhibition of COX-dependent prostanoids synthesis.¹¹ For example, COX-1 inhibition has been associated with decreased platelet aggregation and GI toxicity.^{6,14,20} Prostaglandin I₂ (PGI₂), a prostanoid with cardioprotective properties, is generated by COX-2 and promotes vasodilation and inhibition of platelet aggregation. The inhibition of PGI₂ is thought to be a plausible mechanism for CV risks associated with the use of NSAIDs, such as myocardial infarction.^{5,11} Available data from observational studies strongly suggest that GI and CV events and renal failure are related to total daily dose in patients treated with NSAIDs.^{8,9,29,30}

COX-2 expression appears to be the dominant source of prostaglandin formation in inflammation, and COX-1 inhibition is associated with adverse GI events; consequently, the development of newer NSAIDs has been focused on COX-2 selective agents in order to limit the effects associated with COX-1 inhibition.¹⁰ However, outcome trials demonstrated that agents with increased COX-2 selectivity were also associated with increased risks of CV events.¹³

Since the original observation of elevated risks for CV events among patients in clinical studies of rofecoxib, CV risks associated with the use of these agents has been the subject of intense interest—including numerous observational studies. Nearly 10 years after the original observation that led to standard labeling describing NSAID dose-associated GI and CV risk, McGettigan et al reported a meta-analysis of observational studies. Their analysis confirmed the possibility of dose-related risks of NSAIDs in aggregate. A subanalysis included dose and relative risk (RR) data from 10 or more studies out of a total of 51 observational studies. The analysis revealed that as the NSAID dose increased, CV risks increased for all NSAIDs evaluated, with the exception of naproxen. The CV risk among patients at higher doses of rofecoxib and diclofenac was double that of patients receiving lower doses of these drug products.⁹ A meta-regression model, based on data extracted from the studies used in the McGettigan analysis and information on total daily diclofenac dose, demonstrated a continuous relationship between diclofenac dose and the risk of adverse

GI and CV effects.²⁹ A recent systematic review and meta-analysis of data from 28 observational studies evaluated the GI risks associated with the use of high versus low to medium doses of individual NSAIDs. Daily use of high-dose NSAIDs (defined as diclofenac >75 mg/day; celecoxib >200 mg/day) was associated with a 2- to 3-fold increase in GI complications compared with the use of low to medium doses, with the exception of celecoxib, for which dose-related effects were not demonstrated.⁸

In addition to GI and CV event risks, renal events are linked to the dose of NSAID used. A case-control study using data from a general practitioner database found that NSAID users had a 3-fold higher risk of developing acute renal failure than nonusers in the general population. Although a clear linear dose-response relationship was not observed, the risk was slightly greater in those who received NSAIDs at a higher dose (RR, 3.4; 95% CI, 1.6-7.0) compared with those receiving low-to-medium doses (RR, 2.5; 95% CI, 1.2-5.4).³⁰

Despite the widely held impression that the risk for developing NSAID-related adverse effects increases with duration of treatment, observational studies have demonstrated that even short-term use of NSAIDs (ie, ≤14 days) can increase the risk of serious AEs and that the risk remains elevated throughout treatment.^{31,32} Based on available data linking NSAID dose to the risk of serious adverse GI, CV, and renal effects, multiple medical societies and regulatory authorities worldwide recommend that NSAIDs be prescribed at the lowest effective dose and for the shortest duration possible.^{2,3,13,33-38} Despite these recommendations, higher-dose regimens of several NSAIDs, including meloxicam, celecoxib, and diclofenac, are more often prescribed than low-dose regimens (Table 2).^{19,25,39,40}

Pharmacokinetic Principles in NSAID Selection

NSAID-associated AEs are also influenced by the pharmacokinetic properties of each NSAID product (Table 2).^{19,25,39,40} The selection of an appropriate NSAID should consider the pharmacokinetic properties of available products. Ideally, the goal of NSAID treatment is to rapidly achieve and maintain a drug concentration in the affected site while minimizing the concentrations elsewhere in the body to potentially limit the risks for AEs.⁴¹ Additionally, NSAIDs with longer half-lives and extended-release formulations have been associated with an increased risk of AEs compared with immediate-release formulations.⁴²

