Ranitidine reversed the hyperaemic response in the stomach of rats exposed to immobilization stress

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Abstract

The immobilization stress has been recently recognized to produce marked increase of gastric acid secretion and cause hyperaemia in the stomach . Since ranitidine reduced corpus mucosal blood flow in the stomach to basal levels, it may cause suppression of hyperaemia induced by immobilization stress. In this study, ٥ groups of ٥ rats each were used. The extent of hyperaemia in the glandular mucosa of the stomach of control rats (pretreated with saline) exposed to stress was compared with ranitidine treatment ٣٠ minutes before onset of stress. Gastric hyperaemia elicited in the control rats, while treatment with ranitidine (٢٠ and ٤٠ mg/kg i.m.) ٣٠ minutes before onset of stress, caused a dose – dependent reduction in the gastric hyperaemia response to stress. Furthermore, pretreatment with ranitidine in different doses did not suppress the increase in alanine amino transferase (ALT) activity induced by stress as well as there was no significant difference between plasma cholesterol level in all investigated groups. In conclusion, the present study demonstrates that gastric damage produced by immobilization stress can be protected by ranitidine.

الخلاصـــة

عرف حديثا إن الكرب المقيد للحركة يحدث زيادة واضحة في افراز الحمض المعدي ويسبب الاحتقان الدموي في المعدة . وبما أن عقار الرانتدين يثبط الإمداد الدموي الى الغشاء المخاطي لجسم المعدة الى أدنى مستوى فمن المحتمل أن يسبب منع الاحتقان الدموي المعدي المحدث بواسطة الكرب.في هذه الدراسة استعملت ٥ مجاميع من ٥ جرذان لكل مجموعة. أن امتداد الاحتقان الدموي في المخاطية الغدية لمعدة جرذان السيطرة (المعالجة مسبقا بمحلول الملح الفسلجي) والمعرضة للكرب تم مقارنتها مع المعالجة بالرانتدين قبل٣٠ دقيقة من التعرض للكرب.لوحظ حدوث الاحتقان الدموي المعدي في جرذان السيطرة بينما ادى العلاج بالرانتدين وبجرعة (٢٠ و٤٠ ملغم / كغم من وزن الجسم وعن طريق الحقن بالعضل) قبل٣٠ دقيقة من التعرض للكرب وبشكل يعتمد على الجرعة الى تقليل الاحتقان الدموي المعدي استجابة للكرب . اضافة الى ذلك فان العلاج المسبق بالرانتدين لم يكبح من الزيادة العالية لنشاط خميرة الالنين امينو ترانسفيريز المحدثة بواسطة الكرب ولم تظهر جميع المجاميع المعاملة اختلافات معنوية في تراكيز الكولسترول في البلازما. نستنتج من الدراسة الحالية أمكانية الوقاية من الأذى المعدي المحدث بواسطة الكرب المقيد للحركة بواسطة الرانتدين.

Introduction

Ranitidine is H٢ receptor antagonist competitively inhibit the interaction of histamine with H٢ receptors, lead to inhibit acid secretion in a dose-dependent competitive manner and the degree of inhibition parallels the concentration of the drug in plasma over a wide range[١-٣]. The benefit of ranitidine is reduction of corpus mucosal blood flow in the stomach to basal levels[٤] and to control gastric acid secretion [٥,٦]. Ranitidine is ٥-١٢ times more potent as an inhibitor of gastric acid secretion than cimetidine[١]. It is rapidly absorbed following intramuscular injection, with peak plasma concentration occurring in about ١٥ minutes, and a bioavailability of ٩٠-١٠٠% compared with intravenous injection. It is weakly bound about ١٥% to plasma proteins and its elimination half life about ٢-٣ hours[١,٧,٨].

Immobilization stress belongs to severe stressors[٩] . Rats are a useful model of stress since it induces activation of the hypothalamopituitary-adrenocortical axis[١٠]. Immobilization stress-induced gastric damage is supported by considerable evidence [١١,١٢].

With recent finding of Takeuchi et al[١٣], the stress produced a marked increase of acid secretion and caused gastric hyperaemia .Thus, this study was designed to investigate the protective activity of H_2 blockers (Ranitidine) against stress-induced gastric hyperaemia .

Materials and methods

Male albino rats ١٨٠-٢٦٠ g weight were used. They were housed under standard condition, with ١٠/١٤-h light/dark cycle and ٢٠ °C room temperature, food and water were available.

