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ANTIULCER EFFECT OF FLUVOXAMINE, MIRTAZAPINE AND OMEPRAZOLE IN ASPIRIN INDUCED ULCER IN RATS

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ABSTRACT

Introduction:. Aspirin induced ulcers have a significant incidence and have been treated using many drugs including H2 antagonists and proton pump inhibitors like omeprazole. The antiulcer potential of antidepressants has been observed in indomethacin. However its effect in aspirin induced ulcers requires investigation for potential use. **Objectives:** To compare the antiulcer effect of fluvoxamine and mirtazapine to omeprazole pretreated rats against aspirin induced ulcer by determination of Prostaglandin E2 and glutathione level in gastric antral tissue. **Methodology** The study was conducted with 50 animals divided into 5 groups of 10 each at random. All drugs were administered orally. Group A was given 400mg/kg aspirin only through NG tube.Groups B to E were pretreated with omeprazole 20mg/kg, fluvoxamine 100mg/kg ,fluvoxamine 200mg/kg and mitazapine 60mg/kg respectively, followed by 400ng/kg aspirin 45 minutes later .Ulcer induction was observed with aspirin after four hours when all the rats were killed by intraperitoneal injection of Thiopentol 50mg/kg and dissected. Gastric antral ulcerated tissue was taken for determination of PGE2 and Glutathione. **Results:** The PGE2 and glutathione levels after administration of medicine were recorded for all the groups. PGE2 level of groups A,B,C,D and E were 1.82±0.04 pg/ml , 10.38±0.54pg/ml ,3.62±0.37pg/ml, 10.12±0.19pg/ml and 7.25±0.28pg/ml respectively . Additionally the glutathione levels measured in groups A,B,C,D,E were 6.01±0.12, 56.16±1.62, 38.35±2.26, 53.89±4.09 and 42.55±3.14 nmol/mg tissue respectively . Upon comparison it was noted that all four groups had significantly higher PGE2 and glutathione levels as compared to group A, all with p-values <0.001.**Conclusion** The highest Glutathione and PGE2 levels and thus antioxidant and gastroprotective defense in gastric tissue was provided by omeprazole pre-treatment. Interestingly fluvoxamine 200mg/kg when compared to omeprazole, showed no significant difference in these parameters in its prophylactic antiulcer effect .Fluvoxamine 100mg and mirtazapine 60mg/kg also significantly elevated gastric mucosal glutathione and PGE2 as well but less in comparison to omeprazole, thus afford lesser gastroprotection.

Keywords: Peptic ulcer, aspirin, fluvoxamine, mirtazapine, omeprazole.

INTRODUCTION

Gastric hyperacidity and gastroduodenal ulcer is a very communal universalproblem.[1]Ulcers are generally solitary lesions less than 4cm in width found in following order of decreasing frequency duodenum first portion, stomach or jejunum of Patients with Zollinger Ellison syndrome or near to ileal Meckel diverticulum that encloses ectopic gastric mucosa.[2]

Pakistan is considered amongst the countries with high rate of gastroduodenal pathologies specifically duodenal ulcer.[3]Advanced age, female gender, past history of peptic ulcer, nonselective NSAIDS, use of anticoagulants, corticosteroids with NSAIDS , H-pylori and heavy consumption of alcohol are the risk factors for NSAIDS induced peptic ulcer disease.[4]
Aspirin is an effective NSAID used for inflammatory diseases like rheumatoid arthritis as well as prevention of cardiovascular thrombotic diseases.[5]NSAIDS including high dose of ASA are

considered the most gastrointestinal destructive kind of NSAIDS. Apart from acute side effects belching, epigastric discomfort, bloating.[6]the most significant upper GI side effect is peptic ulcer.[7]

Many factors such as gastric acid secretion and pepsin secretion, gastric microcirculation and prostaglandin E2 are involved in gastric mucosal damage.[8]Numerous studies have suggested the vital role of reactive oxygen species (ROS) and stress in ulcer formation [9,10]A number of defensive antioxidant enzyme system like glutathione peroxidase, catalase are also present in human body.[11]

Multiple drugs are currently used for treatment of gastric ulcer.[12]Recent studies suggested that NSAIDS induced can be prevented by administration of proton pump Inhibitors .[13]

