Controversies in Therapeutics

Non-steroidal anti-inflammatory drugs in patients with peptic ulcer disease: to be considered in certain circumstances

Michael Doherty

Although salicylate and non-aspirin, non-steroidal anti-inflammatory drugs cause acute injury to the gastroduodenal mucosa,[1-3] their role during long term treatment in predisposing to peptic ulcer disease and clinically important complications remains uncertain.[4-11] Common criticisms of existing studies include inadequate design,[9] investigating young volunteers rather than older patients, examining acute and not chronic injury, and focusing attention on aspirin.[7-10] Interpretation is particularly clouded by the prevalence of unsuspected (clinically irrelevant?) gastroduodenal lesions observed endoscopically in patients who take non-steroidal anti-inflammatory drugs, irrespective of their rheumatic condition.[12-16] Well designed case-control studies have nevertheless associated non-steroidal anti-inflammatory drugs with gastroduodenal (and ileal and colonic) bleeding and perforation,[17-21] though ranking of toxicity among such drugs has proved problematic.[7-9] Such difficulties, with the need to distinguish clearly individual and population risks, have been extensively reviewed.[5-11] Against this background, however, it is apparent that non-steroidal anti-inflammatory drugs can adversely affect the gut, elderly women being particularly at risk of significant complications.[17-21] While awaiting results of more definitive studies what is the advice to prescribing doctors?

Patients already taking the drugs

When treating a patient with peptic ulcer disease who is taking non-steroidal anti-inflammatory drugs or for whom such drugs are being considered there are insufficient data to derive authoritative guidelines: individual bias will therefore necessarily enter any strategy of management. Several commonsense considerations, however, seem to be uncontroversial.

Firstly, the rationale for choosing non-steroidal anti-inflammatory drugs over simple analgesics should be reconsidered. Have analgesics been unsuccessful? Is there an inflammatory component to the patient's symptoms? If the patient is already taking a non-steroidal anti-inflammatory drug has definite benefit recently been shown? Although difficult to record, non-steroidal anti-inflammatory drugs are probably unnecessarily prescribed for minor, self limiting conditions.[17]

Prescribing non-steroidal anti-inflammatory drugs to patients with peptic ulcer disease

First consider

- Simple analgesics alone
- Local treatments (physiotherapy, ultrasound, mechanical supports, injection)
- Second line agents to reduce symptoms
- Other correctable predisposing factors (smoking, alcohol consumption, hypovitaminosis C)

If clear indication for such drugs

- Avoid aspirin and indomethacin
- Use one such drug at a time, starting at lower dose range
- Use the patient's (not necessarily the doctor's) choice of effective drug

As yet no authoritative data exist to advise on choosing anti-ulcer agents or how best to prevent relapse.

Secondly, consider other correctable predisposing factors to peptic ulcer disease—for example, smoking, hypovitaminosis C, and alcohol consumption. Smoking particularly often accompanies and is a possible co-factor for ulcers associated with non-steroidal anti-inflammatory drugs.[15,16]

Thirdly, consider alternative, complementary local and systemic treatments for musculoskeletal problems. For example, many patients, particularly elderly women at high risk, have periarticular syndromes or pauciarticular osteoarthritis, which may be treated by local treatments, such as physiotherapy and injections, aimed at resolution rather than amelioration of symptoms alone. Such measures are often omitted, particularly when an inadequate locomotor examination has led to an indefinite diagnosis. In addition, in patients with rheumatoid arthritis effective use of second line agents may reduce the requirement for non-steroidal anti-inflammatory drugs; low doses of corticosteroid, with its possible cytoprotective effect,

