Gastroprotective effect of fluvoxamine and ondansetron on stress-induced gastric ulcers in mice

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Abstract

Objectives: The association between stress and gastric ulcers has been well reported. This study is divided into two parts: the first part of this study is consisted of analyzing the effect of fluvoxamine administration by intracerebroventricular (ICV) and intraperitoneal (IP) injections on stress-induced gastric ulcers. The second part investigates the effect of ondansetron in influencing the protection of the gastric mucous by giving fluvoxamine to the mice before being induced with stress.

Methods: Water immersion restraint stress (WIRS) was used to induce stress. Fluvoxamine 50 and 100 mg/kg by IP injection, fluvoxamine 9.3 µg, and 18.6 µg by ICV injection 30 min before the induction of stress. Meanwhile, single drug and in combination administered to the mice, ondansetron 3 mg/kg was given by IP at 60 min, and fluvoxamine 50, 100 mg/kg orally at 30 min before stress induction.

Results: The obtained results show fluvoxamine 50 and 100 mg/kg by IP, and fluvoxamine 18.6 µg by ICV had significantly reduced ulcer index with $p<0.005$, $p<0.001$, and $p<0.005$ while fluvoxamine 9.3 µg showed the insignificant result. Fluvoxamine 50 mg/kg, fluvoxamine 100 mg/kg, and ondansetron 3 mg/kg monotherapy have a significant reduction in ulcers with $p<0.005$, $p<0.001$, and $p<0.05$, while the combination drugs showed an insignificant reduction in ulcers.

Conclusions: Fluvoxamine with different administration routes and ondansetron monotherapy before stress reduce the occurrence of gastric ulcers, while the combination drugs did not increase the protective effect of the gastric mucosa.

Keywords: fluvoxamine; gastric ulcers; health risk; ondansetron; stress.

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Introduction

Ulcers are described as open sores cut through the thickness of gastrointestinal mucosal [1]. Peptic ulcer is a disorder in the digestive tract characterized by mucosal damage that extends to the submucosa or muscularis propria due to the secretion of pepsin and stomach acid. Peptic ulcer occurs most often in proximal duodenum (duodenal ulcers) and in the stomach (gastric ulcers), and rarely occurs in distal duodenum, jejunum, and in the lower esophagus [2, 3], approximately four million gastric ulcers cases recorded in the world per year [4].

The pathophysiology of gastric ulcers is characterized as an imbalance between aggressive factors (e.g., leukotriene, stomach acid, pepsin, and *Reactive Oxygen Species* [ROS]) with defensive factors (e.g., prostaglandins [PG], mucosal perfusion, and bicarbonates) [5, 6]. *Helicobacter pylori* and prolonged use of nonsteroidal anti inflammatory drug (NSAID) are commonly known as associated with gastric ulcers [7]. Apart from *H. pylori* infection and the use of NSAIDs, gastric ulcers also occur due to stress [8].

Physiological stress triggers the *Hypothalamus–Pituitary–Adrenal* (HPA) axis activation and leads to secrete *Corticotropin-Releasing Factor* (CRF) and affects the secretion *of Adrenocorticotropic Hormone* (ACTH), which stimulates cortisol secretion [9]. Cortisol inhibit phospholipase A2 and lead to a reduction of prostaglandin synthesis [10] and decrease blood flow to the gastric mucosa due to vasoconstriction on the vessels [11].

It has been well documented that the *Selective Serotonin Reuptake Inhibitor* (SSRI) such as fluvoxamine has a mechanism to inhibit the formation of ulcers in the stomach as indicated by a decrease in the value of the *Bax/Bcl-2* ratio in gastric tissue, escalate the expression of Hsp70 protein (one of the markers of gastric defends), reduction of

ulcer index scores and intraluminal bleeding scores [4, 12–14]. Administration of fluvoxamine increases serotonin levels and activates its receptors, for instance, 5-HT_1-5-HT_7. Activation of the 5-HT3 receptor increase gastric acid secretion and affect ulcer formation [15, 16]. The mechanism of the anti ulcer effect of SSRIs may influence by its effect on the brain, so it is necessary to research to see the effect of the direct route of SSRI on the brain by intracerebroventricular (ICV) and compare it with the systemic route by intraperitoneal (IP) and whether the administration of 5-HT3 receptor antagonist (ondansetron) affect the gastric mucosa protection by SSRIs on stress-induced gastric ulcers.

