COMPARATIVE STUDY OF VERAPAMIL, ISRADIPINE AND CIMETIDINE ON THE GASTRIC CHANGES INDUCED BY STRESS OR INDOMETHACIN

By

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ABSTRACT

The influence of the calcuim channel blockers verapamil and isradipine on gastric ulceration and glandular wall mast cell count in rats was investigated and compared with that of cimetidine (H_2 antagonist). Two different models for induction of experimental gastric ulcer were performed; cold restraint stress ulcer and indomethacin-induced gastric ulcer. Restraint at 4°c for 1 h or single bolus dose of indomethacin 30 mg/kg p.o, producod a marked gastric mucosal ulceration in saline pretreated controls. The pretreatment with single I.P injection of either cimetidine (100 mg/kg), verapamil (4 mg/kg) or isradipine (0.5 mg/kg) 30 minutes before cold restraint or indomethacin administration produced a significant reduction in mean gastric ulcer severity score and reduced incidence of ulceration in both macroscopic and microscopic examinations of stomachs of different groups. Both verapamil & isradipine are more or less equally effective in reducing gastric damage produced by either stress or indomethacin, however, cimetidine produced significant greater protective action.

Cold restraint produced a marked decrease in mucosal mast cell count. This degranulating action of stress was prevented with verapamil or isradipine but cimetidine did not produce any significant effect. It is

possible that decreased amine release (Histamine & 5 HT.) from mast cell may be responsible for the antiulcer effect of Ca channel blockers, since mast cell degranulation seems to play an important role in pathogenesis of stress gastric ulcers. Other suggested anti-ulcer mechanisms of Ca^{++} channel blockers are discussed in the light of the available literature, including decreased stomach wall motility, reduced gastric acidity, peripheral & central interference with vagal overactivity, stimulation of gastric PG, synthesis and/or antioxidant action that counteract stimulation of gastric lipid peroxidation produced by stress or indomethacin.

This study proved the potential value of Ca" channel blockers in the management of two different models of experimental gastric ulcers, however, a controlled clinical study is needed before any attempt to extrapolate ulcer therapy in rats to ulcer therapy in man.

INTRODUCTION

A preliminary report of the effects of the calcium channel blocker verapamil (a phenylakylamine derivative) on stress induced gastric ulcer in rats was presented at the 3rd South-East Asian/ Western Pacific Regional Meeting of Pharmacologists in Thailand (Ogle & Tong, 1982). This was later confirmed by (Ogle et al 1985 & 1990). Furthermore, Karim et al (1990) reported that verapamil and cimetidine (a potent H2 receptor antagonist) are equally effective in reducing gastric mucosal ulcerations in response to stress in rats.

The aim of the present study is to investigate whether the antiulcer effect of verapamil is only specific to stress, and the possibility that this protective effect might be shared by other Ca^{++} channel blockers. Therefore, verapamil was tested in two different models of experimental gastric ulcer namely cold restraint stress and indomethacin induced gastric ulcers in rats. Another Ca^{++} channel blocker of different chemical group (a dihydro-pyridine derivative) namely isradipine was similarly tested. At the same time cimetidine was used as a standard drug that

could affect different models of experimentaly induced gastric ulcers (Brunton, 1990).

MATERIAL AND METHODS

Seventy two male albino rats weighing 150-180 gm each were housed under similar conditions and fed similar diet. Rats were randomly divided into nine equal groups, they were fasted for 48 hrs prior to the experiments, but were allowed free access to water one group left as a control non stressed and non treated, received oral and I.P injection of saline 2 ml/kg.

Induction of experimental gastric ulcer was done in the other eight groups; two ulcer models were designed :

A- Cold-restraint Model (Senary & levine, 1967):

Rats to be stressed were put into individual close-fitting tubular restraint cage of wire mesh and exposed to a temperature of 4ºc for one hour. They were pretreated 30 minutes before stress by a single I. P. injection of either saline 2 ml/kg, cimetidine

(Tagamet ampoule, S.K.F.) 100 mg/kg (Karim et al.,l990)., or isradipine powder dissolved in saline (Sandoz) 0.5 mg/kg (Souter et al., 1989). verapamil powder dissolved in saline (Knoll) 4 mg/kg (Ogle et al., 1985). All animals were sacrificed by decapitation after one hour of stress and the stomach were gently dissected out for gross and histological examinations of mucosal lesions and mast cell counting.

