Effect of Clotrimazole on Chemically and Stress Induced Peptic Ulcer

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Abstract:

Clotrimazole, substitutive benzimidazole which is currently available in markets as an antifungal agent, has been studied for its ability to inhibit gastric secretion and to protect the gastric and duodenal mucosa against chemically and stress-induced ulcers. The rationale for drug selection was based on:

1) An imidazole compound omeprazole was the first approved and marketed antiulcer drug, which directly inhibit hydrochloric acid secretion.
2) Some imidazole compounds were shown to alter the levels of prostaglandins, thromboxanes and leukotrienes.

Acid secretion studies were undertaken in pylorus-ligated rats with and without clotrimazole treatment. Experimental gastric lesions were induced by water-immersion restraint stress, indomethacin and absolute ethanol in rats; whereas duodenal ulcers were produced by treatment of rats with cysteamine. The results of this study demonstrated that clotrimazole produce a dose-dependent inhibition of gastric acid secretion in rats. Pretreatment with clotrimazole significantly attenuated the formation of stress-, indomethacin- and ethanol-induced gastric lesions. Clotrimazole also protected intestinal mucosa against cysteamine-induced duodenal ulcers. In conclusion, this study demonstrated that clotrimazole possess significant antiulcer and cytoprotective activity against various experimentally induced gastroduodenal lesions. Although the effects of clotrimazole require further evaluation, the experimental observations derived from this study provide compelling evidence to justify future investigations on the clinical relevance of using such agents in clinical trials.

Keyboards

Clotrimazole, Peptic ulcer, prostaglandin, thromboxanes and leukotrienes.

Introduction

Peptic ulcer disease [PUD] is a major health problem which has a tremendous economical burden on the health institutes [1]. The etiopathology of stress and chemically induced gastric and duodenal ulcer is far from clear. A number of processes have been implicated in the pathogenesis of peptic ulcer including disruption of mucosal blood supply and hypoxic disturbance of

arachidonic acid metabolism via generation of free radical and other mediators, which affect the integrity of gastric mucosa [2,3,4].

The increase in gastric acidity is considered an important contributing factor in the pathogenesis of gastric and duodenal ulcers and is often termed 'aggressive factor' [5]. Prostaglandin E2 (PGE_2) and prostacyclin (PGI_2) are believed to have potent anti-ulcer and cytoprotective properties [6] by retarding the senescence of cells, reducing their exfoliation [7] and preventing stasis of gastric mucosal blood flow [8], induction of superoxide dismutase [9], increasing bicarbonate and mucus secretion and decrease HCl secretion, vasodilation and re-epithelization [10]. Several studies have shown that thromboxaneA2 (TXA_2) is a powerful vasoconstrictor in the stomach of the rat [11], and because of the importance of blood flow in maintaining gastric mucosal integrity [12], TXA_2 may be implicated in the pathogenesis of gastric ulceration. Leukotrienes are the principal mediators of polymorphonuclear-leukocyte-infiltration inflammatory reactions [13], indicating the involvement of leukotrienes in the genesis of cytodestruction of gastric mucosa [14]. Neutrophils have been implicated in the development of inflammation and injury in a number of tissues including the gastric mucosa [15] by releasing a number of substances that result in tissue injury including oxygen derived free radicals (ODFR) such as the superoxide anion, hydrogen peroxide, hypochlorous acid, as well as enzymes such as myeloperoxidase (MPO) and proteases [16, 17].

None of the peptic ulcer treatments is perfect, nor can alter the root causes of ulceration and all have disadvantages. Therefore the main aim of this project is to attempt to identify an imidazole agents, which may have fewer side effects and higher efficacy than currently approved benzimidazole drugs such as lansoprazole. It is known that substituted benzimidazoles inhibit gastric acid secretion by blocking H^+ /K^+– ATPase [58]. In addition, Clotrimazole inhibit the thromboxane A_2 formation [18]

Materials

Chemicals

Indomethacins, cysteamine hydrochloride, crboxymethylcellulose, Absolute alcohol, Diethyl ether, NaOH and HCl are purchased from Sigma chemical company (USA). Clotrimazole (Canesten®) is purchased from Bayer Company (Germany).