Materials and methods

Materials

The materials used were fluvoxamine maleate 5 g (Wako Pure Chemical Industries, Osaka, Japan), ondansetron, normal saline 0.9% (PT. Widarta Bhakti, Pandaan, Pasuruan, Indonesia), tween 80 (Wako Pure Chemical Industries, Osaka, Japan). 1% tween were freshly prepared for solutions and drug suspensions.

Experimental animals and treatments

Male 6–8 week-old mice were used in the experiments. All mice were maintained under the same treatment and freely accessed water and standard chow, and subjected to a 12/12 h light-dark cycle. Experiments were performed under "The Guiding Principles for the Care and Use of Animal Research of Universitas Airlangga No. 683-KE".

After an adaptation period of 2 weeks, 71 mice were randomly divided into two main groups: 36 mice into the comparative groups where fluvoxamine 50 & 100 mg/kg given by IP, and fluvoxamine 9.3 and 18.6 µg given by ICV 30 min before the induction of stress. A total of 35 mice divided into seven groups were treated with a single drug (monotherapy), and in combination, drugs are given to the mice, ondansetron 3 mg/kg given by IP at 60 min and fluvoxamine 50, 100 mg/kg orally at 30 min before stress induction.

Gastric ulcers induction

Induction of stress was conducted following the method of Ji et al. [17]. Stress induction was started 30 min after treated with fluvoxamine or 60 min after treated with ondansetron. All mice were immobilized in a restraint tube and immersed in a water bath to the depth of the xiphoid process at 23 °C for 6 h.

Assessment of gastric mucosal injury

Immediately after 6 h of stress induction, all mice were sacrificed, and the stomachs were removed, opened along the greater curve, and washed with the normal saline. The stomachs were assessed for the severity of intraluminal bleeding, as explained by the following arbitrary scale described by Chiu et al. [18]. Ulcer index (UI) was indicated in terms of gastric mucosal lesions. Gastric tissues were pinned out flat on a corkboard and photographed for lesion assessment. The area with lesion was calculated in square millimeters, and the accumulative area of all sores assessed out of the severity of ulcers [17].

Statistical analysis

All results obtained are expressed as the mean ± standard error of the mean (SEM). One-way ANOVA followed by *Tukey's post-hoc* tests for UI and *Kruskal–Wallis* method followed by *Dunn's post-hoc* test for intraluminal bleeding score were used to evaluate the difference between the treated and control group. p-value <0.05 was claimed statistically significant.

Results

Effect of fluvoxamine given by ICV and IP on stress-induced gastric ulcers

The treatment of mice with *Water Immersion Restraint Stress* (WIRS) model to induce stress on mice produced gastric lesions. The ulcer index in treated groups of fluvoxamine 50, 100 mg/kg (IP) and 18.6 µg (ICV) showed significantly prevented the gastric ulcers as compared to the stress group (Figure 1A). The results for the severity of intraluminal bleeding show only fluvoxamine 100 mg/kg (IP) significantly decreased intraluminal bleeding as compared to the control group (Figure 1B). Meanwhile, the representative photograph of the stomach in both fluvoxamine (IP and ICV) shows that both administrations' route can reduce the occurrence of gastric ulcers. The lesions in the gastric lumen were depicted by the dark spots on the representative photograph (Figure 2). Fluvoxamine given by IP has slightly lesser dark spots' appearance than fluvoxamine given by ICV.

Effect of fluvoxamine and ondansetron on stress-induced gastric ulcers

The ulcer index in treated groups of fluvoxamine 50, 100 mg/kg and ondansetron 3 m/kg (monotherapy) and in combination (fluvoxamine 50 mg/kg + ondansetron 3 mg/kg; fluvoxamine 100 mg/kg + ondansetron 3 mg/kg) showed significantly decreased as compared to the stress group (Figure 3A). Pretreatment mice with high dose of fluvoxamine 100 mg/kg monotherapy and in combination with ondansetron 3 mg/kg significantly reduced the