Twenty five rats were randomly divided into five groups of ٥ rats each. Group ١,٢ were served as controls pretreated with normal saline ٣٠ minutes before the onset of stress .Rats in the groups ٣,٤,٥ were pretreated with ranitidine ١٠,٢٠,٤٠ mg/kg i.m (Kee Pharma Ltd, New Delhi, India) respectively (٢ml/kg) ٣٠ minutes before the onset of stress . The adequacy of the dose level/regimen has been established by the results of preliminary experiments. Group ١ does not exposed to the stress (unstressed animals). The animals in the groups ٢,٣,٤,٥ only were restrained by securing them on their back to a board with the use of adhesive tape for ٣-hr .

At the end of ٣-hr stress, heparinized blood was obtained from the orbital plexus. Plasma alanine amino transferase (ALT) and cholesterol level were determined spectrophotometerically (Cecil, U.K.) using commercially available kits (Syrbo-France). Then the rats were killed by cervical dislocation, and the stomachs were removed, inflated by injecting ١٠ ml of ١% formalin for ١٠ minutes to fix the tissue walls and opened along the greater curvature. The stomach was photographed. The area of hemorrhagic damage was quantified by computerized photoimpact [١٤] .The lesion were acute gastric hemorrhage they are commonly referred to as "stress ulcers" [١٥].

Data were presented as the mean ± S.E. from ٥ rats per group. One-way analysis of variance following least significant difference test were used (١٦) at $p < ٠.٠٥$.

Results

The immobilization stress procedure produced typical hyperaemia in the glandular mucosa of stomach in the control group ٢ pretreated with saline (٢ml/kg i.m.) for ٣٠ minutes before onset of stress (Figure١).

The groups of animals pretreated with ranitidine (٢٠ and ٤٠ mg/kg i.m.) for ٣٠ minutes before onset of stress, caused a dose – dependent reduction in the gastric hyperaemia compared with the control group ٢ (Figure ٢). In contrast, rats pretreated with ranitidine ١٠ mg/kg did not show reduction of hyperaemic area of the stomach compared with ranitidine (٢٠ and ٤٠ mg/kg), while

the gastric hyperaemia did not differ from that in control group ٢ .

ALT activity showed significant ($p< ٠.٠٥$) elevation pretreated with saline or ranitidine in the groups (٢,٣,٤,٥) when compared with the saline – treated animals (unstressed) in the group ١ (Table ١). Plasma cholesterol concentrations were not differ in rats in the group ٢,٣,٤,٥ respectively when compared with saline – treated rats (unstressed) in group ١ (Table ١) .

Table (١): *Effect of pretreatment with ranitidine on plasma cholesterol and alanine amino transferase level in rats subjected to ٣–hr immobilization stress.*

Ranitidine (mg/kg, i.m,) Group	Cholesterol (mg/١٠٠ml)	ALT activities (IU/l)
١- ٠ (absolute control)	٧٨.١±١.٣	٣٢.٧±١٢.٨
٢- ٠ (control)	٧٨.٣±٢.٥	٤٥.٣±١٣.٠*
٣- ١٠	٧٨.٣±١.٥	٤٥.٥±١١.٦*
٤- ٢٠	٧٨.٢±١.٩	٤٤.٩±١٧.١*
٥- ٤٠	٧٧.٩±١.٣	٤٤.٨٥±١٤.٢*

Data are presented as the means ±S.E of ٥ rats/ group. Saline (٢ml/kg i.m.) or Ranitidine (١٠, ٢٠, ٤٠ mg/kg i.m.) was given ٣٠ minutes before the onset of ٣-hr stress, blood samples were obtained immediately after the end of stress.

*Significantly different from the respective absolute control value (١), at $P< ٠.٠٥$.

