BEST PRACTICES IN: NSAIDs for Analgesia of Acute Pain

Use of OTC Medication for Acute Pain Pain is extremely common in the general population,[1] as is the use of over-the-counter (OTC) analgesics.[2] In the United States, OTC analgesics containing nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used.[2] Individuals take these medications on their own or on the recommendation of a health care provider for pain relief. The OTC formulations of the most commonly used NSAID, ibuprofen, are available in 200-mg tablets, labeled for a maximum dosage of 1,200 mg/day (400 mg three times daily).

Rationale for Ibuprofen Use in Acute Pain It has long been known and accepted that acute pain, tissue injury, and inflammation are associated with an increase in the expression of cyclooxygenase (COX), and that COX is the enzyme responsible for converting arachidonic acid to the inflammatory mediators, prostaglandins.[3]

Two isoforms of COX have been identified: COX-1 and COX-2. COX-1, or prostaglandin H1 synthase, is present in most human tissues and has a number of regulatory functions in normal cells, including the maintenance of the gastrointestinal (GI) mucosal integrity.[4] COX-2, or prostaglandin H2 synthase, is found principally in the kidneys and central nervous system[4] and, as demonstrated in animal studies, its expression also is increased in peripheral tissues in response to tissue injury and inflammation.[5]

It has been known for some time that prostaglandins (the biosynthesis of which depends on COX expression, as noted) act at both peripheral neurons and centrally (at specific sites in the spinal cord and brain) to evoke pain.[6]

In a review of randomized controlled trials of oral analgesics for acute pain, Sachs[7] notes that there is consistent and good-quality, patient-oriented evidence that NSAIDs provide analgesia comparable to what can be obtained with the usual starting doses of opiate drugs. Sachs also notes that, based on evidence from several randomized, controlled trials, ibuprofen, in doses of 400 mg (two 200-mg tablets of ibuprofen, as available in the US), should be considered the first-line NSAID for reasons of safety, efficacy, and cost.[7]

NSAID Side Effects Ibuprofen is one of the group of NSAIDs that inhibit COX nonselectively—that is, they inhibit both COX-1 and COX-2—allowing these drugs to achieve anti-inflammatory, analgesic, and antipyretic activity.[8] The inhibition of COX-2 is the primary mechanism by which the nonselective NSAIDs provide analgesia[8]; the simultaneous inhibition of COX-1 is the primary mechanism responsible for the GI side effects associated with NSAID use.[8]

The most common and possibly serious side effects of NSAIDs include GI damage. The risk for GI side effects with nonselective ("conventional") NSAID use is related both to dosage and duration of use. Although GI erosions may occur with acute or chronic use of NSAIDs, the risk of serious GI events—for example, perforated ulcers, obstructions, and bleeding—is greater with chronic, prescription-dose use.[3] Epidemiologic data indicate that among the nonselective NSAIDs, ibuprofen has one of the most favorable GI safety profiles, with a lower relative risk for serious GI events than several other NSAIDs.[9] Furthermore, at lower doses, the GI safety profile of ibuprofen is further improved.[10]

Other possible organ system complications that are associated with chronic, high-dose use of conventional NSAIDs include cardiovascular events (eg, worsening of hypertension, myocardial infarction, stroke, and cardiovascular-related death)[11,12] and nephrotoxicity (eg, fluid retention).[12]

More Attention to Dosage Recommendations Will Reduce Side Effects Risk Clinicians should be aware that some patients do not always follow the label recommendations for dosage on OTC NSAIDS, and, similarly, many users of these drugs are not aware of or are not concerned about the risks of adverse effects that are enumerated and cautioned about on the packaging. A 2003 National Consumers League (NCL) study on OTC pain relievers,[13] conducted by Harris Interactive, showed that of the 4,263 adults surveyed, only 16% said they read everything on the label the first time they take an OTC, and, perhaps even more worrisome, 12% say they never read labels at all. This may lead to serious side effects. For example, an estimated 2% to 4% of individuals who take 2,400 mg/day of ibuprofen (ie, double the maximum daily OTC dose) will develop symptomatic ulcers.[14]

Lee S. Simon, MD
Principal
SDG, LLC.
Cambridge, Mass.

