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Original Article

Gastroprotective and antioxidant effects of fluvoxamine on stress-induced peptic ulcers in rats

Q8 Wael M. Elsaed, PhD [a,b,*], Abelaziz M. Al-Ahmadi [a], Basil T. Al-Ahmadi [a], Q1 Gumana A. Taha [a] and Raghad M. Tarabishi [a]

[a] *Anatomy & Embryology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt*
[b] *Anatomy & Embryology Department, Taibah University, Almadinah Almunawwarah, KSA*

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الملخص

أهداف البحث: يشير مصطلح "القرحة الهضمية الناجمة عن الإجهاد" إلى وجود جروح في الغشاء المخاطي للجهاز الهضمي العلوي نتجت عن الإجهاد. وقد تم تسجيل آثار مضادة للأكسدة ومضادة للتقرّح لبعض مضادات الاكتئاب. إلا أن التقييم النسيجي والتقييم الكيميائي الحيوي للنشاط المضاد للتقرّح لمضاد اكتئاب مشابه، هو " فلوفوكسامين" لم يتم التحري عنهما بصورة كافية. تهدف الدراسة إلى تحديد الفاعلية المضادة للتقرّح لـ "فلوفوكسامين" في إحداث التغيرات النسيجية والكيميائية الحيوية الناجمة عن الإجهاد في الغشاء المخاطي في المعدة.

طرق البحث: تم تقسيم ثلاثين من ذكور الجرذان البيضاء البالغة إلى ثلاث مجموعات من ١٠ جرذان؛ المجموعة الضابطة ومجموعة "القرحة الهضمية الناجمة عن الإجهاد" والمجموعة سابقة المعالجة بـ "فلوفوكسامين" التي تلقت "فلوفوكسامين" لمدة ثمانية أيام قبل التعرض للإجهاد. تم تعريض مجموعة "القرحة الهضمية الناجمة عن الإجهاد" ومجموعة "فلوفوكسامين" إلى طريقة منع الحركة الباردة لاستحداث قُرَح في المعدة. بعد ذلك تم استئصال معداتهم وفتحها واحتساب مؤشرات التقرح. تم فحص العينات بعد صبغها بصبغة "هيموتوكسيلين وإيوسين" وصبغة "بي أي اس" وصبغة "ماسون ثلاثية الألوان" وصبغة "بي سي إن أي" المناعية بالمجهر الضوئي. وتم قياس مستويات علامات الإجهاد التأكسدي في النسيج المعدي ومقارنته بين المجموعات.

النتائج: أظهرت مَعِدات المجموعة سابقة المعالجة بـ "فلوفوكسامين" عدد قُرح أقل بشكل ملحوظ مع حد أدنى من إصابة الغشاء المخاطي مقارنة بالمجموعة المصابة. وأظهر التحسن في مستويات علامات الإجهاد التأكسدي وفي علامات مؤشر قرحة مجموعة "القرحة الهضمية الناجمة عن الإجهاد" فرقا كبيرا بين المجموعات.

الاستنتاجات: فلوفوكسامين كان له أثر معزز للمعدة ضد نشوء القُرح وساعد على شفاء القُرح الموجودة.

الكلمات المفتاحية: فلوفوكسامين؛ الإجهاد؛ القرحة الهضمية؛ قرحة المعدة؛ القرحة الهضمية الناجمة عن الإجهاد

Abstract

Objectives: Stress-induced peptic ulcer disease (SPUD) refers to erosions in the mucosa of the upper gastrointestinal tract that are caused by stress. Some antidepressants are reported to have antioxidant and antiulcer effects. However, histopathological and biochemical evaluation of the anti-ulcer activity of a comparable antidepressant, fluvoxamine, has not been adequately investigated. This study aims to determine the anti-ulcer efficacy of fluvoxamine in reducing stress-induced histopathological and biochemical changes in the gastric mucosa.

Methods: Thirty adult male albino rats were divided into three groups of 10 rats each: the control groups, the SPUD group, and the fluvoxamine-pre-treated group, which received fluvoxamine for eight days before stress exposure. The cold-restraint stress method was used to induce stomach ulcers in the SPUD and fluvoxamine groups. Afterward, the stomachs of rats were removed, opened, and ulcer indices were calculated. Light microscopy was performed following haematoxylin and eosin staining, periodic acid Schiff's, Masson's trichrome staining, and proliferating cell nuclear antigen immunostaining. Gastric tissue levels of oxidative stress markers were measured and compared among groups.

Results: The stomachs of the fluvoxamine-treated rats showed a significantly lower number of ulcers with

Q3 * Corresponding address: Anatomy Department, Taibah University, POX: 42221, Almadinah Almunawwarah, KSA.
E-mail: wzzarina@yahoo.com (W.M. Elsaed)

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minimal mucosal injury compared with those of rats from the SPUD group. The oxidative stress marker levels and SPUD ulcer indices were significantly different among groups.

Conclusion: Fluvoxamine pre-treatment exerted a gastroprotective effect against ulcer development and promoted healing of the developed lesions.

