Review: Misoprostol or COX-2–specific or selective NSAIDs reduce gastrointestinal complications and symptomatic ulcers

Hooper L, Brown TJ, Elliott R, et al. **The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review.** BMJ. 2004;329:948.

QUESTION

In patients taking nonselective nonsteroidal antiinflammatory drugs (NSAIDs), what are the effects of 5 gastroprotective strategies (NSAIDs plus H_2-receptor antagonists, NSAIDs plus proton-pump inhibitors, NSAIDs plus misoprostol, cyclooxygenase-2 [COX-2]–selective NSAIDs alone, and COX-2–specific NSAIDs alone) for preventing gastrointestinal (GI) toxicity?

METHODS

Data sources: 5 databases, bibliographies of relevant studies, and contacting authors.

Study selection and assessment: Randomized controlled trials (RCTs) ≥ 21 days in duration comparing 1 of the 5 gastroprotective strategies with nonselective NSAIDs alone on outcomes of GI toxicity. Quality assessment included randomization procedures, allocation concealment, blinding, and follow-up.

Outcomes: Primary outcomes included serious GI complications (e.g., hemorrhage, hemorrhagic erosions, recurrent upper GI bleeding, perforation, and pyloric obstruction) and symptomatic ulcers.

MAIN RESULTS

112 RCTs (n = 74 666) met the selection criteria. 15 RCTs (n = 2621) compared H_2-receptor antagonists with placebo, 6 RCTs (n = 1358) compared proton-pump inhibitors with placebo, 23 RCTs (n = 16 945) compared misoprostol with placebo, 51 RCTs (n = 28 178) compared COX-2–selective drugs with nonselective NSAIDs, and 17 RCTs (n = 25 564) compared COX-2–specific drugs with nonselective NSAIDs. Effects of serious GI complications and symptomatic ulcers are in the Table.

CONCLUSIONS

In patients taking NSAIDs, misoprostol or COX-2–specific NSAIDs alone reduce serious gastrointestinal complications and symptomatic ulcers more than nonselective NSAIDs alone. Misoprostol, proton-pump inhibitors, and COX-2–selective and COX-2–specific NSAIDs reduce symptomatic ulcers more than NSAIDs alone.

Source of funding: NHS Executive.

For correspondence: Dr. L. Hooper, University of East Anglia, Norwich, England, UK. E-mail l.hooper@uea.ac.uk.

Effects of 5 gastroprotective strategies in patients taking nonsteroidal antiinflammatory drugs at ≥ 21 days*

Outcomes	Number of trials (n)	Comparisons	Weighted event rates	RRR (95% CI)	NNT (CI)
Serious gastrointestinal complications	4 (894)	H_2-receptor antagonist vs placebo	0% vs 0.25%	39% (–280 to 90)	Not significant
	4 (1108)	Proton-pump inhibitor vs placebo	0.36% vs 0.46%	46% (–185 to 90)	Not significant
	10 (11 507)	Misoprostol vs placebo	0.53% vs 0.86%	41% (7 to 62)	306 (161 to 3144)
	19 (22 717)	COX-2–selective NSAIDs vs nonselective NSAIDs	0.18% vs 0.24%	34% (–15 to 63)	Not significant
	11 (21 454)	COX-2–specific NSAIDs vs nonselective NSAIDs	0.45% vs 0.73%	45% (20 to 62)	354 (208 to 1200)
				RRI (CI)	NNH
Symptomatic ulcers	2 (343)	H_2-receptor antagonist vs placebo	0.48% vs 0%	25% (–89 to 1378)	Not significant
				RRR (CI)	NNT (CI)
	2 (343)	Proton-pump inhibitor vs placebo	1.1% vs 9.7%	91% (53 to 98)	12 (8 to 25)
	2 (8913)	Misoprostol vs placebo	0.35% vs 0.89%	64% (33 to 80)	185 (119 to 426)
	16 (21 371)	COX-2–selective NSAIDs vs nonselective NSAIDs	0.41% vs 0.57%	58% (35 to 73)	622 (266 to ∞)
	11 (21 722)	COX-2–specific NSAIDs vs nonselective NSAIDs	1.1% vs 1.8%	51% (38 to 62)	142 (91 to 316)

*Abbreviations defined in Glossary; weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from data in article using a random-effects model.

COMMENTARY

Several important conclusions can be drawn from this review by Hooper and colleagues. First, although the investigators found that COX-2–selective NSAIDs reduced the risk for symptomatic ulcers and gastrointestinal symptoms, no reductions were seen in endoscopic ulcers and ulcer complications. This finding raises concerns that COX-2–selective NSAIDs might actually do more harm than good by masking dyspeptic symptoms and should be avoided in high-risk patients. Second, although COX-2–specific NSAIDs, as a class, seem to reduce the risk for ulcer complications, only rofecoxib has been clearly shown to achieve this goal. Third, the strongest evidence for prevention of NSAID-induced ulcer complications was found with misoprostol, but its use is limited by other adverse effects. Although low-dose misoprostol is better tolerated, it fails to prevent ulcer complications (1). Fourth, no evidence exists from randomized, placebo-controlled trials that proton-pump inhibitors prevent ulcer complications as an adjunct to NSAID therapy.

This meta-analysis did not include direct comparisons of some of the treatment options. It is therefore unknown whether proton-pump inhibitors are more effective than double-dose H_2-receptor antagonists or full-dose misoprostol (2). Although celecoxib was comparable to omeprazole and diclofenac for reducing the risk for recurrent ulcer bleeding (3), neither treatment could eliminate the hazard of ulcers in high-risk patients (4).

Vincent W.S. Wong, MBChB, MRCP
Francis K.L. Chan, MBChB, MD, FRCP, FACG
Chinese University of Hong Kong
Shatin, Hong Kong, China

References

1. **Chan FK, Sung JJ, Ching JY, et al.** Aliment Pharmacol Ther. 2001;15:19-24.
2. **Graham DY.** Helicobacter. 2002;7:1-8.
3. **Chan FK, Hung LC, Suen BY, et al.** N Engl J Med. 2002;347:2104-10.
4. **Chan FK, Hung LC, Suen BY, et al.** Gastroenterology. 2004;127:1038-43.