The Role of Dose Reduction With NSAID Use

Michele L. Matthews, PharmD, CPE, BCACP

Abstract

Effective pain relief with use of nonsteroidal anti-inflammatory drugs (NSAIDs) may come at the cost of an increased risk for serious cardiovascular (CV), gastrointestinal (GI), and renal complications. Research has shown that these adverse events are more likely to occur with higher NSAID dosing and in individuals with a preexisting risk for CV and GI complications. To minimize the potential risk for an adverse event, numerous regulatory bodies and medical societies recommend using the lowest effective NSAID dose for the shortest time necessary. One potential strategy is to offer patients lower doses of standard NSAID formulations. However, efforts to modify physician prescribing behavior may be challenging because of concerns regarding the potential for suboptimal pain management. Another strategy has emerged through use of new technology that produces submicron NSAID formulations. This new technology is also an approach that could provide effective pain relief at low doses. This article reviews the role of dose and duration in the risk for NSAID-associated adverse events, and discusses the potential benefits associated with new low-dose submicron NSAID formulations.

Am J Manag Care. 2013;19(14 suppl):S273-S277

Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a highly effective form of treatment used to manage a number of painful and inflammatory conditions. Serious adverse effects that result from use of NSAIDs most commonly affect the gastrointestinal (GI) tract, the cardiovascular (CV) system, and the kidneys.[1-3] Evidence suggests that there is a strong correlation between the relative risk (RR) for these serious events and the dose and duration of NSAID therapy.

GI Events

Several studies have found an association between NSAID use and the risk for serious GI-related adverse events. For example, a meta-analysis of 28 case-control studies published between 1980 and 2011 calculated the pooled RRs for upper GI complications associated with NSAID use for 8 different prescription NSAIDs. Data from these studies showed that the RR of upper GI complications was approximately 2- to 3-fold greater with use of high daily doses versus low or medium daily doses (**Figure 1**).[1]

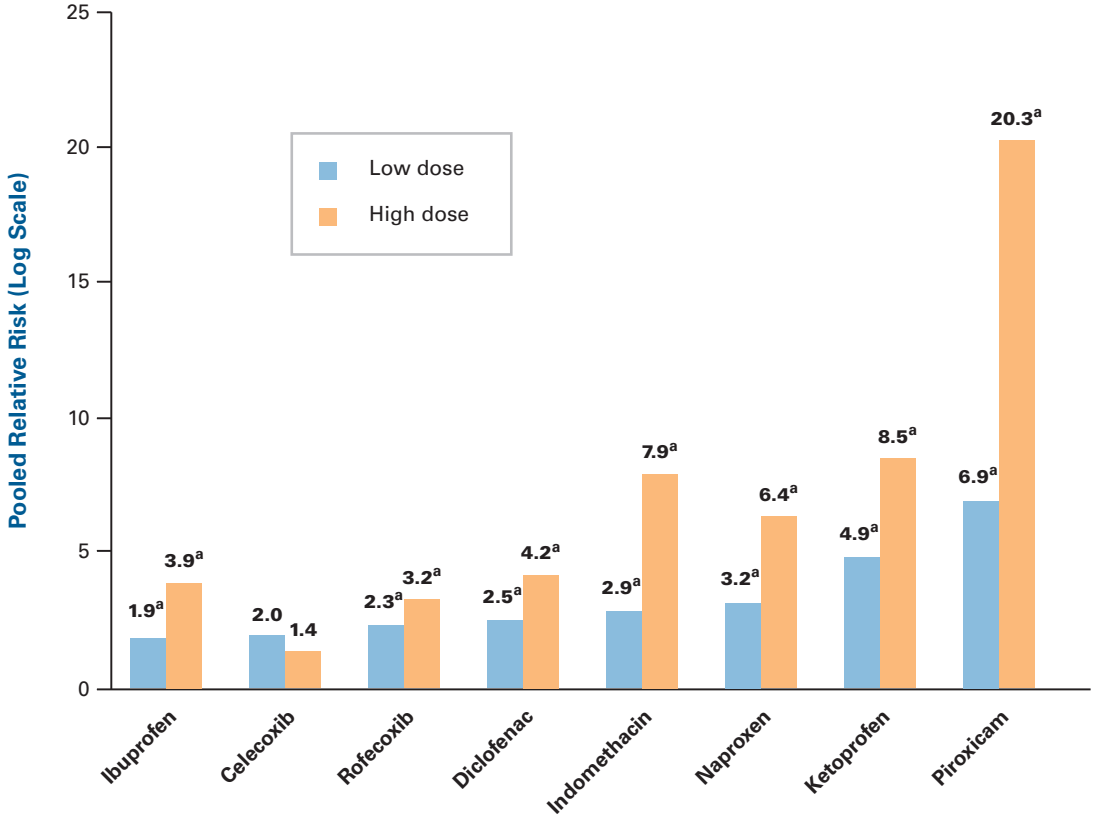
A strong dose-dependent risk was also observed in a separate meta-analysis of individual patient data from 3 case-control studies utilizing conventional dose ranges. The increase in risk for upper GI bleeding was 4- to 8-fold higher for high- versus low-dose indomethacin, naproxen, and diclofenac. This study also found that the RR was highest among short-term users, who had taken an NSAID 1 week previous to the bleed, but had not taken an NSAID 2 to 4 weeks prior.[4]