Animals

Female Wistar Albino rats weighing 180-250 grams, approximately of the same age and fed on standard chow diet were used. They were fasted for 36 hours before experimentation. Only water was allowed ad libitum. The animals were randomly divided into groups. The aqueous solutions of the ulcerogens and clotimazole were freshly prepared before administration

Methods

Ethanol induced gastric ulcer: [19]

clotrimazole were given by gavage in different doses(2.5, 5, 10, 20, 30, 80 and 100 mg/kg). After 30 minutes, the animals were administered 1ml of absolute ethanol by gavage except the animals of control group. After 1 hour, the animals were sacrificed by ether anesthesia. The stomach was removed and opened along the greater curvature, washed with saline and the lesions were assessed. Patcheal lesions of the stomach were scored according to the method described by Schiantarelli,Cadel et al. [20] using the follwing scale: 0= normal mucosa; 1= hyperemic mucosa or up to 3 small patches; 2=4-10 small patches; 3=mor than 10 small or up to 3 medium-sized patches; 4= 4-6 medium-sized patches; 5=More than 6 medium-sized or up to 3 large patches; 6=4-6 large patches; 7= 7-10 large patches and 8= More than 10 large patches or extensive necrotic zone. 'Small-sized patch' was defined as up to 2mm across (maximum diameter); 'medium-sized patch' as between 2mm and 4mm across; and 'large-sized patch' as more than 4mm across.

Indomethacin-induced gastric ulcer:

Indomethacin was suspended in 1% carboxymethylcellulose in distilled water and administered by gavage at the dose of 30mg/kg body weight. Clotrimazole in different doses (2.5, 5 and 10 mg/kg) were given orally 60 minutes prior to indomethacin administration [21]. The animals were sacrificed 7-9 hours after indomethacin administration using ether anesthesia. The stomachs were removed and opened along the greater curvature. After washing with saline, the gastric lesions were quantified. The ulcers were scored according to the methods of Valcavi et al. [22] using the following scale: 10= Deep circular ulcer more than 8mm diameter; 8= Deep circular ulcer between 7 to 8 mm diameter; 7= Deep circular ulcer between 6 t0 7 mm diameter; 6= Deep circular ulcer between 5 to 6 mm diameter; 5=Deep circular ulcer between 4 to 5 mm diameter; 4= Deep circular ulcer between 3 to 4 mm diameter; 3= Deep circular ulcer between 2 to 3 mm diameter; 2= Deep circular ulcer between 1 to 2 mm diameter; 1= Deep circular ulcer less than 1mm diameter; 6= Deep linear ulcer 10mm or more in length and 3= Deep

linear ulcer less than 10mm in length. The scores of each single lesion were then summed to determine the ulcer index which will be represented by lesion area (mm^2).

Stress-induced gastric ulcer:

One hour after clotrimazole treatment in different doses (2.5, 5 and 10 mg/kg) , rats were placed in a restraint cage and immersed vertically to level of the xiphoid process in a water bath (15C°-20C°) for 7-9 hours. Then, the animals were sacrificed using anesthetic ether. The stomachs were removed and opened along the greater curvature. After washing with saline, the gastric lesions were quantified [23]. The ulcers were scored according to the methods of Valcavi et al [22] as in the previous method.

Study of Gastric Secretion Using Pylorus Ligated (Shay) Rats method

Female Wistar Albino rats weighing 180-250 grams, approximately of the same age and fed on standard chow diet were used. They were fasted for 36 hours before experimentation. Only water was allowed ad libitum.

After 30 minutes of clotrimazole administration in different doses (2.5, 5 and 10 mg/kg), the pylorus was ligated under light ether anesthesia, care being taken not cause bleeding or to occlude blood vessels. The animals were sacrificed 6 hours after pylorus ligation [24].

