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EFFECT OF LANSOPRAZOLE ON GASTRIC SECRETION, PROSTAGLANDIN E_2 AND PLASMA GASTRIN IN INDOMETHACIN-INDUCED ULCER IN RATS

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ABSTRACT

The effect of lansoprazole (lansoprazole) (40, 80 mg/kg) daily orally for three weeks on gastric luminal release of prostaglandin E_2 (PGE_2), pH, sodium and potassium ion contents of gastric juice, as well as plasma gastrin level was investigated on indomethacin-induced ulcer in rats. Daily administration of lansoprazole (40 or 80 mg/kg) significantly elevated the intragastric pH and K^+ ion concentration after one, two and three weeks. Sodium ion concentration was only elevated by lansoprazole 80 mg/kg after the same time intervals. Plasma gastrin level was significantly elevated by lansoprazole in a dose dependent manner. On the other hand, lansoprazole in either doses failed to elevate the reduced level of PGE_2 in the gastric lumin induced by indomethacin. In conclusion, lansoprazole caused elevation in intragastric pH value, Na^+ and K^+ ions concentration, it also raised plasma gastrin level in a dose dependent manner, these effects would be related to inhibition of acid secretion. On the other hand lansoprazole failed to elevate the gastric luminal PGE_2 level indicating that it has no cytoprotective effect.

INTRODUCTION

Lansoprazole is a second generation of proton pump inhibitors. Also omeprazole (omep.) is the first drug belonging to this new class. Both lansoprazole and omeprazole are substituted benzimidazole able to inhibit H^+, K^+-ATPase present in the membrane of the parietal cells which is responsible for the last step in the production of acid[1,2]. Since omeprazole and lansoprazole are reversible inhibitors of H^+, K^+-ATPase, the proton pump is inhibited until new enzyme can be synthesized and transported to the canaliculi[3]. For these reasons omeprazole and lansoprazole may present useful alternative acid-suppressants for treatment of ulcer.

Gastrin acts as a physiological stimulant of both gastric acid secretion and gastric mucosal growth and mediates the gastric mucosal proliferation that occurs in response to feeding and an increase in gastric pH [4].It is well known that a low pH in the antrum inhibits the release of gastrin from the G-cells[5].

Stimulation of the release of gastrin occurs when interfering with gastric acid secretion by the use of powerful antisecretagogues[6]. Gastrin then passes into the circulation to the oxyntic mucosa where it stimulates proliferation of the oxyntic mucosal cells[7]. The inhibition of gastric H^+, K^+-ATPase activity by omeprazole in rats is paralleled by an increase in intragastric pH which leads to hypergastrinaemia by stimulating gastrin synthesis and release in the antrum[4].

Postaglandins mainly prostaglandin E_2, are produced by the gastric mucosa. They stimulate mucus, bicarbonate secretion and gastric mucosal blood flow and inhibit acid secretion and hence act as cytoprotectives[8].

The purpose of this study is to investigate effects of lansoprazole on the gastric secretion with special emphasis on the changes in the intragastric pH, Na^+, and K^+ ions concentration as well as plasma gastrin level. The study also extended to evaluate the action of lansoprazole on gastroluminal PGE_2 in indomethacin-induced ulcer in rats in order to investigate any cytoprotective effect of this drug.

MATERIALS AND METHODS

Rats of either sex weighing about 200 g each, were used in the present investigation. They were divided into eight groups each of eight rats. The first group was maintained on regular diet and fasted for 24 hrs. prior to each study and used as general control.

Indomethacin-induced ulcer was performed in the other groups[9]. Indomethacin (25 mg/kg) was given s.c. to rats fasted for 24 hrs. Some animals were killed 7 hrs later and the stomachs were examined to ensure the occurance of ulcer. Rats in which ulcer was induced were divided into **seven groups**:

The first group was used as ulcer control. Rats of the other groups received oral lansoprazole 40 or 80 mg/kg (suspended in polyethylene glycol) daily for 3 weeks. Twenty four hours after the 7th, 14th & 21st days the oesophagi and pylori were ligated and the stomachs removed, and the gastric contents stored for determination of pH, Na^+ and K^+ ions level in two groups of the ulcer rats. The pH of the gastric contents was measured by pH meter microprobe (model MI 506).

