Safety Profiles of Leading Nonsteroidal Anti-inflammatory Drugs

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Recently introduced nonsteroidal anti-inflammatory drugs (NSAIDs) have capitalized on new formulations or unique physical and pharmacologic properties in an attempt to provide a greater margin of gastrointestinal (GI) safety. The use of enteric coatings and nonoral or pro-drug formulations have not necessarily provided the expected safety, but other properties have been identified that appear to be more promising. However, as demonstrated by oxaprozin, considered to be one of the least safe NSAIDs but one of the leading drugs on the US market, success may not be dependent on safety. In contrast, the improved tolerability of 2 other new NSAIDs, nabumetone and etodolac, has been established in clinical trials and limited postmarketing surveillance. This improved tolerability is probably associated with several pharmacologic properties that have been suggested to contribute to GI safety: (1) nonacidic pro-drug formulation; (2) lack of enterohepatic recirculation; (3) a short plasma half-life; and (4) preferential inhibition of cyclo-oxygenase-2 (COX-2). Although these factors may not improve efficacy, their incorporation into the design of drugs suggests that safer NSAIDs may be a clinical reality. However, the safety and clinical value of any new drug for the general population will be validated only through extensive postmarketing surveillance. *Am J Med.* 1998;105(5A): 39S–43S. © 1998 by Excerpta Medica, Inc.

Clinicians have long been aware of the link between nonsteroidal anti-inflammatory drug (NSAID) use and gastropathy. They have also known that not all NSAIDs are "created equal" when it comes to safety; some NSAIDs present a significantly higher risk of upper gastrointestinal (GI) toxicity than do others.[1–4] Over the past decade, clinicians have seen the development of a plethora of new NSAIDs trying to find a specific niche in the $2 billion anti-inflammatory drug market. Despite the promises of improved efficacy and better tolerability, clinicians remain at odds as to whether any one particular NSAID provides an advantage over the others. Most of the newer drugs have tried to capitalize on such unique properties as enteric coating, pro-drug formulation, nonoral administration, or lack of enterohepatic circulation, which may make a particular NSAID safer and thereby distinguish it from the multitude of other NSAIDs.

Some of these properties have only had a modicum of success. Enteric coating offers minimal, if any, benefit for the prevention of NSAID-associated gastropathy. Pro-drug formulation provides no guarantee of safety. For example, the use of sulindac, a pro-drug of sulindac sulfide, is associated with significant toxicity. Alternative routes of administration—parenteral, rectal, or topical—have not provided the safety margin that had been hoped for. Some of these alternative routes of administration may avoid direct topical toxicity to the gastric mucosa, but systemic effects still occur because the drugs are present in the serum. Ketorolac, an NSAID that can be administered either orally or parenterally, has been shown to increase significantly the risk of upper GI bleeding and perforation and is considered to be 5 times more gastrotoxic than other NSAIDs, regardless of its route of administration.[5]

The ability of an NSAID to damage the GI system is dependent on multiple factors. Two factors have recently come into focus, both in terms of their contribution to toxicity and as targets for development of safer NSAIDs: cyclo-oxygenase-2 (COX-2) inhibition and absence of enterohepatic recirculation. Recent indications are that either or both of these properties may be key to providing a gastrointestinally safer NSAID.

COX-2 is the isoform associated with inflammation and disease, and COX-1 is associated with gastroprotection and platelet aggregation; inhibition of COX-1 may lead to NSAID toxicity.[6] Therefore, agents that more spe-

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cifically inhibit COX-2, with a relative sparing of COX-1, should be potentially safer drugs.

Initiation of GI toxicity by an NSAID is most likely to occur via topical damage to the mucosa.[7] The ability of an NSAID to go through enterohepatic recirculation means that the drug will be seen by the GI mucosa twice, thereby doubling the potential for mucosal damage. A recent study[8] in rats given diclofenac or nitrofenac, a nitroxybutylester derivative of diclofenac that does not undergo enterohepatic recirculation, suggests that enterohepatic recirculation is the main factor contributing to the ability of an NSAID to cause enteropathy. Therefore, an NSAID that does not go through this process, i.e., has low or no biliary excretion, should significantly decrease toxicity.