The stomachs were removed, contents collected, volume measured and centrifuged. One milliliter of supernatant was titrated against 0.01N NaOH to determine the acidity using phenolphthalein as indicator and total acid output calculated [25].

Induction of Duodenal Ulcer by Cysteamine Hydrochloride

Female Wistar Albino rats weighing 180-250 grams, approximately of the same age and fed on standard chow diet were used.

Duodenal ulcers were induced by administration of two doses of cysteamine hydrochloride (400 mg/kg in 10% aqueous solution) at an interval of 4 hours according to the method described by Szabo [26]. Clotrimazole in different doses (2.5, 5 and 10 mg/kg)were administered by gavage 30 minutes before each dose of cysteamine hydrochloride and the duodenum was excised carefully and opened along the antimesenteric side. The duodenal ulcers were scored using a scale of 0 to3 where: 0= no ulcer; 1 = superficial mucosal erosion; 2 = deep ulcer or transmural necrosis, and 3 = perforated or penetrated ulcer. The sum of the intensity of each lesion was used as the ulcer index [25].

Statistical Analysis

Data are presented as mean from 4 rats per group. Statistical analyses were performed using the statistical package for social sciences (SPSS) system. Differences with a p value <0.05 were considered significant. Figures are presented as mean ± SEM by using Statistica vr.5.0 program.

Results

Ethanol -Induced Gastric Lesions

The normal control rats have shown no formation of the gastric ulcers. The treatment of rats with one-milliliter absolute ethanol produced extensive gastric lesions in the glandular mucosa of the stomach in 100% of the control animals. These lesions were characterized by multiple hemorrhagic red bands (patches) of different sizes along the axis of the glandular stomach. The ulcer index mean was found to be 7.5 in control animals one hour after ethanol administration.
Pretreatment of rats with clotrimazole at doses of ≥30 mg/kg completely prevented the formation of gastric lesions. Pretreatment of rats with clotrimazole at the doses of 2.5, 5, 10 and 20 mg/kg produce statistically significant inhibition of the formation of gastric lesions, which was dose-dependent (figure 1).

Indomethacin-Induced Gastric Mucosal Damage

All the normal control rats in this group have shown no formation of the gastric ulcers. The administration of indomethacin resulted in production of gastric lesions mainly in the glandular stomach in 100% of the animals. The lesion area in the control group was found to be 24mm² (figure 2).

Pretreatment of rats with clotrimazole at doses of 2.5, 5 and 10 mg/kg produced statistically significant decrease in the intensity of indomethacin-induced ulcers, which was dose-dependent (figure 2).

Water-Immersion Restraint Stress Induced Gastric Lesions

All the normal control rats have shown no formation of the gastric ulcers. The rats exposed to water immersion and restrain stress showed considerable ulcerogenicity in the form of haemorrhagic mucosal lesions in the stomach. There was evidence of intraluminal bleeding in these animals. The lesion area in the control group was 28.25 mm^2 (figure 3).

Pretreatment of rats with Clotrimazole at doses of 2.5,5 and 10 mg/kg produced statistically significant decrease in the intensity of water-Immersion restraint stress induced ulcers in a dose-dependent fashion (figure 3).

Cysteamine-Induced Duodenal Ulcers

All the normal control rats have shown no formation of the duodenal ulcers. Administration of cysteamine hydrochloride produced elongated lesions extending longitudinally down the duodenum. The lesion area of the rats in the cysteamine group was found to be 5.25mm² (figure 4). Pretreatment of rats with Clotrimazole at doses of 2.5 and 5 mg/kg produced statistically significant decrease in the intensity of cysteamine-induced ulcers, which was dose-dependent, complete protection of gastric mucosa was observed in the rats treated with a dose of 10mg clotrimazole /kg body weight (figure 4).

