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EVALUATION OF ANTI-ULCER ACTIVITY OF ESOMEPRAZOLE MAGNESIUM TRIHYDRATE FILM IN WISTAR RATS WITH GASTRIC ULCERATION INDUCED BY INDOMETHACIN

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ABSTRACT

The present study aimed to evaluate the anti-ulcer activity of Esomeprazole magnesium trihydrate by using models of acute gastric lesions in Wistar rats induced by indomethacin and inhibition of gastric cyclo-oxygenase resulting in less formation of prostacyclin. Groups of 4-6 Wistar rats are used. The test drugs are administered orally in 0.1% Tween 80 solution 10 min prior to oral indomethacin in a dose of 20 mg/kg (4 mg/ml dissolved in 0.1% Tween 80 solution). Test drug Esomeprazole magnesium trihydrate and standard drug Misoprostol both are used in a dose of 30mg/kg. Formal-saline (2% v/v) is also injected into the totally ligated stomachs for storage overnight The results showed that Macroscopical and Histopathological changes on Indomethacin induced model showed the edematous, inflammation, degeneration, hemorrhage, appearance of the gastric tissue, where as Esomeprazole magnesium trihydrate (30 mg/kg) treated groups shows regeneration and prevents the formation of hemorrhage and edema. It is conclude that Esomeprazole magnesium trihydrate has good antiulcer activity and high effective in ulcers induced by indomethacin

KEYWORDS: Esomeprazole Magnesium trihydrate, Wister rats, Ulcer-Index, Indomethacin, Anti -ulcers.

INTRODUCTION

Peptic ulcers, which are characterized by the presence of mucosal damage, are predominantly caused by infection with *Helicobacter pylori*, antiplatelet agents such as acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs) such as oral bisphosphonates, potassium chloride, immunosuppressive medications, serotonin reuptake inhibitors, alcohol consumption and cigarette smoking.[1, 4] Anatomically, peptic ulcers occur mostly in the stomach and proximal duodenum. Peptic ulcers are caused by an imbalance between the defensive (mucus secretion, mucosal barrier, blood flow, cellular regeneration and endogenous protective agents) and destructive (acid and pepsin secretion) functions of the gastric system.[13] It is the most predominant of the gastrointestinal diseases with a worldwide prevalence of about 40% in the developed countries and 80% in the developing countries. It is generally recognized that peptic ulcer is caused by a lack of equilibrium between the gastric aggressive factors and the mucosal defensive factors.[2] Based on site of attack, peptic ulcer may be classified as esophageal, duodenal, or gastric. Some other factors, such as bad dietary habits, excessive intake of nonsteroidal anti-inflammatory agents, stress, hereditary predisposition and Helicobacter pylori infection, which is reported to account for more than 70% of cases, are responsible for the development of peptic ulcer diseases.[3, 5]

MATERIALS AND METHODS

Drugs and chemicals

Esomeprazole magnesium trihydrate was obtained from Suven Pharmaceuticals (Vadodara, Gujrat,) and Indomethacin from Glenmark Pharmaceuticals Ltd., Mumbai. Misoprostol and Formal –saline were obtained from Alkem Laboratories Pvt. Ltd., Hyderabad, India. All other chemicals used in this study were obtained commercially and were of analytical grade.

Experimental Animals

Wistar rats (150-200 gm) of either sex, used in the present study, were obtained from the central Animal House facility of MMCP, M.M. University, Mullana (Ambala). All animal protocols were approved by Institutional Animal Ethical committee (IAEC) of the organization (Reg. No. 1355/PO/Re/L/10/CPCSEA).

All animals were maintained under standard conditions of humidity (50±10%), temperature (22±2^{0}c) and light (12 hours light & 12 hours dark). Animals were fed with standard food and water. They were acclimatized for 1 week before examination which was performed in accordance with CPCSEA (committee for the purpose of

control and supervision of experimentation on animals) guidelines.

TREATMENT PROTOCOL FOR ANTI-ULCEROGENIC ACTIVITIES

Ulcer Lesion Index Method

Indomethacin induced ulcers in rats

Nonsteroidal anti-inflammatory agents, like Indomethacin and acetyl-salicylic acid, induce gastric lesions in man and in experimental animals by inhibition of gastric cyclo-oxygenase resulting in less formation of prostacyclin, the predominant prostanoid produced in the gastric mucosa.[6, 11]

