

Do Nonsteroidal Anti-Inflammatory Drugs Cause Lower Gastrointestinal Bleeding? A Brief Review

Jaydev Varma, M.D.

Abstract: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been available for over a decade. Their prime usage has been for the alleviation of pain in rheumatoid arthritis, osteoarthritis, and other painful musculoskeletal and organic syndromes. Physicians and patients have accepted that these drugs can cause irritation of the gastric mucosa and even lead to ulceration and bleeding. While these effects on the gastric mucosa are well researched and documented, the

effects of NSAIDs on the lower bowel are not sufficiently documented, and it is presumed that these agents do not cause any lower gastrointestinal bleeding. Hence, even in the presence of lower gastrointestinal disease, these agents are prescribed by physicians. Because these agents are capable of causing serious or life-threatening disease, a brief review of the effects of NSAIDs on the lower gastrointestinal tract is presented. (*J Am Bd Fam Pract* 1989; 2:119-22.)

Nonsteroidal anti-inflammatory agents have been available for several years. They have a wide spectrum of usage in terms of symptoms and disease states. Some are over-the-counter drugs, and it is not unusual to see these products being promoted on television as well. In the United States, several million prescriptions are written by physicians for NSAIDs annually. The list¹ of the top 200 drugs sold in the United States includes a number of nonsteroidal anti-inflammatory agents (Table 1).

In the face of such extensive usage, physicians encounter numerous side effects in the patients consuming them. One significant side effect of almost all NSAIDs² is the irritation caused to the gastric mucosa, resulting in various symptoms ranging from mild epigastric discomfort to peptic ulceration, perforation, and hemorrhage. While the effects of NSAIDs on the gastric mucosa are well accepted,³⁻⁷ the effects of these agents on the mucosa of the large bowel are not well documented.⁸⁻¹³

NSAIDs are the "elixir of life" for victims of severe arthritis and other painful syndromes. However, the primary care physician, the rheu-

matologist, the surgeon, and the pathologist can view these agents with varied responses because each one of them is exposed to different manifestations or effects of these drugs.

It is true that documentation of these various manifestations would be difficult to substantiate and reproduce.^{2,12,14} There are, however, reports referring to the deleterious effects of NSAIDs on colonic mucosa.^{3,8,9,11,13,15-18} The precise incidence of these occurrences is not known¹⁰; however, estimates are that one episode of gastrointestinal hemorrhage occurs for every 6,000 prescriptions written for NSAIDs.¹⁹

A majority of these agents are prescribed for elderly patients, who may be more susceptible to side effects in the lower bowel as a result of consuming these potent drugs.²⁰ The frequency of gastrointestinal complications is high in the elderly, and there is a significantly worse outcome in patients more than 70 years of age.²⁰

Reports on the side effects of NSAIDs began with the use of indomethacin.^{17,18,21-23} There have been a few studies relating to NSAIDs with lower gastrointestinal bleeding (LGIB),⁸⁻¹¹ ulceration and perforation of colonic ulcers,^{3,11,24} perforation of diverticuli,¹⁷ activation/reactivation of quiescent colitis,^{8,16,25} and perforation and hemorrhage of the large bowel.^{10,22,27,28} Rechallenge with the same drugs has reproduced the rectal bleeding in several of these patients.^{8,11}

From the Department of Family Medicine, Medical College of Georgia, Augusta. Address reprint requests to Jaydev Varma, M.D., Department of Family Medicine, Medical College of Georgia, Augusta, GA 30912-3500.

Table 1. NSAIDs Prescriptions, U.S., 1987.

Refills and New Prescriptions		Refills Only		New Prescriptions	
Rank	Drug	Rank	Drug	Rank	Drug
14	Naprosyn	20	Naprosyn	10	Naprosyn
16	Motrin	22	Motrin	15	Motrin
32	Feldene	31	Feldene	31	Feldene
44	Clinoril	46	Clinoril	55	Clinoril
67	Indocin	100	Nalfon	73	Anaprox
97/105	Ibuprofen	119/121	Ibuprofen	88	Ibuprofen
96	Anaprox	123	Anaprox	93	Dolobid
108	Nalfon	129	Rufen	105	Nalfon
112	Dolobid	147	Dolobid		

Langman and colleagues¹⁰ studied the intake of NSAIDs in 268 patients hospitalized for large-bowel perforation or hemorrhage. This group was compared with age- and sex-matched controls. Patients with bowel cancer, colitis, or Crohn's disease were excluded. In the hospitalized group, 25 patients had small-bowel perforation, 82 had large-bowel perforation, and 161 had gastrointestinal hemorrhage. The report concluded that the intake of NSAIDs was twice as frequent in patients with bleeding or perforation than in their matched controls.