Antidepressants in addition to their use in psychiatric disorders have also been prescribed for a variety of non-psychiatric conditions .[14] The SSRI fluvoxamine has proved to have antiulcer effect due to inhibition of CYP1A2 which is known to produce ROS. Apart from fluvoxamine and an atypical antidepressant mirtazapine has also been shown to have antiulcer activity in rats.[15,9]

Studies on singular antiulcer effects of fluvoxamine and mirtazapine in indomethacin induced ulcer exist .However there is no data available regarding comparison of individual antiulcer potential of fluvoxamine, mirtazapine and omeprazole in aspirin induced gastric ulcer This study was designed to compare the above mentioned gastroprotective role of fluvoxamine, mirtazapine and omeprazole in aspirin induced ulcer in rats. An evaluation of this nature would add to the safety profile of these drugs when administered to psychiatric patients predisposed to or already having peptic ulcer.

MATERIALS AND METHODS

It was a cross sectional analytical study. Male albino rats weighting 190-210g were purchased from NIH. They were housed in standard cages in Postgraduate Medical Institute Lahore.

For this study following materials were also used:

a) Kits for determination of PGE2 (Elisa Kit for PGE2) China (CEA538 GE) and total glutathione (Cell Biolab) USA.

b) Sucrose (Guanghou Jinhuada Chemicals Research Co limited China), Na Phosphate salt (RdH Germany)

c) Sample collection bottles, Eppendorf tubes, disposable tips (China)

d) Cap omeprazole 20mg (Getz Pharma), tablet fluvoxamine 50 mg (Pharm Evo) and tablet mirtazapine 30mg (Obsons).

e) 10 % formalin was used (Merck Germany)

Biochemical parameters were measured at Pakistan Council of Scientific and Industrial research Lahore.

The rats were divided into 5 groups of 10 rats each fasted for 24hours for ulcer induction. All drugs were administered orally.

GroupA: Positive Control. Rats in this group were given aspirin 400mg/Kg orally via nasogastric tube .[16,17]

Group B: Rats were given omeprazole 20mg/kg followed 45 minutes later by aspirin 400mg/Kg . [18]

Group C: Rats were given fluvoxamine 100mg /Kg After forty five minutes aspirin 400mg/Kg was given. .[9]

Group D: Rats were given fluvoxamine 200mg/kg After forty five minutes aspirin 400mg was given.

Group E: Rats in this group were given mirtazapine 60mg/kg .After forty five minutes 400mg/Kg aspirin was given.

Four hours later all the rats were killed by intraperitoneal injection of thiopentol 50mg/kg.[19] A midline incision was given in abdomen, stomach was removed and ulcer induction was confirmed macroscopically. A piece of antral mucosal scrapings from ulcerated area were taken and kept in sodium phosphate buffer for detection of total glutathione. Another piece of antral tissue was also taken and kept in phosphate buffer for determination of PGE2 level in the gastric mucosa.PGE2 and glutathione samples were stored at -80ºC for evaluation of PGE2 and glutathione levels. They were determined according to standard procedure of kit

Sample preparation for PGE2:

Sample were diluted with PBS 10% w/v. Tissues were minced with scissors and placed in shaking

water bath for 20 minutes. Samples were centrifuged at 9000g for 1 minutes.[20] The standard was reconstituted with 0.4ml of standard diluent, and kept for 10 minutes at room temperature, Each tube was mixed thoroughly before the next transfer. 5 dilutions of the standard were made 300 pg/ml, 100pg/ml, 33.33pg/ml, 11.11pg/ml, 3.70pg/ml and the last tube with standard diluent was maintained as the blank at 0pg/ml. Detection Reagent A and detection reagent B was centrifuged before used and with Assay diluent A and B diluted as 1:10. 2800ul was prepared. 20 ml of wash solution was diluted with 580ml of distilled water to prepare a final volume of 600ml wash solution . Solution was aspirated with sterilized tips as required. Further PGE2 levels determination was carried out as per kit protocol.

Determination of Glutathione in gastric tissue of rats:

Sample was washed with isotonic cold saline of 1X PBS with 0.16mg /ml of heparinized tissue was dried and weighed .It was homogenized using glass pestle after adding 5ml of metaphosphoric acid . Then the sample was centrifuged at 12000 rpm for 15 minutes at 4ºCsupernatant was collected and stored at -80ºc.