Procedure

Groups of 4–6 Wistar rats weighing 150–200 g are used. The test drugs are administered orally in 0.1% Tween 80 solution 10 min prior to oral indomethacin in a dose of 20 mg/kg (4 mg/ml dissolved in 0.1% Tween 80 solution). Six hours later, the rats are sacrificed in CO_2 anesthesia and their stomachs removed.[7,8] Formal-saline (2% v/v) is then injected into the totally ligated stomachs for storage overnight.[6,9] The next day, the stomachs are opened along the greater curvature, then washed in warm water and examined under a 10X magnifier. The lengths of the longest diameters of the lesions are measured and summated to give a total lesion score (in mm) for each animal, the mean count for each group being calculated.[10]

Test drug=Esomeprazole magnesium trihydrate 30mg/kg

Standard drug= Misoprostol

The different groups of animals are assigned as follows

Table 1 Different groups of Wistar rats

Groups	Treatment
Group 1	Received vehicle only
Group 2	Served as control group and received Indomethacin (20 mg/kg)
Group 3	Served as standard and received Misoprostol (30 mg / kg)
Group 4	Severed as treatment group and received Esomeprazole magnesium trihydrate (30 mg/kg).

Macroscopic evaluation of stomach

The abdomen was opened, cardiac end of the stomach was dissected out & the content was drained into the glass tube.[11] The volume of the gastric juice was measured and its p^H was determined. The isolated abdomen was examined by a 10X magnifier lens to assess the formation of ulcer. The numbers of ulcers were counted.[12, 14]

Scoring of ulcer

- 0 = Normal coloured stomach
- 0.5 = Red coloration
- 1 = Spot ulcer
- 1.5 = Hemorrhagic streaks
- 2 = Ulcers ≤ 3 but ≤ 5
- 3 = Ulcers > 5

Calculation of ulcer index

- $U_I = U_N + U_S + U_P \times 10^{-1}$
- $U_{I\,=}$ Ulcer index
- U_N = Average of number of ulcer per animal
- U_S = Average of animal severity score
- $U_{P\,=}$ Percentage of animal with ulcer

Determination of percentage protection

$$\% \text{ Protection} = \frac{\text{Control mean ulcer index-test mean ulcer index} \times 100}{\text{Control mean ulcer index}}$$

Statistical analysis

Values are express as mean ±S.E.M. (n=6) observations, statistical comparison as follows: significant at when compared to control group.

RESULTS AND DISCUSSION

Macroscopical and Histopathological Evaluation of Ulcers

Macroscopical changes of Indomethacin induced models shown in figures below. Histopathological changes on Indomethacin induced model showed the edematous, inflammation, degeneration, hemorrhage, appearance of the gastric tissue, where as Esomeprazole magnesium trihydrate (30 mg/kg) treated groups shows regeneration and prevents the formation of hemorrhage and edema.

Table 2 Effects of Esomeprazole magnesium trihydrate on various parameters Indomethacin Induced ulcer in rats

S.No.	Groups	Dose (mg/kg)	Ulcer index	% Protection	P^H of gastric juice
1.	Control	_	13±1.26	_	3.3±.03
2.	Misoprostol	30mg/kg	4.3±0.06	70.38%	4.9±.01
3.	Esomeprazole magnesium trihydrate	30 mg /kg	5.4±0.01	66.93%	4.6±0.03

Values are express as mean ±S.E.M. (n=6) observations, statistical comparison as follows: significant at when compared to control group.