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EDITORIAL COMMENT

Dr Doherty, a rheumatologist, and Dr Hawkey, a gastroenterologist, are not so much disagreeing with each other as highlighting the considerable areas of ignorance surrounding this important and common medical problem of non-steroidal anti-inflammatory drugs and peptic ulcer disease. They both draw attention to the risks of prescribing such drugs to elderly patients, particularly women. In addition, both broadly agree that ibuprofen seems to be comparatively harmless in terms of mucosal toxicity. Against the background of considerable ignorance it would be well to heed their advice to avoid non-steroidal anti-inflammatory drugs unless there is a clear indication and then to tailor the choice of drug to the patient. If circumstances permit a non-steroidal anti-inflammatory drug could be continued to be taken in the presence of a known peptic ulcer while the patient is receiving anti-ulcer treatment. This is, however, an excellent example of when the patient must be brought into the decision making process. Is the benefit derived from treatment with non-steroidal anti-inflammatory drugs sufficient to outweigh the unquantifiable risk of serious bleeding from the ulcer? Generalisations are not possible and clearly each case must be taken on its own merits.—PETER RUBIN, *professor of therapeutics, University Hospital, Nottingham NG7 2UH*

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prevent half of the bleeds associated with non-steroidal anti-inflammatory drugs occurring once every 500 patient years the cost for each life saved would be around £1m. Curtailed prescribing of non-steroidal anti-inflammatory drugs and expanded programmes of joint replacement may be a better bargain.

Should every patient taking non-steroidal anti-inflammatory drugs have endoscopy?

Suspected ulcers should be confirmed endoscopically and monitored for recurrence because so many are silent. Likewise, when treatment is started endoscopy should be performed, but this is impracticable with the current amount of prescribing of non-steroidal anti-inflammatory drugs.

Conclusion

Non-steroidal anti-inflammatory drugs cause significant gastrointestinal morbidity and mortality. Most patients presenting with bleeding have not seen a rheumatologist, are not taking non-steroidal anti-inflammatory drugs for an inflammatory polyarthritis, and probably do not need them.[1] For those who do need the drugs the limited available evidence would convince many prescribers (though not yet the regulatory authorities[23]) that such drugs can be continued during the healing of ulcers. Strategies for prophylaxis are less clear and more pragmatic (box). Meanwhile, some patients with rheumatoid arthritis might inadvertently be receiving prophylaxis as sulphasalazine protects cells of the stomach in animal studies.[24]

Since this article was written misoprostol has become available for prophylaxis of gastric ulcers in patients taking non-steroidal anti-inflammatory drugs and data have been published suggesting that ranitidine may prevent duodenal ulcers.[25]

Prophylactic strategies

Before an ulcer develops

Avoid non-steroidal anti-inflammatory drugs when there is no joint disease, joint disease is inactive, and arthritis is mild, especially in elderly women

- Remember dyspepsia is not a reliable indicator of ulceration

When an ulcer develops

- Confirm endoscopically
- Stop treatment with non-steroidal anti-inflammatory drugs if possible
- Continue treatment if necessary, adding an ulcer healing agent

When an ulcer has healed

- Consider endoscopic surveillance even with maintenance treatment as relapse is often silent.

