Prevention of NSAID-induced gastroduodenal ulcers (Review)

Rostom A, Dube C, Wells GA, Tugwell P, Welch V, Jolicoeur E, McGowan J, Lanas A

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 6

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Prevention of NSAID-induced gastroduodenal ulcers

Alaa Rostom[1], Catherine Dube[1], George A Wells[2], Peter Tugwell[3], Vivian Welch[4], Emilie Jolicoeur[5], Jessie McGowan[6], Angel Lanas[7]

[1]University of Calgary Department of Medicine / Gastroenterology, Foothills Medical Centre, Calgary, Canada. [2]Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada. [3]Centre for Global Health, Institute of Population Health, Faculty of Medicine, University of Ottawa, Ottawa, Canada. [4]Centre for Global Health, Institute of Population Health, University of Ottawa, Ottawa, Canada. [5]Division of Gastroenterology, A-1 Endoscopy Unit, Ottawa, Canada. [6]Institute of Population Health/Ottawa Health Research Institute, University of Ottawa, Ottawa, Canada. [7]University of Zaragoza, Zaragoza, Spain

Contact address: Alaa Rostom, University of Calgary Department of Medicine / Gastroenterology, Foothills Medical Centre, 1403 - 29 St. N.W, Calgary, Alberta, T2N 2T9, Canada. arostom@ucalgary.ca.

Editorial group: Cochrane Upper Gastrointestinal and Pancreatic Diseases Group.
Publication status and date: Edited (no change to conclusions), published in Issue 6, 2011.
Review content assessed as up-to-date: 11 May 2009.

Citation: Rostom A, Dube C, Wells GA, 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.

ABSTRACT

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are important agents in the management of arthritic and inflammatory conditions, and are among the most frequently prescribed medications in North America and Europe. However, there is overwhelming evidence linking these agents to a variety of gastrointestinal (GI) toxicities.

Objectives

To review the effectiveness of common interventions for the prevention of NSAID induced upper GI toxicity.

Search methods

We searched MEDLINE from 1966 to May 2009, Current Contents for six months prior to May 2009, EMBASE to May 2009, and the Cochrane Controlled Trials Register from 1973 to May 2009. Recent conference proceedings were reviewed and content experts and companies were contacted.

Selection criteria

Randomized controlled clinical trials (RCTs) of prostaglandin analogues (PA), H2-receptor antagonists (H2RA) or proton pump inhibitors (PPI) for the prevention of chronic NSAID induced upper GI toxicity were included.

Data collection and analysis

Two independent authors extracted data regarding population characteristics, study design, methodological quality and number of participants with endoscopic ulcers, ulcer complications, symptoms, overall drop-outs, drop outs due to symptoms. Dichotomous data were pooled using RevMan 5.0. Heterogeneity was evaluated using a chi square test, and the I square statistic.

Main results

Forty-one RCTs met the inclusion criteria. All doses of misoprostol significantly reduced the risk of endoscopic ulcers. Misoprostol 800 ug/day was superior to 400 ug/day for the prevention of endoscopic gastric ulcers (RR 0.17, and RR 0.39 respectively, P=0.0055). A dose response relationship was not seen with duodenal ulcers. Misoprostol caused diarrhoea at all doses, although significantly more at 800 ug/day than 400 ug/day (P=0.0012). Misoprostol also reduced the risk of clinical ulcer complications.

Standard doses of H2RAs were effective at reducing the risk of endoscopic duodenal (RR 0.36; 95% CI 0.18 to 0.74) but not gastric ulcers (RR 0.73; 95% CI 0.50 to 1.08). Both double dose H2RAs and PPIs were effective at reducing the risk of endoscopic duodenal and gastric ulcers (RR 0.44; 95% CI 0.26 to 0.74) and RR=0.40;95% CI; 0.32-0.51 respectively for gastric ulcer), and were better tolerated than misoprostol.

Authors' conclusions

Misoprostol, PPIs, and double dose H2RAs are effective at preventing chronic NSAID related endoscopic gastric and duodenal ulcers. Lower doses of misoprostol are less effective and are still associated with diarrhoea. In patients with previous NSAID bleeds, a COX-2 inhibitor alone is equivalent to a tNSAID+PPI, though the re-bleeding rates with both strategies are still relatively high. A strategy of a COX-2 inhibitor+PPI appears to offer the greatest GI safety in high risk patients.

PLAIN LANGUAGE SUMMARY

Medications to prevent NSAID-induced gastroduodenal ulcers

The results of this meta-analysis demonstrate that misoprostol, proton pump inhibitors, and double doses of H2-receptor antagonists are effective at reducing the risk of both gastric and duodenal non steroidal anti-inflammatory (NSAID) medications induced ulcers. In high risk patients, the use of a traditional NSAID + PPI appears equivalent to a COX-2 inhibitor alone. The most effective strategy in high risk GI patients appears to be the combination of a COX-2 inhibitor + PPI.