GRAPH REPRESENTING THE ULCER PROTECTION & ULCER INDEX ARE FOLLOWS

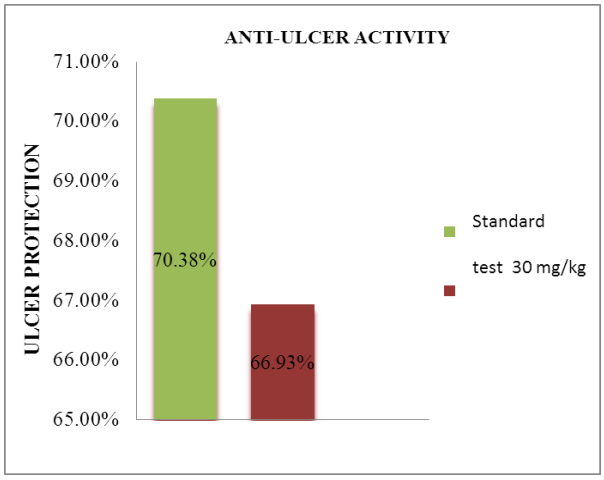

Fig. 1 Graph representing ulcer protection in various groups

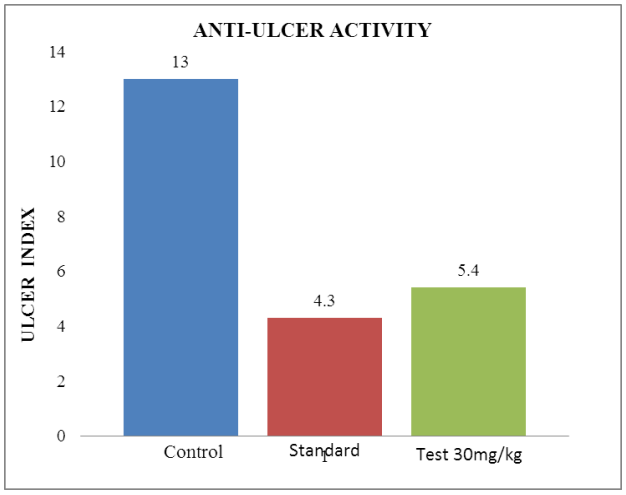

Fig.2Graph representing ulcer index in various groups

MACROSCOPICAL VIEW OF INDOMETHACIN INDUCED GASTRIC ULCER

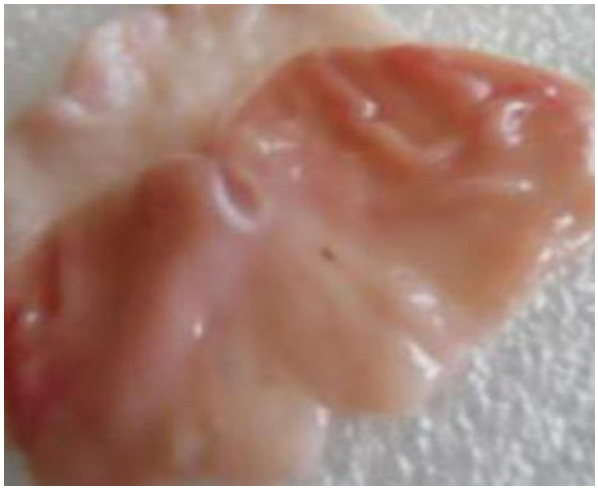

Fig. 3 Normal stomach (without any treatment group)

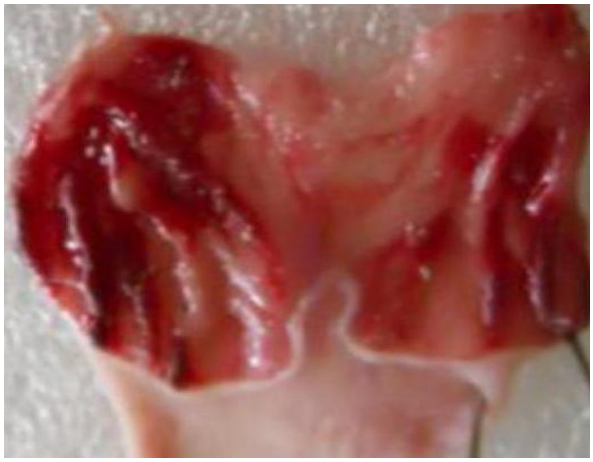

Fig. 4 Ulcer Control stomach (treated with Indomethacin induced ulcer)

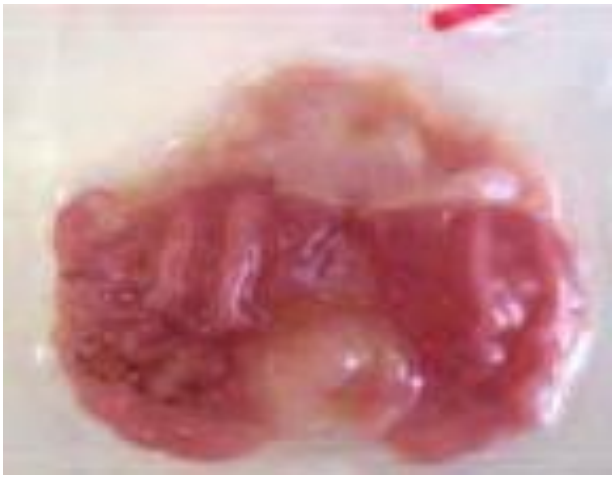

Fig. 5 Standard (treated with Misoprostol 30mg/kg and shows protected mucosal layer)