Assay Principle and Procedure:

Total Glutathione assay kits employ a quantitative assay for measuring the total glutathione content within a sample. Glutathione Reductase reduces oxidized glutathione to reduced glutathione in the presence of NADPH subsequently chromogen reacts with the thiol group of GSH to produce a colored compound that absorbs at 405nm.The total glutathione content in the unknown samples is determined by comparison with the pre-dertermined glutathione standard. The rate of chromophore production is directly proportional to concentration of glutathione in the sample. The rate can be determined from the absorbance change over time.
Five standards of Five standards having concentrations 0.5µM, 0.25µM, 0.125µM, 0.0625µM, 0.03125µM were setup and one as blank. Glutathione levels (nmol/mg tissue) were determined according to standard procedure of kit .

Statistical analysis: Data was entered and analyzed by using SPSS 19.0.Date for GSH, PGE2, was presented for each group by using Mean S.D. Comparison of all above mentioned parameters was performed by using one way ANOVA and Tukey's test.

RESULTS

Prostaglandin PGE2 levels
For PGE2 determination average reading of standards and samples were taken. Standard curve was created by taking PGE2 levels on y axis and absorbance on x axis. Best fit straight line was drawn through standard points. Y=1.0051x2-3.0343x+2.8604 By putting absorbance value in this formula of standard curve concentration of PGE2 in sample was determined (figure 1)
The PGE2 levels after administration of medicine were recorded for all the groups. The group A had level of 1.82±0.04 pg/ml, group B had the highest average of 10.38±0.54 pg/ml and group C, D and E had 3.62±0.37pg/ml, ,10.12±0.19pg/ml and 7.25±0.28pg/ml respectively. (table.1).The difference observed between groups using One Way ANOVA was significant with p-value <0.001.
When pair wise comparison was made between groups it was noted that all four groups had significantly higher PGE2 levels as compare to group A, all with p-values <0.001. Group B had significantly higher level as compare to group C and E with p-values <0.001 and had no significant difference from group D with p-value 0.416. Group D and E had significantly higher value as compare to group C with p-value <0.001. Group D had significantly higher value as compare to E with p-value <0.001.

Glutathione levels: Average of duplicate reading of GSSH standards, samples and negative control was determined. Graph was plotted by taking absorbance on Y axis against incubation time. Second graph was plotted by taking GSSH standards on X axis and concentration of GSSH on Y axis. Y= mx + c. By putting absorbance value in this formula concentration of glutathione in sample was determined Y=1.6148x+0.0174 (figure 2)

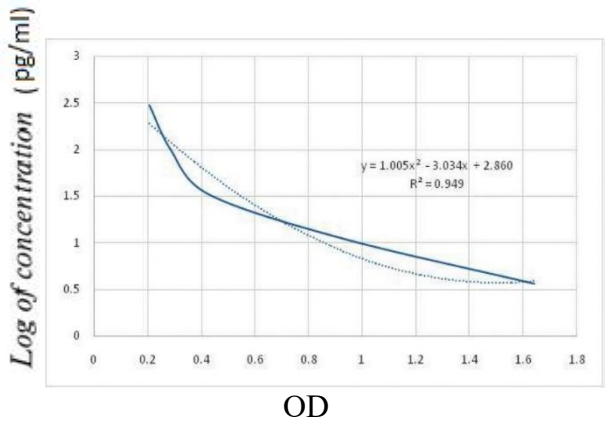

Figure 1: Standard curve for PGE2 concentration

The glutathione levels after administration of medicine were recorded for all the groups. Group A had the lowest glutathione level of 6.01±0.12 nmol/mg of tissue, group B had the highest average of 56.16±1.62, and group C, D and E had 38.35±2.26, 53.89±4.09 and 42.55±3.14 respectively. (table 2).

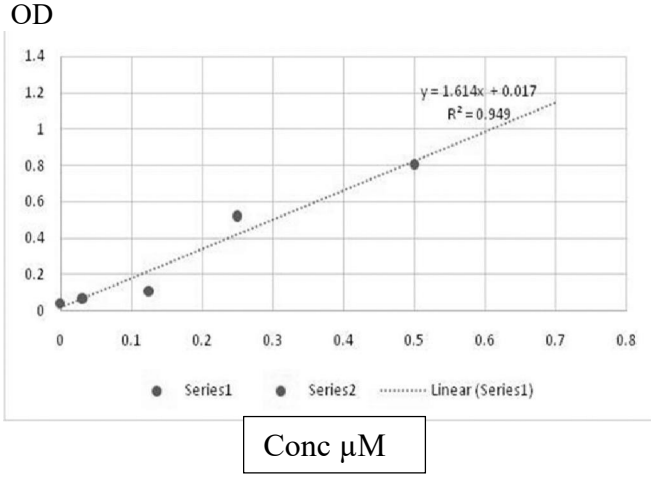

Figure 2: Standard Curve for Glutathione

The difference observed between groups was significant with p-value <0.001
Comparative results between groups for glutathione levels were almost similar to those of prostaglandin.

