Vanadyl sulfate and Lycopene in prevention of Ethanol induced gastric ulcer

Faruk H Aljawad[1], Mohmoud J Jawad[2], Osama K. FadhiL[3]

[1]Prof. Department of pharmacology, Al-Yarmouk University.

[2]Department of pharmacology, Al-Nahrain University.

[3]Department of pharmacology, Al-Yarmouk University.

Abstract

Background:

gastric ulcer is a state resulted from imbalance between the erosive action of acid and pepsin & mucosal defense mechanism in the stomach and may be correlated with antioxidant agents.

Materials and methods:

thirty five healthy albino male rats weighing 200- 220 grams were involved in this study. The animals were allocated to five groups. Each group was given orally one of the following agents: Lansoprazole, Vanadyl sulfate, lycopene and distilled water as control. After five days of treatment ethanol 95% was used orally after one hour of the last dose. The animals were sacrificed one hour later, the ulcer preventive index and free radicales and serum electrolytes were estimated.

Results:

high concentration of ethanol was found to produce a ratio of 100% ulceration in the stomach when administration done orally. The preventative index of both Vanadyl sulfate, lycopene was highly significant when compared to drug control (lansoprazole). All the tested agents produced highly significant changes in free radicals of the gastric tissue increasing GSH and decreasing MDA levels. Serum electrolytes (Na^{+}, K^{+} and Ca^{+2}) were significantly changed by these agents.

Conclusion:

Vanadyl sulfate and Lycopene proved to have preventive effect against ethanol induced gastric ulcer and the possibility to be used after clinical trials for patients with gastric ulcers.

Key words: Gastric ulcers, free radicals, Lansoprazole, Vanadyl Sulfate, Lycopene.

الخلاصة

كبريتات الفناديل ولايكوبين لمنع القرحة المحتثة بالكحول

حدوث القرحة المعدية يعبر عن إختلال الموازنة بين التأثير التأكلي للحامض والببسين والية الدفاع للجدار المخاطي للمعده وما لذلك من علاقة مع البكتريا (H.pylori)

استعمل في الدراسة (٣٥) جرذاً أبيضاً وزعوا على خمسة مجموعات أعطيت لكل مجموعة إحدى المواد التالية لانسوبرازول مضاد للقرحة ،كبريتات الفناديل ولايكوبين وهما من مضادات الأكسدة وكذلك الماء المقطر لوحده كسيطرة وكان أستعمالها لمدة

خمسة أيام متعاقبة وبعد ساعة من آخر جرعة لها أعطي الكحول المركز ٩٥% حيث تم قتل الحيوانات بعد ساعة واحدة من إعطاء الكحول

تم عزل المعدة وإفراغ محتواها وإجراء التثبيت والصبغ لها من أجل حساب عدد التقرحات ومساحتها وحساب معامل الحماية للقرحة بأستعمال المجهر التشريحي وأحتساب الجذور الحرة والكهارل بالمصل أظهرت النتائج أن معامل الحماية من القرحة كان عاليا جدا من قبل لانسوبرازول في حين إنه كان عاليا أيضا لكل من كبريتات الفناديل ولايكوبين مع حدوث تغيرات معنوية معتدة في الجذور الحرة وكذلك مستويات الصوديوم والبوتاسيوم والكالسيوم بالمصل .

الكلمة المفتاح:

كبريتات الفناديل،لايكوبين ،القرحة المعدية ،الجذور الحرة

Introduction

Gastric ulcer takes place as a result of an imbalance between the corrosive action of acid – pepsin and mucosal defense mechanism. It is entirely associated with H. pylori infections and partially with NSAIDs induced injury [1]. Studies showed that some strains of H. pylori have a particular mechanism of injecting the inflammatory agent peptidoglycan from their own cell wall into epithelial stomach cells [2]. H. pylori damage the mucosal defense system by reducing the thickness of the mucus gel layer, diminishing mucosal blood flow and interacting with gastric epithelium during all stages of infection [3]. The reactive oxygen species (ROS) have been shown to play a crucial role in experimental gastric lesion induced by stress, ethanol and NSAIDs. They play a role in prostaglandins synthesis, infiltration of polymorphnuclear leukocytosis, induction of apoptosis and iniation of lipid peroxidation [5]. The present study was performed to investigate the preventive effect of both Vanadyl sulfate and lycopene in comparison to Lansoprazole in ethanol – induced gastric ulcer.

