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Research Article

Comparative study of Captopril and Losartan on gastric ulcer in rats

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ABSTRACT

The mechanism behind ACE inhibitors (ACEI) is increasing PG synthesis, which causes a rapid increase in production of mucus. In contrast AT1 receptor antagonist decreases PG level. In the same time these decrease TNF-α, ICAM-I and neutrophil infiltration in gastric mucosa. In present study the efficacy of Losartan, an AT1 receptor antagonist in ulcer protection was estimated, which was again compared with Captopril. Losartan decrease PG synthesis, but by decreasing TNF-α, ICAM-I and neutrophil infiltration in gastric mucosa it might shows antiulcer activity. In case of Captopril, it occurs by increasing PG synthesis. In this present study it was observed that Captopril as well as Losartan showed ulcer preventive activity in gastric ulcer induced by pylorus ligation method.

Key words: *ACEI, AT1, ICAM-I, Captopril, Losartan, Pylorus ligation*

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INTRODUCTION

Local mechanisms implicated in the mucosal defense are mucus alkaline secretion, mucosal hydrophobicity, rapid epithelial cell renewal, rich mucosal blood flow, mucosal sulfahydryls [1,2] and increased resistance of gland cells in deep mucosa to acid and peptic activity [3]. Numerous studies have indicated that gastro-duodenal protection by prostaglandin include both increases in mucosal resistance as well as decrease in aggressive factors. Peptic ulcer occurs due to the imbalance between aggressive(acid, pepsin) and defensive (mucus, gastric mucosal barrier) factors of gastric mucosa. In the renin-angiotensin system, angiotensin II is an octapeptide generated in the plasma from angiotensin-I by the action of ACE, precursor plasma α 2 globulin and pressure homeostasis. The treatment of peptic ulcer is directed against either reduction of aggressive factors or enhancement of mucosal defense of stomach and duodenum with cytoprotective agents. Prostaglandins form a vital component of gastric mucosal damage. [4] Prostaglandins

may act directly on the parietal cells, reducing both the intra cellular synthesis of cyclic cAMP as well as their own secretary activity. Prostaglandins are also known to stimulate the synthesis of mucus [5, 6]. PGE2 is also believed to increase the surface hydrophobicity of gastric mucosa by increasing surface active phospholipid surfactant. [7] It is reported that ANG-II mediated vasoconstriction is a very important mechanism for ulcer production. The blood flow to the stomach was increased in animals treated with the AT1 receptor antagonist. In cold restraint stress increase in the expression of the pro inflammatory cytokine TNF-α, intra cellular adhesion molecule (ICAM-1) and the number of infiltrating neutrophils in the gastric mucosa, which play crucial roles in the progression of gastric injury [8]. They present evidence that treatment with the AT1 receptor these findings indicate that the anti-inflammatory effects of AT1 blockade could be relevant for the protection of gastric ulcer. In contrast ANG II receptor blocker decreased the prostaglandin level. This study was designed to compare the protective effects of Captopril and Losartan against gastric mucosal lesions induced by pylorus ligation.

MATERIALS AND METHODS

Animals, Wistar rats (140-170 g) of either sex were used. They were kept in polypropylene cages in a centrally air conditioned room at an ambient temperature. Before experiment they kept in 12 hrs. dark and night cycles for 4 days. Antagonist exerts anti-inflammatory actions, In the 5th day they were used for experiment dramatically decreasing the TNF-α and ICAM-1[9], overexpression and the neutrophil infiltration in the gastric mucosa and submucosa and in the venules of the submucosa where AT1 receptors are located. During fasting animals were kept in cages having wire grid bottoms to prevent coprophagia. Animals were randomly distributed into groups consisting of 6 animals. All experimental procedures were carried out in accordance with the guidelines of CPCSEA.

