Effect of zinc sulphate on indomethacin Induced changes in gastric secretion and Ulceration in male albino rats

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ABSTRACT

In the present study the effect of zinc sulphate on indomethacin-induced changes in gastric secretion and ulceration was investigated. Fifty adult male albino rats were used in this work divided into five equal groups. The first (control) group was given intraperitoneal (i.p) distilled water. The second (indomethacin) group was given i.p indomethacin 25 mg /kg. The third, fourth and fifth groups were given i.p zinc sulphate 10, 20, and 40 mg/kg i.p twenty minutes before indomethacin administration.

Indomethacin led to a significant decrease in the volume of gastric juice and acid output with a significant increase in the acid concentration and ulcer index as compared to control group.

Pretreatment with various doses of zinc sulphate led to dose-dependant decrease in the volume, acid concentration and acid output of gastric juice as well as the ulcer index, there was dose-dependant increase in the ulcer prevention indices as compared with group of rats given indomethacin.

Indomethacin showed microscopic great destructive effect on gastric mucosa, while zinc sulphate showed dose dependent improvement in the microscopic destructive effect of indomethacin.

The anti-ulcer effect of zinc sulphate was attributed to decrease in gastric acid secretion, reduction in neutrophils infiltration with increase of mucus secretion and improvement of gastric mucosal blood flow. Zinc sulphate also show stabilizing effect on lysosomes with prevention of release of lysosomal enzymes and scavenging of oxygen-free radicals through its antioxidant effect. We can conclude that zinc sulphate has a better effect in prevention of indomethacin-induced gastric ulceration and can be used as a prophylactic remedy in patients using non-steroidal anti-inflammatory drugs.

INTRODUCTION

Zinc is one of the essential trace elements needed by the body. Zinc is a cofactor for more than 300 enzyme[(1)]. Zinc-containing enzymes are essential for growth, wound healing, reproductive function, immune system and protection against oxygen free radicals damage of cells[(2,3)].

Indomethacin has been shown to induce gastric mucosal damage and ulceration in all animal species[4]. Zinc compounds have been proposed as a new therapeutic agent for gastric ulceration[5]. Although there is evidence for the inhibitory effect of zinc on acid secretion[6,7]. The exact role of zinc sulphate on indomethacin-induced changes in gastric secretion and ulceration is not thoroughly investigated up till now. So the aim of this work is to investigate the effect of zinc sulphate on indomethacin-induced changes in gastric secretion and ulceration.

MATERIAL & METHODS

Fifty adult male albino rats have similar weights (180-200g) were used in this study. They were divided into five equal groups:

- **Group I** (control group): were given intraperitoneal (i.p) saline (2ml/rat).
- **Group II** (Indomethacin-treated group) were given i.p indomethacin (Memphis Chemical Co) in a dose of 25mg/kg[8].
- **Group III** (Indomethacin + zinc sulphate 10mg/kg): were given i.p zinc sulphate (Memphis Chemical Co) in a dose of 10mg/kg twenty minutes before indomethacin.
- **Group IV** (Indomethacin + zinc sulphate 20mg/kg): were given i.p zinc sulphate 20 mg / kg twenty minutes before indomethacin.
- **Group V** (Indomethacin + zinc sulphate 40mg/kg): were given i.p zinc sulphate 40mg/kg twenty minutes before indomethacin.

Zinc sulphate was dissolved in saline and given in the doses mentioned before.

All rats were housed in metal cages with wide meshed- floor to prevent coprophagia. All rats were deprived from food for 48 hours before the experiment while water was allowed ad libitum till one hour before the experiment when it was removed[9].

For the collection of the gastric juice, pyloric ligation was performed under light anesthesia [10] taking care not to interfere with the blood supply of the stomach[11]. Three hours after pyloric ligation, rats were sacrificed with ether over dose[12]. The stomachs were removed their contents were drained into test tubes and centrifuged. The volume of the gastric juice was measured (ml / 3 hours). The titratable acidity was determined (mEq/L)[13]. Titratable acid output was calculated (mEq /3 hours) [14].

The stomachs were opened along the greater curvature , rinsed with saline, dried and stretched as much as possible, then fixed in 10% formalin for 30 minutes. The ulcerated surface was measured by a transparent millimeter (mm) ruler and a magnifying lens, the results for each group were expressed as the ulcer index (U.I)[15]. The preventive index was calculated[16]. Sections of gastric mucosa were stained with hematoxlin and eosin (Hx & E) for histological study; others were stained with periodic acid schiff (PAS) alcian blue to show the mucus content of gastric mucosa. Statistical analysis was carried out using Students "t" test; the results were expressed as mean ± standard error of the mean. P‹ 0.05

was accepted as the level of significance.