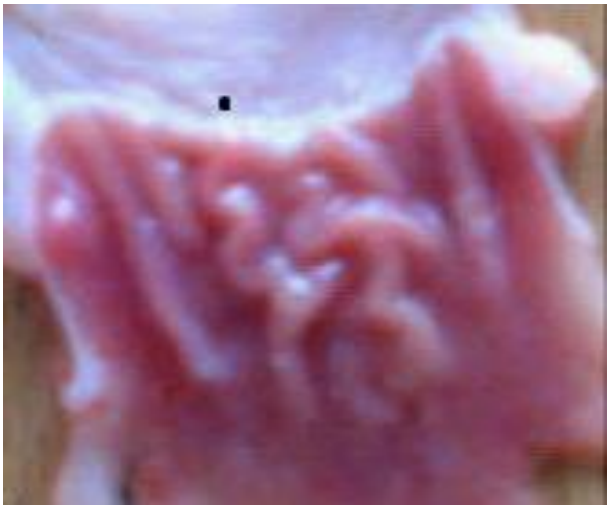

Fig. 6 Test (treated with Esomeprazole magnesium trihydrate and shows protected mucosal layer)

HISTOPATHOLOGY OF INDOMETHACIN INDUCED ULCER METHOD MODEL (HEMATOXIN & EOSINX100)

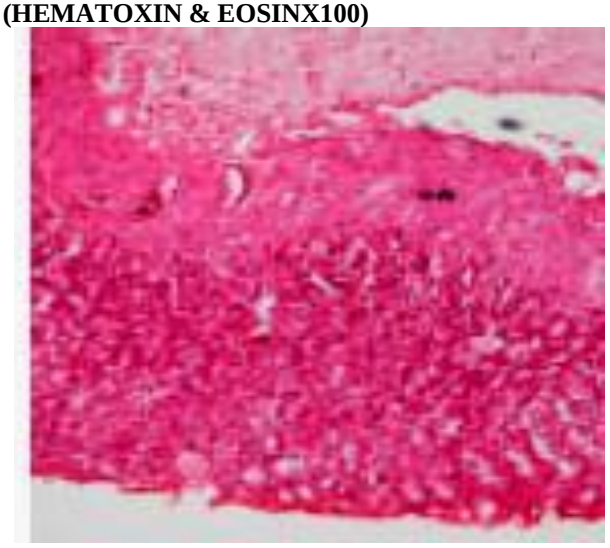

Fig. 7 Indomethacin induced methods shows inflammation & mucosal ulceration control

Fig. 8 Section of gastric mucosal layer shows normal control

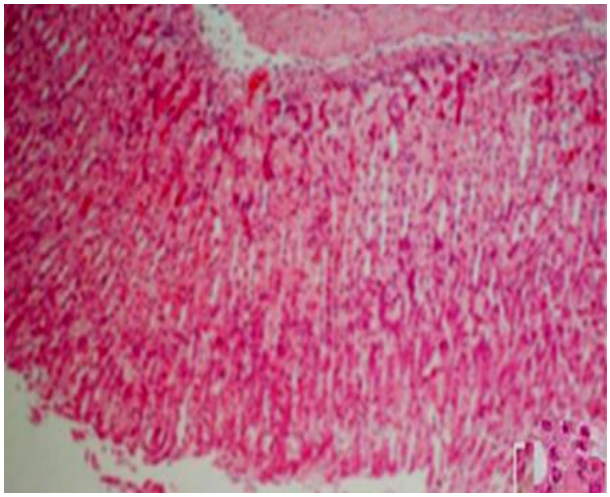

Fig. 9 Standard drug Mesoprostol (30mg/kg) shows no singnifance change in histopathology almost normal appearance

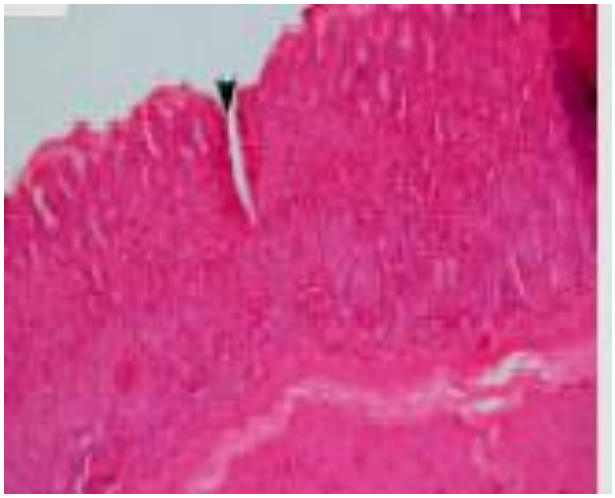

Fig.10 Esomeprazole magnesium trihydrate (30mg/kg) shows no singnifance change in histopathology almost normal appearance

CONCLUSION

Macroscopical and Histopathological changes on Indomethacin induced model showed the edematous, inflammation, degeneration, hemorrhage, appearance of the gastric tissue, where as Esomeprazole magnesium trihydrate (30 mg/kg) treated groups shows regeneration and prevents the formation of hemorrhage and edema.

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