It was noted that all four groups had significantly higher glutathione levels as compare to group A, all with p-values <0.001. Group B had significantly higher level as compare to group C and E with p-values <0.001 and had no significant difference from group D with p-value 0.312. Group D and E had significantly higher value as compare to group C with p-value <0.001 and 0.007. Group D had significantly higher value as compare to E with p-value <0.001.

Group	**PGE2 level pg/ml four hours after administration of aspirin**			
	Mean	**SD**	**Min.**	**Max.**
Group A (Aspirin 400mg/kg)	1.82	0.04	1.76	1.87
Group B (Omeprazole + Aspirin)	10.38	0.54	9.80	11.33
Group C (Fluvoxamine 100 mg/kg + Aspirin)	3.62	0.37	3.34	4.40
Group D (Fluvoxamine 200 mg/kg + Aspirin)	10.12	0.19	9.91	10.46
Group E (Mirtazapine 60mg/kg + Aspirin)	7.25	0.28	6.78	7.66

Table 1: Mean values for PGE2 levels (pg/ml)

Group	**Glutathione level nmol/mg tissue in gastric tissue of rats four hour after ulcer induction**			
	Mean	SD	Min.	Max.
Group A (Aspirin 400mg/kg)	6.01	0.12	5.75	6.13
Group B (Omeprazole + Aspirin)	56.16	1.62	52.36	58.03
Group C (Fluvoxamine 100 mg/kg + Aspirin)	38.35	2.26	36.45	41.95
Group D (Fluvoxamine 200 mg/kg + Aspirin)	53.89	4.09	45.07	58.00
Group E(Mirtazapine 60mg/kg) + Aspirin	42.55	3.14	36.45	47.38

Table 2: Mean values of glutathione (nmol/mg tissue)

DISCUSSION

Aspirin is a widely used non-steroidal anti-inflammatory drug. It produces ulceration in stomach due to inhibition of PGE2 synthesis and by generation of ROS,[21,22] both PGE2 and antioxidants are protective for gastric mucosa.PGE2 regulates functions of GIT like motility and secretion of acid.[23,24]Antioxidants strengthen gastric epithelium and protect tissue from oxidative damage.[21]

Recently peptic ulcer has been found to have strong association with depression[22] and to anxiety disorder as well.[23] Untreated peptic ulcer disease is known to result in complications like obstruction, perforation and cancer.[24]For more than a century, peptic ulcer was managed surgically ,which resulted in high morbidity and mortality rates.[25]But with the introduction of H2 receptor antagonists which suppressed acid secretion , the elective peptic ulcer surgery declined by 85 %.[26] Following these PPI's were used which had a more potent effect on acid suppression.[27]

The treatment of depression could alleviate symptoms of PUD as well. Selective serotonin reuptake inhibitors are used as first line treatment of mild to moderate depression.[28] However they increase the risk of developing upper GI bleed to 2 to 3 folds.[29]Among SSRI paroxetine aggravates formation of gastric ulcer.[30]

So there is need for researching into drugs having both antidepressant and antiulcer potential for patients having mood disorders .The antiulcer potential of fluvoxamine and mirtazapine has been individually investigated only in three studies, two of mirtazapine and one fluvoxamine and all against indomethacin induced ulceration. In this study gastric ulcer was produced in 5 different rat groups by oral administration of aspirin 400mg/kg. Out of those 4 groups were pretreated (prophylactically) given drugs (omeprazole ,fluvoxamine and mirtazapine) .The final effect of these drugs was seen four hours later by determination of gastric ulcerated tissue PGE2 level and glutathione level which is an antioxidant that protects against ROS.