B- Indomethacin Model, (Cho et al.,1985) :

Indomethacin (Indocid, Merck) 30 mg/kg was given orally as a single bolus (cho et al, 1985) to 4 groups of rats, which were pretreated by single I.P. injection of either saline, cimetidine, verapamil or isradipine 30 minutes before administration of indomethacin in the same doses mentioned above. Five hours later animals were sacrificed by decapitation and the stomach was removed for macroscopic and microscopic examination of mucosal lesions and for mast cell counting.

Histopathological Examination :

Stamach were opened along the

greater curvature, washed with saline and pined out flat for gross naked eye examination. The number and severity of discrete areas of damage in gastric mucosa were scored according to the system suggested by (Guth & Hall., 1965), where the severity of the lesions was assessed on a score scale of 1 to 5. The total ulcer score of each group of animals similarly treated was counted and the mean was calculated. The mean ulcer score was then multiplied by the percentage of ulcerated animals in the group to give the ulcer index (U. I.). The preventive index (P. I.) was also calculated according to following equation (Radwan et al., 1989).

Preventive Index = U.I. control-U.I. treated / U.I. control x 100.

After scoring the gross lesions, the stomachs were preserved in 10% buffered formaline for the histopathological analysis, six rectangular pieces from standard sites in each stomach were cut out and prepared for staining with haematoxylin and eosin; and all specimens were unlabelled. The severity of lesions was graded in a standard scale :

0 = intact mucosa, 1 = swelling of the faveolar and superficial parietal cells with oedematous lamina propria, II = superficial erosion due to disruption of damaged faveolar cells, III = erosions involving the upper half the mucosa, surrounded by dilated vessels and IV = necrosis of whole mucosa with inflammatory cell reaction in the submucosa. The mean ulcer score, U.I. and P.I. were calculated as described above.

Histological processing of gastric tissue for stomach wall mast cell counting in toluidine blue-stained tissue sections was carried out by the method of Guth & Hall (1965) and Cho & Ogle (1978a).

RESULTS

The stomachs of non stressed and non treated control rats receiving saline were apparently heathly on gross examination, with no macroscapic evidences of mucosal injury and had a very low ulcer index on histological examination (Table I & III). On the other

hand examination of stomachs of saline pretreated stressed or indomethacin treated group revealed gastric mucosal damage that was visible on gross and histological examination. The incidence of ulceration, mean ulcer score and U.I. were high (Tables I & III).

The histopathological character of the gastric lesions produced by stress or indomethacin could be detected from tables (II & IV) in which the histopathological distribution of lesions were presented according to the scale described. Pretreatment with cimetidine, verapamil or isradipine significantly reduced the severity score and incidence of gastric lesions produced by either stress or indomethacin (Tables I, II, III & IV).

The protective effect of isradipine in the two ulcer models tested was comparable to that of verapamil and did not show any significant statistical difference. However, cimetidine was found to produce more significant protection than either verapamil or isradipine (Tables I & III). It is to be noted that the mean score of ulcer severity, the incidence of ulcerations and U.I. were higher on microscopic than gross evaluation of the same group.

Table (I) shows that, stress markedly lowered mast cell count in the mucosal layer of stomach glandular wall in saline pretreated controls. This degranulating action of stress was abolished by pretreatment with calcium channel blockers but was not affected by cimetidine pretreatment. On the other hand, there were no significant changes in glandular wall mast cell counts in stomachs of all indomethacin treated groups (Table, III).

DISCUSSION

The gross & microscopic examination demonstrated that both stress or indomethacin produced a marked gastric mucosal lesions with incidence of 88.9 and 100 % respectively. The incidence, the severity scores and the characterization of the gastric lesions produced by stress or indomethacin demonstrated in the present study were all in agreement with the characterization of acute stress ulcer

desribed by (Cho and Ogle 1978a and Lau and Ogle 1981). and of indomethacin induced gastric lesion in rats as described by (Cho et al,1979 and Ali et al, l990).

