ORIGINAL RESEARCH

Analgesic activity of omeprazole in pain models in rodents: A preclinical evaluation

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ABSTRACT

Introduction: Omeprazole is a proton pump inhibitor used for acid-related disorders. It exerts an anti-inflammatory effect owing to an inhibition of v-type H^+ K^+ ATPase located on neutrophils thus interfering with the neutrophil function that contributes to inflammation. Previous studies demonstrated omeprazole anti-inflammatory action. This study was planned to evaluate the analgesic action of omeprazole. **Material and methods**: Eighteen albino rats (Wistar strain) of either gender (weight 100-200 g) screened for gross anomaly and divided into 3 random groups of 6 animals each. Groups I, II, and III received omeprazole (10 mg/kg, 20 mg/kg, and 40 mg/kg, per oral each, respectively). The animals in each group served as their own control. Tests used were Haffner's tail clip and Eddy's hot plate method. Recordings done at baseline and after drug administration at 60-, 120-, 150- and 180-minutes using stopwatch. **Result:** Using Haffner's tail clip method, omeprazole showed an analgesic effect clinically at 60 min with high dose in Group III, but this was not statistically significant. With Eddy's hot plate method, omeprazole showed an analgesic effect at a higher dose after 60 minutes of administration in Group III, which was statistically significant but the effect was not sustained. **Conclusion:** Although omeprazole showed analgesic effect at a high dose, the effect was not sustained. Further studies done for a longer duration are needed to establish its analgesic effect.

Key words: Omeprazole, Analgesic, Pain Models, Rodents.

INTRODUCTION

Proton pump inhibitors (PPI) are antiulcer agents which suppress gastric acid secretion by inhibition of H^+K^+ ATPase located on membrane of the gastric parietal cells. Omeprazole is a prototype drug of PPI class that is used to treat acid-related disorders. It decreases acid production by about 80% to 95%.[1] Omeprazole and other PPIs bind covalently with the sulfhydryl group of cysteines in the H^+ / K^+ ATPase and irreversibly inactivate the pump molecules. [1]

Recent studies have shown that omeprazole exerts anti-inflammatory effects independent of the inhibition of gastric acid production.[2] In addition, they have been found to have antioxidant activity[3] and carbonic anhydrase inhibitory activity.[4]

Previous studies have proven the anti-inflammatory, antioxidant and carbonic anhydrase inhibitory action of PPIs. Neutrophil cells have vacuolar (v-type H^+ K^+ ATPase) pump that pumps acid in the cell. These pumps are inhibited by PPIs, thus interfering with neutrophil function. This is responsible for the anti-inflammatory and anti-oxidant action of PPIs.

Wandall[13] demonstrated in an in vitro study that omeprazole reduced chemotaxis and oxidative free radical production induced by bacterial peptide. Yoshida et al[14] demonstrated that lansoprazole and omeprazole, at clinically relevant doses, inhibit the expression of CD-11 and CD18 on neutrophils and neutrophil-dependent adhesion to endothelial cells.

The already marketed drugs like non-steroidal anti-inflammatory drugs exert their analgesic activity because of their anti-inflammatory effect but also exhibit intolerable adverse effects like gastritis, gastrointestinal bleeding, perforation, and analgesic nephropathy. Therefore, a novel, safe, and effective analgesic drug is needed.

Previous studies have evaluated the anti-inflammatory activity using peripheral pain models. The present study was performed with the aim and objectives of evaluating the analgesic activity of omeprazole using central pain models in rodents.

MATERIAL AND METHODS

The study was conducted keeping in mind the principle of the essentiality of animal research. The study was conducted in accordance with the CPCSEA

guidelines.[15] This study was conducted after seeking ethical approval from Institutional Animal Ethical Committee (PGIMS/IAEC/2019/01). The pain models included were the radiant heat method using the hot plate method and the mechanical method using Haffner's tail clip method.

Animals

Albino rats (Wistar strain) of either gender weighing 150-250 gram were procured for study from the central animal house and screened for any gross anomaly. Animals were divided into three groups of six animals each. Group I received omeprazole (10 mg/kg, po), Group II received omeprazole (20 mg/kg, po) and group III received omeprazole (40 mg/kg, po) single dose. The effect of omeprazole was evaluated by using each animal as its own control. The drug was administered by oral gavage technique.