1 Somerville KW, Faulkner G, Langman MJS. Non-steroidal anti-inflammatory drugs and bleeding gastric ulcer. *Lancet* 1986;i:462-4.
2 Armstrong CP, Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. *Gut* 1987;**28**:527-32.
3 Doherty M, Hunt RH, Langman MJS, *et al.* Management of NSAID induced gastrointestinal disturbance. *Ann Rheum Dis* 1987;**46**:640-3.
4 O'Laughlin JC, Silvoso GR, Ivey KJ. Healing of aspirin-associated peptic ulcer disease despite continued salicylate ingestion. *Arch Intern Med* 1981;**141**:781-3.
5 O'Laughlin JC, Silvoso GK, Ivey KJ. Resistance to medical therapy of gastric ulcers in rheumatic disease patients taking aspirin. A double blind study with cimetidine and follow-up. *Dig Dis Sci* 1982;**27**:976-80.
6 Davies J, Collins AJ, Dixon STJ. The influence of cimetidine on peptic ulcer in patients with arthritis taking anti-inflammatory drugs. *Br J Rheumatol* 1986;**2**:54-8.
7 Manniche C, Malchow-Moller A, Andersen JR, *et al.* Randomised study of the influence of non-steroidal anti-inflammatory drugs on the treatment of peptic ulcer in patients with rheumatoid arthritis. *Gut* 1987;**28**:226-9.
8 Agrawal N, Tulane U, Roth S, *et al.* Misoprostol coadministration heals aspirin induced gastric lesions in rheumatoid arthritis patients. *Gastroenterology* 1987;**92**:1290.
9 Rossi AC, Hsu JP, Faich GA. Ulcerogenicity of piroxicam: an analysis of spontaneously reported data. *Br Med J* 1987;**294**:147.
10 Committee on Safety of Medicines. Non-steroidal anti-inflammatory drugs and serious gastrointestinal adverse reactions. *Br Med J* 1986;**292**:1190-1.
11 O'Brien JD, Burnham WR. Bleeding from peptic ulcers and use of non-steroidal anti-inflammatory drugs in the Romford area. *Br Med J* 1985;**291**:1609-10.
12 Jorde R, Bostad L, Burhol PG. Asymptomatic gastric ulcer: a follow-up study in patients with previous gastric ulcer disease. *Lancet* 1986;i:119.
13 Penston JG, Wormsley KG. Long term treatment of duodenal ulcers. *Gastroenterology* 1988;**94**:A349.
14 Rothe SH, Bennett RE, Mitchell CS, Hartman RJ. Cimetidine therapy in non-steroidal anti-inflammatory drug gastropathy. Double-blind long-term evaluation. *Arch Intern Med* 1987;**147**:1798-801.
15 Patrono C, Ciabattoni G, Badrignani P, *et al.* Clinical pharmacology of platelet cyclo-oxygenase inhibition. *Circulation* 1985;**72**:1177-84.
16 Wheatley KE, Poxon VA, Dykes PW, Keighley MRB. Intragastric fibrinolysis in bleeding peptic ulcer disease. *Gut* 1987;**28**:A1402.
17 Daneshmend TK, Stein AG, Bhaskar NK, Hawkey CJ. Abolition by omeprazole of aspirin-induced gastric mucosal injury in humans. *Gut* 1988;**29**:A1442.
18 Bigard MA, Isal JP. Complete prevention by omeprazole of aspirin induced gastric lesions in healthy subjects. *Gut* 1988;**29**:A712.
19 Hogden CAM, Schanker LS, Toco DJ, Brodie BB. Absorption of drugs from the stomach. II. The human. *J Pharmacol Exp Ther* 1957;**120**:540-5.
20 Lanza FL, Aspinall RL, Swabb EA, Davis RE, Rack MF, Rubin A. A double-blind placebo controlled endoscopic comparison of the cytoprotective effects of misoprostol and cimetidine on tolmetin induced gastric mucosal injury. *Gastroenterology* 1987;**92**:1491.
21 Graham DY, Smith JL. Aspirin and the stomach. *Ann Intern Med* 1986;**104**:390-8.
22 Penston J, Carter D, Wormsley KG. Recurrence of duodenal ulcers during maintenance treatment. *Gut* 1987;**28**:A1375.
23 Anonymous. FDA criticises SK&F's Tagamet promotion. *Script* 1988 July 16:16.
24 Cho CH, Ogle CW, Sevilla EL. The protective effects of sulphasalazine against ethanol-induced gastric damage in rats. *Br J Pharmacol* 1987;**92**:31-7.
25 Ehsanullah RSB, Page MC, Tildesley G, Wood JR. Prevention of gastrointestinal damage induced by non-steroidal anti-inflammatory drugs: controlled trial of ranitidine. *Br Med J* 1988;**297**:1017-21.