Rats Gastric Secretion and Total Acid Output in Pylorus-Ligated (Shay)

The control rats' pylorus ligated for 6h resulted in accumulation of 4.85ml of gastric secretions (pgs) and a total acid output (pao) of 363 mEq. Pretreatment of rats with 2.5 mg/kg of clotrimazole insignificantly reduced the gastric secretion volume, while the volume of gastric secretion in the rats treated with 5 and 10mg/kg of clotrimazole was statistically significant reduced (figure5). A significant total acid output, which was dose-dependent, was observed in the rats treated with 2.5, 5 and 10 mg/kg of clotrimazole (figure6).

Discussion

The results of this study indicate significantly the ability of clotrimazole to inhibit the formation of gastric ulcer in rats induced by absolute ethanol. This inhibition is dose dependent and complete protection was achieved at doses >30 mg/kg. The mucus gel adhering to the gastric mucosal surfaces protects the underlying epithelium against acid, pepsin and nercotizing agents such as absolute ethanol and indomethacin [27,28]. Ethanol causes damage of rat gastric mucosa by stasis of blood flow [29]. Therefore, it seemed likely that the gastroprotective activity of clotrimazole against the deleterious effects of ethanol could result, at least in part, from the decreasing of acid secretion [30]. This is accompanied by an increase in PGE_2 production [18, 31], which prevents the stasis of mucosal blood flow [8].

Similarly, pretreatment of rats with clotrimazole significantly protected rats against indomethacin-induced gastric ulcers in a dose-dependent pattern. Gastropathy associated with chronic use of NSAIDs is one of the major public heath problems. Although it has been proposed that a deficiency of endogenous prostaglandins and increase of thromboxane A_2 due to the inhibition of cyclooxygenase by indomethacin which is involved in these effects, the exact pathogenic mechanism remains to be elucidated [32,33]. Clotrimazole causes an increase of PGE_2 production with selective inhibition of thromboxane

synthesis by econazole [18,31]. This may explain the ability of this drugs to significantly inhibit the formation of gastric lesions induced by indomethacin.

Furthermore, the results revealed that pretreatment of animals with clotrimazole protected them against stress-induced lesions, in a dose-dependent pattern. The disturbances of gastric mucosal microcirculation [34,35], altered gastric secretion [36,37] and abnormal gastric motility [38] have been considered to be the pathogenic factors responsible for stress-induced gastric lesions. Numerous recent studies have indicated a substantial role of oxygen-derived free radicals (ODFR) [39] and leukotrienes [40] in mediating stress-induced mucosal injury. The ratio of prostacyclin to thromboxane A_2 is considered to be an important factor in the maintenance of gastric mucosal microcirculation and integrity [22]. The ability of clotrimazole to inhibit this cascade either by inhibiting (ODFR) formation [41,42] or by inhibiting formation of thromboxane and increasing formation of PGE_2 might be responsible for protecting gastric mucosa against stress-induced lesions [18,31].

Pretreatment of rats with clotrimazole significantly protected rats against cysteamine-induced duodenal ulcer, in a dose dependent pattern. The pathogenesis of cysteamine-induced duodenal lesions is far from clear. Cysteamine ulcers are considered to be associated with the hypersecretion of gastrin and hydrochloric acid and decreased mucosal resistance [43,44]]. The anti duodenal ulcer activity of clotrimazole may to a large extent be attributed to its ability to directly inhibit acid secretion by blocking H^+-K^+ ATPase [30].

Pretreatment of rats with clotrimazole produced a dose dependent decrease in the volume and acid output of gastric secretion in Shay rats. The increase in gastric acidity is considered an important contributing factor in the pathogenesis of gastric and duodenal ulcers and is often termed ‘aggressive factor’ [45]. The regulation of gastric acid secretion is complex; endogenous gastrin, histamine, somatostatin and cholinergic mechanisms play major roles in controlling gastric secretions [46]. These entire pathways converge on and modulate the activity of the proton pump of the parietal cells [47]. Clotrimazole possibly decreases acid secretion at the last step by blocking H^+-K^+ ATPase [30].