CV Events

The CV risks associated with NSAIDs also increase with dose, as shown in a large case-control study of more than 58,000 individuals in Denmark. Researchers examined the dose-related risk of death or reinfarction with NSAID use among patients who experienced a first-time myocardial infarction (MI). The most frequently used cyclooxygenase-2 (COX-2) inhibitors were rofecoxib and celecoxib. For traditional NSAIDs, ibuprofen and diclofenac were most frequently used. Researchers identified NSAID dose-related increases in the risk of death following hospital discharge for all 4 of these medications. Overall, the elevated risk of death was greatest with rofecoxib use. A daily dose of less than 25 mg of rofecoxib was associated with a hazard

For author information and disclosures, see end of text.

Figure 1. Pooled Relative Risk of Upper GI Complications With Low Versus High Daily Doses of Individual NSAIDs[1]



GI indicates gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.
[a]$P \leq .05$ compared with nonuse.
Adapted from Castellsague J, Riera-Guardia N, Calingaert B, et al. *Drug Saf*. 2012;35(12):1127-1146.

ratio (HR) of 2.49 (95% CI, 2.11-2.94; P <.0001). By comparison, a higher daily dose of 25 mg or more was associated with a 2-fold greater risk of death (HR, 5.26; 95% CI, 3.90-7.09; P <.0001).[2]

A recent meta-analysis of data from 30 case-control studies that included 184,946 CV events and 21 cohort studies with more than 2.7 million exposed individuals also showed a dose-dependent risk for CV events among NSAID users. Significant increases in the RR of CV events were observed between low and high doses of rofecoxib, diclofenac, and ibuprofen (**Figure 2**).[5]

