Fluvoxamine Provide a Gastro-Protection Against Vitiated Insult

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Abstract

The etiology of peptic ulcer disease is multifactorial and remains an enigma over the last decades. The central parameter is the acid secretion; whose control is under the coordination of gastrin, acetylcholine, histamine, and prostaglandin. The treatment of peptic ulcers is a bi-armed tool, directed toward fighting microbial growth alongside acid suppression. However recent studies reported failure of the therapy due to recurrence of symptoms. Therefore, additional parameters should be considered including patient mood and psychological status. The present study aimed to introduce a new approach to the therapeutic regimen of ulcer disease using commonly used antidepressant drugs (fluvoxamine and fluoxetine) in a laboratory animal model of peptic ulcer induced by stress insult to act as a mood upset model in an attempt to mimic mood changes in human. The study was conducted on 4 groups of laboratory animals using control negative and control positive (misoprostol) against the tested drugs group (fluvoxamine and fluoxetine group). The result confirmed that fluvoxamine confers gastroprotective effects against ulcer insult compared to both fluoxetine or misoprostol groups. These results might significantly mean that antidepressant drugs could be utilized in peptic ulcer diseases or added at low doses to prevent ulcer insults due to whatever precipitating factors, such as, infection, alcohol, smoking, NSAIDs, and stress ulcer.

Keywords: *fluoxetine, fluvoxamine, ulcer score, misoprostol, indomethacin.*

Introduction

Gastric ulcers have been linked to steroidal and non-steroidal medicines, smoking, alcohol consumption, trauma, sepsis, shock, Helicobacter pylori, and stress; with the exception of ulcers, stress is among the most invasive causes that underpin many other disorders, such as depression. Amongst the most prevalent approaches for creating ulcer models is stress[1]. Many individuals with gastrointestinal system ulcers have depression, which is often associated with mental and somatic symptoms[2]. Evidence that some antidepressants can also have anti ulcerative properties[3] is of attention to the present study.

Through the use of tricyclic antidepressants (TCAs) for the management of gastrointestinal ulcer disease was the first known use of antidepressants for Intestinal disease[1]. Fluoxetine, bupropion, dothiepin, maprotiline, mianserin, trimipramine, monoamine oxidase-B (MAO-B) inhibitors, imipramine, amitriptyline, and mirtazapine, have been shown to

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have antiulcer properties[4,56]. In animal models, higher susceptibility to depression and anxiety is linked to ulceration, the same will be valid in human beings[7,8]. Furthermore, typical antidepressants and anxiolytics can greatly minimize the onset of stress ulcers, possibly to a significant degree than typical therapy like cimetidine and antacids[9,10].

Fluvoxamine, an SSRI medication, suppresses the CYP 1A2 enzyme, which has been linked to oxidative damage[11]. Nonetheless, in around 60%–80% of ulcer disorders, the causative factors are unknown, and the pathophysiologic circumstances in the course of sickness are comparable[1]. Higher levels of free radicals (ROS), for example, have been linked to the mechanisms of stress and indomethacin-induced stomach injury[12]. Experimental evidence[1,12] suggest the significant role of oxygen-derived ROS and lipid peroxides (LPO) in immediate gastric injuries generated by nonsteroidal anti-inflammatory medications (NSAIDs) such as indomethacin. Although some SSRIs have been shown to increase upper GIT hemorrhage when coupled with NSAIDs[13], fluvoxamine's protective effects on the CYP 1A2 enzyme and subsequent reduction in cell stress may be advantageous to the digestive system[11]. It's also been observed that boosting redox variables and reducing oxidant parameters are important in the antiulcer action mechanism of mirtazapine, an antidepressant medicine[1]. Unfortunately, no evidence about fluvoxamine's antiulcer activity is presently available. The focus of this research was to look at fluvoxamine's impacts in a rat ulcer model focusing on the histopathological appearance of intestinaltissues.

Materials and Methods

A total of 40 Wistar rats (male, 130-160g, 10-weeks-of-age) were utilized for this study. Under standard laboratory animal conditions suitable for rat breading including temperature 22°C and good air conditioning, the studied groups were housed in animal house facilities provided by the university of Mosul. During the period of study, the rats were fed by commercially available pellet food and with free access to food and water. The researcher has followed the standard rules of laboratory animal breeding and treatment approved by Mosul University's local animal protection committee.