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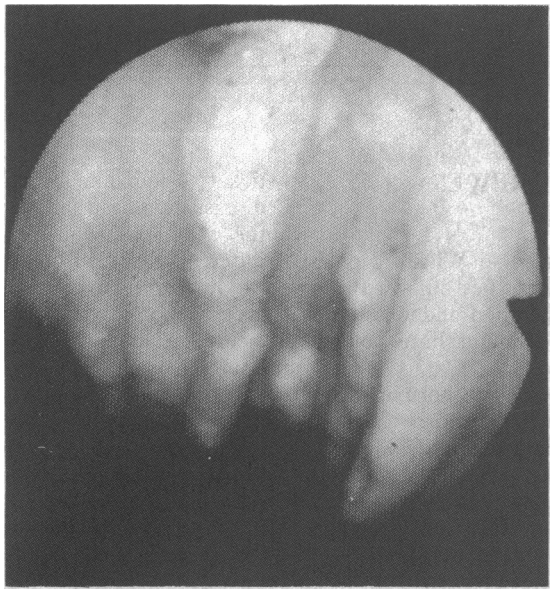
have also been advocated.[1] Such considerations, based on accurately assessing the patient, may avoid altogether or end treatment with non-steroidal anti-inflammatory drugs.

Whether to start treatment

Controversy, however, surrounds continuing or starting treatment with non-steroidal anti-inflammatory drugs in patients with current or past peptic ulcer disease. There are four principal concerns.

Firstly, should non-steroidal anti-inflammatory drugs be given at all? Even after considering the above, some patients with chronic locomotor symptoms find non-steroidal anti-inflammatory drugs undeniably beneficial, and their quality of life is considerably diminished when they are withdrawn. Although the Committee on Safety of Medicines states that non-steroidal anti-inflammatory drugs should not be given to patients with active peptic ulceration,[22] such official advice, predominantly reflecting expectation bias,[23] would result in withdrawal of such drugs in up to 30% of patients with chronic rheumatic disease.[16] The few studies available, however, show that continuing treatment with the drugs little influences the rates of healing obtained with conventional anti-ulcer treatment[16,24-27]: indeed, ulcers may heal spontaneously despite continuing non-steroidal anti-inflammatory drugs.[28] If appropriate non-steroidal anti-inflammatory drugs should therefore still be considered.

Secondly, which non-steroidal anti-inflammatory drug should be prescribed? Salicylate and indomethacin should probably be avoided in peptic ulceration because of their additional direct mucosal toxicity[2-4,6] (in the United Kingdom salicylate is rarely prescribed for arthritis anyway, and indomethacin should be



Gastric erosions as an incidental finding in a patient without dyspepsia

avoided in elderly patients because of frequent side effects in the central nervous system and kidney). Although theoretically attractive, pro-drugs, suppositories, enteric coated or delayed release formulations afford no significant clinical advantage[7 10 29]—systemic rather than local effects remain important.[2 3] Newer non-steroidal anti-inflammatory drugs that spare prostaglandin E_2 merit further investigation.[1] Ibuprofen, especially in low doses seems to be particularly safe,[7 22] but appreciable variation between patients dictates that the choice of drug lies with the patient—taking the doctor's preferred non-steroidal anti-inflammatory drug is pointless if it is ineffective. Usual precautions about prescribing—for example, appropriate dosage and one non-steroidal anti-inflammatory drug only—obviously apply.

Thirdly, which anti-ulcer treatment should be used and for how long? Acute mucosal injury associated with non-steroidal anti-inflammatory drugs is certainly reduced by H_2 antagonists (independently of inhibiting the secretion of acid[30]), sucralfate, and synthetic prostaglandin analogues,[30-34] but long term data in patients are sparse. Most long term studies report good rates of healing with cimetidine or ranitidine,[16 24 26 27] though their usefulness in this situation has been questioned.[28 35 36] Although mucosal protection rather than acid reduction seems theoretically more appropriate,[1 11] good clinical studies to determine the optimum regimens for both healing and preventing relapse in patients receiving long term treatment with non-steroidal anti-inflammatory drugs are still awaited.