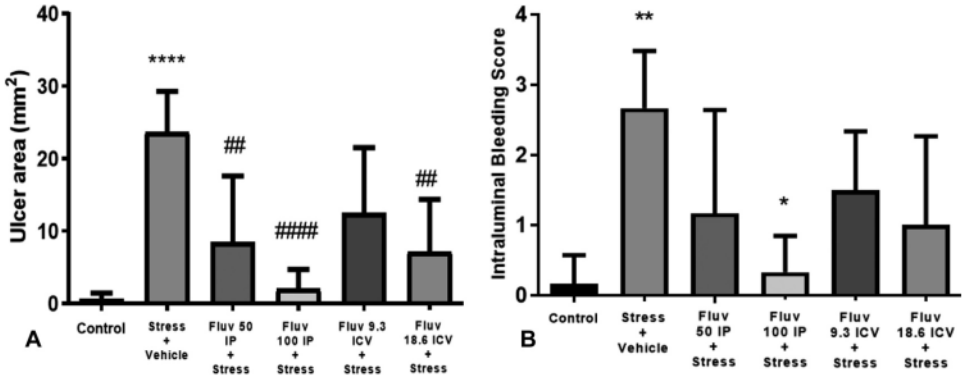

Figure 1: Effect of fluvoxamine given by ICV and IP on stress-induced gastric ulcers.
Effect of fluvoxamine given by ICV and IP decrease gastric ulcers. Ulcer index (A), stress group + vehicle vs. control group; stress group + fluvoxamine 50 mg/kg (IP); stress group + fluvoxamine 100 mg/kg (IP); stress + fluvoxamine 18.6 µg (ICV) group; ****p<0.0001; ##p<0.005; ####p<0.0001; ##p<0.005 vs. stress group + vehicle. Intraluminal bleeding score (B), stress group + vehicle vs. control group, stress group + fluvoxamine IP 100 mg/kg; **p<0.005; *p<0.05 vs. stress group + vehicle. Each column represents mean ± SEM of six mice.

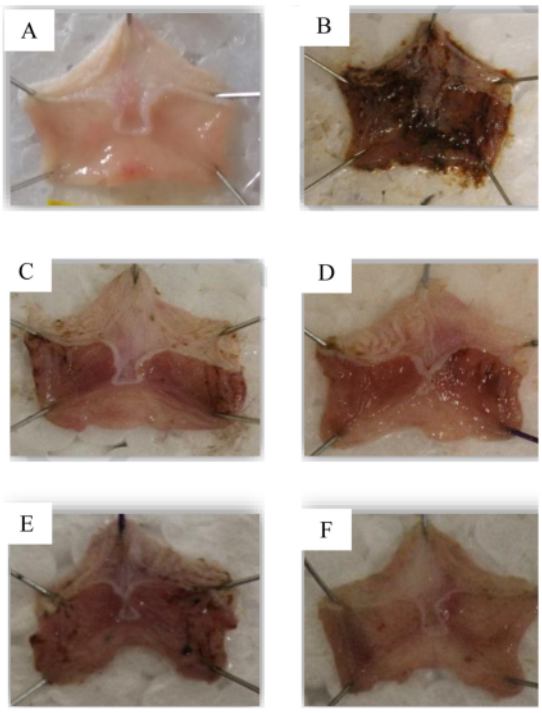

Figure 2: Representative photograph of the gastric lumen of mice. Control group (A), stress + vehicle group (B), fluvoxamine 50 mg/kg (IP) group (C), fluvoxamine 100 mg/kg (IP) group (D), fluvoxamine 9.3 µg ICV group (E), and fluvoxamine 18.6 µg ICV group (F). The blue line indicates the position of the ulcer.

intraluminal bleeding score as compared to the stress group (Figure 3B). The representative photograph of the stomach in both groups of fluvoxamine (monotherapy and combination) reduced the presence of dark spots in the lumen (Figure 4). A high dose of fluvoxamine with and without combination with ondansetron has lesser dark spots' appearance than fluvoxamine low dose and ondansetron monotherapy.

