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EVALUATION OF THE ANTI- GASTRIC ULCER ACTIVITY OF RISPERIDONE IN MALE RATS

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Abstract

Risperidone, though an anti-psychotic drug, have been reported to exhibit anti-ulcer activity. Observation that drugs used in the treatment of gastric ulcer do have recurrence after use, have made the search for a novel drug a continuous one. This study was undertaken to investigate the mechanisms underlying the anti-gastric ulcer activity of risperidone whose anti-ulcer property has not been elucidated in male rats.
Male Wistar rats weighing between 180g and 210g were divided into four groups (n= 6): control (distilled water) and risperidone treated (0.1, 0.3, 0.5 mg/kg) orally daily for 21 days were used in each of the studies. Basal and stimulated gastric acid secretion (GAS) using histamine, pentagastrin, and carbachol were assessed using continuous perfusion method. Malonialdehyde (MDA) concentration, gastric mucus secretion (GMS) and gastric mucus cells count (GMCC) were assessed using spectrophotometric method and calibrated microscopy respectively. Data were analysed using Student's t-test and ANOVA at p= 0.05. The stimulated histamine and pentagastrin GAS (mEq/l) were significantly reduced by risperidone over eighty minutes' period, but not with carbachol. GMS (mg/g tissue $x10^{-2}$) increased significantly in the 0.1mg/kg (1.1±0.1), 0.3mg/kg (1.3±0.1) and 0.5mg/kg (1.4±0.2) risperidone-pretreated groups compared with the control (0.6±0.03) group. There was also a dose-dependent significant increase in the GMCC (mm^2) of the 0.1mg/kg (121.2±5.0), 0.3mg/kg (128.6±2.5) and 0.5mg/kg (129.3±3.8) risperidone treated rats compared with the control (103.3±4.2). The MDA (µmol/L x 10^{-6}) levels in the 0.1mg/kg (0.2±0.01), 0.3mg/kg (0.2±0.01) and 0.5mg/kg (0.1±0.05) risperidone groups were significantly decreased compared to control (0.3±0.09). The study revealed that the anti-gastric ulcer activity of risperidone may be by blocking histamine H_2 and gastrin receptors, increasing gastric mucus secretion, number of gastric mucus cells count and by decreasing lipid peroxidation level.

Keywords: risperidone, gastric ulcer, mucus, gastric acid, malonialdehyde

Introduction

Gastric ulcer is an etiological disease in which several factors such as stress, trauma, sepsis, hemorrhagic shock, burns, *Helicobacter pylori*, steroidal and non-steroidal drugs [1,2,3,4,5] play significant roles. Regardless of great advances in the field of medical science and understanding of the peptic ulcer illness, gastric ulcers aetiology is still not completely understood. Many of these anti-ulcer drugs in use have been found to have adverse effects and there is recurrent infection after a few weeks [6]. Stress as one of the most commonly used methods to produce ulcer models and an aggressive factor in peptic ulcer formation, underlies other diseases such as depression [7,8].

Depression, accompanied by psychotic and somatic symptoms has been reported to be present in most patients with gastrointestinal ulcers [9]. An increased depression [10] and anxiety [11] has been reported to parallel with ulcer development in experimental animals and this holds true in humans [12, 13]. Some anti-psychotic drugs such as perospirone [14] and risperidone [15] have already been reported to have anti-ulcer activity. The successful treatment of gastric lesion depends on augmentation of the defensive factors of the gastric mucosa and blockage of acid secretion [16]. This study was carried out to evaluate further the gastroprotection activity of risperidone where information on these areas are still scarty has not been documented in male Wister rats.

Methods

Risperidone (Jiangsu Suzhong Haixin Pharm CO, China), Histamine acid phosphate (Sigma- Aldrich, St Louis MO), Ketamine Hydrochloride (Rotexmedica, Trittau, Germany), Carbamylcholine chloride (Carbacol: Sigma- Aldrich MO), Pentagastrin (Sigma Aldrich), Trichloroacetic acid (TCA) , Magnesium chloride (Sigma- St Louis, MO), Sodium chloride (Sigma- St Louis, MO), Hydrochloric acid (Sigma- St Louis, MO), Thiobarbituric acid (TBA) (Sigma- St Louis, MO), Alcian blue, Sodium acetate (Sigma- St Louis, MO), Diethyl ether (Sigma- St Louis, MO), Sodium hydroxide (Sigma- St Louis, MO). Chemicals and reagents were of analytical grade.