Eddy's Hot plate method[16-18]

The healthy rats were weighed and numbered. The rats were placed on the electrically heated surface, the temperature of which was set at 55°C. A transparent glass cylinder was used to keep the animal on the heated surface of the plate. The animals were placed on the hot plate and time until either a licking or jumping response was taken as the endpoint. Rats with a reaction time of more than 8 seconds were excluded from the study. A cut-off period of 15 seconds was observed to avoid damage to the paws.[16] The latency was recorded before drug administrations and after 60 minute, 120 minute, 150 minute and 180 minute following oral administration of the drug.

Haffner's tail clip method[17-19]

The rats were weighed and numbered. An artery clip was applied to the root of the tail and reaction time was noted using a stopwatch. Artery clip induces pain. The Animal quickly responds to noxious stimuli by biting to clip/ tail near the location of the clip. After administration of the test drug, the response was noted at 60 minutes, 120 minutes, 150 minutes, and 180 minutes.

Statistical Analysis

The average values of reaction time after each time interval were calculated (Mean ± SD) and compared with the pre-test value by analysis of significance. P value <0.05 was considered significant.

RESULTS

Eddy's Hot plate method

In Group I, mean ± SD of reaction time at baseline, 60 min, 120 min, 150 min and 180 min was 5.29 ± 1.83 seconds, 4.5 ± 1.64 seconds, 5.37 ± 1.65 seconds, 5.96 ± 0.97 and 5.62 ± 1.36, respectively. In Group II, mean ± SD was 5.83 ± 2.6, 4.06 ± 1.28, 4.08 ± 1.16, 6.46 ± 1.54, 6.28 ± 1.41, respectively. In Group III, the findings are as shown in Figure 1. The statistical comparison in group III was statistically highly significant (p value= 0.0001) significant at 60minutes following drug administration but the effect was not sustained.