Sodium and potassium ions concentration in the gastric contents were determined using specific kits. Two separate groups, receiving lansoprazole 40-80

mg/kg in the same manner, were used to estimate plasma gastrin level by radioimmunoassay method[10]. Two other groups, treated by lansoprazole in the same way, were used to measure the gastroluminal PGE_2 using radioimmunoassay technique[11].

Statistical analysis:

The data were presented as means ± SE. Differences between effects were considered to be significant at $P<0.05$. Test of significance was carried out according to Student's "t" test [12].

RESULTS

1- Effect of lansoprazole on intragastric pH:

The mean intragastric pH value of indomethacin -induced ulcer rats in the present work was about 1.8 ± 0.12 and this value remained for 3 weeks. Lansoprazole 40 or 80 mg/kg daily significantly elevated the pH value when compared with control, Table (1).

Table (1): Effect of lansoprazole on intragastic pH in rats (Mean±S.E).

Treatment	Intragastric pH after		
	1st week	2nd week	3rd week
Ulcer control	1.9±0.13	2.1±0.16	2.4±0.21
Lansoprazole (40mg/kg)	3.4±0.42*	5.3±0.38*	4.8±0.24*
Lansoprazole (80mg/kg)	4.3±0.41*	4.8±0.35*	5.6±0.52*

* Significantly different from ulcer control at $P<0.05$

2- Effect of lansoprazole on intragastric sodium and potassium ions concentrations:

The mean value of Na^+ and K^+ ions in ulcer control group was (72.35±2.51) and (4.7±0.11) mEq./l respectively. Lansoprazole (40 mg/kg) did not affect the intragastric content of Na^+ ions after the first, second and third weeks, while lansoprazole (80 mg/kg) daily significantly increased Na^+ ion level after the above mentioned intervals. The greatest increase was observed after the third week from (71.4±4.14) to (132.3±5.76) mEq/l, Fig. (1).

The intragastric concentration of K^+ ion was significantly raised after daily administration of lansoprazole (40 or 80 mg/kg) in a dose dependent way when compared with the ulcer control value. Potassium ion concentration was elevated from (4.3±0.11) to (25.22±1.3) after the first week, from (4.8± 0.13) to (60.3±1.7) after the second week and from (5.2±0.04) to (50.8±2.1) mEq/l after the third week following administration of lansoprazsole 40 mg/kg.

Lansoprazole 80 mg/kg significantly elevated the intragastric K^+ ion concentration about 10 fold. The highest elevation was observed after the third week (from 5.2 ± 0.04 to 54.4 ± 1.5 mEq/l) Fig. (2).

3- Effect of lansoprazole on plasma gastrin level:

The mean plasma gastrin level in ulcer control rats was about (225±20.3) pg/ml. Lansoprazole 40 mg/kg significantly elevated plasma gastrin level from (198.5±15.3) to (460±23.7) pg/ml after the first week, from (226±18.7) to (780±33.4) pg/ml and from (250±22.5) to (960±40.1) pg/ml after the second and third weeks respectively.

The elevation in plasma gastrin level caused by lansoprazole (80 mg/kg) was higher than that induced by lansoprazole (40 mg/kg). The maximal level was reached after the third week (1260±70.4) pg/ml Fig (3).

4- Effect of lansoprazole on gastroluminal PGE_2 level:

The mean level of gastroluminal PGE_2 in ulcer control rats was about (0.34 ± 0.01) ng/ml which is significantly lower than the normal level. No significant change was induced by daily administration of lansoprazole (40 or 80 mg/kg) after one, two and three weeks, Table (2).

Table (2): Effect of lansoprazole on gastroluminal PGE_2 (ng/ml) (Mean±S.E).