Male Wister rats (180- 210g) were used for the study. The choice of male rats was to maintain a fairly constant physiological condition, as gastric acid secretion does vary with oestrous cycle in female rats [17]. The animals were purchased from the Central animal house, College of Medicine, University of Ibadan, Nigeria and housed in clean plastic cages under standard condition 12 hours light and 12 hours darkness. They were fed with commercial rat chow obtained from Ladokun Livestock Feed Limited, Ibadan, Oyo State, Nigeria and water was provided ad libitum. The animals were acclimatized for two weeks before the commencement of the experiment and the study conducted in accordance with the Principles of laboratory animal care of NIH, 1985 [18]. Animals were divided into four study groups; to determine the effect of risperidone on basal and maximal gastric acid secretion, to determine the effect of risperidone on gastric mucus secretion, to estimate the gastric mucus cells count in risperidone pre-treated animals and to determine the antioxidant effect in risperidone pre-treated animals by measuring Malondialdehyde (MDA) concentration. In each study, animals were further allocated into four sub-groups (n=6). Group 1 was the control and received distilled water. Groups 2, 3 and 4 were administered risperidone orally at 0.1mg/kg, 0.3 mg/kg and 0.5 mg/kg respectively for 21 days as earlier reported [15].

Gastric mucus secretion

The rats were sacrificed by cervical dislocation and their stomachs removed and weighed. The glandular portion of each stomach was opened along the lesser curvature. Procedures for measurement of gastric mucus secretion were that described by Corney *et al.,* 1974 [19]. Briefly, the inverted stomachs were soaked for two hours in 0.1% Alcian blue dissolved in 0.16M sucrose buffered with 0.05M sodium acetate, adjusted to pH 5.8 with hydrochloric acid. Uncomplexed dye was removed by two successive washes at 15 and 45 minutes in 0.25M sucrose. Dye complexed with mucus was diluted by immersion in 10ml aliquots of 0.5M Magnesium Chloride for 2 hours. The resulting blue solution was shaken briefly with equal volume of diethyl ether and absorbance of the aqueous phase was measured at 605nm using spectrophotometer. The absorbance of each solution was then used to calculate the various concentrations of dye. The weight of dye (expressed in mg) was deduced using a standard curve. The weight of dye was then expressed over the weight of the stomach, to give the weight of mucus secreted.

Gastric mucus cell count

The rats were sacrificed by cervical dislocation and their stomachs removed. The glandular portion of each stomach was opened along the lesser curvature. Gastric mucus cell count was done by counting the number of gastric mucus cells that stained with H&E, indicated as blue patches. The

gastric mucus cells were counted in five random cubic boxes each with an area of 1 mm^2 using calibrated microscope. This counting method is a modified approach method earlier described [20].

Malondialdehyde concentration (MDA)

The malondialdehyde of the stomach mucosa, a measure of the extent of lipid peroxidative tissue damage was estimated using a standard method [21]. In brief, 0.1 ml of the test sample was mixed with 0.5 ml of 10% TCA, and 0.5 ml of 75% TBA was then added it. The mixture was placed in water bath at 80^{o}C for 45 minutes. The absorbance of the resulting pink colour solution was measured against a reference blank of distilled water at 532 nm. The test sample was calibrated using the MDA as standard and the result was expressed as the amount of free MDA produced or MDA quantified by using the molar extinction coefficient, C of 1.56 x $10^5 M^{-1} cm^{-1}$.

Basal and stimulated gastric acid secretion

The animals were prepared according to the modified continuous perfusion technique [22]. The animals were fasted overnight and were only allowed free access to water so as to provide relatively clean stomach. They were anaesthetized with intraperitoneal injection of urethane solution (25% w/v) at 0.6 ml/100g body weight. The stomach was perfused with normal saline (0.9g/100ml) instead of NaOH. The acidic effluent was collected from the stomach at 10 minute interval and titrated to end point against 0.0025N NaOH using phenolphthalein as indicator.

Histamine-induced gastric acid secretion

After the collection of basal secretion from each animal, a dose of 2.5 ml/100g body weight histamine acid phosphate was injected intravenously through the femoral vein into the rats. Stimulated secretion of gastric contents was later collected at the rate of 1ml per minute for one hour twenty minutes (80 minutes) through gastroduodenal cannula.