Glutathione Levels: Our result analysis began by a comparison of the gastroprotection offered by prophylactic oral administration of our standard drug omeprazole at a dose of 20mg/kg
against an ulcerogenic agent like aspirin. Omeprazole showed significant gastric protection with value < 0.001 by increasing gastric glutathione levels to 833% (56 nmoles/mg tissue) compared to the aspirin group in which the glutathione levels reduced to (6 nmoles/ mg tissue). Pretreatment with fluvoxamine in low dose of 100mg/kg increased the level of gastric glutathione to 539% (38.35nmoles /mg tissue) which was less as compared to omeprazole pretreated group when compared to aspirin group. Prophylaxis with fluvoxamine 200mg/kg further showed a highly significant p value <0.001 and dose dependent increase in glutathione to 259% more as compared to 100mg/kg and 798% greater as compared to aspirin group with p value <0.001. However mirtazapine in a dose of 60mg/kg increased glutathione level to 609% (42.55 nmoles/mg tissue) as compared to aspirin with p value <0.001.

Mirtazapine appeared to be more effective as compared to fluvoxamine 100mg/kg in increasing gastric tissue glutathione levels. It is to be noted that fluvoxamine200mg/kg had no significant difference in glutathione levels as compared to the omeprazole group as both equivalently increased glutathione levels indicative of increasing and proportionate degree of antioxidant gastric mucosal protection against aspirin induced ulcer. This further suggested that fluvoxamine in higher dosage had a significant prophylactic antiulcer effect. These effects are comparable to individual studies done on antiulcer effect of fluvoxamine and mirtazapine .Fluvoxamine in doses of 100mg/kg and 200mg/kg increased glutathione level to 275 % and 387% respectively as compared to ulcer control group (indomethacin).[9] Protective effect of mirtazapine when studied individually showed 46% increase in gastric glutathione level against indomethacin induced ulcer.[15] In both above mentioned studies ulcer was induced by indomethacin which is less commonly used and has more adverse effects. Secondly gastric glutathione was determined 6 hours after indomethacin administration whereas as in our study gastric tissue parameters were evaluated 4 hours later.

PGE2 Levels. In our study protective drugs when given prophylactically to different group of animals increased gastric PGE2 level .When PGE2 levels were compared to aspirin 400mg/kg, omeprazole, fluvoxamine 200mg/kg mirtazapine and fluvoxamine 100mg /kg increased PGE2 levels to 470%(10.38 pg/mg tissue), 456% (10.12pg/mg tissue), 298% (7.25pg/mg tissue and 98% (3.62pg/mg tissue) respectively all with p values <0.001 .These increases

reflected an enhanced cytoprotective potential at baseline as prostaglandin PGE2 on the gastric mucosa maintained gastric mucosal blood flow, secretion of bicarbonate and inhibition of acid secretion which would all prevent formation of an gastric ulcer.[2]

On comparison to omeprazole PGE2 levels, aspirin 400mg/kg decreased PGE2 by 82%. While fluvoxamine 100mg/kg, mirtazapine and fluvoxamine 200mg/kg improved gastric tissue PGE2 levels to 65%, 30% and 2.5% with p values <0.001, <0.001 and 0.416 respectively. Statistically there was no significant difference in p values of omeprazole and fluvoxamine 200mg/kg which showed fluvoxamine in higher dose to be as efficacious as omeprazole for peptic ulcer when given prophylactically. Fluvoxamine understandably showed a similar dose dependent increase in PGE2 levels as it had previously shown for glutathione. This suggested that fluvoxamine in a dose of 200mg/kg has the efficacy to inhibit the effect of aspirin more potently. Therefore another potential mechanism of antiulcer potential of these drugs might be due to increased synthesis of PGE2.

Our results showed the significant gastroprotective effects of fluvoxamine and mirtazapine not only by increasing glutathione but also increasing mucosal PGE2. Fluvoxamine 200mg/kg and mirtazapine 60mg/kg showed better results as compared to fluvoxamine 100mg/kg and they proved to be nearly as efficacious as omeprazole when used prophylactically for peptic ulcer.

This study further pointed out to the importance of the potential, regarding prophylactic treatment of peptic ulcer rather than its therapeutic management once the gastric ulcer has developed. These prophylactic antiulcer effect would also be beneficial in patients of depression predisposed to peptic ulcer.

CONCLUSION

It was concluded that against aspirin induced ulcer, fluvoxamine in higher dose of 200mg has comparable prophylactic antiulcer activity to omeprazole and Fluvoxamine 100mg and mirtazapine 60mg/kg have lesser yet appreciable antiulcer activity.

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