THE EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) ON THE GASTRIC MUCOSA OF ADULT ALBINO RAT AND THE POSSIBLE PROTECTIVE ROLE OF PARACETAMOL: MORPHOLOGICAL AND HISTOCHEMICAL STUDY

THESIS

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Dedication

To my wife Neveen who supported me during all times to perform this work.
To my lovely daughters Anne and Emmy

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin have been widely used clinically as anti inflammatory, analgesic agent, but it has been documented that they produce gastrointestinal injury. Paracetamol is analgesic, antipyretic but differs from other non steroidal anti-inflammatory drugs (NSAIDs) in having no anti-inflammatory activity. The study used 100 male adult albino rats; their weigh ranged 200 and 250. They were divided into four groups. Indomethacin was found to cause severe and dramatic injury to the rat gastric mucosa. When paracetamol given 30 minutes before indomethacin intake, it produced obvious protection of the gastric mucosa against the severe injurious effect produced by indomethacin.

Key words: indomethacin-paracetamol- gastric mucosa- Non-steroidal anti-inflammatory drugs (NSAIDs)

Contents

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin have been widely used clinically as anti inflammatory, analgesic agent. However, its side effect on the GIT is well known one of the most serious adverse effects attributable to NSAIDs ***(Nguyen et al., 1999).***

The exact mechanism of GIT injury produced by NSAIDs is still controversial. Although, it has been proposed that a deficiency of endogenous prostaglandins due to inhibition of cyclooxygenase by NSAIDs is involved in this effect ***(Holvoet et al., 1991***). The exact pathogenic mechanism remains to be elucidated. It has recently been proposed that neutrophil dependent microvascular injuries ***(Bayir et al., 2006)*** and the release of oxygen free radical mediated lipid peroxidation which could be important triggering events that lead to mucosal injury induced by NSAIDs.

Kato and Takeuchi (2006) observed that indomethacin, one of the most potent NSAIDs, induces haemorrhagic gastric ulcers in albino rats. It causes little or no effect on the cellular and nuclear diameter of the parietal and the chief cells associated with reduction of the mucous and the endocrine cells.

Paracetamol (acetoaminophine) is analgesic, antipyretic but differs from other non steroidal anti-inflammatory drugs (NSAIDs)

in having no anti-inflammatory activity and in its selective inhibitory action on prostaglandin synthesis in the brain ***(Omura et al, 1994).***

Van Kolfschoten et al., (1982) reported that paracetamol has no gastrointestinal damaging effect in man and animals. Oral administration of a high dose of paracetamol in rats has been found to antagonize stomach mucosal ulceration by various gastric irritants ،such as ethanol, sodium, hydrochloric acid and NSAIDs.

Kacso and Terézhalmy (1994) stated that paracetamol increased prostaglandin synthesis in gastric tissue in man, so if paracetamol is taken on empty stomach, it produces no effect on gastric mucosa. It has been thought that increased prostaglandin synthesis in gastric tissue was responsible for the antinuclear effect of paracetamol. However ***(Lanza et al., 1998)*** mentioned that paracetamol does not affect prostaglandin level in peripheral tissues.

Another study done by ***Van Kolfchoten (1982)*** on the rat stomach demonstrated that indomethacin inhibits prostaglandin synthesis. Paracetamol alone stimulates the production of prostaglandin but could not prevent the inhibitory action of indomethacin. Preliminary administration, of paracetamol minimizes the inhibitory effect of indomethacin on the

prostaglandin synthesis and in turn its injurious effect on the stomach.

Lanza et al., (1998) concluded that acetaminophen failed to decrease the mucosal injury seen with ibuprofen when given for a period of seven days in combination with acetaminophen.

Aim of the Work

The aim of the present work is to study the effect of NSAIDs (e.g. indomethacine) on the gastric mucosa of adult albino rat and to investigate the possible protective role of preliminary administration of paracetamol.

Review of literature

Blood and nerve supplies of stomach

Campos et al., (2003) reported that the lesser curvature of the stomach is supplied by the right gastric artery inferiorly, and the left gastric artery superiorly, which also supplies the cardiac region. The greater curvature is supplied by the right gastroepiploic artery inferiorly and the left gastroepiploic artery superiorly. The same authors added that both of the fundus and the upper portion of the greater curvature are supplied by the short gastric arteries. The arteries break up at the base of the gastric glands into a plexus of fine capillaries which run upward between the glands anastomosing with each other and ending in a plexus of larger capillaries, which surround the mouths of the glands, and also form hexagonal meshes around the ducts.