RESULTS

As shown in the following table, indomethacin led to a significant decrease in the volume and acid output with a significant increase in the acid concentration in the gastric juice as compared to control group of rats given i.p distilled water.

Pretreatment with zinc sulphate in doses of 10, 20 and 40 mg/kg lead to significant dose-dependent decrease in the volume (2.8 ± 0.4, 2.6 ± 0.2 and 1.8 ± 0.2 ml) acid concentration (75.5±1.3, 63.3±0.8and 57.2±0.7 mEq /liter) acid output (0.213±0.002, 0.182 ± 0.002 and o.163 ± 0.002 mEq/3h) in the gastric juice as compared to group of rats given i.p indomethacin 25 mg/kg only.

As regard ulceration, indomethacin led to a significant increase in ulcer index ($p< 0.005$) as compared to control group given distilled water. Pretreatment with zinc sulphate in doses of 10 , 20 and 40 mg / kg lead to a significant dose-dependent decrease in the ulcer index as compared to group of rats given i.p indomethacin 20 mg/kg only. The preventive indices were 41%, 60% and 76% respectively.

Histological studies of sections of gastric mucosa of rats given indomethacin 25mg/kg stained with Hx&E showed shedding of all layers of gastric mucosa, sever distortion of gastric glands with sever inflammatory cells infiltration (mainly neutrophils). Edema and sever submucosal vasodilatation were also noticed. Sections of the same group stained with PAS/alcian blue showed decrease in the mucus content in the gastric epithelial cells as compared with control group of rats given distilled water.

Sections of gastric mucosa of rats given zinc sulphate in doses of 10, 20 and 40mg/kg stained with Hx & E showed does dependent improve in the gastric mucosa in the form of decrease in destruction of layers of gastric mucosa, distortion of gastric glands, neutrophils infiltration, submucosal edema and vasodilatation. Sections of gastric mucosa of the same groups stained with PAS/alcian blue showed does dependent increase in the mucus content of gastric epithelial cells as compared with group of rats given indomethacin.

Table (1): Effect of pretreatment with various doses of zinc sulphate on indomethacin-induced changes in gastric secretion and ulceration

Group (n= 10) \ Test parameter		Volume (ml)	Acid concentration (mEq/L)	Acid output (mEq/3h)	Ulcer index (mm)	Preventive index (%)
I	Control	5.3 ± 0.5	89 ± 1.8	0.483 ± 0.004	1.6±01	—
II	Indomethacin (25 mg /kg)	3.7± 0.3	98.6 ± 1..9	0.409 ± 0.004	6.6 ± 0.5	—
		P‹ 0.005	P‹ 0.005	P‹ 0.005	P‹ 0.005	
III	Indo + Zinc sulphate (10mg / kg)	2.8± 0.2	75.7 ± 1.3	0.213 ± 0.003	3.9 ± 0.2	41 %
		P‹ 0.005	P‹ 0.005	P‹ 0.005	P‹ 0.005	
IV	Indo + Zinc sulphate (20mg / kg)	2.6± 0.2	63.3±0.8	0.182 ± 0.002	2.8 ± 0.2	60 %
		P‹ 0.005	P‹ 0.005	P‹ 0.005	P‹ 0.005	
V	Indo + Zinc sulphate (40mg / kg)	1.8± 0.2	57.2±0.7	0.163 ± 0.002	1.6 ± 0.1	76 %
		P‹ 0.005	P‹ 0.005	P‹ 0.005	P‹ 0.005	

- n in-between brackets = number of animals.
- Values given are mean ± SE.
- Group II is compared to group I.
- Groups III, VI and V are compared to group II.
- P‹0.005 is significant.

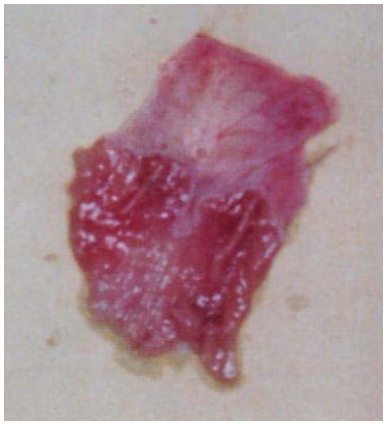

Fig (1): Photomacrograph of stomach of rat of control group shows normal gastric mucosa.