The observed disparity between the gross and the microscopic evaluation scores of gastric lesions in the same animal group was explained by Lacy & Ito,(1982) who stated that although some areas of gastric mucosa were persumed to be entirely normal macroscopically, they were found to be damaged on microscopic examination; hence U. I. was found larger on microscopic than macroscopic evaluation. Miller (1983) concluded that though macroscopic examination may give a rough idea in evaluation of gastric lesions, yet, microscopic examination should be considered for proper evaluation of gastric damage.

Although the exact sequence of events in the etiology of coldrestraint ulcers is not clear,it is likely that stress produces marked nervous system disturbance, which produces an increase in gastrointestinal activity; the effect on the stomach is seen as an increase in motility and gastric acidity which are mediated in part via vagus nerve (cho et al, 1979). The increase in gastric acidity may be in the concentration rather than in the amount (Brodie et al., 1961). Since vagotomy dereased but did not abolish the incidence of stress ulcer (Brodie & Hanson, 1960) and there is histological evidences of severe gastric vascular changes; it is possible that there is also a centrally mediated vascular changes which may alter gastric blood flow resulting in focal ischaemia which disrupts the mucosal barrier causing increased acid backdiffusion which destroys the ischaemic cells (Kawarada et al, 1975).

Guth & Hall (1965) studied microcirculatory and mast cell changes in restraint-induced gastric ulceration and according to their findings, they suggested the following hypothesis; stress gastric mucosal mast cell degranulation with release of vasoactive substances (as histamine and 5HT) gastric mucosal vascular engorgment decreased resistance of mucosal

barrier to acid pepsin digestion muco- sal ulceration. This hypothesis was later confirmed by Cho and Ogle (1978 a&b); Ogle et al, (1985) and Karim et al (1990). The present study add further confirmation, since mucosal mast cell count was found to be significantly lowered in saline pretreated stressed rats. More recently Yegen et al (1990) reported that stress stimulated gastric lipid peroxidation which seems to be the triggering event in the production of gastric ulcers. Lastly, stress induced mucosal damage was found to be associated with a significant fall in gastric mucosal level of prostaglandin E1. (Auguste et al., 1990). Since prostaglandins were assumed to play a significant role in maintaining normal gastric mucosal integrity (Miller, 1983). It could be suggested that reduction of gastric mucosal prostaglandins may be responsible for stress induced ulceration.

The mechanisms of gastic damage by indomethacin or other N.S.A.I. drugs are also complex, they include: direct irritation by these weak organic acids on gastric mucosal membranes and cell components causing their physical destruction and loss of permeability characteristics (Rainsford & Velo,1983), inhibition of active ion transport particularily Na^+ ions with intracellular accumulattion of Na^+, anions and water leading to osmotic swelling of epithelial cells with consequent disruption of these cells (Kuo and Shandaur, 1976); accumulation of high concentration of drug anions in the gastric mucosa results in release of the tissue destructive oxygen radicals (Rainsford, 1984), this could increase gastric lipid peroxidation that may be the triggering factor of cell damage; perturbations of the production of those mediators controlling acid secretion e.g. histamine, acetylcholine and gastrin (Rainsford & Velo, 1982), gastric mucosal ischaemia (Miller, 1983) and lastly inhibition of the cytoprotective gastric mucosal PGs synthesis, (Whittle, et al, 1980).

The present study demonstrated that cimetidine had a marked protective effect against mucosal damage induced by stress or indomethacin. These results offer further

confirmation to the largely accepted role of H2 receptor blockers in preventing stress induced ulceration (Karim et al.,1990) and N.S.A.I. drugs induced gastric mucosal lesions (Konturek et al 1983, and Rainsford & Velo,1983). Verapamil pretreatment was found to produce a significant protection against gastric mucosal damge produced by stress in rats, this finding is in agreement with the earlier reports of Ogle & Tong. (1982); Ogle et al (1985 & 1990) and Karim et al (1990); as well isradipine was found to be equally effective to verapamil in preventing stress induced gastric mucosal damage. This could suggest that the reported protective effect of verapamil against stress induced gastric mucosal damage is not a unique feature of the drug, but it is a property of Ca^{++} entery blockers of other chemical classes like isradipine which is one of dihydropyridine derivatives. This also suggest that Ca^{++} channel blocking activity seems to be involved in the mechanisms of their gastro protective properties.