The animals were sub-classified randomly into four groups of 3 rats each; as follows, Group I (treatment-free control group using sterile water as a reference), Group II (fluvoxaminegroup), Group III (fluoxetine group), and Group IV (misoprostol group). Doses and suppliers are listed in table 1.The administration of the drug solution was manually done daily by orogastric tube (for 3 weeks duration) to overnight fasted rats. The daily doses of drug solution (50 mg/kg) were freshly prepared by dissolving the drugs in sterile water. On the last day, a single dose of indomethacin insult was initiated to create the ulcer model and confirm protection provided by tested drugs, if any.A day before ulcer induction, rats were starved of food but had access to water.

Table 1. The doses, origin, and suppliers of tested drugs.

Tested Drugs	Dose (mg/kg)	Supplier	Country
Fluvoxamine	50	Abbott, Illinois	United States
Fluoxetine	20	Bristol, Berkhamsted	United Kingdom
Misoprostol	20	Pfizer	United State
Indomethacin	30	Medochemie	Cyprus

After 4 hours elapsed following ulcer induction, the laboratory animals were killed for their histopathological studying. The stomachs were then dissected and treated in a 10% buffered formalin solution for 24 hours before being treated in different amounts of alcohol and ultimately in xylene. After that, the tissues were fixed in paraffin, repeatedly sliced to a thickness of 4µm, placed on slides, and stained with hematoxylin and eosin (H&E; Sigma). The samples were then subjected to a blinded histological analysis by a team of experts. A competent pathologist used a Model BM-2101 light microscope to perform a blinded histopathological evaluation on the specimens (Olympus, Yuyao, China). The outcome of tissue remark for injury or lesion were listed in table 2 below.

Table 2. Scores and remark of the all pathological changes

Remark	Score
Almost normal mucosa	0
Vascular congestions	1
One or two lesions	2
Severe lesions	3
Very severe lesions	4
Mucosa full of lesions	5

Results

The sectioning of the stomach of rats following indomethacin exposure revealed histopathological changes at mucosal and submucosal levels compared to the indomethacin-free control group. The mucosa of rats was examined using a light microscope and the result showed the highest score (approximately 5) of structural damage including ulcer formation, erosion formation, necrosis of epithelium of gastric mucosa, hemorrhage, infiltration of inflammatory cells, and dystrophic calcification (score and relevant degree of injury listed in table below). The control group has shown a completely negative outcome for the aforementioned parameters regarding mucosal and submucosal tissues (see Figure 1 and Table 3).

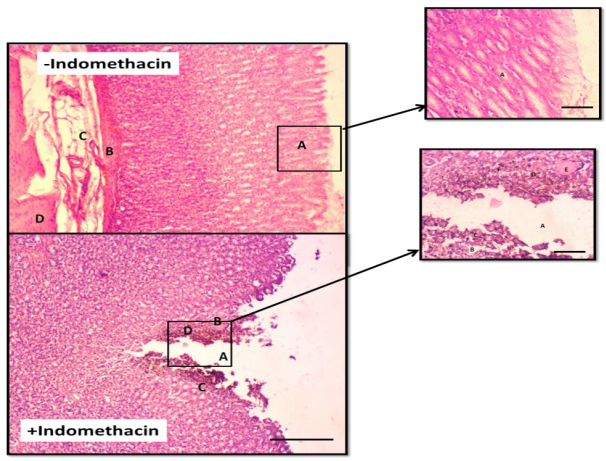

Figure 1. Normal versus an ulcerated histological architecture of the rat stomach. No evidence was noticed of erotic and ulcerative changes of gastric layers mucosa (A), muscularis mucosa (B), submucosa (C) and muscularis (D) in normal compared to the ulcerated stomach by indomethacin; following staining by H&E stain, scalebar100µm.

