EFFECT OF VERAPAMIL AND RANITIDINE ON INDOMETHACIN INDUCED GASTRIC ULCERS IN ALBINO RATS

Thesis submitted in partial fulfillment of the Master Degree in Pharmacology

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"تأثير عقار الفيرابميل و عقار الرانتدين على قرحة المعدة المحدثة بعقار الاندوميثاسين في فئران التجارب"

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TO
My Father
And
My Mother

“Abstract”

The present work studies the effect of verapamil and ranitidine on indomethacin induced gastric ulcers in albino rats. The volume and pH of gastric secretion was estimated and histopathological examination was done.

It was found that indomethacin induced gastric ulcers were significantly reduced by verapamil. This decrease was duration dependent. There was no significant difference between this effect and that produced by ranitidine.

On the other hand, when both verapamil and ranitidine were used together, it was found that there was a significant reduction in the mean ulcer score and histopathological changes compared to that induced by verapamil or ranitidine alone. Gastric acidity and volume of gastric secretion showed significant reduction in the same manner to mucosal changes.

Also, indomethacin and ranitidine increased the gastric motility induced by acetylcholine. Whereas, verapamil decreased the gastric motility. When ranitidine and verapamil were used together there was a decrease in gastric motility in small doses and an increase in gastric motility in large doses.

Key words: indomethacin, ranitidine, verapamil and gastric ulcers.

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Contents

List of Abbreviations

ACh.: ----------Acetylcholine.
AMP: ----------Adenosine Mono Phosphate
PKA: ----------PhosphoKinase A.
ANOVA: ----------One-Way analysis of variance.
AV: ----------Atrioventricular.
Ca^{+2}: ----------Calcium.
cAMP: ----------Cyclic adenosine mono phosphate.
CaSR: ----------Ca^{+2}-sensing receptors.
CCB: ----------Calcium channel blockers.
CCK: ----------Cholecystokinin.
Cl^{-}: ----------Chloride.
CNS: ----------Central nervous system.
COX: ----------Cyclooxygenase.
CSF: ----------Cerebrospinal fluid.
CYP450: ----------Cytochrome p 450.
DAG: ----------Diacylglycerol.
DU: ----------Duodenal ulcer.
ECL: ----------Enterochromaffine like cells.
EGF: ----------Epidermal growth factor.
G_i: ----------G inhibitory.
H. Pylori: ----------Helicobacter pylori.
H^{+}/ K^{+} ATPase: ----------Hydrogen / potassium ATPase.
H& E: ----------Hematoxylin and Eosin.
HCl: ----------Hydrochloric Acid.
HCO_3^{-}: ----------Bicarbonate.
H_2RA: ----------Histamine type 2-receptor antagonist.
H_2 receptors: ----------Histamine type two receptor.
HVA: ----------High voltage-activated.
IP: ----------Inositol phosphate.
IP_3: ----------Inositol trisphosphate.
I.U: ----------Incidence of ulceration
L: ----------Liter.
LH: ----------Lutinizing hormone.
LPS: ----------Lipopolysaccaride.
M.U.S: ----------Mean ulcer score
M_1: ----------$Muscarinic_1$.
M_2: ----------$Muscarinic_2$.
M_3: ----------$Muscarinic_3$.
NO: ----------Nitric Oxide.
NSAIDs: ----------Non steroidal anti-inflammatory drugs.
PG (E, I): ----------Prostaglandins (E and I).
PGG_2: ----------Prostaglandin G_2.
PGH_2: ----------Prostaglandin-H_2.

PIP_2: ----------Phosphatidyl inositol bisphosphate.
PKC: ----------Protein kinas C.
PLC: ----------Phospholipase C.
PSVT: ----------Paroxysmal supraventricular tachycardia.
PTH: ----------Parathrmone.
ROCs: ----------Receptor-operated Ca^{+2} channels.
S.D: ----------Standard Deviation.
TNF: ----------Tumor necrosis factor.
U.I: ----------Ulcer index
US: ---------- Ulcer score
VIP: ----------Vasoactive intestinal peptide.
VOCs: ----------Voltage-operated Ca^{+2} channels.
ZES: ----------Zollinger-Ellison syndrome.

"Introduction"

Acid peptic diseases include gastroesophageal reflux, peptic ulcer and stress–related mucosal injury. In all these conditions, mucosal erosions or ulcerations arise when the caustic effects of aggressive factors (acid, pepsin) overwhelm the defensive factors of gastrointestinal mucosa (mucus and bicarbonate secretion, prostaglandins and blood flow) (***Suerbaum and Michetti., 2002).***

NSAIDs like indomethacin may induce peptic ulcers by several mechanisms. Mainly, they suppress mucosal generation of prostaglandins, which are protective to gastric mucosa (particularly PGI_2 and PGE_2) by inhibition of cyclooxygenase enzyme responsible for their synthesis ***(Konturek, 1995).*** Local irritation of gastric mucosa by NSAIDs is another mechanism as damage to the lipoprotein membrane of the epithelial cells occurs during their absorption. This allows back diffusion of acid in to the gastric mucosa and induces tissue damage ***(Shearman et al., 1984).***

It has been established that Ca^{+2} ions play an important role in activational secretory processes of many gland cells ***(Douglas, 1976).*** The activation of salivary and gastric secretion by secretagogues seems to be dependent on the level of extracellular calcium and these processes have been characterized by an enhanced calcium influx ***(Soll et al., 1993).*** Hence, calcium channel blockers may have a protective action that may play a role in healing of peptic ulcer.

"Aim of the Work"

As the calcium is involved in the regulation of acid secretion in the stomach. There is a possibility that the calcium channel blockers, by blocking the slow calcium channels, may influence the secretion of hydrochloric acid in the stomach and may have a protective effect on the genesis of gastroduodenal ulcers. Therefore, the objective of the present work is to study the effect of verapamil and ranitidine on indomethacin induced gastric ulcers in albino rats.

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