The NCL study also showed that 44% of the survey respondents admitted that they had taken more than the recommended dosage of OTC NSAID products. In fact, those who take NSAIDs more often also tend to take higher-than-recommended dosages.[13] Figure 1, right, summarizes the results of the survey; it indicates how the survey respondents took more medication than recommended and why they did so.

Wilcox and colleagues[15] published a paper in 2005 that discussed the results of the NCL survey along with those from a previous survey conducted by the Roper organization in 1997. Together, the respondents of the two surveys totaled 9,062. In the Roper study, 807 (17%) of 4,799 survey respondents said they used NSAIDs; when the NCL survey was conducted, 3,557 (83%) of the 4,263 individuals who participated used NSAIDs. Wilcox and his colleagues note that ibuprofen-based products were the most frequently used NSAIDs in both surveys (57% Roper, 33% NCL).

Although, as the authors of the Wilcox paper note, the results of the surveys cannot be compared directly because of the relatively small sample size in the Roper study and the fact that the questions were not the same in both surveys, the data are revealing nevertheless. These authors observed that, startlingly, about half of the NSAID users in the two surveys combined admitted that they either did not know or were not concerned about the possible side effects from using these OTC medications.

These studies demonstrate the importance of counseling patients who take OTC NSAIDs for acute pain about the appropriate use of these medications, including dosage and duration, as well as the potential for toxicity. Patients should understand that any OTC medication should be taken as directed on the label unless they are advised by their clinician to use the medication differently.

OTC Ibuprofen Dosage Recommendations For acute pain (such as headache, dysmenorrhea, or mild or moderate musculoskeletal pain not related to disease), a total daily dosage of 1,200 mg of ibuprofen divided into three 400-mg doses provides satisfactory analgesia in most cases. The product label states that this dosage, as an OTC product, should not be used continuously for longer than 10 days unless directed by or under the supervision of a health care provider.

A number of studies have shown that NSAIDs, including ibuprofen, can be as effective for acute pain as are opiate analgesics given in the usual dosages.[7] However, while higher dosages of opiates do result in increased analgesia, this is not the case with NSAIDs. For ibuprofen, specifically, as a study by Laska demonstrated,[16] **no appreciable degree of additional acute analgesic benefit is seen beyond the 400-mg single-dose recommendation** (**Figure 2**). What is seen at higher doses, however—as Sachs has shown from a review of the literature—is an increased risk for toxicity, including potentially serious GI side effects, hepatotoxicity, and nephrotoxicity, and an increased cardiovascular risk.[7]

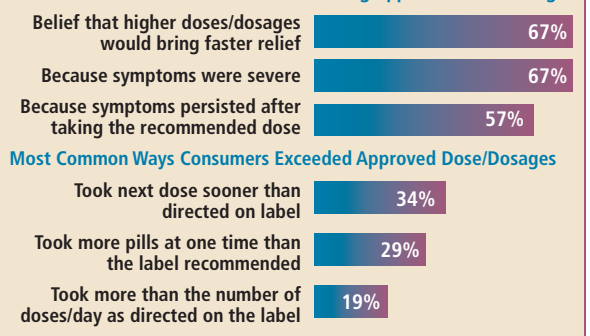
Conclusion NSAIDs such as ibuprofen have been shown to provide analgesia for acute pain, comparable to what can be obtained with the usual starting doses of oral opiate analgesics. Several randomized, controlled trials have supported the recommendation that ibuprofen should be considered as the first-line NSAID for reasons of safety, efficacy, and cost.[7]

Ibuprofen is the most frequently used OTC NSAID and is most effective for acute pain during the first 24 to 48 hours.[7] Patients should be urged to use this agent according to the package labeling—that is, a maximum dosage of 1,200/day (400 mg tid) for up to 10 days.

There is a perception among some consumers that the availability of OTC NSAIDs signifies that there are no risks for side effects with the use of these agents.[13,15] This attitude is reflected in a consumer survey that explored the ways in which individuals exceed recommended dosages of NSAIDs, as well as their reasons for doing so.[13,15] Thus, clinicians should consider routinely addressing the appropriate and correct use of NSAIDs whenever a patient's medications are reviewed.

