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Research Article

ESTIMATION OF THE ANTI-ULCER PROPERTIES OF KETOTIFEN IN ASPIRIN AND SWIMMING STRESS INDUCED ALBINO RATS

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ABSTRACT

Objectives: To study the antiulcer activity of ketotifen on aspirin and swimming stress induced ulcers.

Material and methods: Antiulcer activity of ketotifen was studied using aspirin and swimming induced ulcer model in albino rats. The antiulcer activity of ketotifen1 mg & 2 mg/kg orally was compared with the standard drug ranitidine 10 mg/kg orally. The ulcer index was calculated and other parameters like survival time, hemorrhagic stomach area were determined.

Results: Ketotifen in graded doses i.e. 1 mg and 2 mg/kg orally showed protection against aspirin induced ulcer (ulcer index was reduced) which was statistically significant. However, maximum antiulcer activity was observed at 2 mg/kg oral dose ($p < 0.001$).

Ketotifen in both the doses (1 mg/kg and 2 mg/kg orally) reduced the ulcer index, number of ulcer per stomach, survival time and hemorrhagic area per stomach significantly in stress induced ulcer model.

Conclusion: Ketotifen has antiulcer activity comparable to ranitidine.

Keywords: Antiulcer activity, Aspirin induced ulcer model, Swimming stress model, Ketotifen, ulcer index.

INTRODUCTION

Among the disorders of gastrointestinal tract, peptic ulcers are one of the common disorders with prevalence rate of 3 to 5 %. Peptic ulcers arise due to net imbalances in mucosal offensive and defensive factors[1]. When the offensive effects of acid pepsin outweighs the protective effects of gastric or duodenal mucosa, the result is formation of ulcers.

Histamine is an important factor in the stimulation of acid secretion and the release of histamine is brought by gastrin[2]. There are many evidences which have also suggested that histamine augment gastric acid secretion[3, 4]. The released histamine acts on H_2 receptors of parietal cells and increases the cyclic AMP content[5, 6] which in turn brings secretion of hydrochloric acid.

The ulcer therapy is limited now mainly to reduce the offensive acid secretion. Now, it is known that the gastric mucosa resists auto digestion even though it is exposed to numerous harmful stimuli like reflux of bile, spicy food, micro-organism, substance P, free radicals stress, alcohol, 5 HT, slow reacting substances and PAF[7, 8].

Mast cell stabilizers are extensively used in the treatment of asthma9, allergic rhinitis, persistent diarrhea10, vernal conjunctivitis, apthous stomatitis and eczema. Ulcerative colitis is also treated by mast cell stabilizers like sodium cromoglycate & ketotifen11. Ketotifen decrease enzyme phosphodiaestrase and inhibits the Ca2+ mediated histamine and leukotrines as well as SRS-A. Thus, it impairs hyperemic response mediated by calcitonin gene related peptide (CGRP) 12. The knowledge of antihistaminic action triggers us to explore antiulcer activity which is directly related to gastric secretion.

Prophylactic treatment with mast cell stabilizers appears to protect against the future deregulation of mast cells caused by substance P and restoration of hyperemic response after mucosal injury and acid challenge. The protective effect was reported for duodenal ulcer.

Therefore, the present study has been conducted to investigate the antiulcer property of mast cells orally available ketotifen in albino rats.

MATERIAL AND METHODS

Preparation of drugs

Aspirin- A homogenous suspension of this drug was prepared in equal amount of gum acacia in concentration of 20 mg/ml as a 2 % solution.

Ranitidine- Ranitidine was used as a standard drug for comparison. The solution was prepared in distilled water in concentration of 10 mg/ml.

Ketotifen- Ketotifen was taken as a test drug in concentration of 1 mg/5ml solution.

All drugs were procured from Torrent Company, India. All the solutions were prepared freshly and used on the same day.

Permission for animal study was taken from institutional animal ethics committee before starting the study.

Wistar albino rats of either sex weighing 200 gm were selected. Before experimentation, the rats were fasted for 24 hours, they were deprived of food but free access to water was allowed. The rats were caged having a plate at its base just to avoid coprophagy. A 12 hour light and dark cycle was maintained.

The animals were divided into four groups of 6 animals each. One group received distilled water and served as control, whereas two groups were administered orally with 1 and 2 mg/kg of Ketotifen, respectively. This was continued for 3 days before the experimentation. Fourth group was given Ranitidine (10 mg/kg orally) in each experiment as standard drug for comparison.

The ulcer protective effect of ketotifen was measured as per the method of Hemmati et al (1973) [13] and Brekhman and Dardymov (1969) [14] and Singh et al (1970) [15]. Grading of ulcer was done by a method, described by Wilhelmi and Menasse-Gdynia (1972)[16], which is as follows:

Aspirin induced ulcer:

Grade I - Pin point ulcer.

Grade II - Ulcer smaller than 1mm in diameter.

Grade III- Ulcer up to 2mm in diameter.

