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Gastric Perforation Associated with the Use of Celecoxib

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NONSTEROIDAL antiinflammatory drugs (NSAIDs) are among the most commonly used drugs in the treatment of musculoskeletal disease. NSAIDs inhibit prostaglandin biosynthesis by inhibiting the enzyme cyclooxygenase (COX), the rate-limiting enzyme of prostaglandin synthesis.[1] NSAIDs impair prostaglandin-dependent mucosal protective mechanisms, including gastric blood flow and secretion of gastric mucus, bicarbonate, and surfactant-like phospholipid.[2,3] Two distinct COX isozymes exist: COX-1 is a constitutive enzyme expressed in many tissues, including the gastric mucosa, whereas COX-2 is an inducible enzyme expressed in fibroblasts, macrophages, and other inflammatory mediators.[4,5] Most currently marketed NSAIDs inhibit both COX-1 and COX-2 enzymes with approximately equal potency. Therefore, these NSAIDs inhibit both the inflammatory response (COX-2) as well as the maintenance of regular cellular physiology (COX-1). Selective COX-2 inhibitors were developed with the goal of providing effective antiinflammatory and analgesic activity without causing gastrointestinal side effects.

We report a case in which gastric perforation developed after the administration of celecoxib, a new selective COX-2 NSAID, in a patient recovering from a gastric ulcer.

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Case Report

A 72-yr-old woman with a history of hypertension and osteoarthritis presented to the Pain Management Center for evaluation and treatment of lumbar radiculopathy secondary to spinal stenosis. Her medications included atenolol 25 mg/day, acetaminophen 650 mg every 6 h as needed, and naproxen 1,000 mg/day (initiated 26 days before evaluation). In addition to low back pain, she had been complaining of diffuse burning epigastric pain associated with nausea. A stool sample was guaiac positive. An upper gastrointestinal endoscopy revealed a 5-mm gastric ulcer on the greater curvature of the stomach. Naproxen was discontinued, and omeprazole 20 mg/day was prescribed. Although the epigastric pain resolved after these medication changes, she began to complain of severe lower back pain. Celecoxib 200 mg/day was initiated 12 days after she underwent endoscopy. Within 72 h, she began to complain of severe epigastric pain that required admission to the emergency department. Over the next 3 h she became hypotensive (blood pressure, 75/40 mmHg), tachycardic (heart rate, 150 beats/min), and tachypneic (respiratory rate, 40 breaths/min). An abdominal flat plate radiograph showed free air under the diaphragm. The patient underwent emergency surgery to repair a 2-cm perforated gastric ulcer. The patient tolerated the procedure well, and her vital signs improved postoperatively.

Discussion

Although there is good evidence that selective COX-2 inhibitors significantly reduce the incidence of gastric injury compared with conventional NSAIDs,[6,7] there has been no information regarding their physiologic effects in humans with preexisting mucosal inflammation.

The gastrointestinal tract contains many cells that can express COX-2, such as macrophages, neutrophils, myofibroblasts, and endothelial cells.[8] Prostaglandins produced by COX-2 in the stomach may have a beneficial effect in the setting of acute injury and inflammation. This is suggested by up-regulation of COX-2 messenger RNA in gastric mucosal erosions and ulcers, localization of the COX-2 protein to the base of the ulcer, and loss of COX-2 expression after healing is completed.[9-11] In addition, active gastritis in humans caused by *Helicobacter pylori* has been associated with COX-2 expression.[12] In the presence of inflammation, blocking the production of prostaglandins produced by COX-2 may interfere with

the mechanisms of tissue healing and therefore be deleterious. Studies in rodents showed that selective COX-2 inhibitors delay healing of experimental ulcers.[9,13]

It is currently recommended that NSAIDs be discontinued in patients who develop peptic ulcer disease.[14] However, stopping NSAID therapy may exacerbate musculoskeletal pain. For patients who require continuous NSAID therapy, both omeprazole and misoprostol promote healing and reduce the recurrence rate of gastroduodenal lesions.[15] Because our patient was unable to tolerate her back pain without NSAID therapy, celecoxib and omeprazole were prescribed in the hope of reducing her pain without causing gastrointestinal side effects.

Our patient may have progressed to a gastric perforation despite use of celecoxib. Elderly[16] patients and those with a history of peptic ulcer disease are at greater risk of subsequent ulceration and secondary ulcer complications.[17] Although our patient had no dyspeptic symptoms of any kind during the 12 days when she took no NSAIDs, she presented with a perforated gastric ulcer after 3 days of treatment with celecoxib. This clinical course is consistent with the theory that prostaglandins produced by the COX-2 enzyme participate in the gastric healing process.

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