Pentagastrin-induced gastric acid secretion

Pentagastrin at a dose of 25 µg/kg body weight was administered intraperitoneally [23]. The same procedure as above was uses for pentagastrin-stimulated secretion.

Carbachol-induced gastric acid secretion

Carbachol at a dose of 4 µg/kg body weight was administered intraperitoneally [24]. Also, the same procedure was used here as in histamine-stimulated secretion for the collection of effluent.

Measurement of basal and maximal gastric acid concentration in samples

The acidity of the gastric effluent was determined by calculations using the principle of volumetric analysis. This was used to determine the strength (meq/litre) of the effluents collected.

Statistical analysis

Statistical analysis of data was done using one-way analysis of variance (ANOVA) and Student's t-test for paired data. The data were analyzed using Graphpad prism software version 5 (San Diego, CA, USA) and were expressed as Mean ± SEM (standard error of mean). P-values less than 0.05 ($p \leq 0.05$) were considered statistically significant.

Results

Gastric mucus secretion

In Figure 1, there was significant increase in gastric mucus secretion (mg/g tissue) in the 0.1mg/kg risperidone (1.06 ± 0.11), 0.3mg/kg risperidone (1.31±0.12) and 0.5mg/kg risperidone (1.39±0.20) pretreated rats compared to the control rats 0.60± 0.03 ($p \leq 0.05$). This increase in gastric mucus secretion is dose-dependent.

Gastric mucus cells count

In Figure 2, risperidone caused dose-dependent increase in gastric mucus cells count. These increases were significant with the three doses of risperidone in the treated rats 121.2± 5.04 cells/cm^2, 128.6± 2.46 cells/cm^2 and 129.3 ± 3.73 cells/cm^2 respectively compared to the control rats (103.3± 4.18 cells/cm^2).

Malonialdehyde (MDA) concentration

Figure 3 shows the effect of risperidone on MDA concentration. There was a significant decrease in MDA with 0.1mg/kg risperidone treated rats (0.194 ± 0.0072) as against the control rats (0.257 ± 0.0087) ($p \leq 0.05$). Also, the concentration of MDA concentration in the 0.3mg/kg (0.183 ± 0.0073) and the 0.5mg/kg (0.106 ± 0.0049) risperidone treated rats showed significant decrease compared to the control ($p \leq 0.05$). These decreases were equally dose dependent.

Histamine-induced GAS

Results obtained from this study showed that risperidone decreased gastric acid secretion in experimental animals in a dose dependent manner

compared with the controls. There were significant reductions in gastric acid secretion after histamine administration compared with control (p≤0.05). Between 0-40 minutes, the basal secretion was fairly normal in all the groups. After 40 minutes, histamine was administered intravenously through the femoral vein and 10 minutes later, there was a sharp increase in gastric acid secretion in the control rats, while the risperidone-treated groups showed an inhibition of gastric acid secretion to the normal response of histamine. This was significant with the three doses used compared to the control group (p≤ 0.05).

Effect of risperidone on pentagastrin induced gastric acid secretion

When compared with the normal response of gastric acid secretion to pentagastrin as in the control group, there were significant reductions in gastric acid secretion after pentagastrin administration (25 µg/kg, *i.p.*) in the risperidone pre-treated groups (0.1, 0.3, and 0.5 mg/kg (p≤0.05). Between 0-40 minutes, the basal secretion was fairly constant in all the groups. Between the period 50th – 80th minute's interval, post secretagogues injection, showed significant decrease in gastric output in the pre-treated rats compared to the control rats group.

Effect of risperidone on carbachol induced gastric acid secretion

The basal secretion was similar in all the groups, control and pre-treated (figure 6), however, there were no significant change in gastric acid secretion after carbachol (4 µg/kg, *i.p.)* administration when compared to the control (p≥0.05). The trend was observed in all the groups.