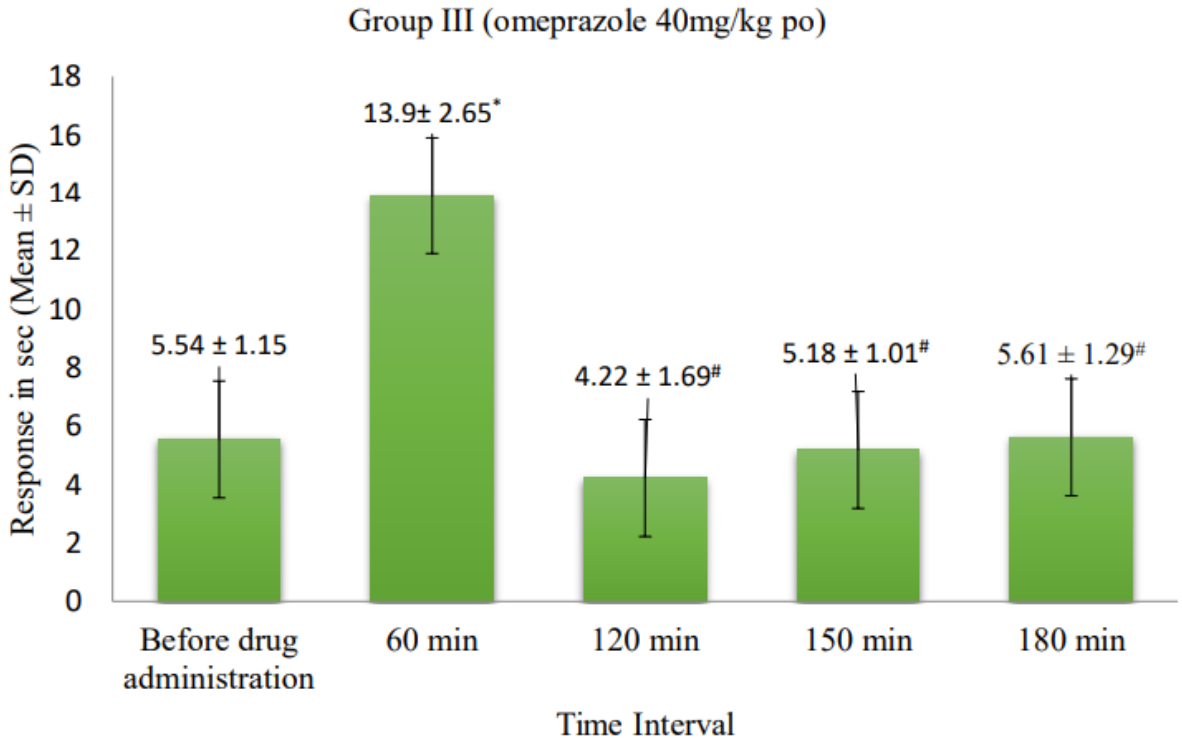

Figure 1: Response of Group III with Eddy's Hot plate method. * refers to p-value <0.0001; #refers to p-value>0.05.

Haffner's tail clip method

In Group I, mean ± SD of reaction time at baseline, 60 min, 120 min, 150 min and 180 min was 1.06 ± 0.2 seconds, 0.94 ± 0.47 sec, 0.96 ± 0.32 sec, 0.83 ± 0.22 sec and 0.88 ± 0.16, respectively. In group II and III the findings are as shown in figure 2 and 3, respectively.

The statistical comparison among different groups was found to be statistically not significant (p value >0.05), although Omeprazole showed analgesic effect clinically at 60 minutes with high doses (40mg/kg p.o).

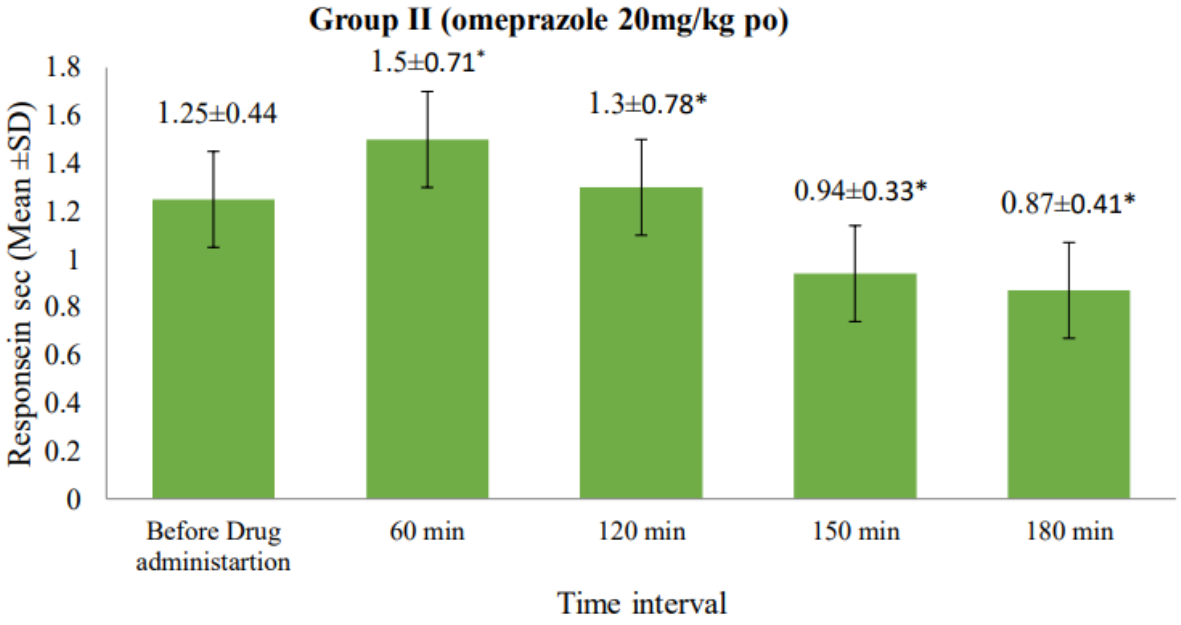

Figure 2: Response of Group II with Hafner's tail clip method. * refers to p value >0.05 on comparison to animals before drug administration animals before drug administration