Later on, the same authors stated that from these meshes the veins arise, and take a straight course into the depth of the mucosa between the glands, to the submucousa where they end either in the superior mesenteric vein, or directly in the portal vein.

Amagase et al., (2003) mentioned that the lymphatics of the stomach are numerous; consisting of a superficial and a deep set, and pass to the lymph glands present along the two curvatures of the stomach.

Campos et al., (2003) observed that the stomach is surrounded by parasympathetic (stimulant) and sympathetic (inhibitor) plexuses, which regulate both the secretory activity and the motor activity of the muscles. The nerves are the terminal branches of the right and left vagi, the former being distributed on the back, and the latter on the front part of the organ. A great number of branches from the celiac plexus of the sympathetic are also distributed to it.

They illustrated that the nerve plexuses are found in the submucous coat and between the layers of the muscular coat as in the intestine. Later on ***Chang et al., (2005)*** discovered that from these plexuses fibrils were distributed to the muscular tissue and the mucous membrane.

Histological Review of the stomach

Karateev et al., (1997) mention that most of the layers of the wall of the stomach appear similar in its different parts. Regional differences are mainly restricted to the appearance of the gastric mucosa.

The Mucosa

Karateev et al., (2001) described that the mucosa is thrown into longitudinal folds (gastric folds or rugae), which disappear when the stomach is fully distended. A network of shallow grooves

divides the mucosa into gastric areas each is (1-5 mm). On the mucosal surface they observed small, funnel-shaped depressions (gastric pits). Almost the entire mucosa is occupied by simple, tubular gastric glands which open into the bottom of the gastric pits.

The same authors added that the structure and cellular architecture of the surface epithelium (simple, tall columnar) is uniform throughout the stomach. It contains mucus-producing cells, surface mucous cells, which form a secretory sheath (glandular epithelium). The mucus is alkaline and adheres to the epithelium. The mucus forms 1 mm thick layer, which protects the mucosa from the acidic contents of the stomach.

Moreover, the surface epithelium is renewed approximately every third day. The source of the new cells is the isthmus i.e. the upper part of the neck, of the gastric glands, where cells divide and then migrate towards the surface epithelium and differentiate into mature epithelial cells ***(Al Moutaery, 2003)[b].***

The same author added that in contrast to the surface epithelium, cellular composition and function of the gastric glands are specialized in the different parts of the stomach.

Gastric mucosal barrier

Al Moutaery,[a] (2003) discovered that the stomach has unique protective characteristics not seen elsewhere in the tract, known as the *gastric mucosal barrier*. The barrier consists of three protective components that together provide extra resistance for the mucosal surface of the stomach. These components include a compact epithelial cell lining, a special mucus covering and bicarbonate ions.

Cell lining

Recently, ***Swarnakar et al., (2005)*** reported that epithelial cells in the stomach were tightly bound to each other. Tight junctions create an impermeable lining that was provided by cell membranes; which consists mainly of lipid; its hydrophobic nature repels fluids that may directly injure the lining.

Mucus Coating

Later on, ***Baschenko et al., (2006)*** added that although gastric glands contain a smattering of mucus producing cells, the principal source of mucus was derived from the columnar epithelium. This mucus was insoluble and forms a protective gel-like coating over the entire gastric mucosal surface. This serves to protect the gastric mucosa from autodigestion by pepsin and erosion by acids and other caustic materials that might damage it

Bicarbonate Ion Production

A detailed discussion about the third layer of the gastric mucosal barrier was added by ***Hatazawa et al., (2007)*** as they emphasized that the gastric glands are interspersed throughout the mucosa consisting of parietal and chief cells; that secrete hydrochloric acid and pepsinogen respectively. An acid environment is essential in converting pepsinogen to pepsin and in activating pepsin as a proteolytic enzyme. Furthermore, ***Filaretova et al., (2007)*** added that bicarbonate production is one of the protective mechanisms of the mucosal surface of the stomach. Bicarbonate is a salt that serves to buffer or neutralize strong acids. Therefore, the epithelium of the gastric mucosa protects itself by secreting mucus coating and the bicarbonate ions that offset the erosive potential of acids.

Cardiac glands

Al Moutaery, [a] (2003) described the cardiac glands in the form of heavily branched tubular glands (similar to the cardiac glands of the esophagus), which contain mainly mucus-producing cells, in addition of the secretory cells characteristic of the principal glands.