Discussion

The results obtained from the study on GAS showed that risperidone affected the normal gastric acid secretory response to histamine (H_2) and pentagastrin stimulation. Histamine (0.1 mg/kg) administration to the different risperidone pre-treated animals, showed complete removal of the normal response to histamine. On pentagastrin secretory response, there were no remarkable changes on the basal secretion of gastric acid with the different doses of risperidone (0.1 mg/kg, 0.3 mg/kg and 0.5 mg/kg). but, when pentagastrin (25 µg/kg) was injected, there was an initial increase in gastric acid secreted followed by significant decrease in gastric output with the risperidone pre-treated used as against the normal expectation whereby the basal secretion increased in the control. From these observations, risperidone appears to cause a complete inhibition of H_2 receptors, but with pentagastrin, there was partial inhibition indicating partial inhibition of CCK-B receptors for gastrin. In both cases, gastric acid secretion (GAS) responses to these secretagogues were fully and partially abolished respectively. The explanation adduced may be a significant depression in intracellular free Ca^{2+}. Since gastrin acts mainly by releasing histamine from the enterochromaffin-like (ECL) cells in the oxyntic mucosa, and also from direct action on parietal cells where they are equally distributed [25,26], similarity in gastric acid secretory response noticed with both drugs is likely affected by the former pathway. Furthermore, it has been reported that prostaglandins do exert inhibitory effects on parietal cells [27]. From this study, apart from antagonizing H_2 and gastrin CCK-B receptors, risperidone may also be potentiating the effect of endogenous prostaglandins leading to inhibition of gastric acid secretion. Acetylcholine from nerve endings have been shown to acts by two possible pathways. First, it releases histamine from the ECL cells, which in turn stimulate acid production and secondly, by interaction with muscarinic (M_3) receptors on the oxyntic cells resulting in increase in intracellular calcium concentration [28]. Thus, the inability of risperidone to decrease acid secretion after carbachol administration may be due to lack of antagonizing effect on the muscarinic receptors.

From this work, there was significant increase in gastric mucus secretion (mg/g tissue) in the risperidone-treated rats compared to the control rats. Similarly, gastric mucus cells count (GMCC) showed a graded increase with increasing doses of risperidone. The possible explanation may likely be linked to potentiating of endogenous prostaglandins. Several other works are in support of this hypothesis [29, 30, 31, 32] and they reported threefold increase in mucus layer thickness when topical prostaglandins and intravenous secretin were administered. Risperidone may equally be generating and potentiating the effect of endogenous prostaglandins which has been reported to be involved in mucosal defense by its stimulation of mucus and bicarbonate secretion [33]. Prostaglandin has also been reported to be important in ulcer healing and protection of gastric mucosal from digestive juice [34, 33].

The study on gastric MDA concentration showed a significant dose-dependent decrease with 0.1mg/kg, 0.3 mg/kg and 0.5 mg/kg risperidone when compared to the control. However, it is known that indomethacin-induced gastric damage is reactive

oxygen species (ROS) mediated via lipid peroxidation [35] and that scavenging these free radicals may play an appreciable role in healing gastric ulcers. Defensive factors such as mucus and reduced lipid peroxidation protect gastric mucosa against a variety of noxious agents-induced damages. The thiobarbituric acid reactive substance (TBARS) has been used as an indicator of lipid peroxidation or free radical scavenging activity in biological samples. These radicals are reported to be involved in acute mucosal ulceration induced by indomethacin [36]. The product of these free radicals, the lipid peroxides, can elicit tissue inflammation [37]. Thus risperidone from this study has been shown to have a strong reducing effect on lipid peroxidation and this could be a good reason for the prevention of mucosal damage. The inhibition of cyclooxygenase (COX) enzymes induced by indomethacin leads to the depletion of endogenous prostaglandins thus leading to decrease of gastric mucus production [38] and generation of reactive oxygen species, which are implicated in the pathogenesis of ulceration [39]. Risperidone was found to have likely scavenged reactive oxygen species as evident in its ability to decrease lipid peroxidation level. The important roles of oxygen-derived ROS and lipid peroxides (LPO) in acute gastric lesions, which are induced by non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, have been supported by experimental data [40, 41]. Similarly, indomethacin has been shown to produce damage via increasing mucosal MDA levels in gastric tissue [42]. Indomethacin causes gastric damage by not only inhibiting cytoprotective prostaglandin synthesis, but also by affecting antioxidant mechanisms, such as MDA. Thus, risperidone appears to exert its anti-ulcer effects by activation of antioxidant mechanisms in stomach tissues. This study showed that risperidone significantly prevented the negative effect of indomethacin on gastric MDA levels at all doses used. This report is supported by earlier work indicating that antioxidant parameters have been shown to be reduced in stomach tissue damaged by indomethacin [43]. The roles of toxic oxygen radicals has also been reported to be involved in indomethacin- induced gastric damage as was determined in etiopathogenesis [35]. Increased levels of reactive oxygen species (ROS) are indicated in the mechanism of both stress and indomethacin-induced gastric damage [44]. Excessive production of MDA and other reactive radicals cause oxidative damage which is represented by measuring lipid peroxidation levels [45]. Lipid peroxidation is an important reason for cell membrane damage; MDA is the end product of lipid peroxidation and is used to determine lipid peroxidation levels [46]. This study revealed that the anti-gastric ulcer activity of risperidone may be by blocking histamine H_2 and gastrin receptors, increasing gastric mucus secretion, number of gastric mucus cells count and by decreasing lipid peroxidation level. However, more detailed studies are necessary to confirm the relevance of this finding and its implications.