Treatment	Gastroluminal PGE_2 (ng/ml) after		
	1st week	2nd week	3rd week
Ulcer control	0.38±0.01	0.36±0.02	0.34±0.01
Lansoprazole (40mg/kg)	0.42±0.02	0.33±0.01	0.40±0.03
Lansoprazole (80mg/kg)	0.35±0.01	0.41±0.02	0.37±0.03

* Significantly different from ulcer control at $P<0.05$

DISCUSSION

The present study revealed that lansoprazole (40 or 80 mg/kg) caused a significant dose dependent elevation in the gastric luminal pH value and plasma gastrin level. These results agree with those obtained by Carlsson et al[13] who reported that the elimination of the inhibitory feedback effect of acid on gastrin secretion leads to hypergastrinaemia.

The above authors reported species difference between rat and man, since gastrin secretion was higher in rat than man. Large doses of inhibitors of gastric acid secretion such as omeprazole or ranitidine may cause sustained hypergastrinaemia[14]. The amount of gastrin in stomach was doublled following 28 days of treatment with omeprazole in rats[15]. A relatively high dose of i.v. omeprazole is required to keep the gastric pH above 4 over 24 hr period[16].

There is a relation between the increase in gastrin level and the pronounced reduction of the intragastric

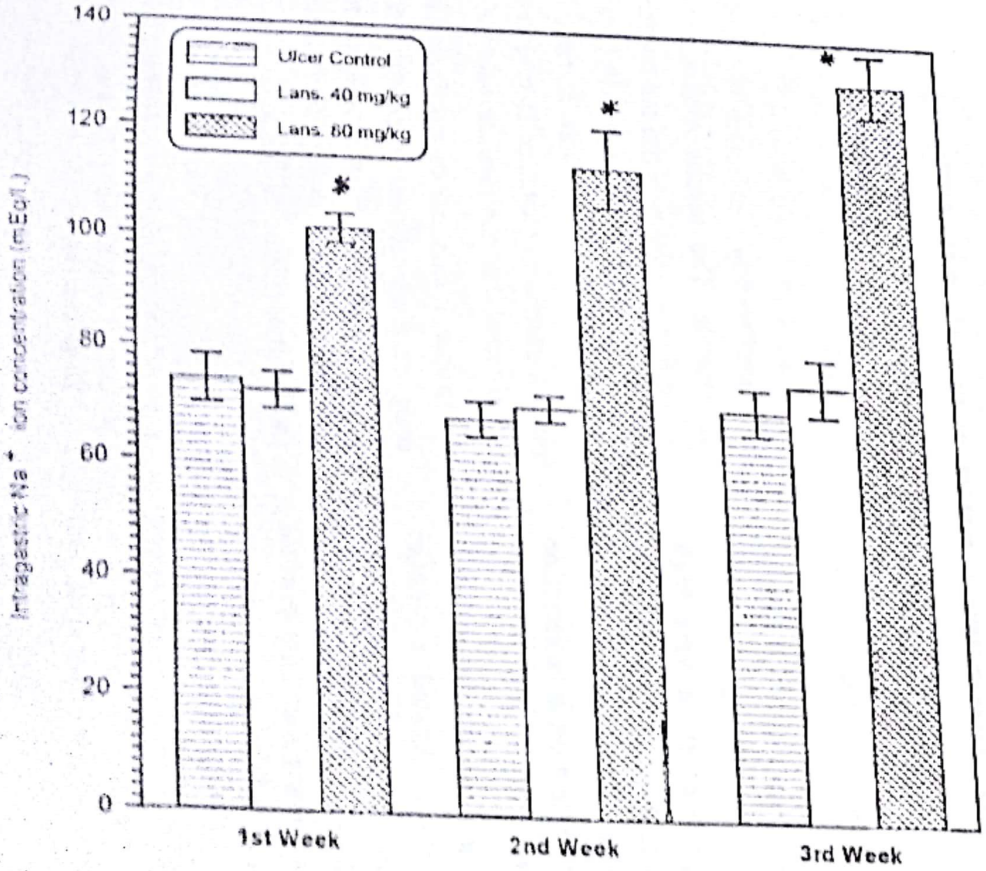

Fig. (1) Effect of lansoprazole on the intragastric Na^+ ion concentration (mEq/l)in rats.