Fourthly, how should progress be monitored? This begs the question of what is being treated. Complications undoubtedly require correction, but poor correlation of symptoms, occult blood loss, and endoscopic findings[7 8 12 14 16] means that one cannot be used to monitor another. Occult blood loss is particularly unhelpful,[37] and undue emphasis on endoscopic appearance may well prove inappropriate.

Conclusions

The high prevalence of unsuspected peptic ulcer disease[12-16] strongly suggests that in most cases no clinical consequences arise from untreated peptic ulcer disease during continuing treatment with non-steroidal anti-inflammatory drugs. What we need to know is which factors (other than being old and female) determine the development of complications so that they (for example, individual non-steroidal anti-inflammatory drugs) may be eliminated and prophylactic approaches tested in high risk patients taking the drugs. Results of well designed studies that answer such questions and provide management guidelines are eagerly awaited.

1 Roth SH, Bennett RE. Nonsteroidal anti-inflammatory drug gastropathy. Recognition and response. *Arch Intern Med* 1987;**147**:2093-100.
2 Fromm D. How do non-steroidal anti-inflammatory drugs affect gastric mucosal defences? *Clin Invest Med* 1987;**10**:251-8.
3 Garner A, Allen A, Rowe PH. Gastroduodenal mucosal defence mechanisms and the action of non-steroidal anti-inflammatory agents. *Scand J Gastroenterol* 1987;**22**(suppl 127):29-34.
4 Graham DY, Smith JL. Aspirin and the stomach. *Ann Intern Med* 1986;**104**: 390-8.
5 Rees WDW, Turnberg LA. Reappraisal of the effect of aspirin on the stomach. *Lancet* 1980;ii:410-3.
6 Somerville KW, Hawkey CJ. Non-steroidal anti-inflammatory agents and the gastrointestinal tract. *Postgrad Med J* 1986;**62**:23-8.
7 Semble EL, Wu WC. Anti-inflammatory drugs and gastric mucosal damage. *Semin Arthritis Rheum* 1987;**16**:271-86.
8 Katzka DA, Sunshine AG, Cohen S. The effect of nonsteroidal anti-inflammatory drugs on upper gastrointestinal tract symptoms and mucosal integrity. *J Clin Gastroenterol* 1987;**9**:142-8.
9 Kurata JH, Elashoff JD, Grossman MI. Inadequacy of the literature on the relationship between drugs, ulcers, and gastrointestinal bleeding. *Gastroenterology* 1982;**82**:373-6.
10 Doherty M, Hunt RH, Langman MJS, *et al.* Management of NSAID induced gastrointestinal disturbance. *Ann Rheum Dis* 1987;**46**:640-3.
11 Sladen G. Peptic ulcer, nonsteroid anti-inflammatory drugs and the rheumatic diseases. *Br J Rheumatol* 1986;**25**:330-2.
12 Silvoso GR, Ivey KJ, Butt JH, *et al.* Incidence of gastric lesions in patients with rheumatic disease on chronic aspirin therapy. *Ann Intern Med* 1979;**91**: 517-20.
13 Sun DE, Roth SE, Mitchell CS, Englund DW. Upper gastrointestinal disease in rheumatoid arthritis. *American Journal of Digestive Diseases* 1974;**19**: 405-18.
14 Caruso I, Bianchi Porro G. Gastroscopic evaluation of anti-inflammatory agents. *Br Med J* 1980;**280**:75-8.
15 Malone DE, McCormick PA, Daly L, *et al.* Peptic ulcer in rheumatoid arthritis—intrinsic or related to drug therapy? *Br J Rheumatol* 1986;**25**: 342-4.
16 Farah D, Sturrock RD, Russell RI. Peptic ulcer in rheumatoid arthritis. *Ann Rheum Dis* 1988;**47**:478-80.
17 Somerville K, Faulkner G, Langman M. Non-steroidal anti-inflammatory drugs and bleeding peptic ulcer. *Lancet* 1986;i:462-3.