The plasma half-life of an NSAID is an additional property that has recently become of interest as a potential basis for determining toxicity. Although, ideally, a longer half-life is desired so that dosing may be maintained on a once-daily basis, a longer half-life has also been associated with increased risk of renal impairment[9] and GI complications.[10] In addition, the potential for a nonaspirin NSAID to inhibit platelet aggregation via its (reversible) inhibition of thromboxane synthesis (a cyclo-oxygenase-dependent prostaglandin required for platelet aggregation) is increased if it has a long plasma half-life.[11] This can lead to a greater risk of GI bleeding, such as in the case of piroxicam, with a half-life of >50 hours.[12]

The relative safety of 3 of the leading NSAIDs on the US market— oxaprozin, nabumetone, and etodolac—will be discussed with respect to the properties outlined above.

Oxaprozin

Oxaprozin has become one of the leading NSAIDs on the US market despite its having a half-life >50 hours and other properties generally not associated with a gastrointestinally safe NSAID.[13] Pharmacokinetic studies suggested that a lack of enterohepatic circulation could provide oxaprozin with a margin of safety compared with other NSAIDs. Although urinary excretion of oxaprozin predominates in humans, an estimated 31% of the drug is recovered as metabolites in the feces, with negligible amounts of free or conjugated oxaprozin.[13] However, if these biliary metabolites do include a glucuronide derivative (as suggested in a review of its pharmacologic profile[14]), the glucuronide conjugate could conceivably be deconjugated back to the parent drug and exacerbate GI toxicity.

Several studies compared the safety of oxaprozin with aspirin, piroxicam, and ibuprofen, and found that it provided better gastric tolerance than those 3 commonly used drugs.[15–19] However, many NSAIDs are better tolerated than aspirin and piroxicam, and these early studies were based on very small numbers of patients. A further retrospective study indicated that oxaprozin was not as well tolerated as aspirin or ibuprofen.[20]

Subsequent to those reports, published in 1986, there has been a dearth of clinical or postmarketing studies on oxaprozin safety. Nevertheless, anecdotal evidence from gastroenterologists and rheumatologists suggests that the risk of gastroduodenal mucosal injury associated with the use of oxaprozin is among the highest of the NSAIDs. This assertion is supported by data obtained from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) database showing a risk factor for serious GI adverse events, adjusted for confounding variables, of 3.72 for oxaprozin.[21] Although this figure is based on only 77 patient-years for the drug, it is the highest adjusted risk rate of all the NSAIDs that were studied.

Nabumetone

Nabumetone is a drug that has recently gained a lot of attention on the basis of its putatively significant increase in efficacy and safety compared with other NSAIDs. Although clinical trials have indicated that its efficacy may not be as good as originally proposed—requiring higher dosages than the recommended starting dose of 1,000 mg/day to achieve its desired reduction in pain and inflammation[22,23]—its GI tolerability, at least at the starting dose, has been demonstrated in numerous studies.

Nabumetone is actually a pro-drug of the active metabolite 6-methoxy-2-naphthylacetic acid (6-MNA). An initial report suggested that 6-MNA was a preferential COX-2 inhibitor[24] and that this accounted for its lack of GI toxicity. Subsequent studies were unable to confirm this observation,[25–27] and it is now believed that its safety is based on 2 other factors. The first is that as a nonacidic pro-drug, nabumetone does not affect the GI mucosa as do the acidic NSAIDs. The second is that nabumetone is metabolized by first-pass hepatic metabolism to 6-MNA, and 6-MNA does not undergo enterohepatic recirculation; it is excreted almost entirely in the urine.

