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Gastroprotective agents use with Nonsteroidal Antiinflammatory Drugs: an Overview

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ABSTRACT

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Non-steroidal Anti-inflammatory Drugs (NSAIDs) are widely used in clinical set up for patient care because of their analgesic, anti-inflammatory and antipyretic properties. Most of the NSAIDs can cause gastrointestinal damage by inhibiting cyclooxygenase-1 (COX-1) enzyme. Strategies are recommended to reduce the risk of NSAIDs associated gastrointestinal (GI) adverse events. Prevention of GI morbidity induced by NSAIDs with co-prescription of Gastro protective agents (GPA) has been clinically approved. Administration of GPA in all NSAIDs users is unnecessary. Selection of GPA mainly depends upon the NSAID related GI risk and also the patient risk factor for GI complication as well as efficacy and tolerability of both NSAID and GPA.

Keywords: Non-steroidal Anti-inflammatory Drugs, Gastrointestinal, Gastro protective agents.

INTRODUCTION

Non-steroidal anti-inflammatory drugs are among the most widely used drugs of all and are used to relive pain for a brief period. They are also often prescribed to the chronic disease patients for long term therapy. It is estimated that 1 to 2% of the world population take at least one Aspirin tablet daily.[1, 2] Non steroidal anti-inflammatory drugs are popular by virtue of their analgesic, anti-inflammatory and antipyretic actions and also valuable agents in the treatment of arthritis and musculoskeletal disorders. These drugs block both the intracellular cyclooxygenase and lipoxygenase enzyme systems, which interferes with the normal inflammatory response and decreases the production of various prostaglandin compounds. Each NSAID has its own pharmacodynamic characteristics and patient response to each drug may vary greatly.[3,4]

Non selective NSAIDs inhibit both COX-1 and COX-2 isoforms of the COX enzyme. Cyclooxygenase-1 is a constitutive enzyme expressed in most tissues including blood platelets and is involved in cell-cell signaling and in tissue homeostasis. Cyclooxygenase-2 is induced in inflammatory cell when they are activated and the primary inflammatory cytokines-interleukin-1 and tumor necrosis factor α are important in this regard. Thus COX-2 is responsible for the production of the prostanoid mediators of inflammation.[5] Anti-Inflammatory action of the NSAIDs is mainly related to their inhibition of COX-2 and their unwanted effect is due to their inhibition of COX-1. The clinical importance of COX-2 selectivity has been investigated. Efficacy is likely to be unaffected but gastrointestinal safety may be improved.[6]

The factors associated with increased risk of NSAID-associated serious complications are mainly history of ulcer, concomitant anticoagulant therapy, advanced age (>65 years), concomitant corticosteroid use, chronic major organ impairment, use of high dose or multiple NSAIDs and severe rheumatoid arthritis.[7,8,9]

Strategies in prevention of NSAID-induced gastrointestinal events are: (1) acetaminophen as the first-line therapy in musculoskeletal disorders (2) use of less gastrointestinal toxic NSAIDs such has selective COX-2 inhibitors (3) use of the lowest effective dose of NSAID (4) concomitant use of gastro protective agents in patients with increased risk.[10] Prevention of NSAID-induced GI morbidity by co-prescription of GPAs has been validated in many clinical studies.[11,12] The use of GPAs has focused on two approaches: prostaglandin replacement (misoprostol) and inhibition of acid secretion (proton pump inhibitors and histamine2-receptor antagonists). Histamine2-receptor antagonists (H2RA) heal almost all NSAID ulcers when the patient discontinues NSAID use. However, in patients who continue NSAID use, H2RA in traditional doses are more effective in healing duodenal ulcers than gastric ulcers.[13,14] Several studies have confirmed the superior efficacy of proton pump inhibitors (PPIs) in the short and longer-term prevention of NSAID-induced ulcers as compared to H2RA.[15] However, prophylactic use of PPIs in all patients is cost-prohibitive even though it is unnecessary.[16]

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Rational and evidence based drug prescribing is one of the main goal in pharmaceutical care so underutilization, as well as inappropriate use of GPAs, can contribute to increased health care costs.[17,18]

NSAIDs INDUCED GASTROINTESTINAL RISKS

The NSAIDs are mainly COX-2 inhibitors and their unwanted effects are due to the inhibition of COX-1. It is believed that the role of COX-1 in gastric protection accounts for the common side effect of upper gastrointestinal symptoms among chronic NSAID users. The risk for serious upper GI events (Perforations, Ulcers and Bleeds) is four times higher in chronic users of NSAIDs than non-users.[19]