Ravi and his colleagues⁸ described 4 patients with NSAIDs-related rectal bleeding. Three were rechallenged with the same drugs (flufenamic acid, mefenamic acid, naproxen) after initial withdrawal and resolution of all symptoms; all 3 patients developed rectal bleeding again.⁸

Ulcerations of the distal transverse colon were observed by Uribe, et al.³ in a patient with rectal bleeding who was receiving NSAIDs. When the drug was discontinued, the bleeding ceased. Subsequent colonoscopy showed that the ulcerations had disappeared, and the mucosa was normal again.

I had a 74-year-old woman patient on long-term clonidine therapy for hypertension who developed lower abdominal pain and bloody diarrhea 24 hours after ingesting 400 mg ibuprofen for two doses 6–8 hours apart. On sigmoidoscopy, the rectum was found filled with burgundy-colored clots, and the rectal mucosa was diffusely congested. The drug was discontinued, and the rectal bleeding stopped in 48 hours. A sigmoidoscopy after 48 hours showed that the rectal mucosa appeared normal.

Schwartz¹¹ has suggested that it may be a presumption that NSAIDs do not cause LGIB and are considered safe when administered to patients with lower bowel disease. He described three patients who developed life-threatening relapse of large-bowel disease while on NSAIDs. One patient developed perforation of a sigmoid diverticulum. Another had a severe relapse of Crohn's disease, and the third had a severe hemorrhage from a right colonic diverticulum.

These histories show that NSAIDs are potentially toxic to the lower gastrointestinal tract whether previously healthy or diseased. There lingers the dilemma of some unresolved questions. For example, how often do these effects occur in the lower bowel? What is the risk of NSAIDs for the lower bowel? What is the mechanism of induction, and what dosages amount to a significant risk? Whatever the answer,²⁶ there seems to be sufficient evidence to indicate that NSAIDs may have deleterious effects on the mucosa of the large bowel. History of previous lower bowel disease and the presence of diverticular disease in a patient should mandate caution in the administration of NSAIDs.

The Dilemma Raised by a Positive Hemoccult™ in a Patient Taking NSAIDs

Physicians routinely perform Hemoccult™ tests in the clinical setting. Much has been written on the sensitivity, specificity, and applicability of this screening tool.²⁹⁻³⁴ In reality, however, we find a variety of clinical dilemmas associated with the practical uses of the Hemoccult™. There are dietary restrictions that need compliance by the patients,³⁰ and the question of false-positives and false-negatives needs to be considered.³⁴⁻³⁶

The patient who is receiving NSAIDs and who has a positive Hemoccult™ poses a tricky clinical dilemma. Nonsteroidal anti-inflammatory drugs have been known to cause gastrointestinal bleeding.³⁷ Pye and associates³⁸ studied 10,931 patients to assess the effects of NSAIDs on the outcome of the fecal occult blood test. A positive result was recorded for 455 persons. Of these, only 50 were taking NSAIDs. The study concluded that a positive test result could not be attributed to NSAIDs. Regardless of one's beliefs that NSAIDs may or may not cause gastrointestinal bleeding, a positive Hemoccult™ is a definitive screening result that needs to be pursued to

rule out other pathology.³⁸⁻⁴⁵ A definite positive Hemoccult™ should mandate one of two approaches. Colonoscopy is preferable; however, this procedure may miss up to 9 percent of adenomas smaller than 1 cm.^{37,41} The other alternative is flexible sigmoidoscopy coupled with an air contrast barium enema. If all these studies are negative, an upper gastrointestinal series would be necessary to complete the diagnostic framework.

In the event that all the above are negative, and in the absence of any symptoms, a conservative approach and follow-up would be prudent. Withholding NSAIDs for a period of time and repeating the test may be considered.⁴⁴ However, if the repeat test is positive, there is added reason to pursue the diagnostics referred to above. On the other hand, if the test is negative, we still are left with the dilemma that the previously positive test may have been due to a bleeding polyp, cancer, angiodysplastic lesion, or NSAIDs. Hence, physicians need to use their discretion on an individual basis.

