# Effect of Econazole Nitrate on Chemically- and Stress-Induced Peptic Ulcer in Rats

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## Abstract :

Econazole nitrate, 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 inhibits 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 econazole nitrate 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 econazole nitrate produces a dose-dependent inhibition of gastric acid secretion in rats. Pretreatment with econazole nitrate significantly attenuated the formation of stress-, indomethacin- and ethanol-induced gastric lesions. Econazole nitrate also protected intestinal mucosa against cysteamine-induced duodenal ulcers. In conclusion, this study demonstrated that econazole nitrate possesses significant antiulcer and cytoprotective activity against various experimentally induced gastroduodenal lesions. Although the effects of econazole nitrate 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.

## Keywords :

Econazole Nitrate, 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 radicals 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 (PGE2) and prostacyclin (PGI2) 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 decreasing HCl secretion, vasodilation and re-epithelization [10]. Several studies have shown that thromboxaneA2 (TXA2) 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], TXA2 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 agent, 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 [30]. In addition, Econazole selectively inhibits the thromboxane A2 formation and increases prostaglandin E2 level [18].

**Materials**

**Chemicals**

Indomethacins, cysteamine hydrochloride, crboxymethylcellulose, Absolute alcohol, Diethyl ether, NaOH and HCl are purchased from Sigma chemical company (USA). Econazole nitrate (Pevaryl®) is purchased from Cilag LTD company (Switzerland).

**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 Econazole nitrate were freshly prepared before administration

## Methods :

**Ethanol induced gastric ulcer:** [19]

Econazole nitrate 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 normal control group. The positive control group was treated with ethanol only. 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 *et al*. [20] using the following scale: 0= normal mucosa; 1= hyperemic mucosa or up to 3 small patches; 2= 4-10 small patches; 3= large more 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 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 except the normal control group. The positive control group was treated with indomethacin only. Econazole nitrate in different doses (2.5, 5 and 10 mg/kg) were given to all animals 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 econazole nitrate treatment in different doses (2.5, 5 and 10 mg/kg) , rats were placed in a restraint cage and immersed vertically to the level of the xiphoid process in a water bath (15C°-20C°) for 7-9 hours except the normal control group. 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 econazole nitrate administration in different doses (2.5, 5 and 10 mg/kg), the normal group was not econazole nitrate. The pylorus was ligated under light ether anesthesia, care being taken not to 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 the 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 form of 10% aqueous solution) at an interval of 4 hours according to the method described by Szabo [26]. Econazole nitrate 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 positive control group was given only cysteamine hydrochloride, while, the normal group was not given neither cysteamine hydrochloride nor econazole nitrate. 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.

**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 econazole nitrate at doses of $\geq$30 mg/kg completely prevented the formation of gastric lesions. Pretreatment of rats with econazole nitrate at the doses of 2.5, 5, 10 and 20 mg/kg produced 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 econazole nitrate at doses of 2.5 and 5 mg/kg produced statistically significant decreases in the intensity of indomethacin-induced ulcers, which was dose-dependent. Complete protection of gastric mucosa was observed in the rats treated with a dose of 10mg econazole nitrate per kg (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 econazole nitrate at doses of 2.5 and 5 mg/kg produced statistically significant decreases in the intensity of water-Immersion restraint stress induced ulcers in a dose-dependent fashion. Complete protection of gastric mucosa was observed in the rats treated with a dose of 10-mg/kg body weight (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 control rats in the cysteamine group was found to be 5.25mm² (figure 3). Pretreatment of rats with econazole nitrate produced statistically insignificant decrease at dose of 2.5 and significant decrease at dose of 5 mg/kg 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 10 mg econazole nitrate /kg body weight (figure 4).

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

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 and 5 mg of econazole nitrate /kg insignificantly reduced the gastric secretion volume, while the volume of gastric secretion in the rats treated with 10 mg econazole nitrate /kg was

statistically significantly reduced (table1). A significant total acid output, which was dose-dependent, was observed in the rats treated with 5 and 10 mg econazole nitrate /kg (table2).

## Discussion:

The results of this study indicated significantly the ability of econazole nitrate to inhibit the formation of gastric ulcer in rats induced by absolute ethanol. This inhibition was 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]. Other study showed the possible role of superoxide and hydroxyl radicals in rat gastric mucosal injury induced by ethanol [3, 45]. Therefore, it seemed likely that the gastroprotective activity of econazole nitrate 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 econazole nitrate 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]. Econazole causes an increase of $PGE_2$ production with selective inhibition of thromboxane synthesis [18, 31]. This may explain the ability of this drug to significantly inhibit the formation of gastric lesions induced by indomethacin.