Furthermore, the present study revealed that the protective effect of Ca entrey blockers against mucosal damage is not confined to stress ulcer since either verapamil or isradipine produced significant protection against indomethacin-induced gastric lesions our findings indicated that the preventive index of either verapamil or isradipine is significantly less than that of cimetidine. In contrast, Karim et al (1990) reported that verapamil and cimetidine were equally effective in reducing mucosal damage in response to stress. This controversy may be explained by the high dose of verapamil used by these investigators 10 and 20 mg/kg versus 4 mg/kg used in the present study.

Despite of the efforts of some investigators to define the sequence of events responsible for the gastroprotective effects of verapamil, yet the mechanisms underlying this property are still elusive. One of the problems is that our current understanding of the pathogenesis of gastric ulceratation is also ill defined (Miller, 1983). If the antiulcerogenic effect of the tested Ca^{++} channel blockers is due to the

Ca" blocking activity, then these drugs can affect many factors involved in the pathogenesis of peptic ulcer depending also on Ca" transport, for example in the present study, verapamil or isradipine pretreatment was found to prevent mast cell degranulation by stress, but cimetidine did not. Similar findings were reported by Ogle et al (1985) and Karim et al., (1990) who studied the effects of verapamil and cimetidine in stress induced gastric damage and suggested that Ca channel blockers could antagonise stress ulcers through prevention of gastric mucosal mast cell degranulation, which leeds to histamine and 5-hydroxytryptamine release (Cho & Ogle, 1978a, 1979). Cochrane et al (1982) and Rock et al (1984) reported that ectracellular Ca" is required for the necessary coupling between stimulation and histamine release from isolated rat mast cells, such finding may explain how Ca' channel blockers could suppress mast cell degranulation.

Verapamil was proved to reduce gastric acid output stimulated by bethanicol in rats with pyloric occlusion (Ogle et al., 1985). Similary, nifedipine (a dihydropyridine derivative) was found to suppress gastric acid hypersecretion in rats (Ibrahim et al., 1988). Moreover, Ca" channel blockers were found to block the effects of gastrin or pentagastrin on gastric secretion in man (Kirkegard et al., 1982 and Sonnenberg et al., 1984). This antisecretory effect of Ca" channel blockers may be through interference with the role of Ca" required for gastric acid secretion (Schwarty& Triggle., 1984). In accordance with this assumption Szelenyi (1980) reported.that the absence of serosal Ca diminish acid secretion. It is noteworthy that decreased histamine release by reduction of mast cell degranulation and/or the interference with vagal overactivity may add further explanation for the antisecretory action of Ca" channel blockers. In contrast, other investigators concluded from in vivo studies in man that verapamil failed to influence acid secretion by histamine, impromidine or sham feeding (Aadland & Berstad, 1983), by pentagastrin (levine et al, 1988). The pos-

siblity of species variation accounting for some of these unequivocal findings cannot be ignored and needs further research (Ogle et al., 1985). However, the antiulcer action of Ca^{++} channel blockers may not be solely due to acid reduction because total acid neutralization failed to effectively prevent glandular ulceration by stress (Dia & Ogle, 1974 and Cho & Ogle., 1979).

Lowered gastric motility after Ca" channel blockers may share in their antiulcer properties, since increased gastric smooth muscle contractility was thought to be a factor in the pathogenesis of ulcer (Cho & Ogle., 1978 a) the Ca^{++} channel blockers could low er gastric motility by interference with Ca" utilization needed for gastric smooth muscle contraction, also prevention of histamine and 5 HT release from stomach mast cells would lead to less H1Histamine and 5 HT receptors mediated smooth muscle contraction, interruption of vagal overactivity through interference with neuromuscular transmission of the motor vagal impulses (Rahaminof, 1970). The further possibility of a central effect of Ca" channel blockers, which could inter-

fere with vagal activity may be considered (Ogle et al., 1985). It is possible that this central effect of Ca^{++} channel blockers may also antagonise the centrally mediated vascular disturbance which may alter gastric blood flow since vascular changes may be as important in the etiology of restraint ulcer as the changes in gastric secretion and motility (Brodie, 1962).