The sectioning of the stomach of rats of the studied groups following indomethacin exposure plus tested agents (fluvoxamine, fluoxetine, and misoprostol) revealed histopathological changes at mucosal and submucosal levels at various levels of severity (see Figure 2 and Table 3) in fluoxetine and misoprostol compared to fluvoxamine group. The mucosa of rats was examined using a light microscope and the result showed the highest scores of structural damage including ulcer formation, erosion formation, necrosis of epithelium of gastric mucosa, hemorrhage, infiltration of inflammatory cells, and dystrophic calcification in fluoxetine and misoprostol group. The fluvoxamine group has shown mild damage (scores close to 0) for the aforementioned parameters regarding mucosal and submucosal tissues (see Figure 2 and Table 3). Fluoxetine and fluvoxamine are SSRI (selective serotonin reuptake inhibitor) which is frequently have been used to manage pain, panic attacks, and alcoholism. Serotonin (5-hydroxytryptamine; 5HT) transporter are thought to be inhibited. Because ulcers are linked to a decrease in serotonin levels in stomach tissues[14,15], researchers

wanted to see if fluoxetine or fluvoxamine could have comparable properties on ulcer onset and development.

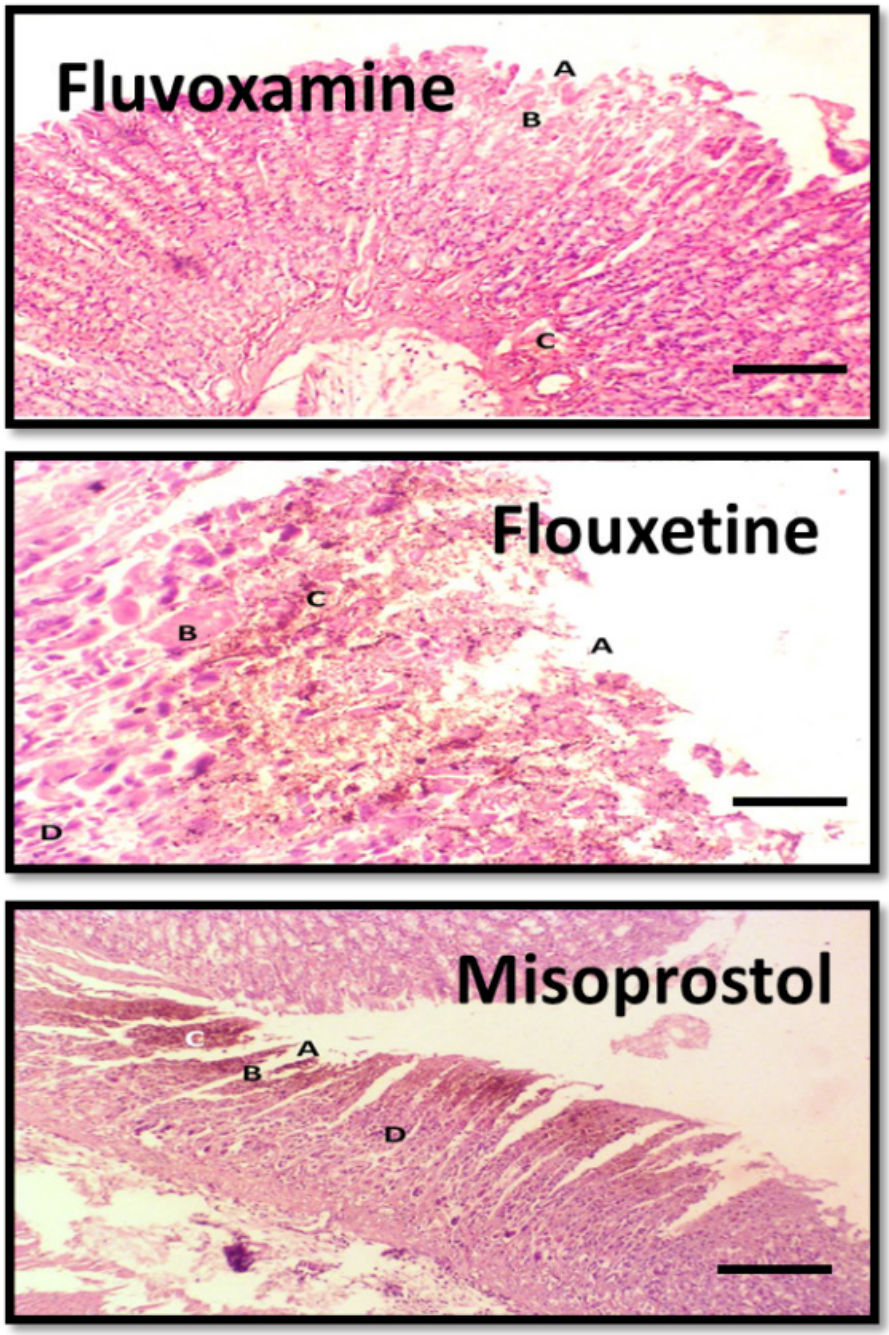

Figure 2. A representative image for the histology of rat stomach in different studied groups. Fluvoxamine showed mild evidence of erosion of gastric mucosa (A), necrosis of epithelium of gastric glands (B), hemorrhage (C), and congestion of blood vessels (D), compared to severe score associated with both fluoxetine and misoprostol group, following staining by hematoxylin and eosin stain, scalebar100µm.

Table 3.Scores of the lesions of the groups of the study.

The lesions	-Drugs	+Indomethacin	+Fluvoxamine	+Fluoxetine	+Misoprostol
Ulcer formation (reaching muscularis mucosa)	0	5	0	2	4
Erosion formation	0	5	1	3	5
Necrosis of epithelium of gastric mucosa	0	5	1	3	4
Hemorrhage	0	5	2	3	5
infiltration of inflammatory cells	0	4	1	2	3
Dystrophic calcification	0	5	0	0	1

Discussion

