Review: misoprostol, double dose $H_2$ receptor antagonists, and proton pump inhibitors reduce GI ulcers in long term NSAID use


QUESTION: In patients requiring long term non-steroidal anti-inflammatory drugs (NSAIDs), are prostaglandin analogues (PAs), $H_2$ receptor antagonists ($H_2$RAs), 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 (1993–99), 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, $H_2$RA, 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.

Main results
36 studies met the selection criteria: 19 trials of misoprostol (PA), 9 of standard dose $H_2$RA, 3 of double dose $H_2$RA, and 5 of PPI. Misoprostol and PPI reduced gastric and duodenal ulcers better than placebo (table). Standard dose $H_2$RA reduced only duodenal ulcers better than placebo (table).

Conclusions
In patients requiring long term non-steroidal anti-inflammatory drugs (NSAIDs), misoprostol, double dose $H_2$ receptor antagonists, and proton pump inhibitors reduce NSAID induced endoscopic gastric and duodenal ulcers. Standard dose $H_2$ receptor antagonists do not reduce gastric ulcers.

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 1.3%. 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 $H_2$RA 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, 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 $H_2$RA 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 $H_2$RA or antacid treatment. 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 antisecretaries. 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?

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