References

1. American druggist, practice of pharmacy. New York: Hearst Business Publication 1988; 198: 40-51.
2. Goodwin JS. Toxicity of nonsteroidal anti-inflammatory drugs. Milwaukee: Department of Medicine, Medical College of Wisconsin.
3. Uribe A, Johansson C, Slezak P, Rubio C. Ulcerations of the colon associated with naproxen and acetylsalicylic acid treatment. *Gastrointest Endosc* 1986; 32:242-4.
4. Biour M, Blanquart A, Moore N, et al. Incidence of NSAID-related, severe gastrointestinal bleeding. *Lancet* 1987; 2:340-1.
5. Ivey KJ. Gastrointestinal intolerance and bleeding with non-narcotic analgesics. *Drugs* 1986; 32(Suppl):71-87.
6. Carson JL, Strom GL, Morse ML, et al. The relative gastrointestinal toxicity of the nonsteroidal anti-inflammatory drugs. *Arch Intern Med* 1987; 147:1054-9.
7. Beard K, Walker AM, Perera DR, Jick H. Nonsteroidal anti-inflammatory drugs and hospitalization for gastroesophageal bleeding in the elderly. *Arch Intern Med* 1987; 147:1621-3.
8. Ravi S, Keat AC, Keat EC. Colitis caused by nonsteroidal anti-inflammatory drugs. *Postgrad Med J* 1986; 62:773-6.
9. Rampton DS. Non-steroidal anti-inflammatory drugs and the lower gastrointestinal tract. *Scand J Gastroenterol* 1987; 22:1-4.
10. Langman MJ, Morgan L, Worrall A. Use of anti-inflammatory drugs by patients admitted with small or large bowel perforations and haemorrhage. *Br Med J* 1985; 290:347-9.
11. Schwartz HA. Lower gastrointestinal side effects of nonsteroidal anti-inflammatory drugs. *J Rheumatol* 1981; 8:952-4.
12. Kraag GR. Rare toxicity with nonsteroidal anti-inflammatory drugs. *J Rheumatol* 1985; 12:1-3.
13. Kaufmann HJ, Taubin HL. Nonsteroidal anti-inflammatory drugs activate quiescent inflammatory bowel disease. *Ann Intern Med* 1987; 107: 513-6.
14. Venning GR. Identification of adverse reactions to new drugs: alerting processes and early warning systems. *Br Med J* 1983; 286:458-60.
15. Boley SJ, DiBiase A, Brandt LJ, Sammartano RJ. Lower intestinal bleeding in the elderly. *Am J Surg* 1979; 137:57-64.
16. Rampton DS, Sladen GE. Relapse of ulcerative proctocolitis during treatment with non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1981; 57:297-9.
17. Coutrot S, Roland D, Barbier J, Van Der Marcq P, Alcalay M, Matuchansky C. Acute perforation of colonic diverticuli associated with short-term indomethacin. *Lancet* 1978; 2:1055-6.
18. Hall RI, Petty AH, Cobden I, Lendrum R. Enteritis and colitis associated with mefenamic acid. *Br Med J* 1983; 287:1182.
19. Langman MJS. Peptic ulcer complications and the use of nonaspirin nonsteroidal anti-inflammatory drugs. *Adverse Drug Reaction Bulletin* 1986; 120:448-51.
20. Cockel R. NSAIDs—should every prescription carry a government health warning? *Gut* 1987; 28:515-8.
21. Day TK. Intestinal perforation associated with osmotic slow release indomethacin capsules. *Br Med J* 1983; 287:1671-2.
22. Levy N, Jasper E. Rectal bleeding and indomethacin suppositories. *Lancet* 1975; 1:577.
23. Alcalay M, Matuchansky C. Acute perforation of colonic diverticula associated with short-term indomethacin. *Lancet* 1978; ii:1055.
24. Bravo and Lowman. NSAIDs and colon ulcers. *Radiology* 1968; 90:113-5.
25. Phillips MS, Fehilly B, Stewart S, Dronfield MW. Enteritis and colitis associated with mefenamic acid. *Br Med J* 1983; 287:1626.
26. Roth SH. What is new in arthritis therapy? Back to the future. *Arch Intern Med* 1987; 147:36-7.
27. Casarella WJ, Galloway SJ, Taxin RN, et al. Lower gastrointestinal tract hemorrhage: new concepts based on arteriography. *Am J Roentgenol* 1974; 121:357.
28. Jacyna MR, Shepherd AN. Perforated ulcer in the elderly. *Lancet* 1985; ii:1309.
29. Norfleet RG. Early detection of colorectal neoplasms. Methods for screening and surveillance. *Postgrad Med* 1986; 79:121-4.
30. Stroehlein JR, Goulston K, Hunt RH. Diagnostic approach to evaluating the cause of a positive fecal occult blood test. *CA* 1984; 34:148-57.
31. Winawer SJ, Andrews M, Flehinger B, Sherlock P, Schottenfeld D, Miller DG. Progress report on con-