Recently, Auguste et al., (1990) reported that verapamil significantly increased PGEI levels in gastric mucosa of stressed and unstressed rats. Since prostaglandins deficiency plays a major role in pathogenesis of stress (Auguste et al, 1990) and indomethacin (Whittle, 1981) induced gastric mucosal damage it seems that the gastric protective effect of Ca^{++} channel block ers is mediated largely via stimulation of PGs synthesis (Auguste et al., 1990). This machanism seems to be of paramount importance, since ethanol induced gastric mucosal damage, which is not mediated solely through inhibition of PGs, (Miller, 1983) could not be antagonised by verapamil (Ogle et al., 1990).

Lastly, recent reports proved that verapamil had an antioxidant effect both in vitro (Shridi & Robak, 1988) and in vivo (Yegen et al., 1990). Since stimulation of gastric lipid peroxidation is thought to be the triggering factor in pathogensis of indomethacin (Rainsford, 1984) or stress (Yegen et al, 1990) induced gastric damage. The antioxidant property of Ca" channel blockers may contribute significantly to their antiulcer effect (Yegen at al, 1990).

The present study demonstrated that Ca" channel blockers from two different chemical groups (Verapamil and Isradipine) have a significant protective effect aganist stress or indomethacin induced gastric lesions. However, because of the differences between the experimental and clinical ulcer states, caution must be taken in any attempt to extrapolate ulcer therapy in rats to ulcer therapy in man. The present study should at least encourage and stimulate detailed controlled clinical study to investigate the gastric antiulcer property of Ca" channel blockers in man, which should certainly add a further advantage for these drugs in clinical practice.
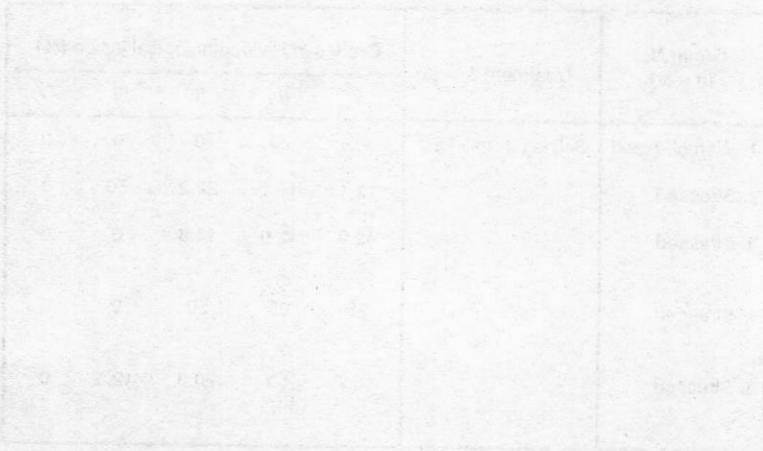
Table (I) : Histopatbological and Gross evaluation of the effects of Cinetidine, Verapanil or Isradipine pretreataent on stress induced gastric damage in Rats.

Group No. (n=8)	Treataent & Dose	Gross Rvaluation				Histopathological Evaluation				Glandular mucosalmst cell count/ 42 o.i.f. (mean± SE)
		Mean Ulcer Score ± . S . E	Incidance of Ulceration	Ulcer Index	Preve- ntive Index	Mean Ulcer Score ± . S . E	Incidance of Ulceration	Ulcer Index	Preve- ntive Index	
1. Non stressed	Saline (2 m / kg)	0	0	0	–	0.25±0.05	25 %	6.25	–	63.5±5.4
2. Stressed	Saline (2 m / kg)	2.11±5.18	77.8 %	164.16	–	2.22±0.90	88.9 %	197.36	–	39.6±2.9
3. Stressed	Cimetidine (100 mg / kg)	0.29±0.01	14.3 %	4.15	97 %	0.71±0.03	57 %	40.47	79.5 %	40.4±3.2
4. Stressed	Verapamil (4 mg / kg)	1.00±0.07	50 %	50.00	69 %	1.13±0.08	73 %	82.49	49.5 %	62.9±5.6
5. Stressed	Isradipine (0.5 mg / kg)	1.07±0.07	50 %	58.50	64 %	1.15±0.08	77 %	88.55	44.1 %	62.3±5.1

