Misoprostol in the prevention of NSAID-induced ulcers in adults

QUESTION
¿What is the effectiveness of misoprostol in the prevention of NSAID-induced ulcers in adults?

CONTEXT	NSAID-induced gastroduodenal ulcers
Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed medications worldwide. There is strong evidence about their gastrointestinal toxicity, causing nausea, dyspepsia and gastroduodenal ulcers. It is thought that this toxicity is due to the inhibition of prostaglandin production. Prostaglandins are a group of substances which protect the intestinal mucosa integrity by maintaining mucosal blood flow, promoting bicarbonate and mucus formation and reducing acid secretion. The introduction of selective inhibitors of COX-2 (coxib) reduced NSAIDs prescriptions, but the discovery of coxib's cardiovascular adverse events raised again NSAIDs prescriptions. There are different gastro-protective agents that are used in combination with NSAIDs to prevent their gastrointestinal toxicity: proton pump inhibitors (PPI), H2 receptor antagonists and prostaglandin analogues like **misoprostol**.	

INTERVENTION	Misoprostol
Endoscopic gastric ulcers Misoprostol compared to placebo reduced the incidence of endoscopic gastric ulcers. There is a dose-response relation being more effective 800 µg than 400-600 µg. *High quality evidence.*	
Endoscopic duodenal ulcers Misoprostol reduced the incidence of endoscopic duodenal ulcers compared to placebo. *High quality evidence.* Misoprostol was not different to ranitidine in the prevention of endoscopic duodenal ulcers. *Low quality evidence.* The PPI are superior to misoprostol in the prevention of endoscopic duodenal ulcers. *Moderate quality evidence.*	
Ulcer complications Misoprostol 800 µg is superior to placebo reducing the incidence of ulcer complications. *High quality evidence.*	
Adverse events Misoprostol produced more withdrawals due to adverse events than placebo or PPIs. *High quality evidence.* Misoprostol compared to placebo produced more withdrawals due to nausea, abdominal pain and diarrhea. *Moderate quality evidence.*	