Furthermore, the results revealed that pretreatment of animals with econazole nitrate 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. Stress causes an increase in superoxide dismutase activity and a decrease in peroxidase

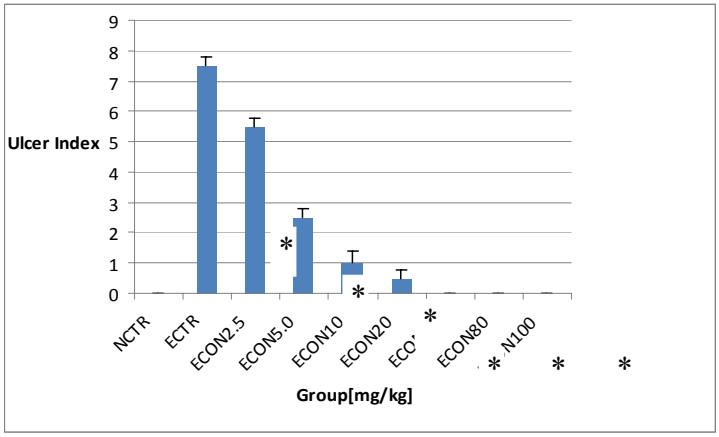
and prostaglandin synthase activity, this creates favorable conditions for accumulation of endogenous $H_2O_2$ and more reactive hydroxyl radical ($OH^-$) [39]. The ratio of prostacyclin to thromboxane $A_2$ is considered to be an important factor in the maintenance of gastric mucosal microcirculation and integrity [22]. The ability of econazole nitrate 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 econazole nitrate 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 econazole nitrate 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 econazole nitrate 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’ [5]. 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]. Econazole nitrate possibly decreases acid secretion at the last step by blocking $H^+$-$K^+$ ATPase [30].

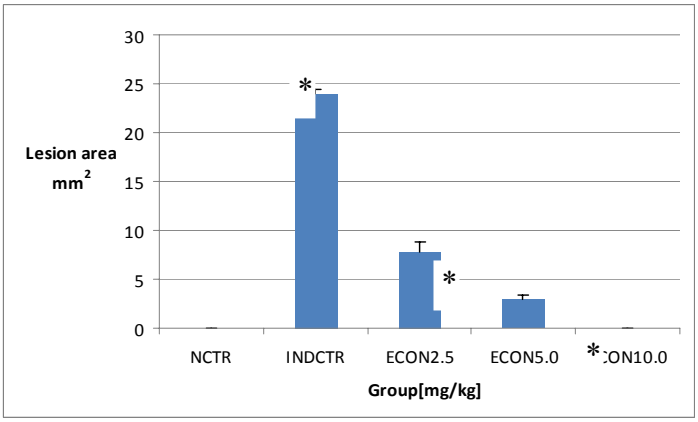
In conclusion, econazole nitrate have gastroduodenal protective activity. Further studies are suggested to shed more light on the role of econazole nitrate in the prophylaxis and/or the treatment of gastrointestinal ulcer diseases.

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



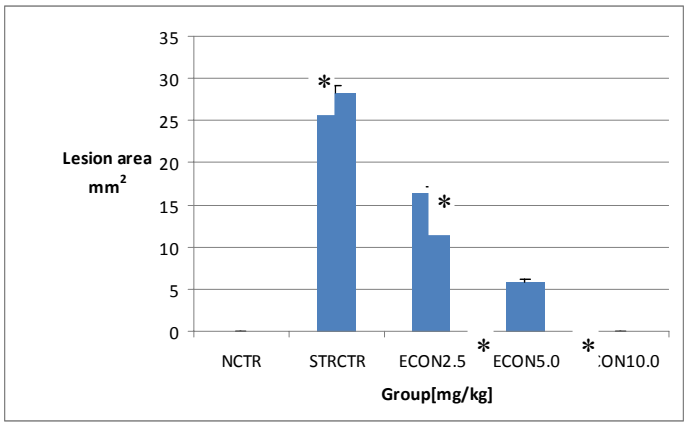

NCTR= control group without any treatment.
ECTR= control group treated with ethanol only.
ECON= test groups treated with ethanol and econazole nitrate in different doses.
* Significant P value of the mean ulcer index for each group vs. the mean ulcer index of ethanol control group using SPSS system. P value < 0.05 is Significant

