

A Practical Approach to Discontinuing NSAID Therapy Prior to a Procedure

The process of stopping NSAIDs should be based on pharmacokinetics, cyclooxygenase selectivity, comorbid renal or hepatic dysfunction, pain level and pain tolerability, overall bleeding risk from specific surgeries or procedures, and overall effect on the patient's well-being during the perioperative timespan.

Maureen Younan

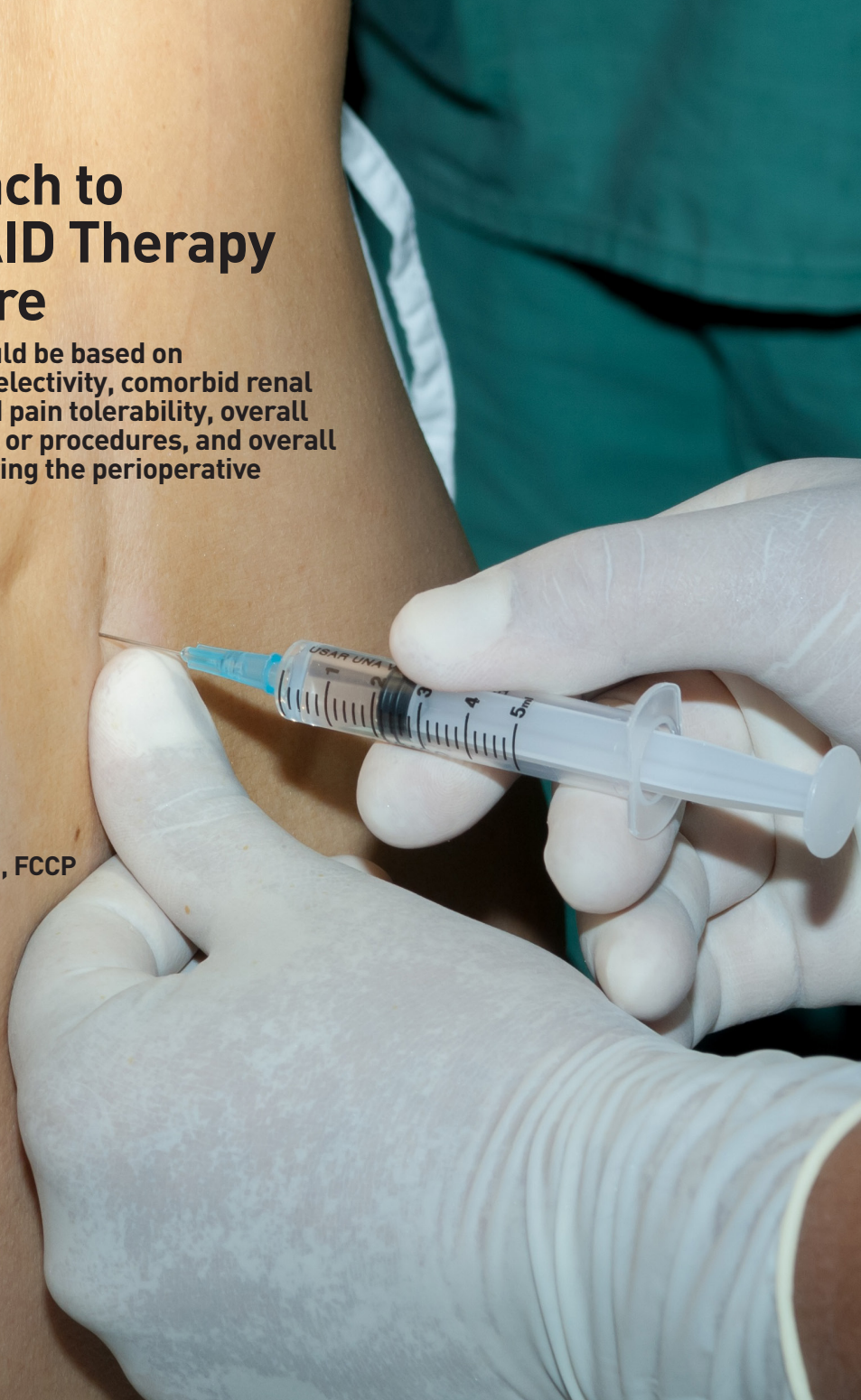
PharmD Candidate 2014
Albany College of Pharmacy & Health Sciences
Albany, New York