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References

1. Mózsik, G., Jávor, T., A biochemical and pharmacological approach to the genesis of ulcer disease. I. A model study of ethanol-induced injury to gastric mucosa in rats. Digest Dis Sci 1988;33:92-105.
2. Davies, G.R., Simmonds, N.J., Stevens, T.R., Helicobacter pylori stimulate antral mucosal reactive oxygen metabolite production in vivo. Gut 1994;35:179-185.
3. Ding, S.Z., Lam, S.K., Yuen, S.T., Prostaglandin, tumour necrosis factor alpha and neutrophils: causative relationship in indomethacin-induced stomach injuries. Eur J Pharmacol 1998; 348:257-163.
4. Feldman, F., Friedman, L.S., Sleisenger, M.H., Sleisenger and Fordtran's Gastrointestinal and Liver Disease. WB Saunders Co, Philadelphia 2002; 615.
5. Hooderwerf, W.A., Pasricha, P.J., Pharmacotherapy of gastric acidity, peptic ulcers, and gastroesophageal reflux disease. In Goodman and Gilman's the pharmacological basis of therapeutics Edited by Brunton, L. New-York: Mc Graw-Hill 2006;967-981.
6. Chan, F.K.L., Leung, W.K., Peptic ulcer disease. Lancet 2002; 360:933-941
7. Brzozowski, T., Konturek, P.C., Chlopicki, S., Therapeutic potential of 1-methylnicotinamide against acute gastric lesions induced by stress: role of endogenous prostacyclin and sensory nerves. J Pharmacol Exp Ther 2008;326:105-116.
8. Kwiecień, S., Pawlik, M.W., Sliwowski, Z., et al., Involvement of sensory afferent fibers and lipid peroxidation in the pathogenesis of stress induced gastric mucosa damage. J Physiol Pharmacol 2007;58(Suppl 3):149-162.
9. Guldahl, M., The effect of trimipramine (Surmontil r) on masked depression in patients with duodenal ulcer. A double-blind study. Scand J Gastroentero 1977; 43:27-31.
10. Pare, W.P., Stress ulcer susceptibility and depression in Wistar Kyoto (WKY) rats. Physiological Behaviour 1989;46:993-998.
11. Glavin, G.B., Vulnerability to stress ulcerogenesis in rats differing in anxiety: a dopaminergic correlate. J Physiol Paris 1993;87:239-243.
12. Sjodin, I., Svedlund, J., Dotevall, G., et al., Symptom profiles in chronic peptic ulcer disease: A detailed study of abdominal and mental symptoms. Scand J Gastroentero