■ **Table 2.** NSAID COX Selectivity, Dose, and Half-life^{19,25,39,40}

NSAID	Preferential Selectivity	Dose	Half-life
Meloxicam	COX 2 ¹⁹	15 mg/day (77% prescribed)	20 hours ⁴⁰
Celecoxib	COX 2 ^{19,25}	>200 mg/ day ⁴⁰ (95% prescribed)	10-12 hours ⁴⁰
Diclofenac (77% is delayed release)	COX 2 ^{19,25}	150 mg/day (80% prescribed)	2 hours ⁴⁰

Pharmacokinetics and Effects on Hyperalgesia

The pharmacokinetic properties of NSAIDs contribute to their efficacy and tolerability in several important ways. These properties include the extent of plasma protein binding; the rate of absorption or time to appearance of therapeutic plasma levels; the distribution of drug in bodily fluids and the drug concentrations at the site of inflammation; and the rate of elimination.⁴ Rapid attainment of therapeutic NSAID plasma concentrations may be a priority in patients with pain because a faster time to peak drug concentration has been correlated with more prompt reduction in measures of pain.⁴³ Examples of NSAIDs with relatively rapid time to maximum concentration include ibuprofen, diclofenac, and etoricoxib. For some agents, the time to maximum concentration may vary substantially depending on the particular drug formulation. For example, diclofenac administered as liquid solutions or immediate-release tablets is associated with a more rapid time to maximum plasma concentration compared with extended-release formulations. Therefore, some patients may prefer NSAIDs administered in solutions or immediate-release tablets such as diclofenac potassium, with a demonstrated more rapid rate of absorption.⁴¹

NSAIDs with certain intrinsic characteristics have been shown to persist in the tissues even after the drug is cleared from the plasma.⁴¹ As illustrated in [Figure 4](#),^{41,44} acidic NSAIDs, especially those that have a short half-life, rapidly become concentrated in the plasma and then diffuse into and out of tissue slowly. This allows for a sustained effect beyond the plasma half-life, a desirable characteristic for duration of analgesia.⁴¹

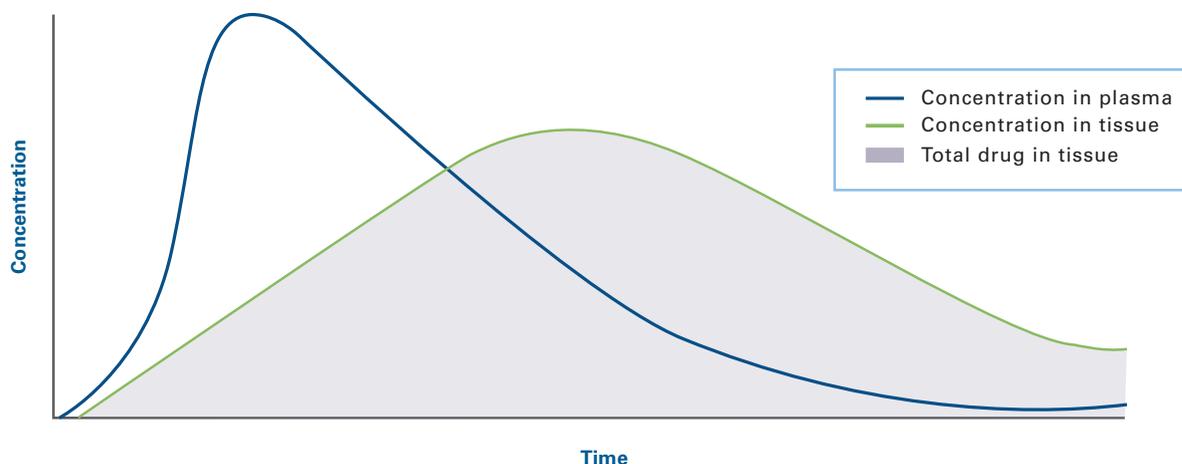
Another important pharmacokinetic property is the elimination half-life ($t_{1/2}$), which is defined as the