In conclusion, clotrimazole have gastroduodenal protective activity. Further studies are suggested to shed more light on the role of clotrimazole in the prophylaxis and/or the treatment of gastrointestinal ulcer diseases.

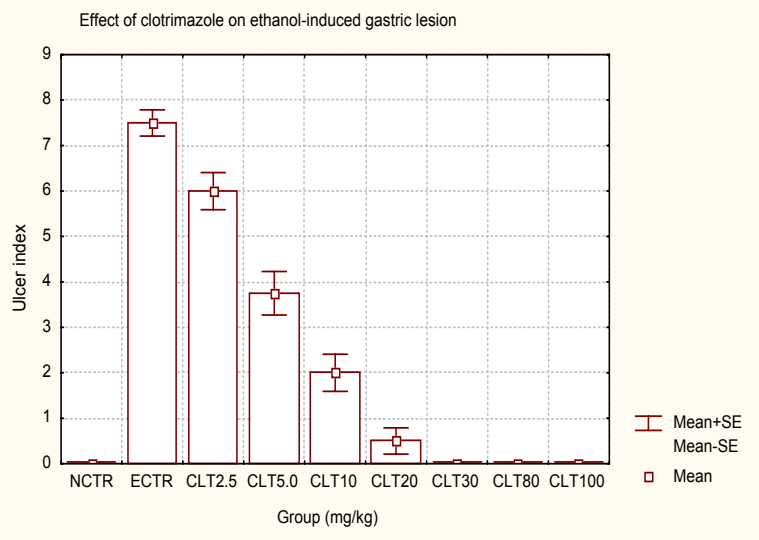

Figure1: Effect of different doses of Clotrimazole (2.5, 5, 10, 20, 30, 80 and 100 mg/kg) on ethanol-induced gastric lesions (1 ml) in experimental female Albino rats.

NCTR= control group without any treatment.
ECTR= control group treated with ethanol only.
CLT= test groups treated with ethanol and clotrimazole in different doses.

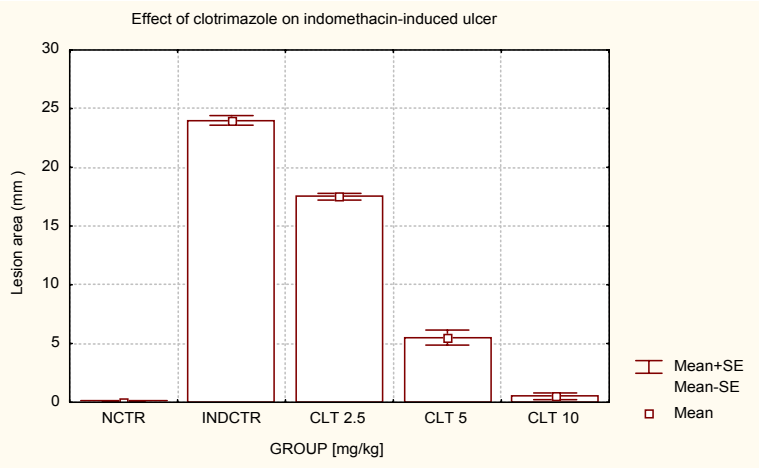

Figure2: Effect of different doses of Clotrimazole (2.5, 5 and 10 mg/kg) on indomethacin-induced ulcer (30 mg/kg body weight) in experimental female Albino rats.