1985; 20:419-427.
13. Feldman, M., Walker, P., Green, J.L., et al., Life events stress and psychosocial factors in men with peptic ulcer disease. A multidimensional case-controlled study. Gastroenterology 1986; 91:1370-1379.
14. Tokuda, I.K., Ohno, Y., Sakamoto, H., et al., Evaluation of perospirone (SM-9018), a novel serotonin-2 and dopamine-2 receptor antagonist, and other antipsychotics in the conditioned fear stress-induced freezing behavior model in rats. Jpn J Pharmacol 1996;72:119-126.
15. Saxena, B., Singh, S., Antistress activity of Risperidone, an atypical antipsychotic drug in rat stress models. Pharmacologyonline 2011;3:98-108.
16. Borelli F, Izzo AA. The plant kingdom as a source of anti-ulcer remedies. Phytother Res 2000;14:581-591.
17. Amure BO, Omole AA. Sex hormones and acid gastric secretion induced with carbachol, histamine, and gastrin. Gut 1970; 11: 641-645
18. Principle of Laboratory animal care. National Institute of Health (NIH) Publication 1985:85-23
19. Corney SJ, Morrissey SM, Woods RJ, A method for the quantitative estimation of gastric barrier mucus. J Physiol 1974;242:116.
20. Li, Ma., Del Soldato, P.J.L. Divergent effects of new cyloxygenase inhibitors on gastric ulcer healing: Shifting the angiogenic balance. Pharmacology 2002;99(20):13243-13247.
21. Gutteridge, J.M.C., Wilkins, C., Copper dependent hydroxyl radical damage to ascorbic acid: Formation of a thiobarbituric acid reactive product. FEBS Letters 1982;137:327-40.
22. Ghosh, M.N., Schild, H.O., Continuous recording of gastric acid secretion in rats. Brit J Pharmacol 1958;21:1396.
23. Fatemah, N.R., Jalal, V., Zakieh, V.A., et al., The effect of acute consumption of paraoxon on basal and pentagastrin-stimulated gastric acid and pepsin secretion in rats. Pak J Physiol 2006;2(2):1-3.
24. Naseri, M.K.G., Mard, S.A., Badavi, M., Effect of Esophageal Distention on Basal and Stimulated Gastric Acid Secretion in Rats. Iran Biomedical J 2007;11(3):177-183
25. Prinz, C., Scott, D.R., Hurwitz, D., et al., Gastrin effects on isolated rat enterochromaffinlike cells in primary culture. Am J Physiol 1994;267:G663-G675
26. Sandvik, A.K., MaÊ rvik, R., Rod, D., et al., Carbachol stimulation of gastric acid secretion and its effects on the parietal cell. Brit J Pharmacol 1998;124:69-74.
27. Soll, A.H., Mechanisms of action of antisecretory drugs: studies on isolated canine fundic mucosal cells. Scand J Gastroentero 1986;21: 1-6.
28. Wilkes, J.M., Kajimura, M., Scott, D.R., et al., Muscarinic receptors of gastric parietal cells. J Membrane Biol 1991;122:97.
29. Kerss, S., Allen, A., Garner, A., A simple method for measuring thickness of the mucosal gel layer adherent to rat, frog and human gastric mucosa: influence of feeding prostaglandin, N-acetyl and other agents. Clin Sci 1982;63:187–195.
30. McQueen, S., Hutton, D., Allen, A., et al., Gastric and duodenal surface mucus gel hickness in rat: effects of prostaglandins and damaging agents. Am J Physiol Gastrointestinal Liv Physiol 1983;245: G388–G393.