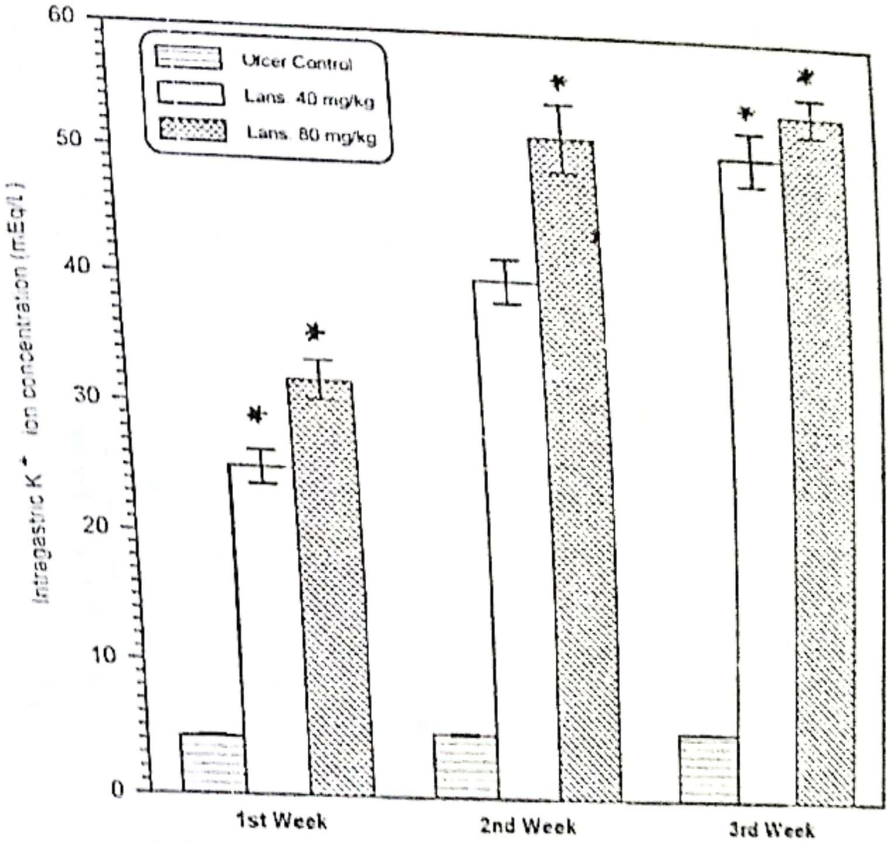

Fig. (2) Effect of lansoprazole on the intragastric K^+ ion concentration (mEq/l) in rats.