Nearly all the clinical trials have suggested that nabumetone is currently one of the safest NSAIDs on the market. Early studies using radiochromium to evaluate the potential for GI bleeding during a 3- or 4-week course of treatment showed that, in contrast to aspirin, which resulted in significant blood loss, there was no difference between nabumetone (at doses of up to 2,000 mg/day) and placebo or no treatment.[28,29]

Endoscopic studies have confirmed that nabumetone, at 1,000 mg/day, causes less gastroduodenal toxicity than do other NSAIDs. When compared with ibuprofen, there was almost a 10-fold decrease in the cumulative rate of ulcers for nabumetone (1,000 mg/day for 12 days; 1.7 versus 15.1; $p < 0.01$).[30] A series of 8 studies lasting between 6 weeks and 6 months compared nabumetone with placebo, aspirin, and naproxen.[31] In these studies, there was no difference in incidence of upper GI perforations,

ulcers, or bleeds between nabumetone and placebo, a lower incidence than that occurring with naproxen or aspirin, and a significantly better endoscopic score at end of trial when compared with naproxen. In a 5-year extension of one of these studies, patients were given nabumetone, ≤1,500 mg/day, or naproxen daily and followed for up to 5 years with annual endoscopies.[32] Over the entire course of this study, there was a consistently and significantly lower risk of developing an ulcer with nabumetone than with naproxen: 1 ulcer with nabumetone compared with 8 with naproxen.

A pooled analysis of clinical trials involving 4,471 patients taking nabumetone for up to 2 years estimated the cumulative frequency of clinically detected perforations, ulcers, and bleeding to be 0.03%. This was more than an order of magnitude better than the comparators, including diclofenac, indomethacin, piroxicam, naproxen, and ibuprofen.[33]

Information obtained from the ARAMIS database confirms the safety of nabumetone; to date, in the 221 patient-years of nabumetone use observed in this study, there have been no serious GI events defined as bleeds or other events requiring hospitalization.[21] However, a more accurate assessment of the GI safety of nabumetone in the clinical setting would come from studies using nabumetone at doses higher than the recommended dose of 1 g/day.

Etodolac

Etodolac is an NSAID that is currently indicated for the treatment of both osteoarthritis and rheumatoid arthritis. Several properties suggest that it may have an improved safety profile over other NSAIDs: preferential COX-2 selectivity, minimal enterohepatic circulation, and a short half-life.

Several in vitro test systems have indicated that etodolac preferentially inhibits COX-2,[27,34–37] with data from 2 of these studies suggesting specific COX-2 inhibition.[27,35] However, the results of in vitro assays are dependent on the assay conditions, and since the conditions used in these 2 studies are likely to overestimate COX inhibition, it is most likely that etodolac is a preferential inhibitor rather than a specific inhibitor of COX-2.

With respect to enterohepatic recirculation, a review of the human clinical pharmacokinetics of etodolac estimates that biliary excretion of etodolac and its metabolites may range between 1% and 16%.[38] Although the half-life of etodolac—7 hours—is not appropriate for once-daily dosing, this short half-life may provide for a safer drug, especially in the elderly, in whom accumulation of drugs with a long half-life may be of concern. Data from endoscopic clinical trials support the contention that these factors do provide a margin of safety for etodolac compared with other NSAIDs.[39–45]

A short-term study (7 days) of etodolac (600 mg/day) in healthy males resulted in endoscopic scores comparable to those with placebo and lower than those with indomethacin, ibuprofen, or naproxen. In several 4-week studies comparing etodolac (400–800 mg/day) with naproxen (1,000 mg/day), etodolac consistently resulted in significantly lower endoscopic scores than the comparator, with fewer gastric and duodenal erosions and ulcers in healthy volunteers[44,45] and in patients with active disease.[39,40,42] Two of these studies demonstrated that, in contrast to naproxen, there was no suppression of mucosal prostaglandin E_2 synthesis and suggested that this accounts, at least in part, for its improved safety.[39,44] Lipscomb et al[45] further demonstrated that although gastric adaptation occurred with both naproxen and etodolac by 4 weeks, naproxen caused more erosions as well as a decrease in gastric mucosal blood flow, as has been shown for other NSAIDs.[46] Etodolac, in contrast, increased the mucosal blood flow, and the investigators suggest that this factor may also contribute to its tolerability.