amount of time needed for the drug plasma concentration to be reduced by half.⁴⁵ In general, there are advantages and disadvantages to drugs with long or short half-lives, depending on the patient and the condition being treated. Examples of NSAIDs with half-life durations longer than 12 hours include piroxicam, naproxen, and meloxicam; NSAIDs with durations shorter than 12 hours include diclofenac and ibuprofen. Although the benefit of drugs with short half-lives includes a fast onset of action, a potential downside is the short duration of treatment effects. This disadvantage can be overcome, however, as the duration of treatment effect may be extended in some cases by altering the drug formulation.⁴¹ Furthermore, some NSAIDs—such as diclofenac, with a short half-life of 1 to 2 hours⁴¹—nevertheless maintain durable inhibition at the active site of COX enzymes. In cell homogenates and in the presence of purified COX-1 and COX-2 enzymes, *in vitro* studies indicate that diclofenac lodges tightly in the active COX binding site. These *in vitro* studies suggest a durable prolonged half-life of COX-2 inhibition lasting from hours to days.⁴⁶ Conversely, NSAIDs with a longer half-life duration require a longer period of time to reach steady-state concentrations but may maintain effects on hyperalgesia for longer durations.⁴² Although the longer half-life of some COX-2 inhibitors may extend the period of clinical efficacy, persistence of these agents in the bloodstream may also allow less opportunity for recovery of COX-2 activity between dose administrations than shorter-half-life COX-2 inhibitors, reducing the beneficial CV and renovascular effects of COX-2 expression.^{14,47}

Pharmacokinetics and Adverse Events

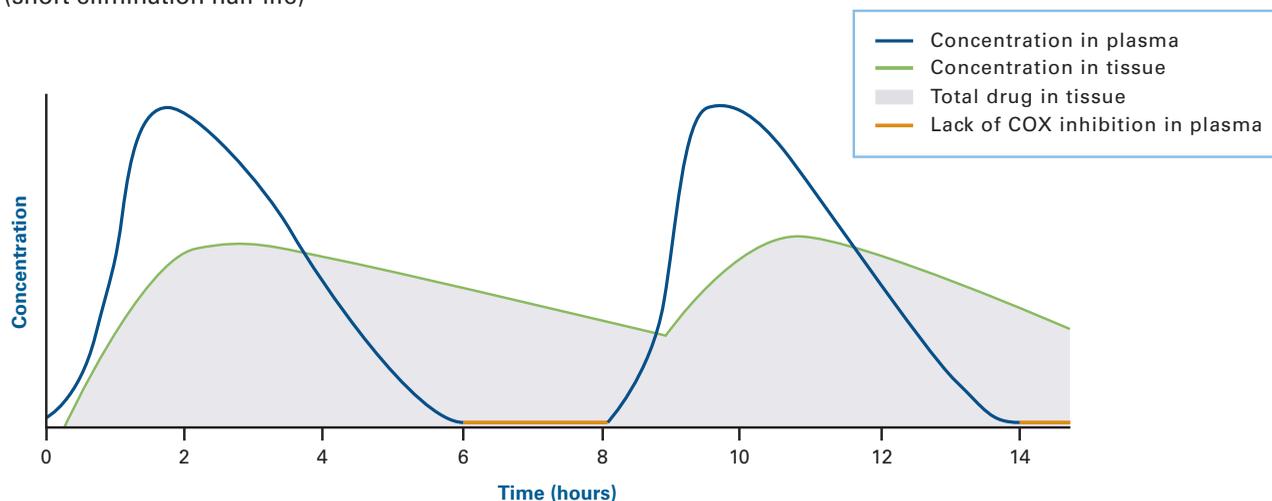
Pharmacokinetic characteristics of NSAIDs influence their safety and tolerability. Longer half-life NSAIDs and sustained-release forms of NSAID drug products, such as diclofenac, are associated with increased gastroerosive effects.⁴² A systematic review of observational studies published between 2000 and 2008, including studies of diclofenac, suggested that long half-life and delayed-release NSAID formulations are associated with a higher risk of GI bleeding and perforation.⁴⁸ A review of estimates of upper GI bleeding/perforation risks for several NSAIDs, according to plasma half-lives reported in 3 observational studies, demonstrated that NSAIDs with half-lives of at least 12 hours were associated with a greater relative risk for developing GI events compared with NSAIDs with half-lives of less