18 Walt R, Katschinski B, Logan R, Ashley J, Langman M. Rising frequency of ulcer perforation in elderly people in the United Kingdom. *Lancet* 1986; i:489-92.
19 Matthewson K, Pugh S, Northfield TC. Which peptic ulcer patients bleed? *Gut* 1988;**29**:70-4.
20 Collier DStJ, Pain JA. Non-steroidal anti-inflammatory drugs and peptic ulcer perforation. *Gut* 1985;**26**:359-63.
21 Langman MJS, 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.
22 Committee on Safety of Medicines. Non-steroidal anti-inflammatory drugs and serious gastrointestinal adverse reactions—2. *Br Med J* 1986;**292**: 1190-1.
23 Rooney PJ, Kean WF. Reinforcement of bias in the medical literature: nonsteroidal anti-inflammatory drugs and the stomach—a case in point. *Br J Rheumatol* 1987;**26**:231-3.
24 Croker JR, Cotton JB, Boyle AC, Kinsella P. Cimetidine for peptic ulcer in patients with arthritis. *Ann Rheum Dis* 1980;**39**:275-8.
25 Gerber LH, Rooney PJ, McCarthy DM. Healing of peptic ulcers during continuing anti-inflammatory drug therapy in rheumatoid arthritis. *J Clin Gastroenterol* 1981;**3**:7-11.
26 O'Laughlin JC, Silvoso GR, Ivey KJ. Healing of aspirin-associated peptic ulcer disease despite continued salicylate ingestion. *Arch Intern Med* 1981;**141**:781-3.
27 Manniche C, Malchow-Moller A, Anderson JR, *et al.* Randomised study of the influence of non-steroidal anti-inflammatory drugs on the treatment of peptic ulcer in patients with rheumatoid arthritis. *Gut* 1987;**28**:226-9.
28 Davies J, Collins AJ, Dixon STJ. The influence of cimetidine on peptic ulcer in patients with arthritis taking anti-inflammatory drugs. *Br J Rheumatol* 1986;25:54-8.
29 Hansen TM, Matzen P, Madsen P. Endoscopic evaluation of the effect of indomethacin capsules and suppositories on the gastric mucosa in rheumatic patients. *J Rheumatol* 1984;**11**:484-7.
30 Hogan DL, Thomas FJ, Isenberg JI. Cimetidine decreases aspirin-induced gastric mucosal damage in humans. *Alimentary Pharmacology and Therapeutics* 1981;**1**:383-90.
31 Kimmey MB, Silverstein FE. Role of H2-receptor blockers in the prevention of gastric injury resulting from non-steroidal anti-inflammatory agents. *Am J Med* 1988;**84**:49-52.
32 Tesler MA, Lim ES. Protection of gastric mucosa by sucralfate from aspirin-induced erosions. *J Clin Gastroenterol* 1981;**3**:175-9.
33 Lanza FL, Aspinall RL, Swabb EA, Davies RE, Rack MF, Rubin A. A double-blind placebo controlled endoscopic comparison of the cytoprotective effects of misoprostol and cimetidine on tolmetin induced gastric mucosal injury. *Gastroenterology* 1987;**92**:1491.
34 Steil D, Ellard KT, Hills LJ, Brooks P. Protective effect of enprostil against aspirin-induced gastroduodenal mucosal injury in man. *Am J Med* 1986; **81**:54-8.
35 O'Laughlin JC, Silvoso GK, Ivey KJ. Resistance to medical therapy of gastric ulcers in rheumatic disease patients taking aspirin: a double-blind study with cimetidine and follow-up. *Dig Dis Sci* 1982;**27**:976-80.
36 Roth SH, Bennett RE, Mitchell CS, Hartman RJ. Cimetidine therapy in non-steroidal anti-inflammatory drug gastropathy. Double-blind long-term evaluation. *Arch Intern Med* 1987;**147**:1798-801.
37 Collins AJ, Du Toit JA. Upper gastrointestinal findings and faecal occult blood in patients with rheumatic disease taking nonsteroidal antiinflammatory drugs. *Br J Rheumatol* 1987;**26**:295-8.