EXPERIMENTAL DESIGN

Pylorus ligation (PL): Rats were fasted for 24 hrs. Before the surgery, Pylorus ligation was performed by a small midline incision in about 1 cm below the xiphoid process under light ether anesthesia. Pyloric portion of the stomach was lifted slightly and ligated avoiding traction to the pylorus and damage to the blood supply. The stomach was replaced carefully and abdomen was closed by interrupted sutures. During the post operative period animals were deprived of both food and water. [11] The animals were sacrificed by heavy ether anesthesia at the end of nine hours. The esophageal region was ligated to prevent the loss of gastric fluid and the stomach was dissected out. The gastric contents were drained into a small beaker and stomach was rinsed with measured quantity of saline. The actual volume of gastric contents was recorded and pH was determined. The contents were subjected to centrifugation at 2000 rpm for 10 min. The supernatant was subjected to analysis for total acidity and free acidity. The stomach was opened along the greater curvature and the pylorus region was examined for ulceration and ulcer index was determined using the equation. [12]

Ulcer index (U.I.) = 10/X

Where X = Total mucosal area /Total ulcerated area.

The stomach contents were subjected to free and total acidity estimation (Hawk et al., 1947). One ml of gastric juice was pipette into a conical flask to which 2 to 3 drops of Topfer's reagent was added and titrated with 0.01 N sodium hydroxide until all traces of red color disappears and the color of the solution turns to yellowish orange. The volume of the alkali added was noted. This volume corresponds to free acidity. Then 2 or 3 drops of phenolphthalein solution was added and titration was continued until a definite red tinge appears. Total volume of alkali added was noted. The volume corresponds to total acidity.

Acidity was calculated by using the formula.

Acidity = Volume of NaOH (ml) x Normality of NaOH × 1000 MEq.

STATISTICAL ANALYSIS

Values are expressed as mean ± standard error of mean (SEM). Statistical significance was determined by unpaired student 't' test for comparison of two group and by one way analysis of variance (ANOVA) followed by Dunnet's test for comparison of more than two groups for all parameters. The statistical analysis was done using computer software (Instant Graph pad, software version 3.0 for windows), values of $p<0.01$ were considered to be statistical significance.

RESULT AND DISCUSSION

In this method there were significant changes in pH, free acidity, total acidity, ulcer index and ulcer scores, but no significant change in the volume of gastric content, free and total acidity in the group of Losartan (10mg/kg, i.p) when compared with standard. Ulcer scores were 1.58±0.193** and 1.66±0.187** in the groups of Captopril and Losartan respectively in comparison of 1.416±0.213** and 2.8 ± 0.412 in the groups of Standard and control respectively. Ulcer index of Captopril and Losartan groups were 0.157±0.0028** and 0.166±0.0032* respectively, where as in standard and control groups it was 0.115**±0.0027 and 0.224 ±0.0036 respectively. So, Captopril and Losartan improved the ulcer score and ulcer index, though the effect of Losartan was lesser than Captopril but both were significant. In case of mucus content determination Losartan didn't improve this as Captopril and Standard groups. Captopril, Standard and Control group showed 37.61±1.08**, 49.44±0.74** and 27.12 ± 0.189 mg of mucus respectively. Gastric pH, volume of gastric content, free acidity and total acidity were also measured. Losartan showed significant effect only in pH parameter, but Captopril had given significant effects to control pH and free acidity. Therefore, the quality of mucosal structure restoration may be a crucial factor in determining future ulcer recurrence and should be paid more attention in evaluation of action of anti ulcer agents.

Fig:1 Photograph of Pylorus ligated rat stomach

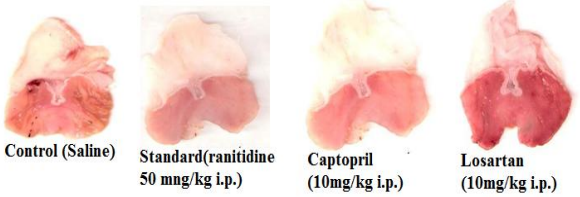

Table 1: Effect of Captopril and Losartan on ulcer scores and ulcer index and mucus content in pylorus ligated rats

Drug	Dose (mg/kg i.p.)	Ulcer scores	Ulcer index	Mucus content(mg)
Control	Saline	2.8 ± 0.412	0.224 ± 0.0036	27.12 ± 0.189
Standard (Ranitidine)	50	1.416±0.213**	0.115±0.0027**	49.44±0.74**
Captopril	10	1.58±0.193**	0.157±0.0028**	37.61±1.08**
Losartan	10	1.66±0.187**	0.166±0.0032**	28.30±1.93

Values are mean ± SEM, n = 6, **p<0.01, when compared with that of the control treated rat.