NCTR= control group without any treatment.
INDCTR= control group treated with indomethacin only.
CLT= test groups treated with indomethacin and clotrimazole in different doses

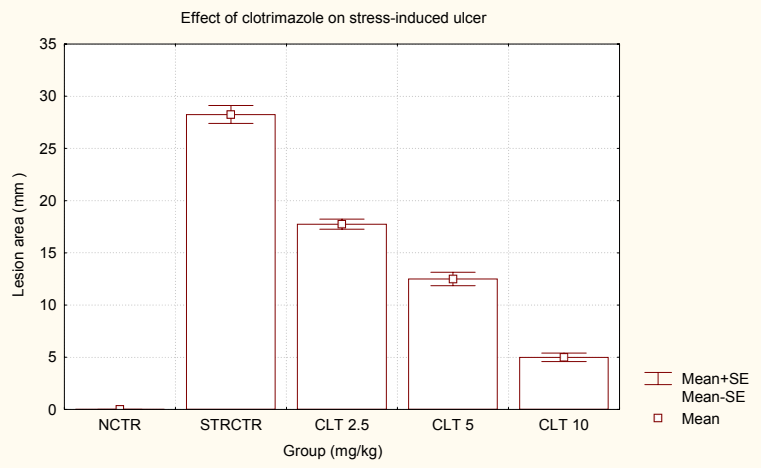

Figure3: Effect of different doses of Clotrimazole (2.5, 5 and 10 mg/kg) on stress-induced ulcer in experimental female Albino rats.

NCTR= control group without any treatment.
STRCTR= control group immersed in cold water.
CLT= test groups immersed in cold water and treated with clotrimazole in different doses

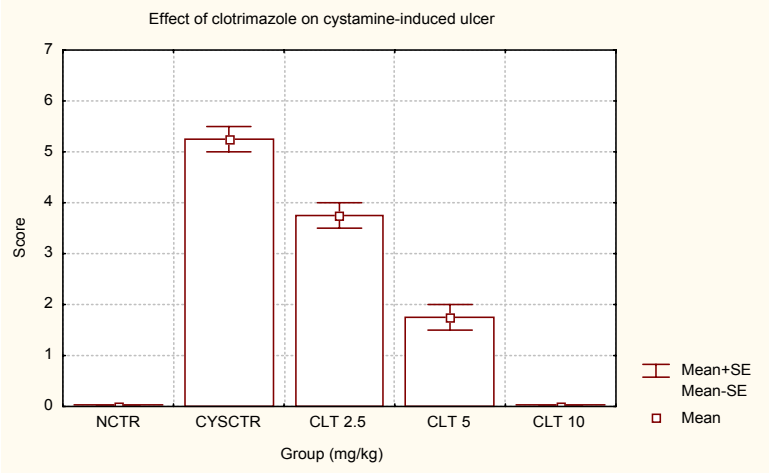

Figure4: Effect of different doses of Clotrimazole (2.5, 5 and 10 mg/kg) on cystamine-induced ulcer (400 mg/kg in 10% aqueous solution) in experimental female Albino rats.

NCTR= control group without any treatment.
CYSCTR= control group treated with cystamine only.
CLT= test groups treated with cystamine and clotrimazole in different doses

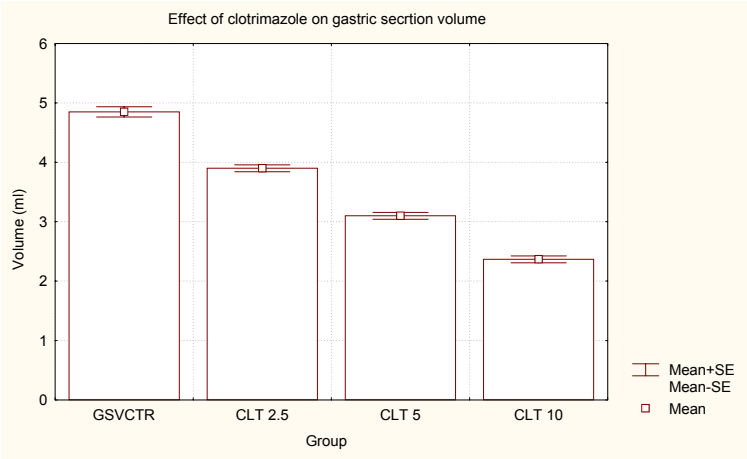

Figure 5: Effect of different doses of Clotrimazole (2.5, 5 and 10 mg/kg) on gastric acid secretion in pylorus ligated (Shay) experimental female Albino rats.