Timothy John Atkinson, PharmD

PGY2
Pharmacy Pain & Palliative Care Resident
Stratton VA Medical Center
Albany, New York

Jeffrey Fudin, BS, PharmD, RPh, DAAPM, FCCP

Adjunct Assistant Professor of Pharmacy Practice
University of Connecticut School of Pharmacy
Storrs, Connecticut
Adjunct Associate Professor of Pharmacy Practice
Albany College of Pharmacy & Health Services
Albany, New York



In 2010, there were a total of 51.4 million inpatient procedures performed in the United States.¹ The perioperative management of chronic medications is an important consideration for healthcare providers.² This entails adequately evaluating all vital signs, including pain, and counseling the patient accordingly.^{3,4}

For many candidates undergoing elective surgery or interventional procedures, non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications for a multitude of chronic and acute pain syndromes.

In 2012, for example, 98 million prescriptions for NSAIDs were filled in the United States. In addition, 23 million Americans reported using over-the-counter NSAIDs daily.⁵

A directive to discontinue NSAIDs prior to surgery or interventional procedure is a serious concern often creating significant angst for chronic pain patients who otherwise rely on these medications to preserve daily function, obtain restful sleep, and maintain comfort.⁶ This review will discuss the historical risks related to NSAID use, appropriate timing for stopping NSAIDs, and other practical guidelines.

Recommendations Vary

Increased bleeding risk from NSAID use in the perioperative period is well known. However, clinicians' recommendations regarding appropriate timing for discontinuation of NSAIDs prior to surgery may be outdated and devoid of scientific evidence specific to unique NSAID half-lives and pharmacology. Minimal clinical studies are available in this area, compelling practitioners to base their decisions on clinical experience, which result in inconsistent recommendations to patients.

Fifteen clinicians responded to an informal email survey the authors sent to pain practitioners nationwide to ascertain their policy on NSAID discontinuation prior to surgery or intervention. The respondents represented a variety of medical specialties, including anesthesiology, pain management, neurosurgery, and pharmacy. Not surprisingly, their answers about the best time to discontinue NSAIDs varied between 0 to 10 days prior to procedure date, with 14% recommending 0 days, 14% recommending 3 days, 29% recommending 7 days, and the majority (43%) of responders recommending discontinuation at 5 days.

Why do practitioners routinely recommend discontinuing NSAID use 5 to 10 days prior to a surgical procedure? Perhaps this is erroneously based on the misconception that all NSAIDs affect platelets similarly to aspirin; that all have the same binding affinity to cyclooxygenase (COX)-1; and that all have an identical half-life. However, the authors suspect that the lack of evidence has influenced most clinicians to take a conservative approach, emphasizing patient safety considering the potential for perioperative bleeding if NSAIDs are continued. This policy may lead to pain patients being left without adequate pain control prior to a procedure.

Historical Record

Willow bark has been recognized for centuries for its antipyretic, anti-inflammatory, and analgesic effects.^{7,8} In 1838, it was purified to salicylic acid, the first NSAID. It was heavily used in inflammatory disorders, limited only by its poor gastrointestinal tolerability. In 1858, salicylic acid was buffered with sodium and acetyl chloride, creating acetyl salicylic acid, significantly improving its gastrointestinal tolerability. It was not produced commercially in significant amounts, however, until a more stable form was produced in 1899 by the Bayer Company and marketed as Aspirin.^{7,8} Aspirin quickly became the most popular painkiller worldwide, commonly used for backache, headache, and arthritis.⁸

Mechanisms of Action

Aspirin's acetyl group confers receptor binding properties unique among all NSAIDs because it binds irreversibly to Ser529 in platelets, which ultimately affects COX-1.⁹ Unlike nucleated cells expressed in body tissues, which can recycle and express new COX enzymes, when COX is *irreversibly* bound in platelets it inhibits platelet aggregation and vasoconstriction for their entire life-cycle (7-10 days).⁹ Aspirin's cardioprotective effect and increased bleeding risk are results of this effect and studies have shown it to be achievable with doses as low as 40 mg per day.⁹