Table 2: Effect of Captopril and Losartan on pH, vol. of gastric content, free acidity and total acidity in pylorus ligated rats

Drug	Dose (mg/kg i.p.)	pH	Vol. of gastric Content (ml)	Free acidity (mEq/l)	Total acidity (mEq/l)
Control (Saline)	-	2.783±0.19	9.2 ± 0.31	47.17±3.28	96.6±3.40
Standard (Ranitidine)	50	5.184±0.22**	8.3 ± 0.22	32.82±2.91**	58.8±2.33**
Captopril	10	4.261±0.13**	8.7 ± 0.17	38.31±3.12**	81.69±4.36
Losartan	10	3.527±0.17**	8.9 ±0.69	43.77±2.21	88.76±4.43

Values are mean ± SEM, n = 6, **p<0.01, when compared with that of the control treated rat.

CONCLUSION

Gastric acid is an important factor for the genesis of ulceration in pylorus-ligated rats. The activation of the vagus-vagal reflux by stimulation of pressure receptors in the antral gastric mucosa in the hypersecretion model of pylorus ligature is believed to increase gastric acid secretion. Captopril increases PG synthesis, which in turn increases mucus production and controls the pH and free acidity. Though Losartan decrease PG synthesis, but as it decrease the over expression of TNF-α, ICAM-1 and neutrophil infiltration, these may be the reasons behind the antiulcer activities of losartan.

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REFERENCES

1. Toma W., Hiruma-Lima C.A., Guerrero R.O. and Souza Brito A.R.M., Preliminary studies of Mammea americana L. (Guttiferae) bark/latex extract point to an effective Antiulcer effect on gastric ulcer models in mice, Phytomedicine 2005, 12(5), 345-350.
2. Harminder D., Chauhan C.K., Shahani S., Study on the action of captopril: A sulfhydryl donar on

rodent ulcer, Indian Journal of pharmacology 2000, 32:25-27.

3. Konturek S.J., Gastric cytoprotection, scand J. Gastroenterol 1985, 28, 543-53.
4. Ko J.K., Cho C.H., Role of non-protein sulfhydryl compounds in gastric adaptive cytoprotection against ehtanol-induced mucosal damage in rate Inflam. Res., 1995, 44, 242-4.
5. Domscheke W. & Domscheke et. al., Prostaglandin stimulated gastric mucus secretion in man, Acta Hepato Gastroenterology 1978, 25, 292-4.
6. Bolton J.P., Palmer D., Cohen M.M., Effects of prostaglandins on gastric mucus production in rats, Surry Forum 1976, 27, 402.
7. Lichtenberg L.M., Richards J.E., Hills B.A., Effects of 16, 16-dimethyl prostaglandin E on surface hydrophobicity of aspirin treated canine gastric mucosa, Gastroenterology 1985, 88, 308-314.
8. Hamaguchi M.T., Watanabi K., Higuch. Mechanisms and roles orf neutrophil infiltration in stress induced gastric injury in rats, Dig Dis Sci 2001, 46, 432-439.
9. Damiano Rizoni Enzo, porteri Alforsa piccoli Effcts of losartan and Enalapril on small arter structrure in hypertensive rats, Hypertension 1998, 32, 305-310.
10. Claudia Bregonzio, Ines Armendo, Hiromichi Ando, Miroslavea Jezova, Gustavo Baiardi Antiinflmmatroy effects of angiotensin II AT1 receptor antogaonism prevent stress-induced gastric injury, Am J. Physiol Gastrointest Liver physiol 2003, 285, G414-G423.
11. Ganguly A.K., A method for quantitative assessment of experimentally produced ulcers in the stomach of the rats, Experientia 1969, 25, 1224.
12. Shay H., Komarov S.A., Fels S.S., Meranze D., Gruenstein H., Siplet H.A., Simple method for the uniform production of gastric ulceration in rat, Gastroenterology. 1945, 5:43-61.