

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 non-steroidal anti-inflammatory drugs (NSAIDs), are prostaglandin analogues (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 (1973-99), 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 randomised 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.

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 placebo (table). Standard dose H₂RA reduced only duodenal ulcers better than placebo (table).

Conclusions

In patients requiring long term non-steroidal 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 +1 613 761 5068.

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 (pl) during non-steroidal anti-inflammatory drug (NSAID) use*

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

COMMENTARY

Traditional NSAIDs cause endoscopic ulcers in up to 40% of patients who have long term exposure, but only 15% of the ulcers ever 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 *et al* reports that double dose H₂RA and PPI treatment 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 mg,² compared with the 75% risk reduction in endoscopic gastric ulcers reported by Rostom *et al*. 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 treatment 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 treatment.²

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 continues to be the best treatment to reduce complications. Diarrhoea, however, is a dose dependent side effect. Because 75% of patients tolerate misoprostol, 800 mg daily, it is a cost effective option (depending on local drug costs).

At least 2 clinical questions still need to be addressed: does *Helicobacter pylori* influence the efficacy of ulcer prophylaxis treatment, and what is optimal treatment 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.

- 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.