Non-Steroidal Anti-Inflammatories-induced Gastrointestinal Damage: Prevention strategies

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Abstract
Non-steroidal anti-inflammatories (NSAIDs) are among the most widely prescribed drugs nowadays. They are used in the treatment of a variety of diseases and are known to cause adverse events in the gastrointestinal tract. These events vary from mild discomfort to bleeding and hospitalization. In this review we discuss the strategies used to prevent these adverse events, how they work and which ones are more effective.

Introduction
Non-steroidal anti-inflammatories (NSAIDs) are among the most widely prescribed drugs nowadays [1]. Millions of NSAIDs are prescribed annually in the U.S.A., and about 30 millions are taken without prescription [2].

There are many known adverse events caused by the use of NSAIDs, such as dyspeptic symptoms, reported by 5-10% of the users [3,4]. If we look beyond dyspeptic symptoms, we can see that a 41% increase in NSAID use was accompanied by a 10% increase in hospitalization for upper GI bleeding (UGIB) [5].

It has been reported that the point prevalence of peptic ulcer disease in patients undergoing NSAID therapy ranges between 10% and 30%, and that is a 10- to 30-fold increase over that found in the general population [6]. These symptoms cause discontinuation of the treatment in 10% of patients [7].

The NSAIDs work by inhibiting cyclooxygenase (COX), the enzyme responsible for prostaglandin production. COX is available in two isoforms, COX-1 and COX-2. COX-1 is expressed in the gastrointestinal tract, probably to maintain the gastric mucosa integrity. COX-2 is induced during inflammatory processes. Based on this information, COX-2 selective inhibitors were developed to spare the GI mucosa (coxibs) [8,9].

Studies have compared the GI tolerability of selective and non-selective NSAIDs. The selective drugs were associated with less gastrointestinal adverse events, but they also cause some level of symptoms in the upper GI, requiring treatment [10,11].

Prevention
The strategy to prevent gastrointestinal (GI) damage is the concomitant use of gastro protective drugs, such as H2-receptor antagonists, misoprostol and proton-pump inhibitors (PPIs). PPIs are significantly better than H2 antagonists and misoprostol in healing NSAID-induced ulceration. The PPIs inhibit the final step in the formation of hydrochloric acid by blocking the H+/K+- ATPase enzyme [12].

The PPIs all have a similar structure: 2-pyridyl-methylsulfinyl benzimidazole; however, they differ according to their chemical stability under acidic and neutral pH, the cayestanes of the proton pump with which they bind, activation under acidic conditions, dissociation constant values, half-lives, bioavailability and metabolism. It is still unclear if the differences in chemical structure of PPIs translate into differences in clinical efficiency, but in a recent short-term (up to 5 days) comparative study, esomeprazole 40 mg treatment provided significantly greater gastric acid suppression than lansoprazole 30mg or pantoprazole 40 mg (all once daily) in patients receiving traditional NSAIDs or coxibs [13].

Since only active proton pumps are inhibited by PPIs and not all pumps are active simultaneously, single doses of PPI do not cause a profound reduction in acid secretion. It takes about 7 days for a PPI to achieve steady state. Patients should be advised that PPIs are not meant for "as needed basis" use for prevention of gastro duodenal ulcers caused by NSAIDs, considering that the acid inhibition will probably be inadequate [14].

Nowadays we can find a variety of clinical trials in the literature that reinforce the benefits of concomitant use of a PPI and NSAID in the prevention of gastro duodenal injuries [15-24].

Studies have suggested that effective PPI protection is only achieved when the patients take 80% of the prescribed PPI and that nonadherence to gastro protective drugs is associated with a 4-fold increased risk of upper gastrointestinal complications among high risk NSAID users, the risk increasing by 16% for every 10% decrease in adherence. In order to ensure adherence to treatment, it has been suggested the development of a fixed-dose combination (FDC) of a PPI and NSAID [25-27].

Clinical trials have been conducted to assess the efficacy of a fixed-dose combination of naproxen and esomeprazole. The FDC significantly reduced the cumulative incidence of endoscopic gastric ulcers compared to EC naproxen administered alone after 6 months of treatment (6% vs 24%, respectively; P<.001). Treatment discontinuation due to adverse reactions combined occurred in 7.9% and 12.5% of patients receiving the FDC and EC naproxen, respectively [28].

The FDC significantly decreased osteoarthritis pain and allowed...
patients to increase their physical function: WOMAC pain subscale 18% improvement at 12 weeks (-42.0 for VIMOVO vs -35.6 for placebo, P<0.05) (29) There was no comments about adherence, but the treatment has proven its efficacy.

The use of NSAIDs should be appropriate to each type of patient. It is important to take into consideration the concomitant use of other drugs, previous GI events, age and other risk factors. For those without previous GI events, no use of aspirin and younger than 65, the NSAID can be used alone. For patients aged >65 years and at low risk, an NSAID alone was considered ‘uncertain’. For patients with a previous gastrointestinal event or who concurrently received aspirin, an NSAID alone was rated as ‘inappropriate’, and either a cyclo-oxygenase-2-specific inhibitor or an NSAID + proton pump inhibitor was rated as ‘appropriate’. Finally, for patients with a previous gastrointestinal event and on aspirin, an NSAID or cyclo-oxygenase-2-specific inhibitor in conjunction with a proton pump inhibitor was rated as ‘appropriate’ [29,30].

Clinicians and managed care entities need to balance the risks, benefits and costs of NSAIDs, cyclooxygenase-2-specific inhibitors and the prophylactic use of proton pump inhibitors according to each patient [30].

References