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



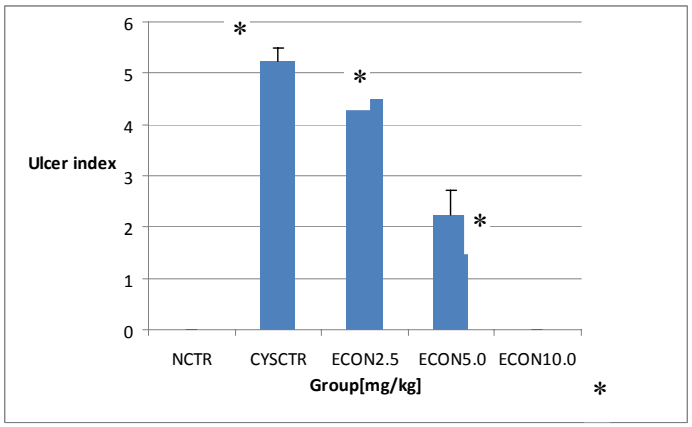

NCTR= control group without any treatment.
INDCTR= control group treated with indomethacin only.
ECON= test groups treated with indomethacin and econazole nitrate in different doses.
* Significant P value of the mean ulcer index for each group vs. the mean ulcer index of indomethacin control group using SPSS system. P value < 0.05 is significant.

Figure3: Effect of different doses of econazole nitrate (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.
ECON= test groups immersed in cold water and treated with econazole nitrate in different doses.
* Significant P value of the mean ulcer index for each group vs. the mean ulcer index of stress control group using SPSS system. P value < 0.05 is significant.

Figure4: Effect of different doses of econazole nitrate (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.
ECON= test groups treated with cystamine and econazole nitrate in different doses.
* Significant P value of the mean ulcer index for each group vs. the mean ulcer index of cysteamine control group using SPSS system. P value < 0.05 is significant.

**Table (1)**

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

| | | Gastric secretion volume (ml) | | | |
|---|---|---|---|---|---|
| **Group** | **Dose mg/kg** | **Mean** | **Standard Error Mean** | **P Value*** | **% Decrease**** |
| GSVCTR | - | 4.85 | 0.15 | 1 | - |
| Econazole nitrate | 2.5 | 4.55 | 0.1 | 0.105 | 6.19 |
| Econazole nitrate | 5 | 4.05 | 0.15 | 0.118 | 16.49 |
| Econazole nitrate | 10 | 2.7 | 0.1 | 0.03 | 44.33 |

GSVCTR= control group with ligated pylorus.

*P value of the mean gastric secretion volume for each group vs. the mean gastric secretion volume of pylorus ligated control group using SPSS system. P value < 0.05 is Significant and P value ≥ 0.05 is insignificant.

** % Decrease in mean ulcer score of drug treated animals.

**Table (2)**

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

| | | Total acid output (mEq) | | | |
|---|---|---|---|---|---|
| **Group** | **Dose mg/kg** | **Mean** | **Standard Error Mean** | **P Value*** | **% Decrease**** |
| GAOCTR | - | 363 | 13 | 1 | - |
| Econazole nitrate | 2.5 | 300.1 | 14.9 | 0.148 | 17.33 |
| Econazole nitrate | 5 | 206.7 | 11.7 | 0.048 | 43.06 |
| Econazole nitrate | 10 | 78.4 | 5.6 | 0.013 | 78.4 |

GAOCTR= control group with ligated pylorus.

* P value of the mean total acid output for each group vs. the mean total acid output of pylorus-ligated control group using SPSS system. P value < 0.05 is Significant and P value ≥0.05 is insignificant.

** % Decrease in mean ulcer score of drug treated animals.

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# تأثير نترات الايكونازول على القرحة المعدية والعفجية في الجرذان

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**الملخص :**

تشمل الدراسة معرفة تأثير دواء من مشتقات الأميدازول (نترات الايكونازول) على القرحة المعدية والعفجية الناتجة عن التأثير الكيميائبي أوالكرب 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 االموثينات والثرومبوكسان واليكوترايين.

أستحدثت القرحة المعدية عن طريق استخدام الايثانول و الاندوميثاسين و عن طريق غمس الجرذان في الماء البارد (الكرب)،بينما تم استحداث القرحة العفجية عن طريق استخدام مركب السيستامين تمت.دراسة كمية إفراز الحمض المعدي بطريقة ربط الفم المعدي السفلي للجرذان المعالجة بالكلوتريمازول أو غير المعالجة (مجموعة الضبط أو التحكم).

أوضحت نتائج الدراسة قدرة نترات الايكونازول على خفض مستوى الافرازات المعدية بشكل مطرد مع كمية الجرعة من الدواء (بنسبة تصل الى ٨٠٪ ), كما أن المعالجة المسبقة بنترات الايكونازول قللت من تكون القرحة المعدية الناتجة من الايثانول والاندوميثاسين والكرب (بنسبة تصل الى ١٠٠٪)، كمااستطاع نترات الايكونازول حماية والعفج من القرحة الناتجة بواسطة السيستامين.

من نتائج هذا البحث أنه سلط الضوء على فعالية نترات الايكونازول ضد التقرحات المعدية والعفجية التجريبية، والتي تحتاج الى المزيد من البحث لدراسة امكانية استخدامها في تجارب سريرية.