Note: Animals in the group(١) did not exposed to immobilization stress (absolute control)

Discussion

Ranitidine is H٢ receptor antagonists, which lead s to inhibit acid secretion[١,٢,٣], and reduce corpus mucosal blood flow in the stomach to basal levels[٤]. The role of endogenous corticosterone in stress – induced gastric damage has been debated . Weisis , Murphy et al [١٧,١٨] found that the degree of ulceration after stress were correlated positively with the level of plasma corticosterone . Furthermore, Al – Mohaisen et al , Retana et al [١٩,٢٠] found that plasma corticosterone increased ٣-٤ fold after single acutely immobilization stress . These studies suggested that immobilization stress influenced the hypothalamic- pituitary-adrenal axis in rats by elevating the level of plasma corticosterone . Thus, on the basis of these studies, corticosterone increases during immobilization stress. In addition, gastric damage produced by immobilization stress was mainly attributable to the elevating of plasma corticosterone leading to suppression of gastric cytoprotective properties prostaglandin biosynthesis [٢١,٢٢,٢٣] . Since prostaglandins synthesized in the

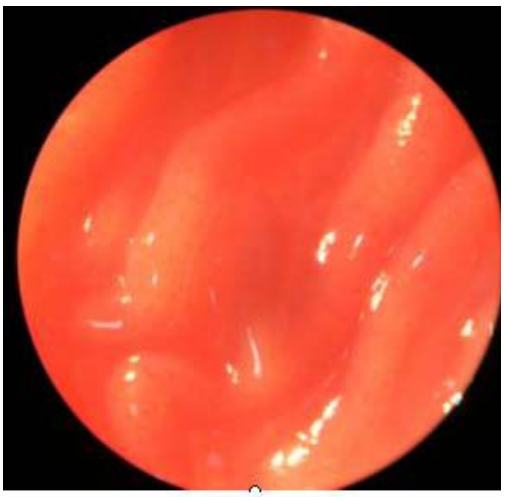
mucosa, stimulate mucus and bicarbonate secretion, decrease acid secretion [٢٤,٢٥,٢٦]

This experiment clearly indicated that pretreatment with ranitidine before onset of stress, can provide substantial

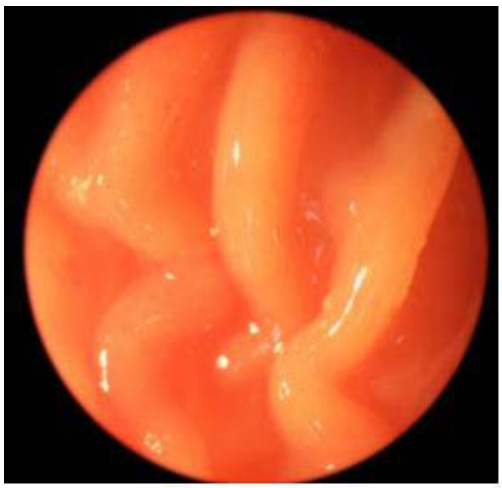
Gastro-protection, and the extent of hyperaemia in the corpus region of the stomach were reduced in a dose – dependent way. These results were consistent with the finding of Pique et al[٤] which is related with reduced corpus mucosal blood flow in the stomach to basal levels that lead to suppression hyperaemic response to stress . In addition to that, Hardman, et al[٣] found that H_2 blockers inhibit gastric acid secretion in a dose-dependent manner; with a degree of inhibition parallels to plasma concentrations of the drug .

In the present study, pretreatment with ranitidine (٤٠ mg/kg) was effective in reducing the gastric hyperaemia .This result was consistent with finding of Nissen[٨] that serum concentration necessary to inhibit ٥٠% of stimulated gastric acid secretion are estimated to be ١٠٨٠-٢٨٢٠ ng/ml following single (٣٠mg/kg i.m.) doses serum concentration of ranitidine hydrochloride are in this range for ٦-٨ hours .

In the present experiments, ranitidine in different doses did not suppress a stress-induced increase in ALT activity .Thus, this results consistent with Fernández, et al and Senba et al[٢٧,٢٨] who reported that immobilization stress in mice increased plasma ALT activity, a marker of liver damage caused by C-Fos protein accumulation in the liver .



(Figure ١): *The immobilization stress produced typical hyperaemia in the glandular*



(Figure ٢): *Pretreated with Ranitidine (٤٠ mg/kg i.m.) for ٣٠ minutes before onset of stress,*

change in response to immobilization stress .

In present study, plasma cholesterol concentrations were not affected in stress rats pretreated with saline or ranitidine when compared to the saline – treated animals (unstressed). This is consistent with Hershock et al[٢٩] who found that cholesterol level did not

In conclusion, ranitidine is capable of reducing the severity of immobilization stress – induced gastric hyperaemia . These beneficial effects of ranitidine are attributable to its inhibitory effects on

acid secretion and decreased corpus mucosal blood flow in the stomach to basal level during stress.

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