Traditional NSAIDs *reversibly* inhibit COX enzyme, but may compete with aspirin for the binding site. For this reason, patients requiring aspirin for prevention of cardiovascular disease should be counseled to take it at least 30 minutes prior to non-aspirin NSAIDs to receive the intended cardioprotective effects.⁹ There are more than 6 distinct chemical classes of NSAIDs with significant differences in pharmacology, pharmacokinetics, and COX selectivity, all of which

contribute to their unique efficacy and safety profile.^{10,11}

Arachidonic acid is hydrolyzed from the phospholipid bilayer of cellular membranes by phospholipases and converted into prostaglandins via cyclooxygenase enzymes.⁹ There are 2 major subtypes of the cyclooxygenase enzyme, COX-1 and COX-2. COX-1 is constitutively expressed in most cells and is responsible for GI mucosa protection, renal homeostasis, and hemodynamic stability.¹²⁻¹⁵ Prostaglandins produced by the COX-1 enzyme are further metabolized into thromboxane A₂ (TXA₂) and prostacyclin I₂ (PGI₂), which are produced in equal amounts to maintain a balance.⁹ In platelets, TXA₂ increases platelet aggregation and vasoconstriction.^{14,16} In tissues and vessels, PGI₂ inhibits platelet aggregation and thrombosis formation.^{9,14}

Unlike COX-1, COX-2 is expressed only in the brain, kidney, colon, and vessels. However, its expression can be induced by cytokines at the site of inflammation.^{12,13,11,17} COX-2 produces PGI₂ and PGE₂, but not TXA₂, and is believed to be the primary mediator of pain and inflammation.¹¹ PGE₂ is the primary prostaglandin produced in the presence of inflammation and has an interesting concentration-dependent effect. At low levels, PGE₂ will favor platelet aggregation and vasoconstriction whereas at high levels, PGE₂ inhibits platelet aggregation and promotes vasodilation.^{9,12,14}

Determining Bleeding Risks

Because COX-1 inhibition directly affects platelet aggregation, the degree of COX-1 inhibition by an NSAID plays an integral part in determining a patient's bleeding risk.^{9,12}

Theoretically, NSAIDs with COX-2 greater than COX-1 inhibition will have an increased analgesic benefit while minimizing bleeding risk. The NSAIDs currently marketed vary in

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$$t_{1/2 \text{ (terminal)}} = \frac{0.632 \times \text{volume of distribution}}{\text{plasma clearance}} \quad \text{VS.} \quad t_{1/2} = \frac{0.693}{k}$$

Figure 1. Comparison of terminal half-life to half-life. Specifically to NSAIDs, these pharmacokinetic terms may be used interchangeably due to the high protein-binding characteristic of NSAIDs. NSAIDs, non-steroidal anti-inflammatory drugs

their degree of COX-1 to COX-2 inhibition and selectivity; and familiarity with these properties can be useful to determine bleeding risk. In fact, since celecoxib (Celebrex) has an 11-hour half-life, it is reasonable to begin therapy at least 55 hours prior to a procedure (5 half-lives) to reach steady state in advance. The final preemptive dose could be given with dinner the evening prior to a scheduled procedure in order to reduce inflammation perioperatively.

COX-2 inhibition should be avoided in patients with known cardiovascular risk. Two of the most potent COX-2 selective inhibitors, rofecoxib (Vioxx) and valdecoxib (Bextra) were removed from the market for their association with an increased risk of serious and potentially fatal cardiovascular thrombotic events.¹⁸ Nonacetylated salicylates, such as salsalate (Disalcid) and choline magnesium trisalicylate (Trilisate), are viable alternatives. Nonacetylated salicylates are prodrugs to salicylic acid; they minimally inhibit COX-1, are thought not to inhibit renal blood flow, and do not adversely affect platelet function.¹⁹⁻²²

Pharmacokinetics

In the absence of prospective randomized trials, the pharmacokinetics of each NSAID is the most reliable guide for discontinuation prior to surgery. In the presence of reversible/competitive binding, pharmacokinetic parameters such as protein binding, steady-state

concentrations, and terminal half-life are useful tools to predict how long the drug remains in the body.²³⁻²⁵ Steady-state concentration occurs when the rate of drug administration equals drug elimination and is achieved after 5 half-lives.^{23,24} Half-life is the amount of time required to decrease an administered dose by 50% in the plasma.^{23,24} Terminal half-life, however, is the amount of time required for plasma concentration to decrease by 50% after steady-state concentration has been established.²⁵ Terminal half-life can be calculated only when the decrease in drug plasma concentration equals that of drug elimination.²⁵ The equation for terminal half-life takes into consideration the drug's volume of distribution (Vd) and clearance from the plasma (Figure 1).²⁵

