COXIBs AND THE GASTROINTESTINAL TRACT: A PROMISE FULFILLED?

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Gastro-intestinal mucosa possesses an array of defensive mechanisms and non-steroidal anti-inflammatory drugs (NSIADs) have a deleterious effect on most of them. This results in a mucosa less able to cope with even a reduced acid load. As a consequence, GI symptoms and lesions (as well as their life-threatening complications, like bleeding and perforation) are so common, especially in the elderly population, to have been considered an "emerging epidemic" [1]. Many attempts have been made in the past to reduce GI toxicity of NSAIDs but have all been disappointing, making pharmacological prevention strategies (with either misoprostol or proton pump inhibitors, PPIs) worthwhile and cost-effective [1, 2]. However, the discovery of two different isoenzymes of cyclo-oxygenase (COX) allowed the development of selective inhibitors of the inducible enzyme (i.e. COX-2), giving the hope of having drugs (often incorrectly referred to as Coxibs) endowed with anti-inflammatory and analgesic activity but devoid of GI toxicity [3]. Compared to traditional NSAIDs, these drugs do spare COX-1 activity and therefore do not reduce prostaglandin (PG) concentration of the gastric mucosa. Large clinical trials have shown that the incidence of both non-complicated and complicated gastro-duodenal ulcers is significantly reduced in patients taking selective COX-2 inhibitors, but this benefit appears to be lost when low-dose aspirin is given. Although – compared to traditional NSAIDs – dyspepsia is significantly reduced in patients taking COX-2 selective compounds, it still represents a troublesome symptom in about 25% of subjects. In high-risk patients (like those with previous ulcer bleeding), the use of selective COX-2 inhibitors achieves a prevention of re-bleeding similar to that obtained with the combination of traditional NSAIDs with a PPI. However, re-bleeding is completely prevented only when the PPI is added to a COX-2 selective NSAID [2, 3]. Trials with capsule endoscopy have shown that celecoxib (and probably the other non acidic members of the class) is less damaging for the intestinal mucosa and radioisotope studies have demonstrated that all the selective COX-2 inhibitors investigated do not increase fecal blood loss. Although the clinical significance of these data is still uncertain, the rate of serious lower GI clinical events (i.e. bleeding, perforation, obstruction, ulceration or diverticulitis) as well as the incidence of anemia are significantly reduced when selective NSAIDs are used [2, 4]. Although still not the ideal anti-inflammatory compounds, COX-2 selective inhibitors have fulfilled to some extent the expectations underlying their development and should currently be regarded as a GI safer alternative.

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