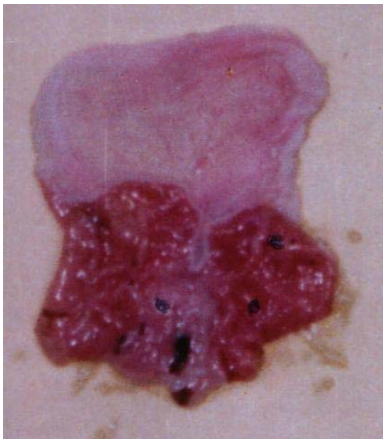

Fig (2): Photomicrograph of stomach of rat of indomethacin group shows multiple ulcers.

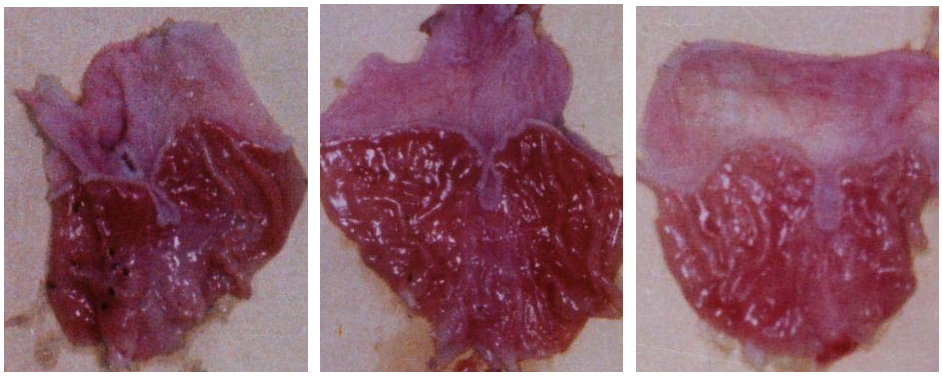

Fig. (3): Photomicrographs of stomachs of rats pretreated with zinc sulphate 10mg/kg (a), 20 mg /kg (b) and 40 mg /kg (c) show dose-dependent improvement of gastric mucosa and decrease in ulcer index

DISCUSSION

Indomethacin has been shown to cause gastrointestinal damage[17]. Indomethacin has been shown to cause gastric ulceration by several mechanisms including inhibition of prostaglandin (PGE_2 & PGI_2) synthesis[18], increase gastric acid secretion[19], increase gastric motility[20], reduction in gastric mucus secretion[21], decrease in gastric mucosal blood flow[22], increase neutrophils infiltration at the site of damage[23], reduction in nitric oxide synthesis[24], decrease of lysosomal membrane stability with release of lysosomal enzymes[25], release of oxygen free radicals with increase lipid peroxidation[26].

Zinc compounds prevent gastric ulceration in different experimental models such as pyloric occlusion, reserpin-induced ulcer, necrotizing agents-induced ulcer, platelet activating factor –induced ulcer and cold restraint –induced ulcer[27].

In the current study indomethacin led to a significant decrease in the volume of gastric juice and gastric acid output which may be due to direct inhibition of acid secreting cells[28]. Pretreatment with zinc sulphate in doses of 10, 20 and 40 mg/kg led to a dose-dependent decrease of volume of gastric juice and total acid output. These results are in agreement with *Cho et al.*[29] and may be attributed to reduction of carbonic anhydrase activity[30].

In the current study indomethacin led to marked ulceration of gastric mucosa particularly in body of the stomach. Zinc sulphate pretreatment led to a significant dose-dependent prevention in indomethacin –induced gastric ulceration. These results are in agreement with those of *Esplugues et al*[31] Joseph et al [32] and *Dillon et al*[33].

Indomethacin led to a marked submucosal vasocongestion and edema accompanied by mucosal ischemia which may be an element in the pathogenesis of ulcerogenic effect of indomethacin[34]. Zinc sulphate pretreatment led to a significant reduction in this vasocongestion and edema in a dose dependent manner with improvement of the gastric mucosal blood flow. These results are in agreement with those observed by *Cho et al*[35] and may be due to mild stimulation of prostaglandin synthesis[28].

The present study showed that indomethacin led to a significant decrease in mucus production by the gastric mucosal cells. This result is in agreement with result observed by[36] and may be due to inhibition of endogenous prostaglandins[37]. Zinc sulphate pretreatment led to a significant increase in mucus production by the gastric mucosal cells in a dose-dependent manner. This result is in agreement with the result observed by *Bandyopadhyay and Bandyopadhyay*[38] and may be due mild stimulant effect on prostaglandin synthesis[28].