Keywords: Fluvoxamine; Gastric ulcer; Peptic ulcer; Stress; Stress-induced peptic ulcer

Introduction

Peptic ulcer disease (PUD) is a common disease worldwide.[1] PUD occurs as a defect in the mucosa of the stomach or duodenum that exceeds the muscularis mucosa.[2] PUD follows gastric mucosal injuries as a result of imbalance between the defensive and the aggressive factors affecting the mucosa.[3,4] Many factors contribute to the development of PUD, of which environmental factors such as psychosocial conditions and stress are the most outstanding.[5]

Stress is an acute hazard/risk to homeostasis that excites an allostatic or adaptive response. Stress affects the function of the gastrointestinal tract either in short or long-term impacts.[5] Studies revealed that stress contributes to the formation of PUD and is frequently used to produce PUD in experimental animal models.[6]

Stress-induced peptic ulcer disease (SPUD) or stress-related gastric mucosal lesions occur as a typical stress-induced organ injury.[7] SPUD incidence is increasing worldwide and is considered a significant cause of pain and distress, with an accompanying impairment of quality of life.[8] The onset and modulation of SPUD may be caused by various types of stress,[9] of which several types of major physiologic harms, including trauma, CNS injury, burn injury, major surgical procedures and critical illnesses are the most common.[10] The pathogenesis of SPUD is not clearly discussed in previous research, but it differs from ordinary PUD in symptoms and risk factors.[7] It has been suggested that in SPUD there is insufficient blood microcirculation, which results in accumulation of reactive oxygen species (ROS) with accompanying lipid peroxidation and subsequent loss of normal cellular functions.[11]

Being a serious gastrointestinal disorder, PUD demands a well-targeted therapeutic approach.[12] Numerous drugs are available for the treatment of PUD, involving anti-acids, H_2 receptor antagonists, and proton pump inhibitors[13]; however, clinical evaluation has revealed major side effects, drug interactions, and incidences of relapse from these drugs.[14]

Tricyclic antidepressants have been reported to be used for their antioxidant effects.[15] They were the first antidepressants used for the treatment of PUD.[16] Although some selective serotonin reuptake inhibitor (SSRI) drugs have gastric side effects that might progress to gastrointestinal bleeding if used in combination with indomethacin,[17,18] over time, other antidepressants have been shown to possess variable degrees of anti-ulcer action.[19–21] Alternatively, novel anxiolytics have gastroprotective effects in experimental animals.[22] Some drugs have shown other, more beneficial GIT effects, such as increasing gastric contractility[23] and decreasing stomach and intestinal distension.[24]

Fluvoxamine is an SSRI broadly prescribed for depression[25] and is used for treating obsessive-compulsive disorder.[26] This drug inhibits CYP1A2,[25] an enzyme known to be involved in ROS generation.[27] Unlike most SSRIs, which enhance upper GIT bleeding, fluvoxamine is postulated to be beneficial in the management of PUD.

The combined antioxidant and antidepressant effects of fluvoxamine favours its use in treatment of SPUD. However, the histopathological and biochemical changes associated with its anti-ulcer activity are not fully elucidated. Thus, the aims of this study is to examine the histopathological and biochemical changes in the gastric mucosa induced by stress, and to investigate the effects of fluvoxamine on stress-induced ulcers.

Materials and Methods

Thirty adult male eleven-week-old albino rats (130–150 g average body weight), obtained from the Mansoura Animal House were used in this study. Animals were housed in the Mansoura Faculty of Medicine Animal House under standard laboratory conditions. Commercial standard pellet diet was used for feeding, with free access to food and water. The animals were acclimatized to standard laboratory conditions (according to Mansoura University IRB protocols); the temperature was 20 ± 1 °C, with a 12:12-h light–dark cycle for 10 days before the experiment. To prevent coprophagy, a grid floor was placed in each cage. The animals were randomly assigned to three groups of 10 animals each: Group I (the control group), Group II (the SPUD group), and Group III (the fluvoxamine-treated group). Groups I and II received sterile water, while Group III received fluvoxamine solution by an orogastric tube for 8 days before stress induction.

The fluvoxamine solution was prepared by dissolving 50 mg film-coated fluvoxamine tablets (Solvay, Cairo, Egypt) in sterile water. The solution was prepared just prior to dosing at a concentration of 50 mg/kg,[21] and administered daily to 12-h fasted rats by an orogastric tube as a pre-treatment (for 1 day) and repeated for 7 consecutive days.

Induction of SPUD in 12 h-fasted rats of Groups II and III using the cold immobilization restraint method as previously described.[28] Rats were tied to a wooden plank and immersed individually in cold water (6 ± 0.6 °C) for 6 h. Q4 The same procedure was repeated daily for 7 days.[7] At the assigned time, the animals were sacrificed under diethyl ether anaesthesia, the abdomens were opened at the midline and the stomachs were gently removed, washed with saline, opened at the greater curvature, and photographed with a digital camera (Canon 650D).

The total ulcer surface area was measured from the photographs after considering the drawing scale. Ulcer severity was scored by the sum of the total ulcer surface area

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