In an 8-week double-blind endoscopic study[43] comparing the efficacy and safety of etodolac with tenoxicam in an older population (mean age, 70.7 years) with osteoarthritis, there were only 2 confirmed ulcers in each study arm. Endoscopic scores were significantly better with etodolac than with tenoxicam, and there was no significant difference between baseline endoscopic scores and those at 8 weeks of etodolac treatment.

The main problem with the studies discussed above is that the patient populations were small. Only one study,[47] based on European postmarketing surveillance, has utilized a large population to estimate the cumulative ulcer rate of etodolac. In this population of >51,000 patients with rheumatoid arthritis, the cumulative ulcer rate for etodolac was 0.04%. However, this study was based on spontaneous reporting rather than on prospectively collected data. In the United States to date, the largest database for this type of epidemiologic data collection is the ARAMIS database, which has information based on 88 patient-years of etodolac use with no reports of serious GI events and a risk factor of 0.[21]

SUMMARY

Although the NSAID armamentarium has continued to increase since the introduction of this class of drugs, it has only recently been determined that specific factors may help predict the comparative safety of NSAIDs: COX-2 inhibition, absence of enterohepatic recirculation, shorter half-life, and nonacidic pro-drug formulations. One or several of these factors can also be incorporated into the design and synthesis of new compounds that may potentially provide safer anti-inflammatory and analgesic activity. Two drugs currently in clinical use appear to provide decreased GI toxicity: etodolac and nabumetone. Although clinical trials are important in the initial deter-

mination of the relative safety and efficacy of new and developing drugs, it is the combination of postmarketing surveillance and a continuing dialogue between gastroenterologists and rheumatologists regarding use of NSAIDs and incidence of serious adverse events that will confirm the safety of any new drug.

