

Review: Misoprostol, double-dose H₂-receptor antagonists, and proton-pump inhibitors reduce GI ulcers in long-term NSAID use

Rostom A, Wells G, Tugwell P, et al. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database Syst Rev.* 2000;(4):CD002296 (latest version 21 Aug 2000)(also published in *J Rheumatol.* 2000;27:2203-14).

QUESTION

In patients requiring long-term nonsteroidal anti-inflammatory drugs (NSAIDs), are prostaglandin analogs (PAs), H₂-receptor antagonists (H₂RAs), and proton-pump inhibitors (PPIs) effective at reducing NSAID-induced gastrointestinal (GI) ulcers?

DATA SOURCES

Studies were identified by searching MEDLINE (1966 to January 2000) and EMBASE/Excerpta Medica (to February 1999), the Cochrane Controlled Trials Register (1973 to 1999), *Current Contents* (6 mo before January 2000), and conference proceedings; by reviewing bibliographies of retrieved studies, including reviews; and through personal contact with experts and companies.

STUDY SELECTION

2 reviewers independently selected randomized controlled trials published in any language. Studies were selected if they examined PA, H₂RA, or PPI effects on preventing NSAID-induced upper GI toxicity in adults; if the duration of NSAID exposure was > 3 weeks; and if endoscopic ulcers were ≥ 3 mm in diameter. Studies that used healthy participants were excluded.

COMMENTARY

Traditional NSAIDs cause endoscopic ulcers in up to 40% of patients who have long-term exposure, but only 15% of the ulcers ever become clinically manifest, with an annual incidence of serious complications of approximately 1.5% (1). Older patients (> 65 y) and those with past peptic ulcer or comorbid conditions are at high risk.

The meta-analysis by Rostom and colleagues reports that double-dose H₂RA and PPI therapy similarly reduce the risk for gastric and duodenal ulcers. In the absence of head-to-head trials, however, the results should be viewed cautiously. It has not been established that a reduction in ulcers will translate into a similar reduction in complications. The Misoprostol Ulcer Complication Outcomes Safety Assessment (MUCOSA) trial reported a 40% risk reduction for ulcer complications with misoprostol, 800 µg (1), compared with the 75% risk reduction in endoscopic gastric ulcers reported by Rostom and colleagues. The number needed to treat (NNT) to prevent complications is uncertain (NNT 264, 95% CI 132 to 5709)‡ and is probably overestimated by using endoscopic ulcer rates.

Standard-dose H₂RA therapy was not protective against gastric ulcers. The risk for ulcer complications may be higher in those long-term NSAID users who are rendered symptom free on standard H₂RA or antacid therapy (2).

DATA EXTRACTION

2 reviewers independently extracted data on study methods, patient characteristics, interventions, outcome, and study quality (Jadad scale). The main outcome was number of patients with endoscopic ulcers.

MAIN RESULTS

35 studies met the selection criteria: 19 trials of misoprostol (PA), 9 of standard-dose H₂RA, 3 of double-dose H₂RA, and 5 of PPI. Misoprostol and PPI reduced gastric and duodenal ulcers better than did placebo (Table). Standard-dose H₂RA reduced only duodenal ulcers better than did placebo (Table).

Occurrence of endoscopic ulcers in patients receiving misoprostol (miso), standard- or double-dose H₂-receptor antagonist (st-H₂RA or dd-H₂RA), or proton-pump inhibitor (PPI) treatments for ≥ 3 months compared with placebo (PI) during nonsteroidal anti-inflammatory drug (NSAID) use*

Comparisons	Ulcer	Weighted event rates	RRR (95% CI)	NNT (CI)†
Miso vs PI	Gastric	2.5% vs 12.9%	75% (67 to 82)	10 (9 to 12)
	Duodenal	2.6% vs 6.1%	54% (34 to 69)	29 (20 to 53)
st-H ₂ RA vs PI	Duodenal	11.5% vs 25.9%	64% (26 to 82)	29 (17 to 84)
dd-H ₂ RA vs PI	Gastric	2.0% vs 5.5%	56% (26 to 74)	7 (5 to 17)
	Duodenal	3.4% vs 13.6%	74% (35 to 89)	10 (7 to 25)
PPI vs PI	Gastric	6.6% vs 19.6%	61% (45 to 73)	8 (6 to 13)
	Duodenal	1.7% vs 10.3%	81% (60 to 91)	12 (9 to 20)

*Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article using a fixed-effects model.

†Calculated for endoscopic, not clinical, outcomes.

CONCLUSIONS

In patients requiring long-term nonsteroidal anti-inflammatory drugs (NSAIDs), misoprostol, double-dose H₂-receptor antagonists, and proton-pump inhibitors reduce NSAID-induced endoscopic gastric and duodenal ulcers. Standard-dose H₂-receptor antagonists do not reduce gastric ulcers.

Source of funding: No external funding.

For correspondence: Dr. A. Rostom, Division of Gastroenterology, Ottawa Hospital-Civic Site, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada. FAX 613-761-5068. ■

In high-risk patients requiring long-term NSAIDs, clinicians now have a choice: Switch to a Cox-2 inhibitor, or prescribe ulcer prophylaxis with misoprostol or potent antisecretories. Misoprostol definitely reduces ulcer complications. Diarrhea, however, is a dose-dependent side effect. Because 75% of patients tolerate misoprostol, 800 µg daily, it is probably a cost-effective option (depending on local drug costs).

At least 2 clinical questions still need to be fully addressed: Does *Helicobacter pylori* influence the efficacy of ulcer prophylaxis therapy, and what is optimal therapy for the large number of high-risk patients taking low-dose aspirin for cardiovascular prophylaxis?

Nicholas J. Talley, MD, PhD
University of Sydney
Penrith, New South Wales, Australia

‡ NNT and CI calculated from data in reference 1.

References

- Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1995;123:241-9.
- Singh G, Ramey DR, Morfeld D, et al. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch Intern Med.* 1996;156:1530-6.