31. Allen, A., Carroll, N.J.H., Adherent and soluble mucus in the stomach and duodenum. Digest Dis Sci 1985;30: 55S–62S.
32. Allen, A., Gastrointestinal mucus. In: Handbook of Physiology. Gastrointestinal Physiology. Salivary, Gastric, Pancreatic, and Hepatobiliary Secretion. Bethesda, MD. Ed. American Physiology Society 1989;6(III):359–
33. Wallace, J.L., Prostaglandins, NSAID's, and Gastric mucosal protection: Why doesn't the stomach digest itself? Physiol Rev 2008; 88: 1547-1565.
34. Seno, K., Joh, T., Yokoyama, Y., et al., Role of mucus in gastric mucosal injury induced by local ischaemia/reperfusion. J Lab Clin Med 1995;126:287-293.
35. Naito, Y., Yoshikawa, T., Yoshida, N., Kondo, M., Role of oxygen radical and lipid peroxidation in indomethacin-induced gastric mucosal injury. Digest Dis Sci 1998;43:30S-34S.
36. Vaananen, P.M., Meddings, J.B., Wallace, J.L., Role of oxygen-derived free radicals in indomethacin-induced gastric injury. Am J Physiol 1991; 261: G470-G475.
37. Link, E.M., Inflammation and a mechanism of hydrogen peroxide cytotoxicity. In: Free radicals: From basic science to medicine (Poli, G., Albano, E. and Dianzani, M.U., eds.) Birkhauser Verlag 1993:113-123.
38. Nam, S.Y., Kim, N., Lee, C.S., Gastric mucosal protection via enhancement of MUC5AC and MUC6 by geranylgeranylacetone. Digest Dis Sci 2005;50:2110-2120.
39. Corfield AP, Carroll D, Myerscough N, Probert CS. Mucins in the gastrointestinal tract in health and disease. Frontline Bioscience 2001;6:D1321-D1357.
40. Jainu, M., Devi, C.S., Gastroprotective action of Cissus quadrangularis extract against NSAID induced gastric ulcer: role of proinflammatory cytokines and oxidative damage. Chem Biol Interac 2006;161:262-270.
41. Bayir, Y., Odabasoglu, F., Cakir, A., et al., The inhibition of gastric mucosal lesion, oxidative stress and neutrophil-infiltration in rats by the lichen constituent diffractaic acid. Phytomedicine 2006;13:584-590.
42. Odabasoglu, F., Halici, Z., Cakir, A., et al., Beneficial effects of vegetable oils (corn, olive and sunflower oils) and alpha-tocopherol on anti-inflammatory and gastrointestinal profiles of indomethacin in rats. Eur J Pharmacol 2008;591:300-306.
43. Hassan, A., Martin, E., Puig-Parellada, P., Role of antioxidants in gastric mucosal damage induced by indomethacin in rats. Method Find Exp Clin 1998;20:849-54.
44. Itoh, M., Guth, P.H., Role of oxygen-derived free radicals in hemorrhagic shock-induced gastric lesions in the rat. Gastroenterology 1985;88:1162-1167.
45. Peralta, C., Rull, R., Rimola, A., et al., Endogenous nitric oxide and exogenous nitric oxide supplementation in hepatic ischemia-reperfusion injury in the rat. Transplantation 2001;71:529-36.
46. Nielsen, F., Mikkelsen, B.B., Nielsen, J.B., Andersen HR Grandjean P. Plasma malondialdehyde as biomarker for oxidative stress: reference interval and effects of life- style factors. Clin Chem 1997;43:1209-14.