GSVCTR= control group with ligated pylorus.
CLT= test groups with ligated pylorus and treated with clotrimazole in different doses

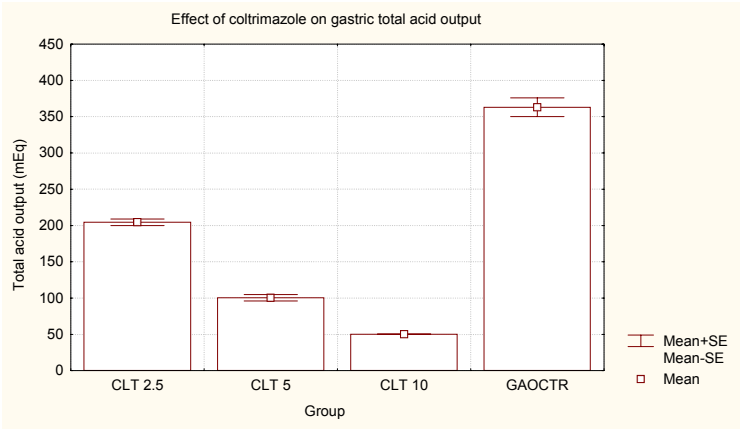

Figure 6: Effect of different doses of Clotrimazole (2.5, 5 and 10 mg/kg) on gastric total acid ouput in pylorus ligated (Shay) experimental female Albino rats.

GAOCTR= control group with ligated pylorus.
CLT= test groups with ligated pylorus and treated with clotrimazole in different doses.

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تأثير الكلوتريمازول على القرحة المعدية والأثنى عشرية

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الملخص :

تشمل الدراسة معرفة تأثير دواء من مشتقات الأميدازول (كلوتربمازول) على القرحة المعدية والاثني عشرية الناتجة عن التأثير الكيميائبي أو الضغوط النفسية وتأثيرها على افرازات المعدة لحامض الهيدروكلوريك. ولقد تم اختيار هذا المركب بناء على أن :

١) الاوميبرازول وهو من مشتقات الاميدازول كان أول دواء يرخص في السوق للاستعمال كمضاد للقرحة ويعمل على تثبيط مضخة البروتونات مباشرة.

٢) لتأثيرها على مستوى بعض المركبات مثل البروستاغلاندين والثرومبوكسان واليكوتراين.

أستحدثت القرحة المعدية عن طريق استخدام الايثانول والاندوميثاسين و عن طريق غمس الجرذان في الماء البارد (الضغط النفسي)، بينما تم استحداث القرحة الأثني عشرية عن طريق استخدام مركب السيستامين تمت.دراسة كمية إفراز الحمض المعدي بطريقة ربط الفم المعدي السفلي للجرذان المعالجة بالكلوتريمازول أو غير المعالجة(مجموعة ضابطة).

أوضحت نتائج الدراسة قدرة الكلوتريمازول على خفض مستوى الافرازات المعدية بشكل مطرد مع كمية الجرعة من الدواء (بنسبة تصل إلى ٨٠٪)، كما أن المعالجة المسبقة بالكلوتريمازول قللت من تكون القرحة المعدية الناتجة من الايثانول والاندوميثاسين والضغط النفسي (بنسبة تصل إلى ١٠٠٪)، كمااستطاع الكوتريمازول حماية الأثنى عشر من القرحة الناتجة بواسطة السيستامين.

من نتائج هذا لبحث أنه سلط الضوء على فعالية الكلوتريمازول ضد التقرحات المعدية والاثني عشرية التجريبية. والتي تحتاج إلى المزيد من البحث لدراسة إمكانية استخدامها في تجارب سريرية.