Indomethacin led to marked increase in neutrophil infiltration in the gastric mucosa, this result is in agreement with the observation of[39]. This may be a result of increase in the expression of intracellular adhesion molecule I and the release of oxygen free radicals and protease[40]. This increased neutrophil infiltration may be involved in the pathogenesis of gastric mucosal injury. Zinc sulphate pretreatment led to a significant reduction of neutrophil infiltration. This result is in agreement with that of *Naito et al*[41] who attributed this to the antioxidative and anti-inflammatory properties of zinc.

Indomethacin–induced gastric mucosal injury may be due to decreased lysosomal membrane stability and release of lysosomal enzymes[28]. Zinc salts have been shown to increase lysosomal membrane stability in many experimental ulcer models which decrease the release of lysosomal enzymes[42].

As indomethacin increases release of oxygen free radicals with increase of lipid peroxidation[26], thus the protective action of zinc sulphate against indomethacin-induced gastric ulceration may be partly through its anti-oxidative effect It was found that zinc sulphate significantly reduces the superoxide radicals and inhibit lipid peroxidation in vitro and in vivo[43, 44].

It is concluded that zinc sulphate produced its anti-ulcer effect through different mechanisms including decrease in gastric secretion, reduction in neutrophil infiltration in gastric mucosa, increase in mucus secretion, improvement in gastric mucosal blood flow, stabilization of lysosomal membrane and through its anti-oxidant effect. So it is advisable to introduce zinc compounds in the remedies as a prophylactic agent used in patients with liability to gastrointestinal erosions and also as an important trace element in the treatment of patients with active peptic ulcer.

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تأثير كبريتات الزنك علىالتغيرات المحدثة بعقار الإندوميثازين فى الإفراز و التقرح المعدى فى ذكور الفئران البيضاء

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قسم الفيسيلوجى كلية طب الأزهر

يهدف هذا البحث إلى دراسة تأثير كبريتات الزنك علىالتغيرات المحدثة بعقار الإندوميثازين فى الإفراز و التقرح المعدى فى ذكور الفئران البيضاء.وقد أستخدم فى هذا البحث خمسون فأرا قسمت إلى خمس مجموعات متساوية الأولى ضابطة والثانية أعطيت اندوميثازين (25مجم/كجم) وأعطيت الثالثة والرابعة والخامسةكبريتات الزنك (١٠،٢٠،٤٠مجم/كجم) بالترتيب قبل الأندوميثازين بعشرين دقيقة.

وقد تم قياس حجم العصارة المعدية ، تركيز حمض الهيدروكاوريك ، الدفع الحامضى، معامل التقرح ومعامل الوقاية من التقرح فى كل مجموعة من المجموعات الثلاثة .

وقد أدى الحقن البريتونى لعقار الإندوميثازين إلى زيادة ذات دلالة إحصائية فى تركيز الحمض المعدى وإلى نقص ذو دلالة إحصائيةفى حجم العصارة وكذلك الدفع الحامضىبالمقارنة بالمجموعة الضابطة.

كما أدى الحقن البريتونى لعقار الإندوميثازين إلى إحداث العديد من القرح فى الغشاء المخاطى المبطن لجدار المعدة .

وقد أدى الحقن البريتونى المسبق لكبريتات الزنك إلى نقص مطرد ذو دلالة إحصائيةفى حجم العصارة و تركيز الحمض المعدى و كذلك الدفع الحامضىبالمقارنة بالمجموعة التى أعطيت الإندوميثازين فقط كذلك أدى الحقن البريتونى المسبق لكبريتات الزنك إلى نقص مطرد ذو دلالة إحصائية فى معدل التقرح فى الغشاء المخاطى وكذلك حماية هذا الغشاء من التاثير التقريحى للإندوميثازين ، وكان معدل الحماية هو ٤٠ ٪ ، ٦٠ ٪ ، ٧٦ ٪ للجرعات ٤٠، 20، ١٠مجم /كجم على التوالى.

وقد أوضح الفحص المجهرى لجدار المعدة التأثير التدميرى للإندوميثازين على أنسجة جدار المعدة وكذلك أوضح هذا الفحص المجهرى لجدار المعدة التأثيرالتحسينى المطرد لكبريتات الزنك على أنسجة جدار المعدة.

من هذه الدراسة يتضح أن كبريتات الزنك تحمى المعدة من التأثير التقريحى للإندوميثازين وبالتالى ننصح بإضافة عنصر الزنك ألى الأدوية التى تسبب قرحة المعدة وكذلك أعطاؤة لمرضى قرحة المعدة للمساعدة فى إلتئام هذه القرح .