Discussion

The preventive effect of fluvoxamine was analyzing in mice using the WIRS model to induced stress. In the present study, the obtained results show administration by IP and ICV injection can reduce the occurrence of gastric ulcers. The ICV route's administration goal is to bypass the *Blood–Brain Barrier* (BBB) and other mechanisms that restrict the distribution of drugs to the brain [18]. The IP administration route is included as a parenteral route. However, the pharmacokinetics of drugs that are given by IP is comparable to the oral administration due to the primary route of absorption towards the mesenteric vessels, depleted within the portal vein, and traversed the liver [19]. Our previous study showed fluvoxamine 50 and 100 mg/kg have a protective effect against the gastric mucosa [4, 14]. Based on previous research conducted by Schreiber et al. [20], it was found that the IP dose of 50 mg/kg was equivalent to a dose of 9.3 µg given by ICV, and

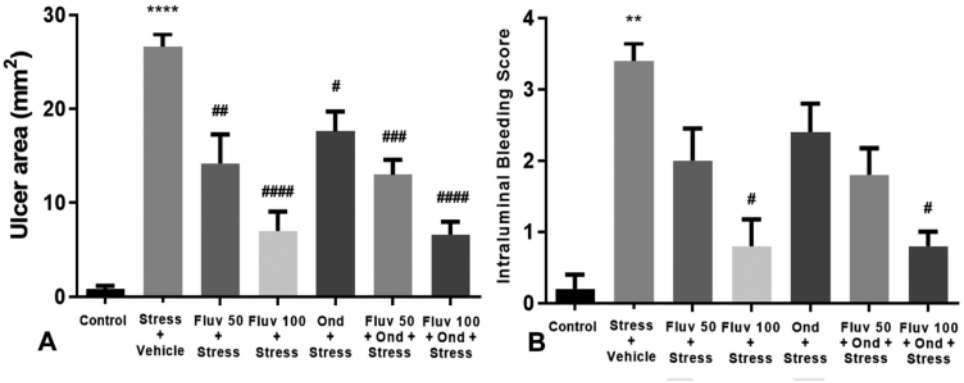

Figure 3: Effect of fluvoxamine and ondansetron on stress-induced gastric ulcers.
Effect fluvoxamine and ondansetron decrease gastric ulcers. Ulcer index (A) stress + vehicle, stress + fluvoxamine 50 mg/kg, stress + fluvoxamine 100 mg/kg, stress + ondansetron 3 mg/kg, stress + fluvoxamine 50 mg/kg + ondansetron 3 mg/kg, stress + fluvoxamine 100 mg/kg + ondansetron 3 mg/kg; ****p<0.0001 vs. the control group; ####p<0.0001, ###p<0.0005, ##p<0.005, #p<0.05 vs. stress group. Intraluminal bleeding score (B) **p<0.005 vs. control group; #p<0.05 vs. stress group. Each column represents the mean ± SEM of five mice.

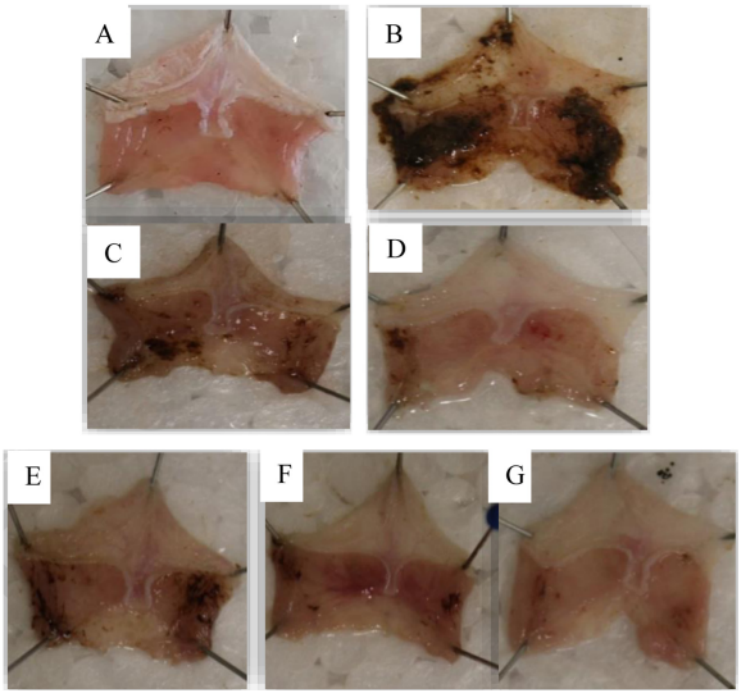

Figure 4: Representative photograph of the gastric lumen of mice.
Control group (A), stress + vehicle group (B), fluvoxamine 50 mg/kg group (C), fluvoxamine 100 mg/kg group (D), ondansetron 3 mg/kg group (E), fluvoxamine group 50 mg/kg + ondansetron 3 mg/kg group (F), and fluvoxamine group 100 mg/kg + ondansetron 3 mg/kg (G).