o.i.f. = Oil immersim field (1000 X).
*   Significant difference from the saline pertreated stressed group (P< 0.05)
+   Significant difference from the Cimetidine pretreated stressed group (P<0.05)
$ Non significant difference from the Verapamil pretreated stressed group (P< 0.05)
N.B.   All treatment were given 30 minutes before stress as a single I.P. injection

Table (II) : Histopathological distribution of stress induced gastric lesions in Rats pretreated with Cimetidine, Verapamil or Isradipine.

Group No. (n = 8)	Treatment & dose *	Grades of Histopathological lesion (%)				
		0	I	II	III	IV
1. Non stressed	Saline (2 ml / kg	75	25	0	0	0
2. Stressed		11.1	11.1	22.2	50	0
3. Stressed		42.9	42.9	14.3	0	0
4. Stressed		25	25	50	0	0
5. Stressed		16.7	50	20.8	12.5	0

*   All treatments mere given 30 minutes before stress as a single I . P . injection .

Table (III) : Histopathological and gross evaluation of the effects of Cimitidine, Verapamil and Isradipine on Indo methacin induced gastric lesions in Rats .

Group Treatment & Dose	Gross Evaluation				Histopathologica Evaluation				Gandular mast cell count / 42 o.i.f. (mean+
	Mean Ulcer Score ±S.E.	Incidance	Ulcer Index	Preventive Index	Mean Ulcer Score ±S.E.	Incidance	Ulcer Index	Preventive Index	
1. Saline (2 ml / kg P. 0 & I. P.	0	0 %	0	——	0.25±0.14	25.0 %	6.25	——	63.5±5.4
2. Indomethacin & Saline (2 ml / kg)	2.66±0.17	100 %	266	——	2.98±0.16	100.0 %	298.00	——	61.9±4.9 #
3. Indomethacin & Cimitidine (100 mg / kg)	0	0 %	0	100.0 %	0.67±0.03	66.7 %	44.69	83.4 %	62.2±5.1 #
	0.67±0.04 *+	33.3 %	22.3	91.7 %	1.00±0.08 *+	76.7 %	76.70	71.6 %	62.1±5.2 +#
4. Indomethacin & Verapamil (4 mg / kg)	0.67±0.04 *+$	33.3 %	22.3	91.7 %	1.33±0.07 *+$	89.0 %	118.37	56.2 %	63.9±5.8 #

*   Sigbificant difference from Indomethacin treated group   2   (P<0.05) .
+   Sigbificant difference from Cimetidine pretreated group   3   (P<0.05) .
$ Non Sigbificant difference from Verapamil pretreted group   4   (P<.05).
#   Non Sigbificant difference from Control group   1   (P>0.05).
N.B. All treatments were given as a single I.P. injection 30 minutes before indomethacin administration .

Table (IV) : Histopathological distribution of Indomethacin induced gastric lesions in Rats .

Group No.	Treatment & dose *	Grades of Histopathological lesion (%) 0				
		0	I	II	III	IV
1.	Saline 2 ml kg (p. o. & I.P)	75	25	0	0	0
2.	Indomethacin & Saline (2 ml / kg)	11.1	11.1	22.2	50	0
3.	Indomethacin & Cimetidine (100 mg / kg)	33.3	66.7	0	0	0
4.	Indomethacin & Verapomil (4 mg / kg)	33.3	33.3	33.3	0	0
5.	Indomethacin & Isradipine (.05 mg / kg)	0	66.7	33.3	0	0