REFERENCES

1. Taha AS, Dahill S, Sturrock RD, et al. Predicting NSAID related ulcers assessment of clinical and pathological risk factors and importance of differences in NSAID. *Gut.* 1994; 35:891–895.
2. Henry D, Lim LL-Y, García Rodríguez LA, et al. Variability in risk of gastrointestinal complications with individual nonsteroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ.* 1996;312:1563–1566.
3. Fries JF, Williams CA, Bloch DA. The relative toxicity of nonsteroidal antiinflammatory drugs. *Arthritis Rheum.* 1991; 34:1353–1360.
4. Singh G, Terry R, Ramey DR, et al. Comparative GI toxicity of NSAIDs. (Abstr.) *Arthritis Rheum.* 1997;40(suppl):S115.
5. García Rodríguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal antiinflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med.* 1998;158:33–39.
6. Vane J. Towards a better aspirin. *Nature.* 1994;367:215–216.
7. Schoen RT, Vender RJ. Mechanisms of nonsteroidal antiinflammatory drug-induced gastric damage. *Am J Med.* 1989;86:449–458.
8. Reuter BK, Davies NM, Wallace JL. Nonsteroidal anti-inflammatory drug enteropathy in rats: role of permeability, bacteria, and enterohepatic circulation. *Gastroenterology.* 1997;112:109–117.
9. Henry D, Page J, Whyte I, et al. Consumption of nonsteroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects: results of a case-control study. *Br J Clin Pharmacol.* 1997;44:85–90.
10. Henry D, Dobson A, Turner C. Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs. *Gastroenterology.* 1993;105:1078–1088.
11. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J Clin Pharmacol.* 1995;35:209–219.
12. Kaufman DW, Kelly JP, Sheehan JE, et al. Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. *Clin Pharmacol Ther.* 1993;53:485–494.
13. Janssen FW, Jusko WJ, Chiang ST, et al. Metabolism and kinetics of oxaprozin in normal subjects. *Clin Pharmacol Ther.* 1980;27:352–362.
14. Lewis AJ, Carlson RP, Chang J, et al. The pharmacological profile of oxaprozin, an antiinflammatory and analgesic agent with low gastrointestinal toxicity. *Curr Ther Res.* 1983;34:777–794.
15. Poiley JE, Spindler JS, Clarke JP, Brame CL. Nonsteroidal antiinflammatory drug therapy in rheumatoid arthritis: a comparison of oxaprozin and ibuprofen. *Semin Arthritis Rheum.* 1986;15(suppl 2):59–65.
16. Appelrouth DJ, Chodock AL, Miller JL, Powell WR. A comparison of single daily doses of oxaprozin with multiple daily doses of ibuprofen for the treatment of rheumatoid arthritis. *Semin Arthritis Rheum.* 1986;15(suppl 2):54–58.
17. Barber JV, Collins RL, Kitridou RC, et al. The efficacy and safety of single daily doses of oxaprozin in the treatment of rheumatoid arthritis: a comparison with aspirin. *Semin Arthritis Rheum.* 1986;15(suppl 2):47–53.
18. Kolodny AL, Klipper AR, Harris BK, et al. The efficacy and safety of single daily doses of oxaprozin in the treatment of osteoarthritis: a comparison with aspirin. *Semin Arthritis Rheum.* 1986;15(suppl 2):72–79.
19. Powell WR, Miller JL, Sheldon WB. Once-daily oxaprozin and piroxicam compared in osteoarthritis. *Semin Arthritis Rheum.* 1986;15(suppl 2):80–85.
20. Dahl SL, Ward JR. Efficacy and tolerability of oxaprozin in the elderly. *Semin Arthritis Rheum.* 1986;15(suppl 2):40–46.
21. Singh G, Terry R, Ramey DR, et al. Comparative GI toxicity of NSAIDs. (Abstr.) Paper presented at: XIX ILAR Congress of Rheumatology; June 8–13, 1997; Singapore.
22. Makarowski W, Weaver A, Rubin B, et al. The efficacy, tolerability, and safety of 1200 mg/d of oxaprozin and 1500 mg/d of nabumetone in the treatment of patients with osteoarthritis of the knee. *Clin Ther.* 1996;18:114–124.
23. Weaver A, Rubin B, Caldwell J, et al. Comparison of the efficacy and safety of oxaprozin and nabumetone in the treatment of patients with osteoarthritis of the knee. *Clin Ther.* 1995;17:735–745.
24. Meade EA, Smith WL, DeWitt DL. Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other non-steroidal anti-inflammatory drugs. *J Biol Chem.* 1993;268:6610–6614.
25. Churchill L, Graham AG, Shih C-K, et al. Selective inhibition of human cyclo-oxygenase-2 by meloxicam. *Inflammopharmacology.* 1996;4:125–135.
26. Young JM, Panah S, Satchawatcharaphong C, Cheung PS. Human whole blood assays for inhibition of prostaglandin G/H synthases-1 and -2 using A23187 and lipopolysaccharide stimulation of thromboxane B_2 production. *Inflamm Res.* 1996;45:246–253.
27. Riendeau D, Percival MD, Boyce S, et al. Biochemical and pharmacological profile of a tetrasubstituted furanone as a highly selective COX-2 inhibitor. *Br J Pharmacol.* 1997;121: 105–117.
28. Lussier A, Davis A, Lussier Y, Lebel E. Comparative gastrointestinal blood loss associated with placebo, aspirin, and nabumetone as assessed by radiochromium (^{51}Cr). *J Clin Pharmacol.* 1989;29:225–229.
29. Lussier A, LeBel E. Radiochromium (chromium-51) evaluation of gastrointestinal blood loss associated with placebo, aspirin, and nabumetone. *Am J Med.* 1987;83:15–18.
30. Roth SH, Tindall EA, Jain AK, et al. A controlled study comparing the effects of nabumetone, ibuprofen, and ibuprofen plus misoprostol on the upper gastrointestinal tract mucosa. *Arch Intern Med.* 1993;153:2565–2571.
31. Roth SH. Upper gastrointestinal safety with nabumetone. *J Rheumatol.* 1992;19(suppl 36):74–79.
32. Roth SH, Bennett R, Caldron P, et al. A longterm endoscopic evaluation of patients with arthritis treated with nabumetone vs naproxen. *J Rheumatol.* 1994;21:1118–1123.
33. Lipani JA, Poland M. Clinical update of the relative safety of nabumetone in long-term clinical trials. *Inflammopharmacology.* 1995;3:351–361.
34. Glaser K, Sung M-L, O Neill K, et al. Etodolac selectively inhibits human prostaglandin G/H synthase 2 (PGHS-2)