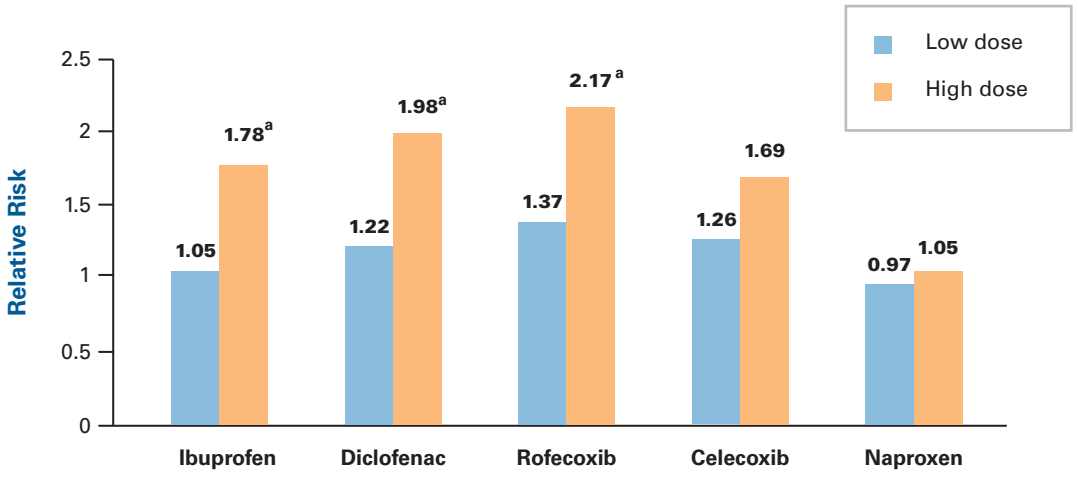
A separate retrospective, case-control study of 716,395 individuals aged 50 to 85 years found an increased RR of MI of 1.35 for NSAID users compared with nonusers. This study also found that duration of treatment played a role in the CV risks associated with NSAID therapy. Users who stopped treatment between 3 months and 1 year in advance had a risk level similar to that of nonusers (RR, 1.02). When duration of NSAID treatment increased from 1 month to 3 or more years, the RR of MI increased from 1.13 to 1.53.[6]

Acute Renal Failure

Several studies have reported a dosage effect for NSAID use and nephrotoxicity.[7] A nested case-control study of 386,916 individuals aged 50 to 84 years in the general population in the United Kingdom examined several factors to determine the RR for renal failure associated with NSAID use. Data showed that dose; duration of use; and previous history of hypertension, heart failure, and diabetes were among the factors associated with an elevated risk for renal failure. The study found a dose-dependent effect regardless of the type of NSAID used. When compared with nonusers of NSAIDs, the RR of renal failure among individuals using NSAIDs was 2.51 with low/medium daily doses and 3.38 with high daily doses.[3]

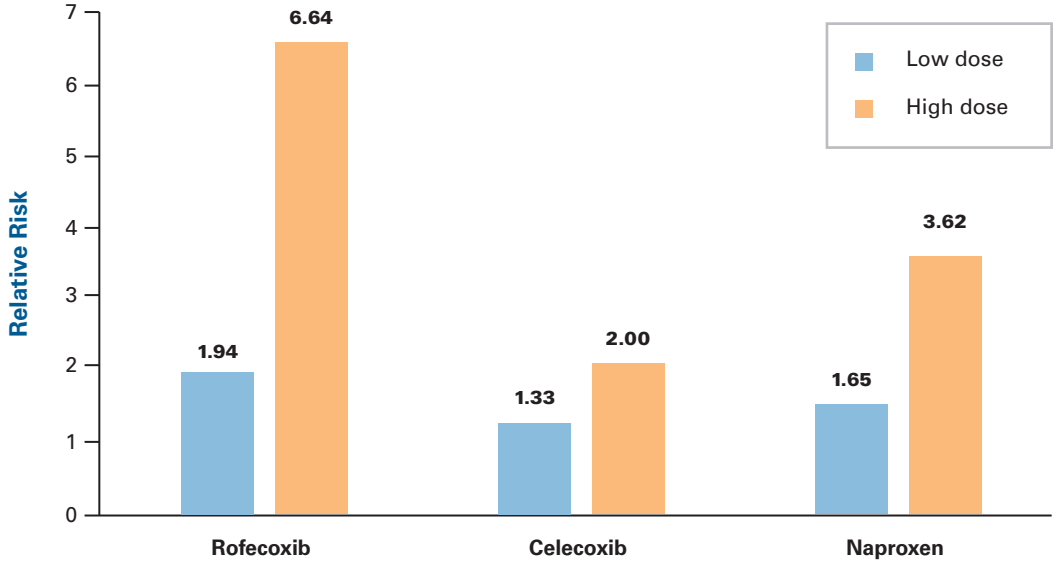
A separate study examined the association between NSAID use and hospitalization for acute renal failure among 4228 new NSAID users and 84,540 matched control subjects older than 65 years in Quebec. The adjusted RR of acute renal failure for rofecoxib was 6.64 for daily doses greater than 25 mg and 1.94 for daily doses less than 25 mg. A dose-depen-