*   Indomethacin was given as a single oral dose (30 mg / kg), other treatments were giv en as a single I.P. injection 30 minutes hefore indomethacin .
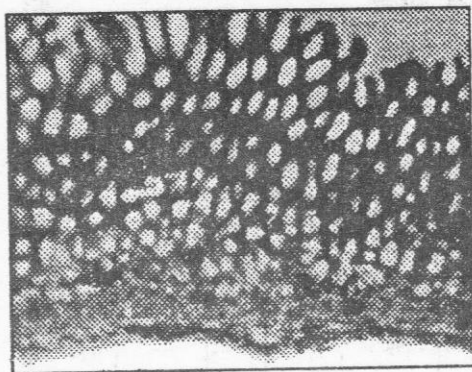
Figo 1 : Normal gastric mucosa in control group (Hx. & E. X 100).
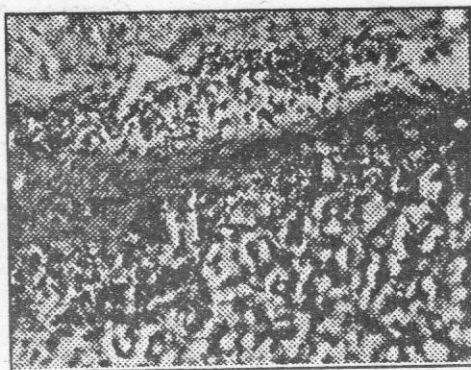

Fig. 3 : Excessive inflammatory infiltrate in mucosa and submucosa of stressed rat (Hx. & E. X 100).
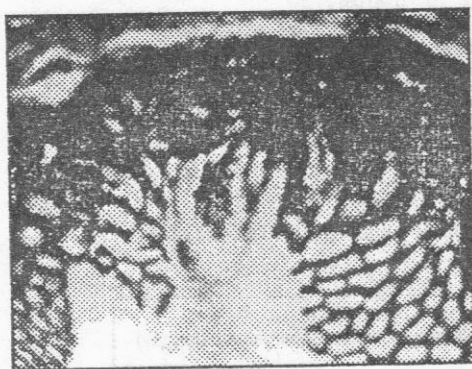

Fig. 2 Degenerative changes in foveal cells of gastric pits and mild superficial erosion in stressed rat (Hx. & E. X 100).
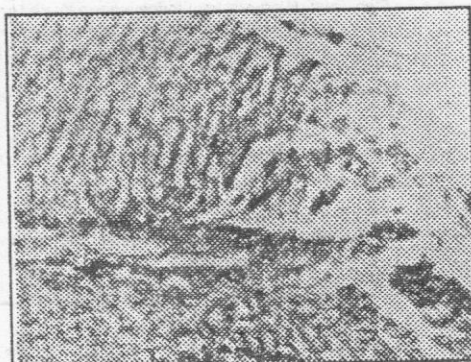

Fig. 4 : Deep erosion in indomethacin treated rat (Hx. & E. X 100).
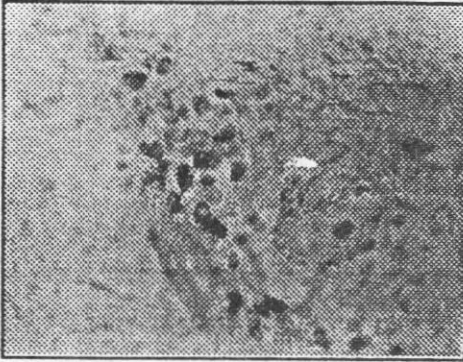
Fig. 5 : Mast cell with posit toludine
blue stain are arranged perivas-
cular in control non stressed rat
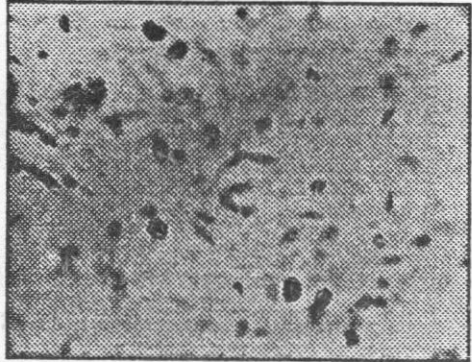(Toludine blue X 100).