- controlled trial of fecal occult blood testing for the detection of colorectal neoplasia. *Cancer* 1980; 45:2959-64.
32. Ostrow JD, Mulvaney CA, Hansell JR, Rhodes RS. Sensitivity and reproducibility of chemical tests for fecal occult blood with an emphasis on false-positive reactions. *Am J Dig Dis* 1973; 18:930-40.
 33. Gilbertsen VA, McHugh R, Schuman L, Williams SE. The earlier detection of colorectal cancers: a preliminary report of the results of the Occult Blood Study. *Cancer* 1980; 45: 2899-2901.
 34. Winawer SJ, Andrews M, Miller CH, Fleisher M. Review of screening for colorectal cancer using fecal occult blood testing. New York: Memorial Sloan-Kettering Cancer Center, 1980.
 35. Simon JB. Occult blood screening for colorectal carcinoma: a critical review. *Gastroenterology* 1985; 88:820-37.
 36. Brandeau ML, Eddy DM. The workup of the asymptomatic patient with a positive fecal occult blood test. *Med Decis Making* 1987; 7:32-46.
 37. Rozen P, Ron E, Fireman Z, et al. The relative value of fecal occult blood tests and flexible sigmoidoscopy in screening for large bowel neoplasia. *Cancer* 1987; 60:2553-8.
 38. Pye G, Ballantyne KC, Armitage NC, Hardcastle JD. Influence of non-steroidal anti-inflammatory drugs on the outcome of faecal occult blood tests in screening for colorectal cancer. *Br Med J* 1987; 294:1510-1.
 39. Jensen J, Kewenter J, Haglind E, Lycke G, Svensson C, Ahrent C. Diagnostic accuracy of double-contrast enema and rectosigmoidoscopy in connection with faecal occult blood testing for the detection of rectosigmoid neoplasms. *Br J Surg* 1986; 73:961-4.
 40. Ganiats TG, Norcross WA. Cost-effectiveness of fecal occult blood screening. *West J Med* 1987; 146:486-7.
 41. Welch R. More targeted approach to colon cancer screening advocated. *Fam Pract News* 1988; July 1-14:16.
 42. Fedotin MS, Ginsberg BW. Practical considerations in screening for colorectal cancer. *Mod Med* 1988; 56:127-35.
 43. Bahrt KM, Korman LY, Nashel DJ. Significance of a positive test for occult blood in stools of patients taking anti-inflammatory drugs. *Arch Intern Med* 1984; 144:2165-6.
 44. Niv Y. Influence of non-steroidal anti-inflammatory drugs in faecal occult blood tests. *Br Med J* 1987; 295:446.
 45. Doran J, Hardcastle JD. Bleeding patterns in colorectal cancer: the effect of aspirin and the implications for faecal occult blood testing. *Br J Surg* 1982; 69:711-3.

GLEANINGS FROM A COMMONPLACE BOOK — *NJP*

"Boredom and the restless search for diversion show how much each man hates and tries to escape from himself."
Lucretius

"The young man knows the rules; the old man the exceptions."
O.W. Holmes, M.D.

". . . While you may, live happy amid joys; live mindful ever of how brief your time is."
Horace

"To flee vice is the beginning of virtue, and to have got rid of folly is the beginning of wisdom."
Horace

"A man behind the times is apt to speak ill of them, on the principle that nothing looks well from behind."
O.W. Holmes, M.D.

"A wise physician skilled our wounds to heal
Is more than armies to the public weal."
Author Unknown