A drug's Vd is a theoretical quantitative measure of total drug concentration in the plasma and tissue.²⁵ There is an inverse relationship between Vd of a drug and its ability to bind to plasma protein. NSAIDs are greater than 90% plasma protein bound particularly to albumin.^{26,27} The Vd of NSAIDs is minimal because the high percentage of protein binding decreases the amount of available unbound active drug in the serum.^{26,27} It requires about 5 termination half-lives for a drug to be eliminated from the plasma (Table 1).²³

Practically then, it seems most logical for a clinician to use 5 termination half-lives to determine the best

time for NSAID discontinuation prior to surgery or intervention to assure complete elimination from the body. Since NSAIDs are not widely distributed in the plasma due to their ability to strongly bind to albumin, it makes sense that clinicians should base NSAID discontinuation in large part on half-life. Moreover, half-life and terminal half-life could be used interchangeably under these circumstances, with the caveat that it is not practical in patients who have hypoalbuminemia. Calculations based on 5 half-lives of a NSAID are significantly shorter than the generally recommended suggestion of 7 to 10 days. Table 2, page 50, provides the half-lives of available NSAIDs and recommendations for discontinuation prior to surgery, to aid prescribers in making clinical decisions.

Potential Exceptions To Guidelines

Despite the confusion surrounding NSAID discontinuation prior to surgery outlined previously, some professional organizations provide guidance in agreement with a pharmacokinetic approach using 5 half-lives as a standard.²⁸⁻³⁰ However, these guidelines do not explain the reasons for using pharmacokinetic principles to aid in clinical decision-making, or provide a quick resource for easy access to relevant pharmacokinetic parameters. In general, to determine when to discontinue NSAID prior to surgery, we recommend calculations based on 5 half-lives of the NSAID, but there are some potential exceptions and individual patient factors that require consideration.

COX-2 selective inhibitors are not associated with increased bleeding risk in the perioperative setting and these agents may be considered for pain control in patients who are not at an increased risk for a thromboembolic

Table 1. Drug Concentration in the Body as a Function of Increasing Half-Lives

Number of Half-Lives	Percentage of Dose Remaining, %	Percentage of Dose Eliminated, %
0	100	0
1	50	50
2	25	75
3	12.5	87.5
4	6.25	93.75
5	3.125	96.875

event. Data is available that suggest COX-2 selective inhibitors are safe in the perioperative setting.³¹⁻³³ In a study by Noveck et al, parecoxib sodium, an injectable COX-2 specific inhibitor approved only in Europe, was given with heparin and compared with heparin alone. The study demonstrated an analgesic effect with the combination without increasing surgical bleeding risk compared with the control.³⁴

Although not labeled as COX-2 inhibitors, both meloxicam (Mobic) and etodolac (Lodine) are more COX-2 selective than celecoxib.³⁵ Meloxicam's ratio of COX-2/COX-1 inhibition is approximately 80:25, and it has not been found to have significant effects on platelets or increased bleeding risk.³⁵⁻³⁷ Short-term use of traditional NSAIDs may present less risk, as shown recently with intravenous ibuprofen, approved in 2009. IV ibuprofen demonstrated perioperative effectiveness with minimal risk in 3 phase 3 clinical trials.³⁸⁻⁴⁰ Other potentially useful strategies for continued NSAID use perioperatively include temporarily switching a patient to an NSAID with a short half-life for continued anti-inflammatory and analgesic effects closer to their surgery. Non-acetylated NSAIDs, theoretically, may be an additional analgesic option for patients but no randomized or case-controlled studies have been published.¹⁹⁻²²

Individualize Care

To individualize therapy, clinicians must consider a patient's unique medical history, including diseases that may alter pharmacokinetics and increase bleeding risk. Clinicians should examine this information, combined with the inherent bleeding risk associated with each specific type of surgery, before making recommendations about discontinuation (Table 2).