Figure 2. Pooled-Adjusted Relative Risk of Cardiovascular Events With Low-Medium Dose NSAIDs Versus High-Dose NSAIDs, Compared With Nonuse[5]



GI indicates gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.
[a]$P \leq .05$ for dose effect.

Figure 3. Relative Risk of Acute Renal Failure for High- and Low-Dose NSAID Use[8,a]



NSAID indicates nonsteroidal anti-inflammatory drug.
[a]Adjusted for several covariates including age, sex, comorbidities, current use of aspirin, and healthcare utilization.

dent trend for increased risk was also seen with celecoxib and naproxen (Figure 3).[8]

Recommendations From Regulatory Bodies and Medical Societies

Following recognition of the potentially serious adverse CV and GI events associated with nonselective NSAIDs, numerous regulatory bodies and medical organizations from around the world issued guidance on appropriate use of these agents for symptom control. The US Food and Drug Administration (FDA) issued an advisory in 2005 warning of the risks associated with NSAID use. The FDA recommended using "the lowest effective dose for the shortest duration consistent with individual patient treatment goals."[9] A few months later, the European Medicines Agency issued a press release recommending that patients "take the lowest effective dose of non-selective NSAIDs for the shortest time necessary to control symptoms."[10]

Table. Recommendations From Regulatory Bodies and Medical Societies on Minimizing the Risk of NSAID-Associated Adverse Events[9-17]

Organization	Recommendation
Regulatory Bodies	
US Food and Drug Administration	Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals
European Medicines Agency	All patients should take the lowest effective dose of nonselective NSAIDs for the shortest time necessary to control symptoms
Health Canada	To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration
UK National Institute for Health and Clinical Excellence	Oral NSAIDs/COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time
Medical Societies	
American Gastroenterological Association	Risks may be decreased through attention to risk factors and use of co-therapy. Risk can be reduced through the use of the lowest effective dose for the shortest duration of time
American College of Rheumatology	If a patient and provider agree to utilize an NSAID, then the lowest effective dose should be considered first line. Low doses of NSAIDs are safer than high doses
American Heart Association	For patients with a prior history of or at high risk for cardiovascular disease, use of COX-2 inhibitors for pain relief should be limited to patients for whom there are no appropriate alternatives, and then, only in the lowest dose and for the shortest duration necessary
American Geriatric Society	Dosing for most patients requires initiation with low doses followed by careful upward titration, including frequent reassessment for dosage adjustments and optimum pain relief and for adverse effects
Osteoarthritis Research Society International	NSAIDs should be used at the lowest effective dose, but their long-term use should be avoided if possible

COX-2 indicates cyclooxygenase-2; NSAID, non-steroidal anti-inflammatory drug.

Other regulatory bodies issued similar recommendations,[11,12] as did several medical organizations, including the American College of Rheumatology and the American Gastroenterological Association.[13,14] A consistent message from all of these organizations is that NSAIDs are effective in treating pain, but should be used at the lowest effective dose for the shortest time necessary. The Table provides a summary of these recommendations.[9-17]

Strategies for Dose Reduction

Until recently, the only option for lower-dose oral NSAID use was for physicians to offer a lower dose of an existing standard NSAID formulation. However, this approach could lead to suboptimal pain management.[7]

One novel approach to improving safety through lower dosing involves the use of a new technology. This technology relies on a manufacturing process that can produce drug particles that are approximately 10 times smaller than conventional drug particles.[18] The decreased particle size increases the total surface area of the particle, which allows for faster dissolution of the drug.[19]

Conclusion

Although NSAIDs are associated with serious GI, CV, and renal adverse events, these side effects tend to occur most often at high NSAID doses. Physicians should also be mindful that the increased risks are present even with short-term therapy. Utilizing low NSAID doses for the shortest duration necessary to control symptoms, in accordance with regulatory and medical society recommendations, may lead to better outcomes by mitigating the risk for potentially serious side effects. For patients at risk of developing NSAID-associated side effects, additional risk reduction may be obtained by selecting an NSAID with a minimal GI or vascular risk profile. Use of new NSAID formulations is also an approach that could provide effective pain relief at low doses.