versus human PGHS-1. *Eur J Pharmacol.* 1995;281:107–111.
35. Kawai S, Nishida S, Kato M, et al. Comparison of cyclooxygenase-1 and -2 inhibitory activities of various nonsteroidal anti-inflammatory drugs using human synovial cells and platelets. (Abstr.) Paper presented at: XIX ILAR Congress of Rheumatology; June 8–13, 1997; Singapore.
36. Laneuville O, Breuer DK, Dewitt DL, et al. Differential inhibition of human prostaglandin endoperoxide H synthases-1 and -2 by nonsteroidal anti-inflammatory drugs. *J Pharmacol Exp Ther.* 1994;271:927–934.
37. Adams L, Neuman RG, Sachs J, Bralow SP. Efficacy and gastric safety of etodolac as determined in cultured human gastric and synovial cells. (Abstr.) *Gastroenterology.* 1990; 98(suppl):A14.
38. Brocks DR, Jamali F. Etodolac clinical pharmacokinetics. *Clin Pharmacokinet.* 1994;26:259–274.
39. Russell RI. Endoscopic evaluation of etodolac and naproxen, and their relative effects on gastric and duodenal prostaglandins. *Rheumatol Int.* 1990;10(suppl):17–21.
40. Taha AS, McLaughlin S, Sturrock RD, Russell RI. Evaluation of the efficacy and comparative effects on gastric and duodenal mucosa of etodolac and naproxen in patients with rheumatoid arthritis using endoscopy. *Br J Rheumatol.* 1989;28:329–332.
41. Lanza F, Rack MF, Lynn M, et al. An endoscopic comparison of the effects of etodolac, indomethacin, ibuprofen, naproxen, and placebo on the gastrointestinal mucosa. *J Rheumatol.* 1987;14:338–341.
42. Bianchi Porro G, Caruso I, Petrillo M, et al. A double-blind gastroscopic evaluation of the effects of etodolac and naproxen on the gastrointestinal mucosa of rheumatic patients. *J Intern Med.* 1991;229:5–8.
43. Perpignano G, Bogliolo A, Puccetti L. Double-blind comparison of the efficacy and safety of etodolac SR 600 mg u.i.d. and of tenoxicam 20 mg u.i.d. in elderly patients with osteoarthritis of the hip and of the knee. *Int J Clin Pharmacol Res.* 1994;14:203–216.
44. Laine L, Sloane R, Ferretti M, Cominelli F. A randomized, double-blind comparison of placebo, etodolac, and naproxen on gastrointestinal injury and prostaglandin production. *Gastrointest Endosc.* 1995;42:428–433.
45. Lipscomb GR, Wallis N, Armstrong G, et al. Gastric mucosal adaptation to etodolac and naproxen. *Aliment Pharmacol Ther.* 1995;9:379–385.
46. Taha AS, Angerson W, Nakshabendi I, et al. Gastric and duodenal mucosal blood flow in patients receiving nonsteroidal anti-inflammatory drugs influence of age, smoking, ulceration and *Helicobacter pylori*. *Aliment Pharmacol Ther.* 1993;7:41–45.
47. Etodolac safer than other NSAIDs? *Scrip.* 1991;1616:28.