Renal or hepatic dysfunction can affect bleeding risk, which may necessitate NSAID discontinuation because of effects on the pharmacokinetic parameters including protein binding, volume of distribution, and clearance. For example, renal failure and nephrotic syndrome can negatively affect an NSAID's ability to bind to albumin.²⁶ This results in an increased fraction of unbound drug and increased volume of distribution, the latter of which causes increased drug concentrations within tissue. Ultimately, disease states affecting renal function can result in an increased elimination half-life due to the increased amount of time required to completely metabolize and excrete the NSAID. Chronic hepatic insufficiency may also result in either increased or decreased elimination half-life attributable to hypoalbuminemia, the result of which could be decreased tissue uptake or an increase in free drug for excretion.²⁶ Moreover, chronic hepatic

insufficiency may limit the liver's ability to eliminate the NSAID resulting in decreased plasma clearance and increasing the elimination half-life.²⁵

As clinicians, we have a responsibility to provide individualized care to our patients. A patient's dependence on an NSAID for continued pain control and ability to function must be weighed against true NSAID-associated bleeding risk based on the drug's uniqueness, not on conjecture. To appropriately balance the needs of specific patients with risk of bleeding requires an understanding of NSAID pharmacology, pharmacokinetics, and COX selectivity, and most importantly it is a decision that should be scientifically-based. An improved understanding of these parameters justifies the recommendation for discontinuation of an NSAID at 5 half-lives prior to surgery since as outlined here, unlike aspirin, NSAID binding is reversible.

Summary

Discontinuation dates for NSAIDs are frequently based on hearsay or conservative estimates without scientific support or evidence-based guidelines. Until such time that data are available prospectively, these decisions should be based on what we do know. Therefore, clinicians should consider discontinuing NSAIDs based on pharmacokinetics, COX selectivity, co-morbid renal or

Table 2. NSAID Discontinuation Recommendations Based on Half-Lives of NSAIDs in Normal Subjects

Drug (Brand)	t _{1/2} , h	5t _{1/2} , h	Discontinuation, d
Salicylic Acids and Esters			
Choline Magnesium Trisalicylate (Generic)	9-17	45-85	4
Diflunisal (Generic)	8-12	40-60	3
Phenylacetic Acids			
Diclofenac (Cambia, Cataflam, Flector, Pennsaid, Solaraze, Voltaren, Zipsor, Zorvolex, generic)	2.3	11.5	1
Carbocyclic and Heterocyclic Acids			
Etodolac (Lodine, generic) ^a	7.3 ±/ 4	36.5 +/- 20	3
Indomethacin (Indocin, generic)	4.5	22.5	1
Ketorolac (Sprix, generic)	≈ 5.3	26.5	2
Sulindac (Clinoril, generic)	16-18	80-90	4
Tolmetin (Tolectin, generic)	2-6	10-30	3
Propionic Acids			
Fenoprofen (Nalfon, generic)	2-3	10-15	1
Flurbiprofen (Ansaid, generic)	7.5	37.5	2
Ibuprofen (Advil, Motrin, generic)	1.8-2.0	9-10	1
Ketoprofen (Generic)	1.6-4	8-20	1
Naproxen (Aleve, Anaprox, Naprosyn, generic)	12-17	60-85	4
Meclofenamate (Generic)	3-4	15-20	1
Enoloic Acids			
Nabumetone (Generic)	26	130	6
Meloxicam (Mobic, generic) ^a	15-20	75-100	5
Piroxicam (Feldene, Therafeldamine, generic)	50	250	11
COX-2 Inhibitors			
Celecoxib (Celebrex) ^a	11	55	3

COX, cyclooxygenase, NSAIDs, non-steroidal anti-inflammatory drugs

^a COX-2 selectivity: etodolac>meloxicam>celecoxib. If the clinician chooses to discontinue these medications due to presumed perioperative risk, the recommended times are listed. However, in the absence of significant bleeding risk, such as during CABG surgery or with thromboembolic disease, these medications could theoretically be continued safely to provide preemptive and perioperative analgesia.

hepatic dysfunction, pain level and tolerability, overall bleed risk associated with specific surgeries or procedure types, and overall impact to the patient’s well-being during the perioperative timespan.

Authors’ Bios: *Maureen Younan, PharmD Candidate, is a pharmacy intern at the Albany College of Pharmacy & Health Sciences.*

Timothy John Atkinson, PharmD, is

a PGY2, Pharmacy Pain & Palliative Care Resident at the Stratton VA Medical Center in Albany, New York.

Jeffrey Fudin, BS, PharmD, RPh, DAAPM, FCCP, is an Adjunct Assistant Professor of Pharmacy Practice, University of Connecticut School of Pharmacy in Storrs, Connecticut. Dr. Fudin also is Adjunct Associate Professor of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, in Albany, New

York, and a Clinical Pharmacy Specialist in Pain Management at the Samuel Stratton VA Medical Center, in Albany.

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