Materials and Methods

Thirty five healthy albino male rats weighing 200- 230 grams were used in this study. They were supplied by animal house of Al-Nahrin College of Medicine. They were fed daily on oxoid pallet, food with held 24 hours before sacrifying the animals in the 5^{th} day but allowing excess of water. The animals were allocated to five groups with seven rats in each. Each group was given orally one of the followings:

Group I (control) - received 1.5 ml of distilled water as a single daily dose for 5 days

Group II (ulceration) - received 1.5 ml of distilled water as a single daily dose for 5 days

Group III (drug control) - received 30mg/ kg Lansoprazole in 1.5 ml of distilled water as a single daily dose for 5 days

Group IV - received 50mg/kg Vanadyl sulfate in 1.5 ml of distilled water as a single daily dose for 5 days

Group V - received 60mg/kg Lycopene in 1.5 ml of distilled water as a single daily dose for 5 days

All the animals except group I were given 1.5 ml ethanol 95% orally after one hour following the last dose of tested drugs then one hour after the administration of ethanol all the animals were sacrificed later. The main parameters used in the study concern the gastric ulcer include: the number of lesions, total lesion length, total lesion surface area, the preventive index, biochemical estimation of free radicals in gastric tissue extract glutathione (GSH), malondialdehyde (MDA) levels and serum Ca^{+2} , Na^{+}, and K^{+} levels.

Stomach tissue Preparation

The rats' stomach was separated and removed then opened along greater gastric curvature. Washing with physiological saline then immersed in freshly prepared phosphate buffer with PH 8. The gastric tissue were harvested from the sacrificed animals and the pieces were put in 10% neutral formalin solution embedded in paraffin then stained and examined by dissecting microscope binocular type Heerbrugy to measure the parameters of ulcer. Blood samples were collected by intracardiac aspiration; they were put in centrifuge at 3000 RPM for 15 minutes. The separated serum used for biochemical estimation of serum $Ca^{+2,}$ Na^{+}, and K^{+} levels by electrolyte analyzer. All data were analyzed using SPSS version and paired sample t- test with level of significance ($P<0.05$).

Results

Ethanol was found to be highly effective to induce gastric lesions with ratio of 100% when used orally in rats. The results of Vanadyl sulfate and Lycopene revealed highly significant preventive index equal to 75.38 ± 2.66 and 50.31 ± 4.78 respectively as compared with Lansoprazole 99.06 ± 0.25 (as shown in table 1) . All the drugs showed high significant changes in free radicals of gastric tissue extract increasing GSH, and decreasing MDA levels. Serum electrolytes also showed significant changes, the serum Na^{+} level highly decreased with Lycopene while serum Ca^{+2} level highly increased with Vanadyl sulfate as compared with lansoprazole (shown in table 2).

Discussion

Ethanol in large dose causes gastric mucosal lesions in rats, include ulcers and erosions similar to that occurred in peptic ulcer with extensive visible hemorrhage. Most of these lesions were occurred in the glandular portion of rat stomach while the non- glandular portion remained intact [4]. Using distilled water alone (group I) produced no changes in all parameters including the serum electrolytes while ethanol (group II) caused damage to gastric mucosa associated with production of free radicals leading to increased lipid peroxidation and damage of the cells [6,15] the obtained results showed that gastric tissue extract of MDA levels increased while GSH levels decreased these results were compatible with other results after administration of ethanol [7]. Lansoprazole a proton pump inhibitor Group III acts by irreversible binding to H^{+}- K^{+} ATPase pump and effectively suppress the gastric acid secretions[8,14] .Also it significantly change GSH and MDH level, for these reasons it has a powerful gastroprotective activity.

These result similar to others when they used esomeprazole against ethanol induced ulcer [9]. Lansoprazole increases serum K^+ and Na^+ levels significantly due to Proton Pump inhibitor (PPI) action. Vanadyl sulfate is an oxidative form of vanadium (group IV) it is important for normal bone growth & as a cofactor for enzyme reaction [10]. It is beneficial for diabetes hyperlipidemia and heart diseases [11]. Our study showed that Vanadyl sulfate has a preventive effect to ethanol induced ulcer. This effect is supported by increased GSH and decreased MDA levels of gastric tissue extract accompanied with significant increase in Na^+ and highly significant Ca^{++} levels but no available data are present. Lycopene is the most powerful antioxidant carotenoids quencher of single oxygen (group V). It is a potent neuroprotective, antiproliferative, antimutagentic, anti- inflammatory agent [12]. It provides protection against free radical tissue damage caused by DNA. Lycopene extract may prevent colon, uterus, prostate, bladder, and pancreatic carcinoma [13]. The obtained result of lycopene showed that this agent has significant preventive effect against ethanol induced ulcer due to antioxidant activity. This effect supported by increase GSH and decreased MDA levels of gastric tissue extract. Lycopene is a phenolic compound that present in plants and has highly significant lowering effects to Na^+ levels. The preventive effect of both tested drugs is related to their positive action on antioxidant system. In conclusion, there is possibility to use these agents for patients with predisposing to peptic ulcer, but these results should be confirmed by clinical trials.

Table.1 The effect of Lansoprazole & tested Agents on ulcers parameters (No. of ulcer, total length of ulcers, total area of ulcers & preventive index).