BACKGROUND

Description of the condition

Non-steroidal anti-inflammatory drugs (NSAIDs) are important agents in the management of arthritic and inflammatory conditions, and are among the most frequently prescribed medications in North America and Europe (Fries 1990; Wallace 1996). However, there is overwhelming evidence linking these agents to a variety of gastrointestinal (GI) toxicities (Fries 1990; Stalnikowicz 1993; Smalley 1996; Fries 1991; Griffin 1988; Bollini 1992; McMahon 1997; Gabriel 1991; Langman 1994; MacDonald 1997; Armstrong 1987; Silverstein 1995). Common side effects such as nausea and dyspepsia correlate poorly with serious adverse GI events (Silverstein 1995; Larkai 1987). While endoscopic ulcers can be documented in up to 40% of chronic NSAID users (Stalnikowicz 1993), it is estimated that as many as 85% of these never become clinically apparent (Silverstein 1995; Maetzel 1998). Serious NSAID induced GI complications such as haemorrhage, perforation or death are much less common, occurring collectively with an incidence of about 1.5% per year (Silverstein 1995). However, the number of individuals prescribed NSAIDs and the potential for life-threatening adverse events make NSAID toxicity an important clinical and economic problem.

Description of the intervention

In the late 1990s, evidence from non-clinical and early clinical trials suggested that the gastrointestinal (GI) safety of the newer cyclooxygenase-2 (COX-2) selective NSAIDs may be such that a fundamental change in clinicians' choice from the use of standard NSAIDs with a gastro-protective agent to monotherapy with a COX-2 selective NSAID (COX-2 inhibitors) was on the horizon. However, much has changed since then in the NSAID field. The release of the cyclo-oxygenase-2 selective inhibitors (COX-2s) brought about significant changes in the NSAID market place. Traditional nonselective NSAIDs (tNSAIDs) prescription numbers fell rapidly, to be replaced by COX-2 prescriptions. Additionally, overall NSAID prescriptions rose in number suggesting that

clinicians were starting COX-2s on patients who were not considered candidates for tNSAIDs. The rise of COX-2s continued until 2004 when greater data regarding their cardiovascular and other toxicities became available, leading to the withdrawal of most of these agents from the market over the following years. Non-naproxen tNSAIDs were also suggested to have important cardiovascular toxicity, leading to considerable uncertainty amongst clinicians treating patients with arthritis and other pain disorders as to the choice of agent to use (Rostom 2009; Rostom 2009b).

How the intervention might work

NSAIDs are believed to cause gastroduodenal mucosal injury through their inhibition of mucosal prostaglandin production. Prostaglandins promote mucosal integrity through several mechanisms including: maintenance of mucosal blood flow; promoting mucosal bicarbonate formation; promoting mucosal mucus formation; and reducing mucosal acid secretion. Three intervention classes were assessed in this review: misoprostol; H2RAs; and PPIs. H2RAs and PPIs are believed to exert their gastro-protective effects from NSAID gastroduodenal injury through the reduction of gastric acid secretion. Prostaglandin analogues such as misoprostol are believed to exert their gastro-protection by restoring mucosal prostaglandin effects (Rostom 2004).

Why it is important to do this review

NSAIDs are amongst the most commonly prescribed medications worldwide, and are associated with important gastrointestinal harms. The introduction of COX-2's with their greater GI safety resulted in important declines in tNSAID prescriptions. However, with the discovery of cardiovascular (CVS) and other adverse effects associated with COX-2s, practitioners are returning to prescribing tNSAIDs with a gastro-protective agent in an effort to overcome some of the adverse GI effects of tNSAIDs.

OBJECTIVES

The primary objective of this study was to systematically review the available literature on the effectiveness of the prostaglandin analogue (PA) misoprostol, H2-receptor antagonists (H2RA), and proton pump inhibitors (PPI) for the prevention of NSAID induced upper GI toxicity, among patients requiring chronic NSAID use. The secondary objectives were to review the effect of these agents on NSAID induced GI symptoms, and to assess the relationship between the effectiveness of PAs at various doses and their associated drug induced adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials were eligible for this meta-analysis.

Types of participants

Participants were eligible if they had taken NSAIDs for greater than 3 weeks and were enrolled for the prophylaxis of NSAID-induced ulcers.

Types of interventions

Interventions that were examined include: H2-antagonists, proton pump inhibitors and misoprostol each used for the prophylaxis of NSAID induced gastroduodenal ulcers.

Types of outcome measures

Primary outcomes

For each study, the number of participants with: endoscopic ulcers; ulcer complications (haemorrhage, perforation, pyloric obstruction or death); symptoms (nausea, vomiting, dyspepsia, abdominal pain or diarrhoea); overall drop-outs; and drop outs due to symptoms were identified. Included studies were also classified into primary or secondary prophylaxis trials and by the time periods of outcome measures.

The primary outcomes were:

- endoscopic ulcers (gastric, duodenal and gastroduodenal);
- clinical ulcer complications.

Secondary outcomes

The secondary outcomes were:

- symptoms;
- drop-outs and drop outs due to symptoms

Search methods for identification of studies

Electronic searches

Randomized controlled clinical trials (RCTs) of PA, H2RA or PPIs for the prevention of NSAID induced upper GI toxicity were identified in accordance with published recommendations (Haynes 1994; Hunt 1997). This included identification of articles

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.