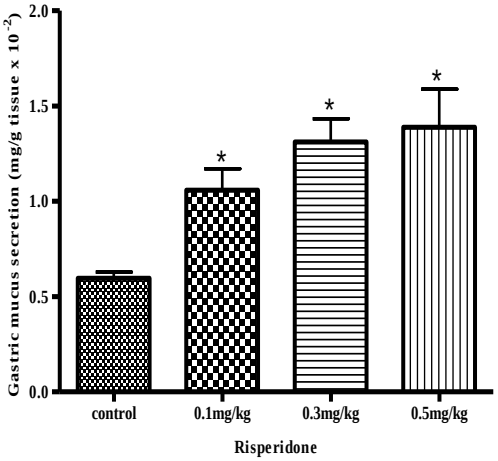

Figure 1. Effect of risperidone on gastric mucus secretion

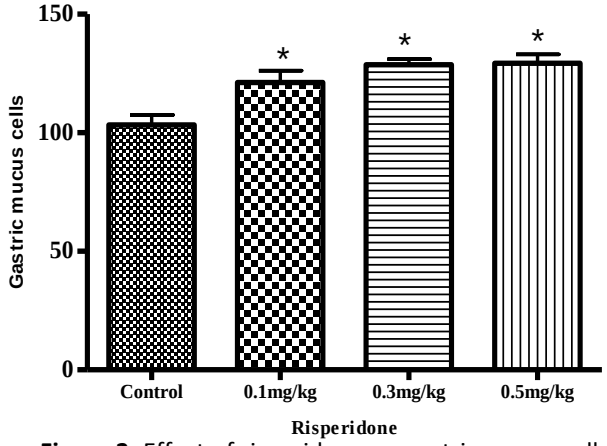

Figure 2. Effect of risperidone on gastric mucus cells count

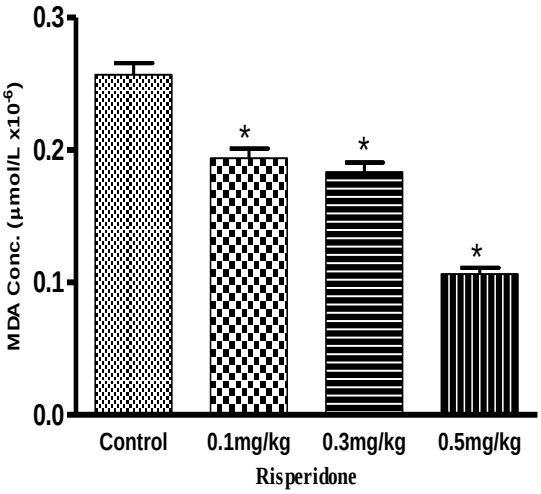

Figure 3. Effect of risperidone on malonialdehyde (MDA) concentration

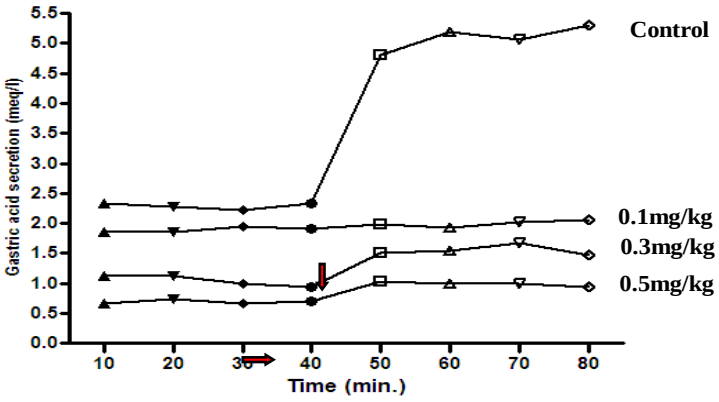

Figure 4. Effect of risperidone on gastric acid secretion induced by histamine

= Before arrow shows basal secretion

= Arrow indicates point of injection of histamine administration, *i.v.*

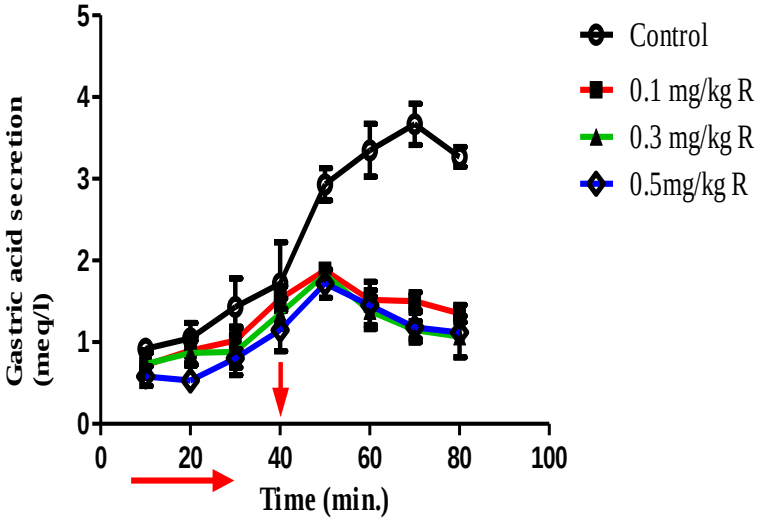

Figure 5. Effect of risperidone on gastric acid secretion induced by pentagastrin

= Before arrow shows basal secretion.

= Arrow indicates point of injection pentagastrin administration, *i.p.*

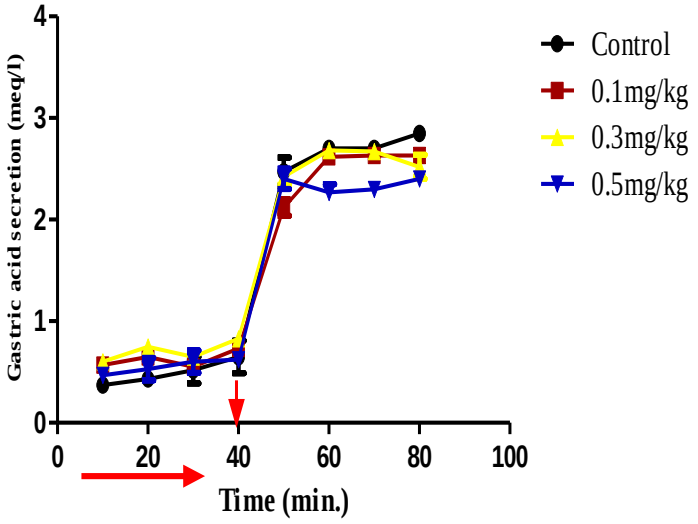

Figure 6. Effect of risperidone on carbachol induced gastric acid secretion

= Before arrow shows basal secretion

= Arrow indicates point of injection of histamine administration, *i.p.*