Grade IV- Ulcer above 2mm in diameter.

Stress induced ulcer: Grading was done by dividing the stomach arbitrarily into four quadrants and calculation of hemorrhages according to the affected as follows:

Grade I - haemorrhages in one quadrant.

Grade II - haemorrhages in two quadrants.

Grade III- haemorrhages in three quadrants.

Grade IV- haemorrhages in four quadrants.

Mean ulcer scores for each animal were calculated and ulcer index was determined. The glandular portion of the stomach was opened along the greater curvature and the severity of hemorrhagic erosion was assessed and grading was done with the help of magnifying lens.

RESULTS

Aspirin induced ulcer

Aspirin (200 mg/kg) produced all grades of ulcer in 100 % animals.

Ketotifen in graded doses i.e. 1 mg and 2 mg/kg orally showed protection against aspirin induced ulcer (ulcer index was reduced) which was statistically significant. However, maximum antiulcer activity was observed at 2 mg/kg oral dose ($p < 0.001$) (Table 1).

Ranitidine (10mg/kg p.o.) produced highly significant ($p < 0.001$) antiulcer activity against aspirin induced ulcer.

Table 1: Effect of ketotifen on aspirin induced gastric ulcer

Groups (n = 6)	Dose (mg/kg p.o.)	Number of ulcer (mean ± SEM)	Ulcer index (mean ± SEM)
D.w.	10 ml	0.0 ± 0.02	0.00
Aspirin	200	9.0 ± 0.02	3.0 ± 0.15
Ketotifen	1	1. ± 0.86	1.0 ± 0.17
Ketotifen	2	1.0 ± 0.001***	0.25±0.06**
Ranitidine	10	0.16±0.16***	0.16±0.16***

n= number of animals, D.w.= Distilled water, *p <0.05 **p<0.01 ***p<0.001

Table 2: Effect of ketotifen on swimming stress induced gastric ulcer

Groups (n=6)	Dose (mg/kg p.o.)	Survival time (Mean ± S.E.M.)	Number of ulcer in total stomach area (Mean ± S.E.M.)	Ulcer index mean± S.E.M.	Hemorrhage in total stomach area
D.w.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Aspirin	200	3.8 ±0.17***	3.00 ± 0.00***	0.8 ± 0.00	1.0 ± 0.00***
Ketotifen	1	4.0 ± 0.15***	0.60 ± 0.16***	0.15 ± 0.04**	0.10 ± 0.04***
Ketotifen	2	4.5 ± 0.15***	0.40 ± 0.12***	0.15 ± 0.04	0.05 ± 0.02***
Ranitidine	10	5.6 ± 0.00***	0.01 ± 0.00***	0.01 ± 0.00***	0.01 ± 0.00***

n=number of animals, D.w.= Distilled water, *p<0.05 **p<0.01 ***p<0.001

Swimming stress induced gastric ulcer

Ketotifen in both the doses (1 mg/kg and 2 mg/kg orally) reduced the ulcer index, number of ulcer per stomach, survival time and hemorrhagic area per stomach, significantly. It also increased mean survival time. However, maximum effect was seen in 2mg/kg dose. Ranitidine 10 mg/kg significantly reduced the ulcer index, number of ulcer and has hemorrhagic area per stomach on stress induced gastric ulcer (Table 2).

DISCUSSION

In the present study, the significant reduction was seen in ulcer index in aspirin induced model and significant decrease in hemorrhagic areas, increase in survival time in swimming stress induced ulcer. It shows its cytoprotective effects.

Mechanism of gastric acid secretion as discussed by martin et al[12] proposes that gastric secretion is modified by many factors including anxiety. Anxiety affects the functioning of central nervous system and especially vagal activity in swimming stress. Anxiety also affects histaminergic and gastrinergic neurotransmissions and the functioning of the proton pump. Antiulcerogenic effect of ketotifen may be due to its antihistaminic action[5, 17, and 19]. The review of literature shows that mast cell stabilizers have antihistaminic, anticholinergic and vagolytic activity[19]. By just extrapolation of this particular fact Ketotifen's action on ulcer production can be explained.

The anti ulcer activity also confirm our finding with earlier study with other mast cell stabilizer i.e. sodium cromoglycate[20, 21]. Although, there is no direct reference of ketotifen as to having antiulcer properties (mast cell stabilizer) but we got the potent anti-ulcer activity like sodium cromoglycate which is also a mast cell stabilizer.

If more studies are conducted in this direction, there could be a new approach in the treatment of gastric ulcers in future.

CONCLUSION

From the above study, it was found that when compared with ranitidine; ketotifen showed nearly equal effect on both parameter i.e. aspirin and swimming stress induced gastric ulcer which is highly significant. It shows that ketotifen has potent antiulcer activity like other mast cell stabilizers. In future, the mast cell stabilizers can be most effective drugs for the prevention and treatment of peptic ulcers. For this, further studies are required.

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