Fluvoxamine's antiulcer impact in animals was studied in the present research utilizing an indomethacin-induced ulcer model. Fluvoxamine's beneficial effects were compared to fluoxetine and misoprostol to confirm that the action is specifically related to fluvoxamine. Fluvoxamine was demonstrated to reduce indomethacin-induced ulcers selectively versus the same member of its group-fluoxetine. Fluvoxamine's antiulcer activity was found to prevented indomethacin-induced ulcers more effectively than misoprostol.

As compared to several other NSAIDs, indomethacin has been demonstrated to cause more gastrointestinal injury in rats[16]. As a result, it seems to be the medication of choice for producing ulcer lesions. Antidepressant medicines have indeed been demonstrated in numerous trials to reduce histamine release from mast cells, limit stomach acid secretion, and block leukotriene (LTC4, D4, E4) receptors, resulting in antiulcer actions[17]. Beyond those mechanisms, redox lipid peroxidation is the most important dominant driver in indomethacin-induced stomach injury.Fluvoxamine, an SSRI, inhibits the CYP 1A2 enzyme, which is known to create reactive oxygen species (ROS)[9].

Intrinsic 5-HT plays a role in gut function modulation, inhibiting stomach acid production while boosting mucus secretion[7]. The current findings revealed that indomethacin and alcohol decreased stomach serotonin concentration, which is consistent with prior research that established that lesions developed in parallel with serotonin deficiency in stomach tissues[14]. Comparable to the CNS, the enteric nervous system has a serotonin reuptake mechanism that is suppressed by serotonin reuptake inhibitors. This might reflect why fluvoxamine was able to maintain the rats' gastric lesionsminimumcompared to misoprostol or fluoxetine, whereas fluoxetine from the same class of fluvoxamine was unable to do so, the reason behind that is unclear[13,18].

In rats, indomethacin (INDO) induced severe stomach mucosa lesions. Animal primed with fluoxetine, fluvoxamine, or misoprostol lowered ulcer scores to various extents. However, fluvoxamine seems to be the most effective one (see Figure 2 and Table3).

Conclusion

We discovered that fluvoxamine possesses antiulcer properties. Indomethacin induces stomach injury through its potent irritation and systemic damages. Fluvoxamine but not fluoxetine seems to

activate its antiulcer actions in gut tissues via activating serotonin pathways and further investigation was required to confirm the differences between the mechanism of fluoxetine and fluvoxamine.