Author affiliations: Department of Pharmacy Practice, School of Pharmacy, Boston, MCPHS University, Boston, MA; Brigham and Women's Hospital, Pain Management Center, Chestnut Hill, MA.

Funding source: This supplement was sponsored by Iroko Pharmaceuticals, LLC.

Author disclosure: Dr Matthews has no relevant financial relationships with commercial interests to disclose.

Authorship information: Concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

Address correspondence to: E-mail: Michele.Matthews@mcphs.edu.

REFERENCES

1. Castellsague J, Riera-Guardia N, Calingaert B, et al; for Safety of Non-Steroidal Anti-Inflammatory Drugs (SOS) Project. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). *Drug Saf*. 2012;35(12):1127-1146.

2. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation*. 2006;113(25):2906-2913.

3. Huerta C, Castellsague J, Varas-Lorenzo C, García Rodríguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *Am J Kidney Dis*. 2005;45(3):531-539.

4. Lewis SC, Langman MJ, Laporte JR, et al. Dose-response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. *Br J Clin Pharmacol*. 2002;54(3):320-326.

5. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med*. 2011;8(9):e1001098.

6. García Rodríguez LA, 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*. 2008;52(20):1628-1636.

7. McCarberg B, Gibofsky A. Need to develop new nonsteroidal anti-inflammatory drug formulations. *Clin Ther*. 2012;34(9):1954-1963.

8. Schneider V, Lévesque LE, Zhang B, Hutchinson T, Brophy JM. Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: a population-based, nested case-control analysis. *Am J Epidemiol*. 2006;164(9):881-889.

9. Public health advisory - FDA announces important changes and additional warnings for COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). US Food and Drug Administration website. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm150314.htm. Published April 7, 2005. Accessed September 16, 2013.

10. Press release on the cardiovascular safety of non-selective NSAIDs. European Medicines Agency website. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000201.jsp&mid=WC0b01ac058004d5c1. Published August 2, 2005. Accessed September 16, 2013.

11. Basic product monograph information for nonsteroidal anti-inflammatory drugs (NSAIDs). Health Canada website. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/nsaid-ains/nsaids_ains-eng.php. Published November 23, 2006. Accessed September 16, 2013.

12. National Collaborating Centre for Chronic Conditions. Osteoarthritis: national clinical guideline for care and management in adults. London: Royal College of Physicians;2008.

13. Wilcox CM, Allison J, Benzuly K, et al. Consensus development conference on the use of nonsteroidal anti-inflammatory agents, including cyclooxygenase-2 enzyme inhibitors and aspirin. *Clin Gastroenterol Hepatol*. 2006;4(9):1082-1089.

14. Desai SP, Solomon DH, Abramson SB, et al. Recommendations for use of selective and nonselective nonsteroidal antiinflammatory drugs: an American College of Rheumatology white paper. *Arthritis Rheum*. 2008;59(8):1058-1073.

15. Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation*. 2007;115(12):1634-1642.

16. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons; Ferrell B, Argoff CE, Epplin J, et al. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57(8):1331-1346.

17. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*. 2008;16(2):137-162.

18. SoluMatrix. iCeutica web site. http://iceutica.com/solumatrix. Accessed October 2, 2013.

19. Manvelian G, Daniels S, Gibofsky A. A phase 2 study evaluating the efficacy and safety of a novel, proprietary, nano-formulated, lower dose oral diclofenac. *Pain Med*. 2012;13(11):1491-1498.