

GASTROINTESTINAL PROTECTION BY NO FROM NSAIDS INDUCED INJURY

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Abstract : One of the most deleterious side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) is gastric injury. In order to prevent this, attempt has been made to make novel nitric oxide (NO) releasing NSAIDs. The NO-releasing moiety (nitroxybutylester), which is combined with NSAIDs, has been shown to be responsible for gastrointestinal protection. Various NO-releasing NSAIDs have been compared with their parent compounds and marked decrease in gastrointestinal side effects were observed in the former case. Various animal studies have been done in this context. However, exact mechanism of action of NO-releasing NSAIDs is not clear.

Key words: NSAIDs gastric injury NO nitroxybutylester

INTRODUCTION

Non-steroidal anti-inflammatory agents (NSAIDs) have earned a bad reputation in the clinical setup because in long term use, they significantly cause gastrointestinal side effects. Most common amongst them are gastric ulceration, bleeding, perforation and an increased risk of bleeding from preexisting peptic ulcer disease (1).

The mechanism of action of NSAIDs is well established. They interfere in the prostaglandin cascade by interrupting the cyclooxygenase enzyme which is responsible for prostaglandin synthesis. Since mucosal prostaglandins decrease gastric acid secretion and further appear to exert a cytoprotective effect, inhibition of prostaglandin biosynthesis is believed to account for the erosions, ulcerations and bleeding caused by NSAIDs (2).

Nitric oxide (NO) is a small, short-lived, diatomic molecule present in the gas form. It was studied extensively after 1988 but its physiological role in human body is yet to be established. Since it is involved in diverse

physiological events, variety of diseases may occur due to overproduction or underproduction of NO (3). NO similar to prostaglandins appears to play a vital role in gastric mucosal defence (4).

GI protection by NO

NO is a free radical gas biosynthesised in mammalian cells through the oxygenation of one of the guanidino nitrogen atoms of L-arginine by the help of a group of enzymes called Nitric Oxide Synthase (NOS). Various forms of NOSs are distributed in the cells and tissues according to their function (3). NO has a half life of seconds. It is inactivated by oxygen, haemoglobin, and reductants like methylene blue and potentiated by a free radical scavenger like superoxide dismutase. NO causes vasodilation, stimulation of mucosal secretion, and interference with neutrophil endothelial adhesion (5, 6, 7). It was initially identified as an endothelium-derived relaxing factor (EDRF) but has since been shown to be released from many cell types in addition to the endothelial cells, such as neurones, neutrophils, platelets, macrophages and smooth muscle cells (8). NO promotes capillary integrity,

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inhibits leucocyte adherence and activation, and scavenges oxygen radicals (9). Animal studies under constitutive conditions have suggested that prostaglandins, enteric neuronal reflexes, and NO synthesis all contribute to the protection of gastric mucosa (10). NO or drugs that generate NO exogenously (e.g., glyceryl trinitrate, sodium nitroprusside) have been reported to reduce the severity of gastric mucosal injury in experimental models (11,12). Nitric oxide regulates several humoral and cellular responses in inflammation. It regulates inflammatory erythema and oedema and has cytotoxic action against microorganisms. It has both pro- and anti-inflammatory reactions depending upon the type and phase of the inflammatory reaction. Nitric oxide seems to mediate some destructive effects of proinflammatory cytokines such as Interleukin 1 (13).

Under basal conditions, intestinal NO serves an antiinflammatory role (14). It is assumed that sensitisation to nociception is due to an increase in the concentration of cAMP/Calcium ions in the sensory neurones. The stimulation of arginine/NO/cGMP pathway may counteract the effect of increased cAMP concentration. Examples of analgesics that act via this mechanism are peripherally acting opiates and dipyrone (15).

NO releasing NSAIDs - A novel approach

Several strategies have been used to reduce the incidence of gastric injury caused by NSAIDs. These include, enteric coating, parenteral or topical administration, prodrug concept, and coadministration of either suppressors of gastric acid secretion or exogenous prostaglandins. However, none of the approach has yet been proved successful to have a significant impact on the untoward effects of NSAIDs (1).

The digestive system is one of the major sources of NO, which, by virtue of its smooth muscle-relaxing and vasodilating properties, appears to play a key role in the regulation of GI motility, mucosal blood flow and

gastroprotection (16). The recent approach is to reduce the GI toxicity of NSAIDs by incorporation of nitric oxide-releasing moiety to these compounds which is similar to the other NO-releasing compounds (4,18,19,20). The incorporated NO-releasing moiety was nitroxybutylester (Fig. 1). The assumption behind this class of NSAIDs is that NO, by maintaining gastric mucosal blood flow, and preventing leucocyte adherence within the gastric microcirculation, may counteract the untoward effects of cyclooxygenase suppression (21) so that mucosal injury does not occur. The nitroxybutylester moiety has been incorporated in various NSAID derivatives including flurbiprofen, ketoprofen, and diclofenac. The possible importance of exogenous NO in protecting the stomach from ulcer formation induced by NSAID have recently been reported (4). Lipopolysaccharide (LPS) on exogenous administration induces the expression of an inducible type of nitric oxide synthase (iNOS) in rat stomach. When given with flurbiprofen, LPS also reduced the gastric mucosal damage elicited by flurbiprofen (17).

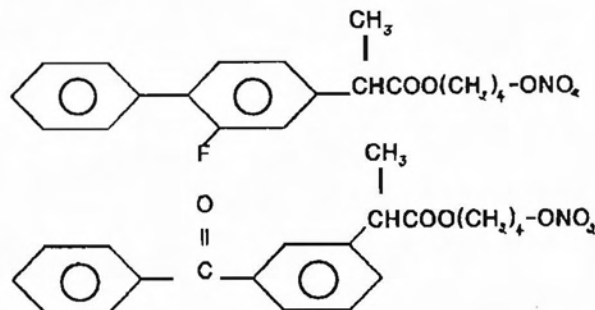


Fig. 1 : Structures of two NO-releasing NSAIDs.
(i) Flurbiprofen nitroxybutylester, and
(ii) Ketoprofen nitroxybutylester (Ref 22)

Conclusion

When the antiinflammatory and antipyretic activities of NO-releasing NSAIDs were compared to their parent compounds, the addition of NO-releasing moiety to a number of common NSAIDs markedly reduced their toxicity in the GIT without interfering with

their ability to inhibit the prostaglandin synthesis. Despite evidence that these agents generate NO in rat *in vivo*, these compounds did not significantly affect systemic blood pressure (4, 18). Experimental evidence suggests that NO-releasing NSAIDs have been shown to suppress the prostaglandin synthesis in stomach (4), in the intestine (20) and at the site of peripheral inflammation (4) as effectively as the parent NSAID.

However, the mechanism of action of such compounds is not clear. Nitroflurbiprofen

(containing NO moiety) was found to be significantly less damaging to the gastric mucosa than flurbiprofen even when the compounds were administered systemically which leads to the conclusion that the former compound does not act merely as a prodrug (4). Further, only animal studies are reported till date to support this concept. Further work is, therefore, required in this context to establish the role of NO-releasing NSAIDs in inhibiting NSAID induced gastric injury.

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