100 mg/kg IP was equivalent to 18.6 µg ICV. The results in present study showed the IP administration greater than ICV. This can be due to serotonin levels in the gastrointestinal (GI) tract higher than in the brain. Serotonin is found about 80% in the GI track and the remnant being divided between the central nervous system (CNS) and the platelets [21].

Fluvoxamine works by blocking the reuptake of serotonin transporter (SERT), subsequently increase extracellular serotonin (5-HT) levels [22]. Serotonin administration has pharmacological effects, which inhibit gastric acid secretion, stimulate mucus discharge, stimulate the intestinal secretion, and stimulate ionic and mucus secretion [23, 24]. Serotonin on the brain may play a role in activating

the vagus nerve, and releasing serotonin in the brain due to stress increase gastric acid secretion, leading to an increased risk of gastric ulcers. Serotonin causes activation of 5-HT3 receptors, which increase the activity of the vagus nerve [25]. The vagus nerve is a nerve that allocates a two-way affinity between the stomach and brain, consisting of afferent nerve fibers that send messages from the stomach to the CNS, and laden efferent that convey motor information from the dorsal motor nucleus to the stomach muscles [26].

The second part of this research examines the effect of 5-HT3 receptor antagonist (ondansetron) in influencing the protection of the gastric mucous by giving fluvoxamine to the mice before being induced with stress. 5-HT3 receptor antagonist prevent serotonin to bind with 5-HT3 receptor on GI vagus nerves and the chemoreceptor trigger zone (CTZ) on the brain [27] The administration of fluvoxamine (monotherapy) at a dose of 50 and 100 mg/kg protect the gastric mucosa marked by reducing intraluminal bleeding score and UI. The results support the previous studies [4, 14–16]. Administration of ondansetron 3 mg/kg monotherapy to stress-induced gastric ulcers in a representation shows a reduction in the occurrence of ulcers. Monotherapy of ondansetron provides this gastroprotective effect according to the results of previous studies [28, 29]. Ondansetron reduce gastric ulcers in several gastric ulcer induction methods, and it is thought that through several mechanisms. Ondansetron reduce gastric acid secretion, reduce total acidity, and increase mucus secretion [28].

The combination drug by adding ondansetron 3 mg/kg showed mucosa's protection against the stress group. The protection was characterized by a substantial reduction in the ulcer index and a significant reduction in intraluminal. However, these results show less significant protection when compared with the fluvoxamine monotherapy group. This can emerge from 5-HT receptor competition. Based on previous study showed co administration of ondansetron with SSRI significantly increase levels of extracellular 5-HT and partially blocked the suppressant effect on dorsal raphe nucleus [30]. SSRI decrease the potentiation of 5-HT3 receptor via pharmacodynamic competition. This combination increase the potential accumulation of 5-HT because of receptors competition [31].

Previous studies have shown a pro ulcerogenic effect via 5-HT3 serotonin receptors while an anti ulcerogenic effect via 5-HT4 serotonin receptors [30]. In this study, the results show that blocking or inhibiting the 5-HT3 serotonin receptor with ondansetron can act as an anti ulcer. It supports the results of previous studies, which state that the 5-HT3 receptor is a pro ulcer. However, since the actual mechanism of SSRI's antidepressant effect on stress-induced gastric ulcers is not known to involve serotonin and its receptors or it may have other mechanisms, it is necessary to carry out further research to examine with other receptors besides 5-HT3 to determine the antidepressant effect of SSRIs on stress-induced gastric ulcers.

Conclusions

The SSRI (fluvoxamine) with different administration routes and 5-HT receptor antagonist (ondansetron) as monotherapy before stress can reduce the occurrence of gastric ulcers, while the combination drugs did not increase the protective effect of the gastric mucosa. Moreover, further research on the actual mechanism of SSRI's antidepressant effect on stress-induced gastric involving serotonin and its receptors is needed.

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Ethical approval: All experiments were conducted at the Animal Research Laboratory of Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia, in accordance with the Guidelines for the Care and Use of Laboratory Animal issued by approved by by National Institutes of Health revised in 1985. The Ethics Committee of Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia, approved the study protocol.

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