Mucosal injury caused by NSAIDs likely occurs by several different mechanisms and it can be divided into topical and systemic effects. Most NSAIDs, including aspirin are carboxylic acid derivatives and consequently not ionized in the acidic pH found in the stomach. The nonionized drug is readily absorbed across the gastric mucosa into the pH-neutral mucosa where it is ionized and temporarily trapped within the epithelial cells. The high intracellular concentration of drug induces cellular injury and ultimately causes damage to the gastrointestinal mucosa. The main cause for pathogenesis of NSAIDs induced ulcer is by the systemic effects exhibited by the post-absorptive inhibition of gastrointestinal cyclooxygenase activity. Indeed, peptic ulcer disease has been demonstrated in humans following the intravenous and intramuscular administration of NSAIDs, which suggests a systemic mechanism of action. Cyclooxygenase, which is present in at least two isoforms in humans, is the principal enzyme involved in the biochemical conversion of membrane phospholipids and arachidonic acid into prostaglandins. Various prostaglandins may either prevent or potentiate the inflammatory response. Like most tissues, healthy gastric and duodenal mucosa constitutively expresses COX-1, which produces prostaglandins that act locally in the stomach and duodenum to help protect against mucosal injury. In contrast, the expression of COX-2 occurs largely in response to inflammatory mediators and generates various prostaglandin effectors that are responsible for attenuating the inflammatory response.

From a gastrointestinal standpoint, the ideal NSAIDs would inhibit the inducible COX-2 isoform, thereby reducing inflammation, without acting on COX-1 and its constitutively expressed cytoprotective effectors. Most NSAIDs, including aspirin and ibuprofen inhibit COX-1 and COX-2 equally. However, some NSAIDs, such as celecoxib, selectively inhibit COX-2 and exhibit less suppression on the locally protective gastric prostaglandins. The inhibition of COX-1 and the loss of the protective gastrointestinal prostaglandins may cause a local ischemic injury by reduction in mucosal blood flow at the sub mucosal and mesenteric levels. While associated with less gastrointestinal toxicity, selective COX-2 inhibitors are still associated with some risk for gastrointestinal toxicity particularly at higher doses and in high risk patients.[19]

Oesophagus:

The effect of NSAIDs on the esophagus reported less in number. Some studies had shown a higher incidence of esophageal strictures in patients taking NSAIDs.[20, 21] An endoscopy performed on 50 patients who had taken Indomethacin for at least a year showed, 10 (20%) had erythema, erosions, or ulcers in the esophageal mucosa.[22]

Stomach and Duodenum:

Many patients taking NSAIDs complain of symptoms related to dyspepsia, abdominal pain, ulcers, hemorrhage, and acute perforation. Now it is clear that NSAIDs can damage the gastro duodenal mucosa. Evidence of mucosal injury may occur within weeks to a few months of starting NSAID therapy. The mucosa of the stomach is protected from noxious agents (cytoprotection) by numerous defensive mechanisms including the secretion of mucus and bicarbonate, mucosal blood flow, local production of prostaglandins and rapid cellular repair. By decreasing the local cellular production of prostaglandins, NSAIDs cause a disruption of these protective measures. There is subsequent increased permeability to acid and pepsin within the damaged mucosal cell, and erosions and ulcers may result.[23,24]

McCarthy DM reviewed eight articles surveying patients on long-term NSAID therapy, one study noted a 46-fold greater chance of gastric ulcer and 8-fold increase for duodenal ulcer when compared with the normal population.[25]

Small Intestine:

One study had shown the evidence of increased small intestine permeability, ileal inflammation, blood loss, protein-losing enteropathy and bile salt malabsorption due to NSAID ingestion. Similar study have showed no signs of distal small bowel inflammation in arthritis patients not taking NSAIDs. .[26]

Non-steroidal anti inflammatory drugs reduce the local cellular production of prostaglandin leading to increased mucosal permeability allows the luminal substances and bacteria to damage the mucosa; finally it results in secondary adverse effects. Occasional clinical reports have linked NSAIDs to small bowel disease.[27]

Colon:

A case report showed NSAIDs damage colonic mucosa, wherein ulcerative colitis developed in patients taking NSAIDs, after the drug stopped, the patients improved, and then they relapsed on resuming NSAID therapy.[28]

A case study report shown that patient developed thin colonic strictures after several years of NSAID (diclofenac) therapy. The patient also had a history of anemia and ulcers in the ascending colon. The other case study report described two patients developed colonic bleeding due to ulcers in the right side of the colon, with diclofenac treatment.[29,30]

PHARMACOTHERAPEUTIC STRATEGIES FOR PREVENTION AND TREATMENT OF NSAID RELATED ULCERS:

Several strategies are recommended to reduce the risk for NSAID associated gastrointestinal adverse events. First, risk may be reduced by use of non-NSAID analgesics such as acetaminophen, but this strategy is unlikely to be sufficient in all patients or in those with more severe disease. Second, the use of the minimum effective dose of NSAID may reduce the risk for complications. Third, co-therapy with gastro protective agents may be necessary in patients at high risk for complications. Although these agents reduce the risk for gastrointestinal events, each is associated with its own spectrum of side effects. In addition, increased medication burden (cost and compliance issues) must be considered, particularly in elderly patients who are likely to be receiving multiple medications for concomitant conditions. Recommendations for the treatment of NSAID related dyspepsia and mucosal injury are summarized in Table 1.[31]