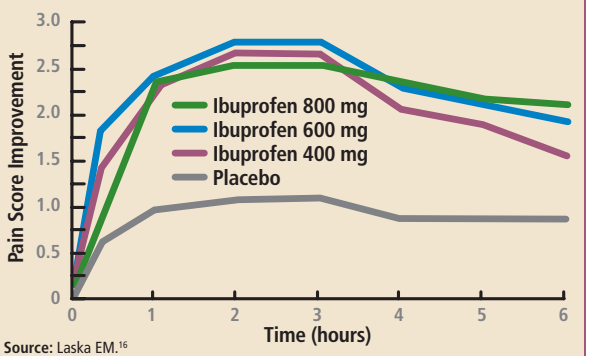
Consumers who take an OTC NSAID for acute pain—such as that associated with dental procedures (root canal therapy, tooth extractions), musculoskeletal pain, dysmenorrhea, and tension headaches—will likely achieve a good level of analgesia.

Figure 1. Consumer Misuse of OTC Analgesics*



Source: Adapted from National Consumers League survey.[13]
*A total of 4,263 consumers were surveyed; data shown above are based on responses from 3,557 of consumers who reported using OTC nonsteroidal anti-inflammatory drugs.
Note that some respondents gave more than one reason.

Figure 2. Pain Improvement With Ibuprofen at 400-, 600-, and 800-mg Doses



Source: Laska EM.[16]
In a study by Laska, improvements in pain scores reached a maximum at ibuprofen doses of 400 mg. Doses of 600 and 800 mg did not demonstrate a dose-related advantage.

References

1. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. *Lancet*. 1999; 354:1248-1252.
2. Top 200 brand drugs by retail sales in 2006. Available at http://www.drug topics.com/drugtopics/article/articleDetail.jsp?id=423632&refresh= 1196636701429. Accessed December 2, 2007.
3. Simon LS. *Gastroenterol Clin North Am*. 2001;30:1011-1025.
4. Scheiman JM. *Gastroenterol Clin North Am*. 1996;25:279-298.
5. Seibert K, Zhang Y, Leahy K, et al. *Proc Natl Acad Sci SA*. 1994;91:12013-12017.
6. Malmberg A, Yaksh T. *Science*. 1992;257:1276-1279.
7. Sachs CJ. *Am Fam Physician*. 2005;71:913-918.
8. Crofford LJ, Lipsky PE, Brooks P, et al. *Arthritis Rheum*. 2000;43:4-13.
9. Henry D, Mc Gettigan P. *Int J Clin Practice*. 2003;135:43-49.
10. Henry D, Lim L L-Y, Garcia Rodrigues LA, et al. *Br Med J*. 1996;312:1563-1566.
11. Moskowitz RW. *Osteoarthritis Cartilage*. 2007;15:849-856.
12. Munir MA, Enany N, Zhang J-M. *Anesthesiol Clin*. 2007;25:761-774.
13. National Consumers League 2003 Over-the-Counter Pain Medication Study. Available at: http://www.nclnet.org/otcpain/harrisesummary.htm. Accessed October 16, 2008.
14. Motrin (ibuprofen). New York, NY; Pharmacia & Upjohn, Division of Pfizer; January 2006.
15. Wilcox CM, Cryer B, Triadafilopoulos G. *J Rheumatol*. 2005;32:2218-2224.
16. Laska EM. *Clin Pharmacol Ther*. 1986; 40:1-7.

This supplement was produced by the customized publication department of Elsevier/International Medical News Group (IMNG). Neither the editor of Internal Medicine News, the Editorial Advisory Board, nor the reporting staff contributed to its content. The opinions expressed in this supplement are those of the faculty and do not necessarily reflect the views of the supporter or of the Publisher.

Editorial support provided by Joanne Still and Elsevier/IMNG.
Faculty Disclosure: **Dr Simon** previously served as the Division Director of the Arthritis, Analgesic & Ophthalmologic Drug Product Division at the US Food and Drug Administration Center for Drug Evaluation and Research. He is a Principal in SDG, LLC., a consulting company.