PROTECTION FROM NSAID-INDUCED GASTROINTESTINAL DAMAGE

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ABSTRACT

Increased understanding of the damaging and protecting factors in the gastrointestinal tract opens up possibilities of safer use of NSAIDs or the development of safer NSAIDs in preventing gastrointestinal tract damage. Highly effective gastric acid suppression can successfully prevent both duodenal and gastric lesions associated with NSAIDs. The development of synthetic prostaglandin analogues and drugs with a selective prostaglandin effect has been shown to be successful, although the side-effects of current prostaglandin analogues limits their use. Selective prostaglandin drugs such as etodolac have been shown in prospective endoscopic studies significantly to reduce damage, and this is associated with less suppression of gastrointestinal prostaglandins than conventional NSAIDs.

Keywords: NSAIDs, gastrointestinal damage

INTRODUCTION
Non-steroidal anti-inflammatory drugs (NSAIDs) are increasingly used. Over 20 million prescriptions for NSAIDs are issued in the UK per year, comprising 5% of all prescriptions written, and over 100 million per year in the USA [1,2]. These drugs are increasingly used in elderly patients, and more than 50% of NSAID prescriptions are written for patients over the age of 65. NSAIDs are responsible for significant morbidity and mortality. Thirty-two to thirty-six per cent of patients taking NSAIDs develop gastric or duodenal ulceration, and the risks of ulcer complications such as gastrointestinal haemorrhage and perforations have increased three- to six-fold in recent years. Sixty-five to seventy per cent of patients on NSAIDs develop dyspeptic symptoms, but there is a poor correlation between symptoms and endoscopically proven ulceration. Up to 50% of endoscopically confirmed ulcers are asymptomatic. Lesions associated with NSAIDs are most commonly found in the antral area of the stomach and the duodenum, but any part of the gastrointestinal tract may be involved. The small intestine has been found to be more commonly affected than previously considered, and lesions associated with NSAIDs have been demonstrated in the small intestine at enteroscopy [3]. A recent postmortem study of 713 patients [4], of whom 249 had taken NSAIDs in the six months before death and 469 had not taken NSAIDs, found gastric and duodenal lesions in 54 (21.7%) in those taking NSAIDs compared with 57 (12.3%) in those not on NSAIDs ($p < 0.001$). Small intestinal ulceration was found in 21 (8.4%) of those taking NSAIDs compared with 3 (0.6%) in those not on
Increased numbers of lesions were also found in the colon. All patients had died of conditions not associated with NSAIDs.

Widespread damage associated with NSAIDs may thus occur throughout the gastrointestinal tract.

The pathogenesis of NSAID-associated damage is complex and not yet fully worked out. There is initially a local topical effect followed by biochemical cellular damage and a tissue reaction, with increased mucosal permeability, which alters the relationship between the luminal damaging factors and the mucosal defence system. NSAIDs inhibit cyclo-oxygenase enzymes (COX), altering the metabolism of arachidonic acid, and reducing eicosanoid production. There are two distinct COX molecules (COX-1 and COX-2). COX-1 is involved in synthesizing prostaglandins in response to physiological stimuli, these being involved with gastrointestinal protection such as the mucus–bicarbonate barrier, the regulation of cell division and microvascular integrity. COX-2 is induced at sites of inflammation mediated by cytokines and endotoxins, and is associated with pain. Complex cellular biochemical changes such as uncoupling of oxidative phosphorylation in mitochondria leading to depletion of ATP production and the impairment of energy-dependent barrier function, and reactive oxygen radical release associated with neutrophil movements are also likely to be involved in the pathogenesis of damage. Other factors likely to be involved are alterations in mucosal blood flow, cellular proliferation and migration at the ulcer edge, maturation of granulation tissue at the ulcer base and the inhibition of formation of new blood vessels, angiogenesis. A complex interaction of these factors is likely to be involved.

Additional damaging factors may include acid, pepsin, bile acids and *Helicobacter pylori* in the stomach and duodenum; and bile, pancreatic secretions and other bacteria in the small intestine and colon. Protective factors include prostaglandins, which are important in maintaining the mucus–bicarbonate barrier, cellular integrity and restitution, and mucosal blood flow. Nitric oxide is also likely to be an important protective factor.

The prevention of NSAID-associated gastrointestinal damage may utilise some of these factors. These include possible reduction of damage associated with gastric acid or *H. pylori*, the use of synthetic prostaglandin analogues or by the development of newer NSAIDs which may cause less damage to mucosal defence systems either by causing less depletion of gastrointestinal protective prostaglandins or by the generation of nitric oxide.

An attractive theoretical option would be the development of an NSAID which had selective COX-2 inhibition.

**ACID**

There have been a number of studies assessing the possible prevention of NSAID-associated gastric and duodenal ulceration by the use of gastric acid-reducing agents. In most patients requiring NSAIDs, especially those with rheumatoid arthritis, it is not practical to stop NSAID therapy, and thus acid-reducing drugs would be given along with NSAIDs.