Drug	Dose	No. of ulcer	Total length of ulcers(mm)	Total area of ulcers (mm^2)	preventive Index
Ethanol	1.5 ml 95%	8.86 ± 0.4	10.35± 0.68	129.47± 0.19	
Lansoprazole	30 mg/kg	0.71± 0.18 **	2.29±0.64**	128 ± 0.32**	94.06 ± 0.25**
Vanadyl sulfate	50 mg/kg	2.29± 0.36 **	8.87± 0.66	32.00 ± 3.46**	75.38 ± 2.66**
Lycopene	60mg/kg	6.00 ± 0.72 **	7.90 ±0.72*	63.95± 6.21**	50.31± 4.78**

* Significant at $P < 0.05$ compared with group I (induced ulcer)

** highly significant at $P < 0.001$ compared to group I (induced ulcer)

Table.2 The effect of Lansoprazole & tested Agents on GSH, MDA levels in gastric tissues of serum electrolytes to levels of Na^{+}, K^{+}, and Ca^{++}

Drug	**Dose**	**GSH nmoL/ mg**	**MDA nmoL/ mg**	**Na^{+} mmoL/L**	**K^{+} mmoL/ L**	**Ca^{++} mmoL/ L**
D.W	1.5ml	741.15 ±15.20	8.59± 0.23	118.14±3. 88	5.41± 0.17	0.78 ±0.06
Ethanol	1.5 ml 95%	470.00 ± 10.69	18.82± 0.42	131.43± 0.20	5.84± 0.08	0.62 ±0.06
Lansoprazole	30 mg/kg	609.55 ±16.64**	13.66 ±0.55**	149.00 ± 3.11**	6.97 ±0.34**	0.65 ±0.02
Vanadyl sulfate	50 mg/kg	777.14 ± 23.17**	10.62 ± 0.92**	142.00 ± 0.01*	5.49 ± 0.18	0.86 ± 0.05**
Lycopene	60mg/ kg	508.07 ±24.32	13.90± 0.36**	119.71± 1.34**	6.07 ±0.22	0.67± 0.05

* Significant at $P < 0.05$ compared with group I(induced ulcer)

** highly significant at $P < 0.001$ compared to group I (induced ulcer)

References:

1. Laurence DR, Bennett PN & Brown MJ clinical pharmacology 10th Ed. Churchill Livingstone – London 2008, p.568 – 573.

2. Jerome V, Catherine C & Boneca IG nodl responds to peptidoglycan by the helicobacter pylori cag pathogenicity island. Nature Immunol 2001, 5 1166- 74.

3. Turkkan E, Uslan I, Acarturk G, Topak N & kahraman A, Does Helicobacter pylori induced inflammation of gastric Mucosa determine the Severity of Symptoms in functional dyspepsia, J Gastro euterol 2009, 44,66-70.

4. Krish nendu G, parag k, Aditi B, Russel JR and Snehasikta S Hydrogen peroxide – mediated down regulation of Matrix metallo protease -2 in indomethacin – induced gastric ulceration is blocked by melatonin and other free radicals, Biology and medicine 2006, 41, 911-925.

5. Beck pL, Lee SS, Mcknight G and Wallace JI characterization of spontaneous and, ethanol induced gastric damage in Cirrhotic rat gastroenterology 1992, 103, 1048 – 1055.

6.Vanisree AJ, Mitra k and shymala Cs, Anti ulcerogenic effect of UI 409 against experimentally induced gastric ulcer in rats, Indian. J pharmacol 1996, 28, 265- 268.

7. AL- Rejaie Inhibition of ethanol – induced gastric mucosal damage by carvedilol in male albino rats. Int. J of Pharmacology 2009, 5: 146 – 154.

8. Mycek MJ, Harvery RA, champe P and Fisher B. Lippincott's illustrated Review's Pharmacology 5th Ed. Williams and Wilkins 2010.

9. Al Jawad FH and AL Sabah E some medicinal plants versus esomeprazole in prevention of ethanol induced ulcer. J. AL- Nahrin medical College Impress, 2011.

10. Hendler SS, Rorvik D, Fleming T, Deutsch M and Wyblec Vanadine PDR For nutritional Supplements Montvale NJ 2001, Medical Economics Co 459-460

11. BodenG, chen X, Ruiz J, effcts of Vanadyl Sulfate on Carbohydrate metabolism in Patients with non- insulin dependent diabetes mellitus Metabolism 45, 1130-1135.

12. Hininger LA, Meyer- Wenger A, Moser U, Wright A, Southern Setal No Significant effect of Leutin, Lycopene or beta- Carotene Supplemention on biological markers of Oxidaline Stress and LDL Oxidizability in health adult Subjects J AM. Coll. Nutri 2001, 20(3) 232-238.

13. Raom, Rao AV, Fleshner N, khachi k Fand kucuk O prostate Cancer Prevention, the role of nutrition Lycopene Prevention chronic Dis 2002 1(1) 15-18.

14. Faruk H Al-jawad , Mohmud J. Jawad Vasodilators versus Lansoprazole in prevention of ethanol induced gastric ulcer , The new Iraqi J. of medicine Vol 9 No1 2013, 7-11.

15. Faruk H Al-jawad , Mohmud J. Jawad, Ahmed H. Ismail Gastroprotective effect of antioxidants in ethanol induced gastric ulcer , The new Iraqi J. of medicine Vol 9 No 1 2013, 88-95.