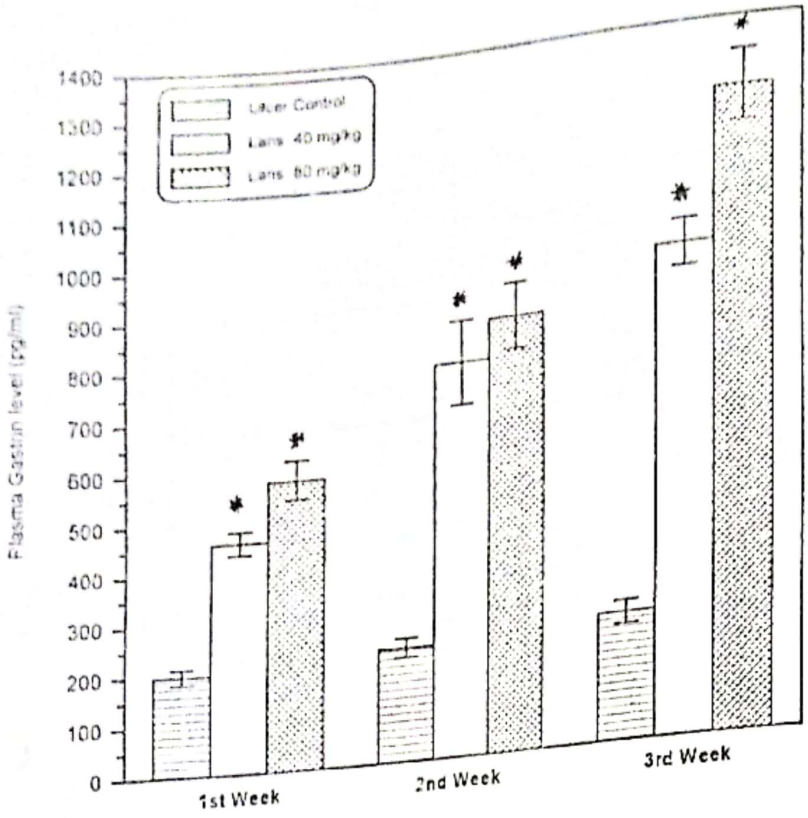

Fig. (3) Effect of lansoprazoleon plasma gastrin level (pg/ml) in rats.

acidity and elimination of acid inhibition of gastrin release from the antrum. The effect of omeprazole on gastrin secretion is dose dependent since very high doses of omeprazole lead to a reversible hypergastrinaemia while moderate daily dose which also has a significant inhibitory effect on acid secretion does not significantly influence gastrin levels [17].

The present study showed a significant elevation in intragastric K^+ ion concentration induced by either doses of lansoprazole. Sodium ion concentration was only increased by lansoprazole 80 mg/kg after the first, second and third weeks. This means that lansoprazole increases intragastric Na^+ and K^+ ion concentration which may be secondary to inhibition of acid secretion due to inhibition of H^+, K^+-ATPase or it may be related to continued activity within the parietal cells such as active transfer of other ions beside hydrogen and potassium [18].

We found that the gastric luminal PGE_2 level was not significantly affected by either doses of lansoprazole. The results obtained by Goto et al[19] proved that, omeprazole did not improve the decrease in mucosal PGs produced by water immersion stress-induced gastric ulcer in rats. In vitro study on rabbits gastric mucosal cells revealed that omeprazole did not modulate the media content of PGE_2[20].

In conclusion, lansoprazole is considered a useful drug for the treatment of peptic ulcer since it elevates the gastroluminal pH and rises plasma gastrin level, but it has no cytoprotective effect since it did not change the luminal release of PGE_2

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تأثير اللانسوبرازول على الإفراز المعدى والبروستاجلاندين E_2 والجاسترين فى البلازما فى الفئران المصابة بالقرحة باستخدام الإندومثاسين.

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يشمل هذا البحث دراسة تأثير عقار اللانسوبرازول (٤٠ , ٨٠ مجم/كجم) يوميا ولمدة ٣ أسابيع على البروستاجلاندين E_2 والأس الهيدروجينى ومحتوى العصارة المعدية من أيونات الصوديوم والبوتاسيوم .كما تم تعيين نسبة هرمون الجاسترين فى بلازما الدم لدى الفئران المصابة بقرحة المعدة الناتج عن عقار الأندوميثاسين. أثبتت التجارب فى هذا البحث أن اللانسوبرازول بجرعتيه المستخدمة يرفع مستوى الأس الهيدروجينى وأيون البوتاسيوم فى العصارة المعدية بعد أسبوع وأسبوعين وثلاثة أسابيع بدرجة ملحوظة بينما لم يحدث ارتفاعا واضحا فى نسبة أيون الصوديوم فى العصارة إلا بالجرعة ٨٠ مجم/كجم بعد نفس الفترات الزمنية السابقة. ارتفعت نسبة هرمون الجاسترين ارتفاعا واضحا معتمدا على الجرعة بينما فشل اللانسوبرازول بجرعتيه فى رفع المستوى المنخفض للبروستاجلاندين E_2 فى عصارة المعدة والناتج عن القرحة المستحدثة فى الفئران. نستنتج من هذا البحث أن عقار اللانسوبرازول يمكن الاعتماد عليه كعلاج قرحة المعدة لما له من تنأثير رافع للأس الهيدروجينى ونسبة هرمون الجاسترين فى بلازما الدم ولكن فشله فى رفع نسبة البروستاجلاندين E_2 ينفى انتماءه للأدوية الحامية لجدار المعدة.

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