Conflict of Interest: Nil

Source of Funding: Self

Ethical Clearance: Taken from College of Pharmacy Research Ethics Committee

References

1. Dursun H, Bilici M, Albayrak F, Ozturk C, Saglam MB, Alp HH, Suleyman H. Antiulcer activity of fluvoxamine in rats and its effect on oxidant and antioxidant parameters in stomach tissue. BMC gastroenterology. 2009 Dec;9(1):1-0.
2. Maguire A, Douglas I, Smeeth L, Thompson M. Determinants of cholesterol and triglycerides recording in patients treated with lipid-lowering therapy in UK primary care. Pharmacoepidemiology and drug safety. 2007;16:S228.
3. Ma J, Vaillancourt R, Boddam R, Auger S, Sampalis J. Association between antidepressant use and prescribing of gastric acid suppressants. The Canadian Journal of Psychiatry. 2006 Mar;51(3):178-84.
4. Gabry KE, Chrousos GP, Rice KC, Mostafa RM, Sternberg E, Negrao AB, Webster EL, McCann SM, Gold PW. Marked suppression of gastric ulcerogenic and intestinal responses to stress by a novel class of drugs. Molecular psychiatry. 2002 Jun;7(5):474-83.
5. Abdel-Salam OM, Nofal SM, El-Shenawy SM. Evaluation of the anti-inflammatory and anti-nociceptive effects of different antidepressants in the rat. Pharmacological research. 2003 Aug 1;48(2):157-65.
6. Almulathanon AA, Mohammad JA, Fathi FH. Comparative effects of metformin and glibenclamide on the redox balance in type 2 diabetic patients. Pharmacia. 2021 Apr 13;68:327.
7. Yamaguchi T, Hidaka N, Suemaru K, Araki H. The coadministration of paroxetine and low-dose aspirin synergistically enhances gastric ulcerogenic risk in rats. Biological and Pharmaceutical Bulletin. 2008 Jul 1;31(7):1371-5.
8. Almukhtar H, Garle MJ, Smith PA, Roberts RE. Effect of simvastatin on vascular tone in porcine coronary artery: Potential role of the mitochondria. Toxicology and applied pharmacology. 2016 Aug 15;305:176-85.
9. Spina E, Santoro V, D'Arrigo C. Clinically relevant pharmacokinetic drug interactions with second-generation antidepressants: an update. Clinical therapeutics. 2008 Jul 1;30(7):1206-27.
10. Zainal AA, Al-Hamamy FA. Effect of Telmisartan Versus Captopril on Insulin Resistance in Hypertensive Type 2 Diabetic Patients. Mosul Journal of Nursing. 2014 Dec 15;2(2):99-106.
11. Schlezinger JJ, White RD, Stegeman JJ. Oxidative inactivation of cytochrome P-450 1A (CYP1A) stimulated by 3, 3′, 4, 4′-tetrachlorobiphenyl: production of reactive oxygen by vertebrate CYP1As. Molecular pharmacology. 1999 Sep 1;56(3):588-97.
12. Bayir Y, Odabasoglu F, Cakir A, Aslan A, Suleyman H, Halici M, Kazaz C. The inhibition of gastric mucosal lesion, oxidative stress, and neutrophil-infiltration in rats by the lichen constituent diffractaic acid. Phytomedicine. 2006 Sep 11;13(8):584-90.
13. Halford JC, Harrold JA, Boyland EJ, Lawton CL, Blundell JE. Serotonergic drugs. Drugs. 2007 Jan;67(1):27-56.
14. Debnath S, Guha D. Role of Moringa oleifera on enterochromaffin cell count and serotonin content of experimental ulcer model.
15. Al Asmari A, Arshaduddin M, Elfaki I, Kadasah

S, Al Robayan A, Al Asmary S. Aripiprazole an atypical antipsychotic protects against ethanol induced gastric ulcers in rats. International journal of clinical and experimental medicine. 2014;7(8):2031.

16. Salem Sokar S, Elsayed Elsayad M, Sabri Ali H. Serotonin and histamine mediate gastroprotective effect of fluoxetine against experimentally-induced ulcers in rats. Journal of immunotoxicology. 2016 Sep 2;13(5):638-51.
17. Berg A, Redeen S, Ericson AC, Sjöstrand SE. Nitric oxide-an endogenous inhibitor of gastric acid secretion in isolated human gastric glands. BMC gastroenterology. 2004 Dec;4(1):1-9.
18. Peng L, Gu L, Li B, Hertz L. Fluoxetine and all other SSRIs are 5-HT2B agonists-importance for their therapeutic effects. Current neuropharmacology. 2014 Jul 1;12(4):365-79.