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Prevention and Management of NSAID-Induced Gastropathy

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ABSTRACT. Nonsteroidal antiinflammatory drugs (NSAIDs) are the most frequently prescribed medication for chronic pain. Gastrointestinal complications from NSAID treatment are a major cause of morbidity and mortality. In the majority of patients, NSAID induced gastropathy is superficial and self-limiting. However, peptic ulcers develop in some patients and may lead to hemorrhage, perforation, or death. NSAIDs can cause gastrointestinal damage via topical injury of the mucosal barrier, systemic inhibition of prostaglandin synthesis or a combination of both. Risk factors for NSAID related complications include age > 60 years, history of ulcer disease, concomitant corticosteroid or anticoagulant use, high dose therapy, and multiple NSAID use. Identifying high-risk patients is critical in order to minimize risk. Factors suggested to predict the safety of NSAIDs include selective COX-2 inhibition, absence of enterohepatic circulation, shorter half-life, and nonacidic pro-drug formulations. The COX-2 selective NSAIDs, celecoxib and rofecoxib, have been recently marketed and appear to have less GI toxicity. Long-term studies and post marketing surveillance are needed to confirm the safety of the COX-2 inhibitors. Proton pump

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inhibitors and misoprostol are the only agents proven beneficial in preventing GI adverse effects from NSAIDs.

KEYWORDS. Nonsteroidal antiinflammatory drugs, gastropathy, risk factors, prostaglandins, COX-2 inhibitors

INTRODUCTION

Aspirin was the most widely used drug in the world at the turn of the century. It was also known to be toxic to the stomach. In the 1950s, additional nonsteroidal antiinflammatory drugs (NSAIDs) became available with the hope of reducing the gastrointestinal (GI) and other side effects associated with aspirin.[1] Today, NSAIDs are the most frequently prescribed medication for chronic pain and remain the most widely used drug category for the treatment of rheumatoid arthritis, osteoarthritis, fibromyalgia, connective tissue diseases, spondylo-arthropathies, gout, musculoskeletal injuries, and dysmenorrhea.[2] Twenty million Americans regularly use over-the-counter and prescription NSAIDs[3] and more than 30 million people in the United States consume NSAIDs.[4,5] Celecoxib set an industry record in its first year on the market generating 19 million prescriptions for approximately 7 million patients. Worldwide, 100 million prescriptions are written annually for NSAIDs. This number accounts for 4.5% of all prescriptions.[1,2,6] In addition, over-the-counter (OTC) NSAID sales are significantly increasing, as more products become available.[1] Thus, the potential exists for patients to supplement prescribed NSAIDs with OTC products. Approximately 33% to 50% of patients who die of ulcer-related complications had recently ingested NSAIDs.[7] Patients over the age of 60 years account for 40% to 60% of those who use NSAIDs and are at a higher risk of GI toxicity because of declining renal function, decreased endogenous prostaglandins, concomitant medical conditions, and polypharmacy.[6]

EPIDEMIOLOGY

Gastrointestinal complications from NSAID treatment are a major cause of morbidity and mortality. In the U.S., an estimated 16,500

deaths per year are associated with complications from NSAID use in arthritis patients alone.[8] Patients with rheumatoid arthritis have a 1.5% chance of hospitalization and a 0.22% chance of death associated with the use of NSAIDs. Approximately 107,000 hospitalizations per year occur as a result of NSAID-induced gastropathy. On average, a patient has a 20% chance of experiencing gastrointestinal toxicity with 1% to 3% of these patients suffering from a life-threatening GI bleed or perforation.[6] At an average cost of $10,000 to $15,000 per hospitalized patient, over $1 billion is spent annually on gastrointestinal complications alone.[3,8] The economic burden is tremendous, and augmented by additional factors including lost wages and postoperative care.

