WWJMRD 2022; 8(12): 34-35
www.wwjmrd.com
International Journal
Peer Reviewed Journal
Refereed Journal
Indexed Journal
Impact Factor SJIF 2017: 5.182 2018: 5.51, (ISI) 2020-2021: 1.361
E-ISSN: 2454-6615

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Evaluation of Hyperalgesic activity of oral Pantoprazole in Albino Mice

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Abstract
This study was developed to know the heat and chemical induced nociception behaviour of albino mice under influence of oral Pantoprazole. Heat was induced by Eddy's hot plate, maintained at constant temperature of 55 degree Celsius. Chemical induced nociception behaviour of albino mice was done by freshly prepared 0.6% Acetic acid solution in the volume of 10ml/kg. Under Eddy's hot plate method mice shows their nociception behaviour by licking the paw or jumping the limbs. Under chemical induced method albino mice shows their nociception behaviour by abdominal contractions. Pantoprazole comes under class of proton pump inhibitors which is used for treatment of various disease related to gastrointestinal tract as peptic ulcer, gastroesophageal reflux disease, dyspepsia, Zollinger Ellison Syndrome etc. Lansoprazole should not prescribe with non-steroidal anti-inflammatory drugs as examples -Ibuprofen, Diclofenac, Aceclofenac, Etoricoxib etc, because lansoprazole can increase hyperalgesic activity of NSAIDS. Lansoprazole can increase pain threshold when it is given with NSAIDS. In hot plate method four groups has been created, each group contains 6 albino mice. Total 24 mice have been placed in hot plate method. Group one has been created as control group. In this group 10 ml/kg distilled water is administered orally, once daily four 10 days, an hour before test procedure. Each animal of group 2,3 and four is administered 1mg/kg, 2mg/kg, 3mg/kg orally once daily for 10 days an hour before test procedure. Drug treatment schedule for chemical induced method will be same as hot plate method.

Keywords: Nociception, Substance-P, Somatostatin, NK1R, Pantoprazole.

1. Introduction
Pantoprazole is one of the proton-pump inhibitors used to treat gastric ulcers; gastroesophageal reflux disease (GERD), Zollinger Ellison syndrome (ZES). It is also used in combination therapy of *H. pylori*, bacteria that causes ulcers.[1] It has been reported that lansoprazole increases plasma levels of gastrointestinal peptides like substance P, gastrin, motilin, somatostatin.[2] Substance P (SP) and its receptor, the neurokinin 1 receptor (NK1R), participate in the neural processing of a range of noxious and stressful stimuli. In the spinal cord, SP contributes to nociception and disruption of the NK1R decreases or ablates the late-phase response to peripheral injury.[3] Hence, this study will be undertaken to evaluate the influence of lansoprazole on heat-induced and chemical-induced nociception behaviour in albino mice.

2. Materials and Methods
Albino mice (Swiss strain) weighing between 25–30 g of either sex will be used for this study. They will be housed in clean polypropylene cages in groups of four and maintained at room temperature between 27–31°C with standard laboratory feed and water ad libitum. Animals will be divided into two sets. Each set will consist of 4 groups with 6 animals in each group. The test drug lansoprazole will be administered in doses based on earlier studies.[4] The test drug is available along with bicarbonate as sachet will be dissolved in distilled water and administered orally. Drug solution will be prepared just before administration. The study will be chronic. In which study, drugs/ vehicle will be administered once daily for ten days Two models will be used for evaluation of nociceptive behaviour. Each model will have four groups, each group having 6 animals. Number of

animals used in each group & treatments received in both chronic studies are shown in below-given Table 1

Table 1: Drug treatment schedule for chronic study for 0.6%v/v Acetic acid induced writhing.

Group	Dose	No. of animals	Route of Drug Administration
Group I–Control Distilled water	10ml/kg	6	Oral – once daily for 10 days,1hr before test procedure
Group II-Pantoprazole	1 mg/kg	6	Oral – once daily for 10 days, 1hr before test procedure
Group III- Pantoprazole	2 mg/kg	6	Oral once daily for 10 days, 1hr before test procedure
Group IV- Pantoprazole	3 mg/kg	6	Oral once daily for 10 days, 1hr before test procedure

Total number of animals required for this study- 48
For Nociception assay two models viz, Eddy's hotplate method and Chemical-induced writhing test will be used.

Hot plate method [5]
In this method, heat is used as a source of pain. All animals will be placed individually on Eddy's hot plate, maintained at a constant temperature 55°C and the time taken by the animal for the reaction either by licking the paw or jumping or raising the limbs which ever was observed first will be taken as the end point. Animals having basal reaction time not exceeding 15 seconds were included in the study. Reaction time will be noted before and 15, 30, 60, 90 and 120 minutes after the drug or vehicle administration in each animal.

Writhing test [6]
Freshly prepared 0.6% acetic acid solution in the volume of 10 ml/kg will be administered intraperitoneally to each animal which received either the vehicle (Group I) or the test drug Pantoprazole (Groups II-IV) 1 hour before the challenge. The time of onset writhing and the number of abdominal contractions or writhing in the following 15 minutes will be recorded.

3. Results
All animals will be placed individually on Eddy's hot plate, maintained at a constant temperature 55°C and the time taken by the animal for the reaction either by licking the paw or jumping or raising the limbs which ever was observed first will be taken as the end point. Animals having basal reaction time not exceeding 15 seconds were included in the study. Reaction time will be noted before and 15, 30, 60, 90 and 120 minutes after the drug or vehicle administration in each animal. In another method freshly prepared 0.6% acetic acid solution in the volume of 10 ml/kg will be administered intraperitoneally to each animal which received either the vehicle (Group I) or the test drug lansoprazole (Groups II-IV) 1 hour before the challenge. The time of onset writhing and the number of abdominal contractions or writhing in the following 15 minutes will be recorded. The data will be analyzed by one-way ANOVA. Post-hoc comparisons will be performed by applying Dunnett's test. p & lt; 0.05 will be considered statistically significant.

4. Conclusion
Pantoprazole increases plasma levels of gastrointestinal peptides like substance P, gastrin, motilin, somatostatin. [2] Substance P (SP) and its receptor, the neurokinin 1 receptor (NK1R), participate in the neural processing of a range of noxious and stressful stimuli. Hence, this study was undertaken to evaluate the influence of lansoprazole on heat-induced and chemical-induced nociception behaviour in albino mice.

5. Statistical Analysis
The data will be analyzed by one-way ANOVA. Post-hoc comparisons will be performed by applying Dunnett's test. $p < 0.05$ will be considered statistically significant.

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