Fig. 7 : Relative increase in mast
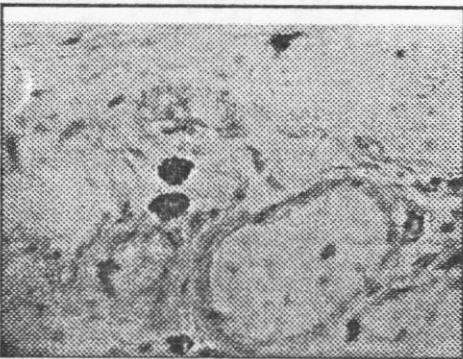cells in rat treated by verabamil
before stress (Toludine blue X
100).

Fig. 6 : Extensive decrease in num-
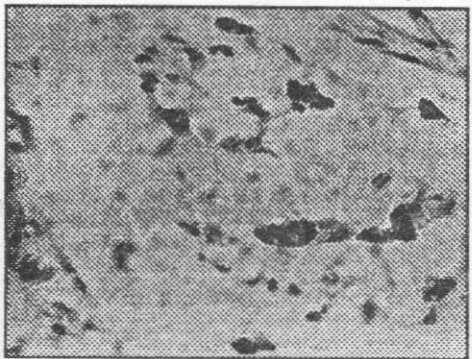ber of mast cell in stressed rat
(toludine blue X 160).

Fig. 8 : Normal appearance of mast
cells in erosive ulcer caused by
indomethacine (Toludiue blue X
160).

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بسم الله الرحمن الرحيم

الملخص العربي

دراسة مقارنة لتأثير كل من الفيراميل والازراديبين والسيميتدين على التغيرات المعديه المستحثه بالاندوميثاسين أو الاجهاد الانفعالى

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أجرى هذا البحث ...

لدراسة تأثير قافلات قنوات الكالسيوم (فيراباميل والازراديبين) بالمقارنة بالسميتدين على تقرحات المعده فى الفئران البيضاء .

وقد تم إحداث التقرحات المعدية بطريقتين مختلفتين الأولى الاجهاد الانفعالى وذلك بتقييد حركة الفئران ووضعها فى درجة حرارة ٤م لمدة ساعة والثانية : باعطاء ٣٠مجم/كجم من عقار الاندوميثاسين جرعه واحده بالفم للفئران البيضاء ... وقد تبين من البحث أن حقن ١٠٠مجم/كجم من السيميتدين ٤٠مجم/كجم من الفيراباميل أو ٥ مجم/كجم من الازراديبين فى الغشاء البرتيونى للفئران قبل إحداث التقرحات المعد ية سواء بالانفعال أو بالاندوميناسين بنصف ساعة يحدث انخفاضاً ملحوظاً فى متوسط عدد وشدة التقرحات المعدية سواء بالعين المجردة أو الميكروسكوب ...

وقد تبين أن كلا من الفيراباميل والازراديبين لهما نفس التأثير الوقائى تقريباً ضد حدوث التقرحات المعدية، أما السيميتدين له تأثير وقائى أكبر وأكثر وضوحاً إذا قورن بهما .....

وقد وجد أن الانفعال يحدث نقصا فى عدد خلايا الماست فى جدار المعده نتيجة تهالكها.

وتبين أن كلا من الفيراباميل والازراديبين يقلل من تهالك خلايا الماست الموجودة فى جدار المعده بدرجة كبيرة ولكن السيميتدين ليس له تأثير ملحوظ ... ومن الممكن أن يكون تقليل خروج الامينات مثل الهستامين والسيروتونين من خلايا الماست هو المسئول عن التأثير الوقائى لقافلات قنوات الكالسيوم ضد

حدوث التقرحات المعدية ... حيث أن تهالك هذه الخلايا وخروج الامينات منها يلعب دوراً هاماً فى حدوث القرحة المعدية...

وعلى الرغم أن هذه الدراسة تثبت الأهمية المتوقعة لقافلات قنوات الكالسيوم فى علاج نموذجين مختلفين لقرحة المعدة فى الفئران البيضاء ... فإن هذا التأثير ليس بالضرورة ينطبق على الانسان ولذلك يجب التحقق من تأثير قافلات قنوات الكالسيوم على حالات قرحة المعدة فى الانسان قبل أن ننصح باستخدامها أكلينيكياً لعلاج مثل هذه الحالات.