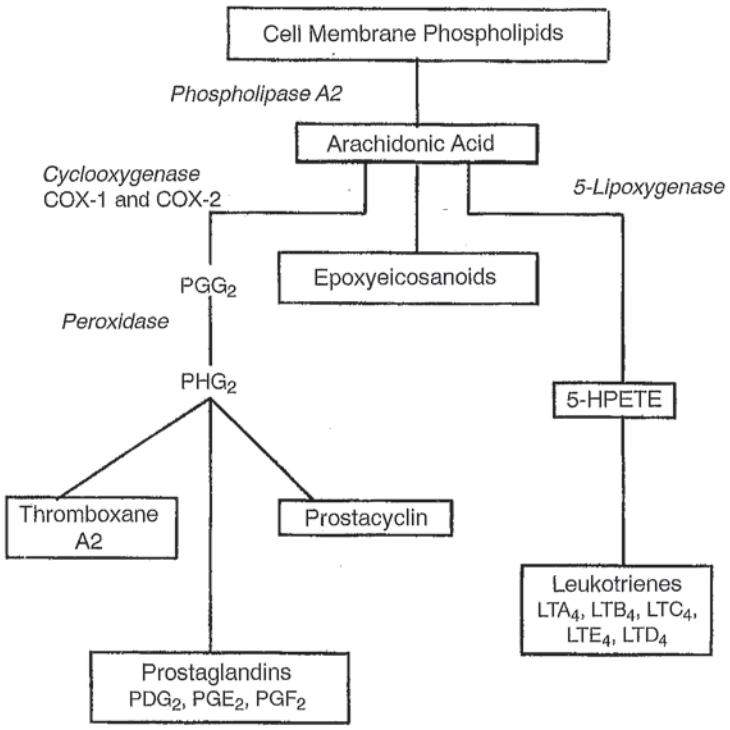
GASTRIC MUCOSA AND PROSTAGLANDINS

The gastric mucosa is continuously exposed to both endogenous and exogenous injurious agents such as acid, pepsin, bile acids, food ingredients, bacterial products, and drugs.[9] These irritants induce "adaptive cytoprotection" by stimulating bicarbonate and mucus secretion, increasing mucosal blood flow, increasing mucosal cell restitution, and inhibiting acid secretion.[1] Prostaglandins (PGs) mediate the adaptive or proliferative response. Two enzymes are responsible for catalyzing the conversion of arachidonic acid to prostaglandins: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)[7,2] (Figure 1). COX-1 is constitutive, present in most tissues, and unaffected by steroids. COX-1 maintains physiologic functions such as gastric mucosal integrity, renal function, and platelet homeostasis. In general mucous and bicarbonate secretion, induced by PGs, parallels acid secretion and in doing so maintains homeostatic balance.[2,10-16] COX-2 is found in a limited number of cell types, is induced by cell injury, is steroid inhibitable, and facilitates prostaglandin production in response to injury.[2,10-13] The non-selective NSAIDs inhibit both COX-1 and COX-2, but show varying affinities for the two enzymes. The newer agents, like celecoxib and rofecoxib, inhibit only COX-2.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

NSAIDs, by inhibiting cyclooxygenase, reduce prostaglandin synthesis. Prostaglandins exert pain by sensitizing nerves through the

FIGURE 1



formation of edema and cellular exudation. NSAIDs inhibit this effect and in doing so reduce inflammation and pain. In addition, NSAIDs exert analgesic and antiinflammatory effects through a secondary mechanism of inhibition of leukotriene B_4 production. All NSAIDs are highly protein bound, primarily to albumin, and are metabolized chiefly by hepatic biotransformation and excreted renally.[2,7] The non-selective NSAIDs inhibit both COX isoforms to some degree with the more GI toxic agents demonstrating greater COX-1 inhibition.

The ideal NSAID would retain analgesic and antiinflammatory properties while sparing the toxicity associated with COX-1 inhibition.[14] In fact, the specific factors that predict safety of NSAIDs are selective COX-2 inhibition, shorter half-life, absence of enterohepatic recirculation, and nonacidic pro-drug formulations. Agents designed to capitalize on these properties include nabumetone and etodolac.

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