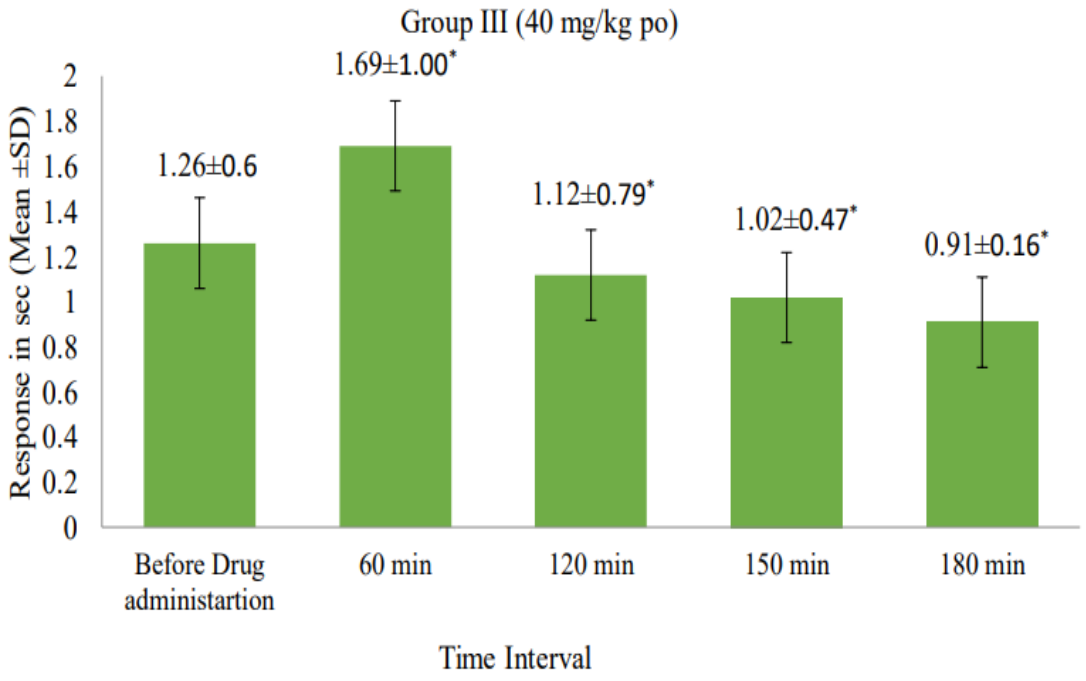

Figure 3: Response of Group III with Haffner's tail clip method; * refers to p-value > 0.05.

DISCUSSION

Omeprazole apart from reducing the acid secretions also act by inhibiting the release of inflammatory mediators and chemotaxis. The studies published previously elaborated the anti-inflammatory action of omeprazole.[11-14] The present study was carried out to evaluate the analgesic activity of omeprazole.

The pain models used to evaluate the analgesic activity were Haffner's tail clip method and Eddy's hot plate method. The study animals were divided into

3 groups of 6 animals each and were administered omeprazole 10mg/kg, 20mg/kg and 40 mg/kg per orally. The animals actedas their own controls.

No study in literature could be found which evaluated the analgesic activity using central animal pain models.

Chanchal et al found that omeprazole at 50mg/kg/day p.o for 14 days reduced neuropathic pain when compared with control.[11] El Nezhawy et al[12] demonstrated that omeprazole (50 mg/kg, po) significantly inhibited the carrageenan-induced acute paw inflammation. Our study intended to evaluate the analgesic action using central animal pain models and found that omeprazole showed analgesia at high dose (40mg/kg po) after 60 minutes of administration that was not clinically significant in Haffner' s tail clip method but was statically significant with Eddy's hot plate method although the effect was not sustained.

Limitations of the study are that it included only minimal number of animals and therefore further studies are needed to elaborate the analgesic activity of omeprazole. Other battery of tests involving peripheral pain models could have been included in the study but because of technical requirements were not the part of study.

CONCLUSION

Although omeprazole showed analgesic effect at high dose but the effect was not sustained. Further studies are needed to establish its analgesic activity.

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