■ **Figure 4.** Initial and Latent Drug Accumulation in the Plasma and Joint Fluid Over Time^{41,44}



Acidic NSAIDs, especially those that have a short half-life, rapidly become concentrated in the plasma and then diffuse into and out of tissue slowly. This allows for a sustained effect beyond the plasma half-life, a desirable characteristic for duration of inhibition of hyperalgesia. Adapted from Brune K, Furst DE. *Rheumatology (Oxford)*. 2007;46(6):911-919.

■ **Figure 5.** Typical Plasma and Tissue Concentration Profile of Acidic NSAIDs Such as Diclofenac and Ibuprofen (short elimination half-life)⁴⁷



Plasma and tissue pharmacokinetics of multiple doses of an NSAID (such as diclofenac or ibuprofen) with a short half-life. As shown, periods between doses may permit recovery of COX enzyme function in the central compartment (ie, blood, vessel walls, and kidneys). Adapted from Brune K. *Curr Med Res Opin*. 2007;12:2985-2995.

than 12 hours.⁴⁸⁻⁵¹ Treatment with the delayed-release formulation of diclofenac was shown to increase the risk of acute myocardial infarction compared with the immediate-release diclofenac drug products.⁵²

It has been proposed that low-dose NSAIDs with short half-lives and dosing intervals of up to 8 hours could permit the recovery of vasoprotective COX-2

dependent prostaglandins.⁴¹ Figure 5⁴⁷ depicts the plasma and tissue pharmacokinetics of multiple doses of an NSAID (such as diclofenac or ibuprofen) with a short half-life. As shown, periods between doses may permit recovery of COX enzyme function in the central compartment (ie, blood, vessel walls, or kidneys).⁴⁷ Increased COX-2 activity may result in vasodilation and

Report

inhibition of platelet aggregation.^{10,14,47} These potential vasoprotective effects with short-half-life NSAIDs may also translate into a lower risk of impaired renal function. An 802-patient study conducted by Stürmer et al estimated creatinine clearance in patients undergoing total joint replacement and determined the influence of medications on the risk of a patient developing impaired renal function, defined as creatinine clearance less than 60 mL/min. Adjusting for patient-specific factors and use of other potentially renal-active drugs, NSAIDs with half-life durations of less than 4 hours did not significantly increase the risk of developing impaired renal function (odds ratio [OR], 1.1; 95% CI, 0.7-1.9); in contrast, NSAIDs with half-life durations of at least 4 hours were found to be significantly associated with impaired renal function (OR, 2.6; 95% CI, 1.2-5.7).⁵³

Conclusion

The ideal NSAID is more selective for COX-2 than COX-1, and achieves levels of COX-2 inhibition required to achieve pain relief while minimizing the potential for CV harm associated with sustained COX-2 inhibition. Selection of an NSAID to meet these requirements should include consideration of the intrinsic physiochemical, pharmacokinetic, pharmacodynamic, and formulation-specific factors that are known to affect the efficacy, tolerability, and safety of these agents. Appropriate NSAID therapy utilizes the lowest effective dose necessary for efficacy while minimizing the risk of serious AEs. Pharmacokinetic characteristics that combine early plasma levels, prolonged therapeutic levels in tissue, and rapid clearance from plasma are desirable. It has been proposed that a short half-life potentially allows for the recovery of COX activity and minimizes the risks for serious GI, CV, and renal effects.

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Authorship information: Analysis and interpretation of data (TSH, CR); drafting of the manuscript (TSH, CR, PPG); critical revision of the manuscript for important intellectual content (TSH, CR, PPG); administrative, technical, or logistic support (CR); and supervision (CR, PPG).

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