Summary of evidence	
Benefits	A Cochrane systematic review (39 RCTs) was found [1]. It assessed the use of misoprostol (23 RCTs) for the prophylaxis of NSAID-induced gastroduodenal ulcers. The studies included patients treated with NSAID during at least 3 weeks. The review showed that misoprostol compared to placebo reduced the risk of developing **endoscopic gastric** (11 RCTs, 351 events, RR 0.26, 95% CI 0.17 to 0.39) and **duodenal ulcers** (8 RCTs, 133 events, RR 0.42, 95% CI 0,22 to 0,81) in the long term (12 weeks). The absolute risk reduction was of 10.7% and of 2.5% respectively. All evaluated dosages reduced the risk of developing endoscopic ulcers. A **dose-response relation** was found for endoscopic gastric ulcers, but not for duodenal ulcers. Misoprostol was superior to ranitidine (150 mg twice daily) in the prevention of gastric ulcers (2 RCTs, 19 events, RR 0.12, 95% CI 0.03 to 0.51) but not in the prevention of duodenal ulcers (2 RCTs, 4 events, RR 1.00, 95% CI 0.14 to 7.05). Misoprostol compared to PPIs was inferior in preventing duodenal ulcers (1 RCT, 37 events, RR 0.25, 95% CI 0.11 to 0.56) and there were no differences in preventing gastric ulcers (2 RCTs, 120 events, RR 1.61, 95% CI 0.85 to 3.06). One study found that misoprostol 800 µg compared to placebo reduced the risk of **ulcer complications** (8843 patients, 49 events, RR 0.49, 95% CI 0.27 to 0.89) at 3-24 months. Misoprostol at inferior doses (400-600 µg) did not reach a significant difference.
Risks	Misoprostol showed a slight increase in **dropouts due to adverse events** compared to placebo (12 RCTs, 11021 patients, 533 events, RR 1.26, 95% CI 1.07 to 1.48) and to PPIs (3 RCTs, 65 events, RR 0.48, 95% CI 0.29 to 0.78). Misoprostol compared to placebo presented a great risk of withdrawals due to **nauseas** (6 RCT, 533 events, RR 1.26, 95% CI 1.07 to 1.48), **diarrhea** (10 RCT, 667 events, RR 2.36, 95% CI 2.01 to 2.77) and **abdominal pain** (6 RCT, 11098 events, RR 1.36, 95% CI 1.20 to 1.55). When analyzing by dose, only the dose of 800 µg showed a statistically significant excess risk of withdrawals due to diarrhea (RR 2.45, 95% CI 2.09 to2.88) and abdominal pain (RR 1.38, 95% CI 1.17 to 1.63)**.** Misoprostol compared to ranitidine also presented a great risk of withdrawals due to abdominal pain (1 RCT, 20 events, RR 3,00, 95% IC 1.11 to 8.14). There were no differences in the withdrawals due to dyspepsia, constipation, flatulence or vomiting when compared to placebo.
Applicability	The results showed a benefit of misoprostol compared to placebo in the prophylaxis of NSAID-induced gastroduodenal ulcers, especially in gastric ulcers.
Comment	The results showed that misoprostol reduced the risk of developing endoscopic gastric and duodenal NSAID-induced ulcers and their complications (doses of 800µg/day), despite it was associated with adverse events, especially at high doses. Lower doses were associated with less adverse events (diarrhea) but they were less effective in the prevention of endoscopic gastric ulcers. The effects of low doses of misoprostol on the prevention of ulcer complications are not known. It is difficult to establish the relative efficacy of different prophylactic drugs because head-to-head comparisons usually use less effective doses of the comparison drug. It seems that misoprostol is superior to ranitidine in the reduction of gastric ulcers and that omeprazol is superior to misoprostol in the prevention of duodenal ulcers, not being differences in the prevention of gastric ulcers. Misoprostol was associated with more adverse events than the other drugs (H2 receptor antagonists and PPI).
Costs	A health technology assessment which evaluated the cost-effectiveness of five therapeutic strategies for rheumatoid arthritis was found [2]: 1) NSAID without prophylaxis, 2) NSAID with H2 receptor antagonists 3) NSAID with misoprostol, 4) NSAID with PPIs, 5) COX-2. Compared to NSAID alone, NSAID with misoprostol and NSAID with H2 receptors antagonists did not have an additional cost to prevent an endoscopic ulcer. In contrast, NSAID with PPI and COX-2 had an additional cost of £454 (£251 a £877) and £301 (£189 a £418) respectively to prevent an ulcer.

NSAID: Non steroidal anti inflamatory drugs.

1. Rostom A,Dube C,WellsGA, Tugwell P,Welch V, Jolicoeur E,McGowan J, Lanas A. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD002296. DOI: 10.1002/14651858.CD002296.
2. Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al. A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling. Health Technol Assess 2006;10(38).

TABLA	GRADE evaluation of clinical outcomes.								
Number of studies (N))	**Outcome**	**Comparison**	**Evidence type**	**Quality**	**Consistency**	**Direct evidence**	**Precision**	**GRADE**	**Comments**
11 (3.641)	Endoscopic gastric ulcers	Misoprostol Placebo	4	-1	0	0	0	High	Quality: Doubs in allocation concealment. Moderate heterogeneity justified in the subgroups analysis. There is a dose-response relation.
2 (599)		Misoprostol Ranitidine	4	0	0	0	-2	Low	Very low number of events.
2 (917)		Misoprostol PPI	4	-1	0	0	-1	Low	Considerable heterogeneity (I^2=60%) probably due to different doses. Very low number of events.
8 (2.785)	Endoscopic duodenal ulcers	Misoprostol Placebo	4	-1	0	0	0	Moderate	See comments in “endoscopic gastric ulcers””.
2 (599)		Misoprostol Ranitidine	4	0	0	0	-2	Low	Very low number of events.
1 (570)		Misoprostol PPI	4	0	0	0	-1	Moderate	Only one RCT. Very low number of events.
2 (9.276)	Ulcer complications	Misoprostol Placebo	4	0	0	0	0	High	
12 (11.021)	Adverse-events dropouts	Misoprostol Placebo	4	0	0	0	0	High	
3 (1019)		Misoprostol PPI	4	0	0	0	0	High	
Evidence type: 4 = RCT; 2 = Observational; 1 = no analytic /expert opinion									