Table 1: COX, cyclo-oxygenase; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor

Recommendations for the treatment of NSAIDs related d yspepsia and mucosal injury	
Clinical situation	**Recommendation**
Dyspepsia	Empirical treatment with H2 receptor antagonist or PPI; individualize therapy
Helicobacter pylori infection	Treatment to eradicate infection in patients with a history of peptic ulcer; PPI therapy
Active gastro duodenal ulcer: NSAID discontinued NSAID continued	 Treatment with H2 receptor antagonist or a PPI Treatment with a PPI
Prophylactic therapy	Treatment with a PPI or misoprostol or a COX-2 (preferential) or selective NSAID

Misoprostol:

Many data indicates that misoprostol is effective in the prevention of ulcers. But poor compliance in proper dosing frequency and relatively high rate of adverse events has led to improper usage and it is the important concern in usage of misoprostol. . One study found that lower doses of misoprostol are better tolerated. However, the drug has to be taken at least twice daily to provide effective prophylaxis against NSAID related ulcers.[32] Misoprostol may also be effective in the treatment of patients with established NSAID associated ulcers, but comparative studies suggested that the proton pump inhibitors (PPIs) are substantially more effective in NSAID associated ulcer patients.[33]

Sucralfate:

Sucralfate, a basic aluminum salt of sucrose octasulfate, forms an ulcer adherent complex at duodenal ulcer sites, protecting the ulcer and promoting healing. It may also inhibit pepsin activity in gastric fluid. Sucralfate has been shown to be effective in the treatment of NSAID associated duodenal ulcers, particularly when the NSAID administration is stopped. But it is not effective in the treatment or prevention of NSAID related gastric ulcers.[34]

H2 receptor antagonists:

H2 receptor antagonists modulate gastric pH through the competitive inhibition of the action of histamine at H2 receptor sites on the gastric parietal cell. The efficacy of the H2 antagonist famotidine at high dose (double the usual dose) for preventing ulcers in patients receiving long-term therapy with NSAIDs was examined in a double blind, parallel group, randomized study, the percentage of patients with gastro duodenal ulcers were significantly lower in the famotidine 20 mg group (4%) and the 40 mg group (2%) compared with the placebo group (13%). Although this agent has been shown to be effective in preventing ulcers in patients taking NSAIDs, H2 receptor antagonists are not recommended for routine treatment of asymptomatic patients for a variety of reasons, including their potential to mask dyspeptic symptoms associated with mucosal injury.[34,35]

Furthermore, data suggested that the H2 receptor antagonists are less effective in healing gastro duodenal ulcers than PPIs, whether or not NSAIDs are continued, and are inferior in preventing ulcer recurrence.[36]

Proton pump inhibitors:

Proton pump inhibitors (PPIs) act by binding irreversibly to resident proton pumps (H^+/K^+ATPase), thus inhibiting the final common pathway for acid secretion. Proton pump inhibitors are administered as prodrugs that are activated in

the acidic environment of the parietal cell secretary canaliculus, once converted to their active form; PPIs bind to cysteine residues in the proton pump and inhibit acid secretion into the canalicular lumen.[37]

Omeprazole, the most extensively studied PPI, has a protective effect against NSAID-related mucosal injury. Because of its potent acid-inhibiting property, it prevents duodenal ulcer (DU) in patients taking NSAIDs. There is evidence that omeprazole also protects against gastric ulcer (GU). Three large Randomized Controlled Trials have been carried out by comparing omeprazole with placebo, misoprostol, and ranitidine for the prevention of GU and DU. Overall, omeprazole significantly reduced the total number of NSAID-related ulcers when compared with placebo and ranitidine. It was more effective than misoprostol in preventing DU, and equally so in reducing GU.[37, 38]

CONCLUSION

The most common side effect of NSAIDs therapy relates to gastrointestinal damage. A wide variety of disorders may develop in patients taking NSAIDs, ranging from minor dyspepsia to life-threatening ulcer bleeding or perforation. Although NSAIDs induced gastropathy has been the complication most evaluated, other parts of the gastrointestinal tract including the esophagus, small bowel and colon may be seriously injured, leading to mucosal inflammation, hemorrhage, and obstruction due to strictures. The treatment of NSAID gastropathy depends on the clinical situation and anatomic area involved of the patient.

Gastro protective agents in all NSAID user patients are unnecessary. Gastro protective agents selection in NSAID user mainly depends upon the NSAID related gastrointestinal risk, the selection must be individualized according to the patient's risk factors for gastrointestinal complications, as well as the efficacy and tolerability of both the NSAID and gastro protective co-therapy.

Rational drug use and evidence based medicine practice required among hospital physicians about possible NSAID-induced gastrointestinal complications, as well as sufficient knowledge about recommended drug of gastroprotectives in NSAID-induced ulcer prophylaxis and gastrointestinal toxicity of different types of NSAIDs.

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