INHIBITION OF STEROID INDUCED GASTRIC ULCERS IN FORESTOMACHECTOMIZED ALBINO RATS BY PHENOBARBITAL

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Summary: Oral administration of 2.5 *mg* of prednisolone/100 *gm* B.W. to starved forestomachectomized albino rats for three days induces 5-7 acute gastric ulcers with a severity of 3+ in 83% of the rats in the corpus comparable to human gastric ulcers with an ulcer index of 17.1. When 15 *mg* of Phenobarbital/100 *gm* B.W. was concomitantly administered with prednisolone either orally or subcutaneously prevents the formation of steroid induced ulcers probably due to their insensitization of gastric epithelium to corticoid ulcerogenic induction. This preliminary observation may have a therapeutic value as this sedative has a common usage. It is suggested that forestomachectomized rats are best suited for ulcerogenic experiments.

Key words : forestomachectomized albino rats, prednisolone, steroid induced ulcers, gastric ulcers, corticoids, phenobarbital

INTRODUCTION

Clinical and experimental evidences indicate that adrenocortical secretions are involved in the initiation, formation and severity of gastric ulcers (3,17,22). Subcutaneous administration of heavy doses of these steroids to starved rats, rabbits and dogs induces severe gastric ulcers comparable to human gastric ulcers (1, 4, 8, 11, 12, 15 and 21). These steroid induced gastric lesions may be due to increased acid-pepsin secretion, histamine release, diminution of mucous secretion and/or vascular dilatation resulting in localised haemorrhagic thrombosis (4, 6, 5, 11, 12, 14, 8, 15, 18 and 7). In the rat, the thin translucent, nonsecretory forestomach is not comparable to any portion of the human stomach and therefore ulcerations in that region are not comparable (2, 16, 19). Therefore forestomachectomized rats were employed successfully in this laboratory in inducing gastric ulcers in the corpus comparable to human gastric ulcers. It has been shown that, potent steroids administered orally has a direct ulcerogenic effect on gastric mucosa (9). Administration of anticholinergic drugs seems to prevent forestomach as well as glandular ulcers in starved and Shay rats (13). As barbitarates are known to reduce the secretions during the period of sedation, it would be of interest to study their effect on corticoid induced gastric ulcers in the forestomachectomized albino rats.

MATERIALS AND METHODS

Male albino rats of Holtzman's strain weighing 140-150 g (90-100 days old) were starved for 24 hr to ensure that their stomachs were empty. Under light ether anaesthesia, forestomachectomy was performed along the limiting ridge after stitching both the walls without damaging the gastric blood vessels or causing traction to the stomach or block the oesophageal passage. Postoperative care of feeding chopped potatoes, boiled minced Hindustan Lever rat feed and

administering 1 *ml* of 5% glucosaline and 25-100 IU of Streptopenicillin was undertaken for 5 days. Thereafter normal feeding with water *ad lib* was ensured. Generally normalcy is achieved 10 days after operation and the rats can survive for 3 months or more (9, 10).

The forestomachectomized rats were starved in individual cages for 48 hr with water *ad lib* and thereafter 2.5 *mg* prednisolone (Calbiochem, USA)/100*g* body weight in 1 *ml* of 0.9% saline suspension was administered orally by intragastric tubation, once a day, for 3 days. 15 *mg* of phenobarbital (May & Baker)/100 *g* body weight in 1 *ml* of saline was given orally or subcutaneously 30 minutes after prednisolone treatment. Suitable controls were maintained. They were autopsied by cervical dislocation on the 3rd day of treatment, 6 hr after the last administration of drugs. The stomachs were dissected out, opened along the greater curvature and examined for ulceration using a binocular microscope (x 10). The number of ulcers and their size were recorded and the ulcer index was calculated as per the method described by Robert and Nezamis (11) and Sheriff (20). The ulcerated region was sectioned and stained in Harri's haemotoxylin eosin for histological observations. The weight of liver and adrenals were also recorded.

RESULTS

Forestomachectomy: Though albino rat is extensively used in gastroenterological research, its stomach is unique in having a thin, translucent, nonglandular forestomach which is not comparable to any portion of the human stomach. Only the corpus and the antrum are comparable to the respective regions of the human stomach (2, 16, 19). As the forestomach interferes with ulcerogenic experiments, forestomachectomy was performed and these rats become normal 10 days after operation and can survive for 3 months or more in our laboratory (9, 10).

Ulcerogenic effect of prednisolone in starved forestomachectomized abino rats (*Table I*: *Figs*, 1 & 2): In saline treated starved forestomachectomized controls, the glandular region (corpus) shows slight inter-tissue haemorrhages without any erosion of gastric epithelium. Administration of prednisolone per os causes considerable damage to the gastric mucosa resulting in the formation of 5-7 acute ulcers wherein the gastric mucosa is eroded upto muscularis mucosa or submucosa (severity 3+) in 83% of the rats, with the result, the ulcer index is as high as 17.1 (Figs. 1 & 2). Perforated ulcers are rare and the antrum is free from any type of erosions.

Efficacy of phenobarbital in inhibiting the prednisolone induced gastric ulcers (*Table I; Figs.* 3 & 4) : It is interesting to note that administration of phenobarbital either orally or subcutaneously concomitantly with prednisolone prevents or inhibits steroid induced gastric ulcers in almost all the rats except in one showing a single haemorrhagic spot. The gastric mucosa, muscularis mucosa, submucosa and muscularis externa are perfectly normal

(Figs. 3 & 4). Prednisolone treatment reduces the body weight with slightly heavy liver. Phenobarbital treatment has no significant effect either on body weight, liver or adrenals in relation to prednisolone treated rats. Probably this may be due to the insensitization of gastric mucosa to the ulcerogenic action of corticoids.

TABLE: Antiulcerogenic effect of phenobarbital in prednisolone treated forestomachectomized albino rats (2 days starvation+3 days treatment) 2.5 *mg* prednisolone/100 *gm* B.W. 15 *mg* phenobarbital/100 *gm* B.W.

Group	*Treatment*	*% Reduction in body weight*	*Mortality*	*Gastric ulcers/rat M ± S.E.*				*Organ weight/100 gm B.W. M ±S.E.*	
				No. of ulcer	*Severity in +++*	*% Incidence*	*Ulcer index*	*Liver gm*	*Adrenals mg*
A	Starved rats +Saline	(5) 24.64	—	—	—	—	—	2.34 ± 0.01	45.98 ± 0.05
B	+Prednisolone	(6) 27.39	16.66	5.50* ± 1.25	3.30* ± 0.60	83.0	17.1	3.26 ± 0.04	34.55 ± 1.83
C	+Prednisolone +Phenobarbital (Oral)	(7) 24.32	14.30	—	—	—	—	3.12 ± 0.10	36.29 ± 1.89
D	+Prednisolone +Phenobarbital (Subcutaneous)	(5) 25.04	20.00	—	—	—	—	4.14 ± 0.08	31.56 ± 1.88

Number in parenthesis indicates the number of rats
Ulcer index — No of ulcers/rat+severity + % incidence X 10^{-1}
M ± S.E. — Arithmatic mean ± Standard error

P Values
* P<0.001

DISCUSSION

It has been well documented that subcutaneous administration of heavy doses of adrenocorticoids to experimental animals causes gastric ulceration in the corpus comparable to human gastric ulcers (1, 4, 8, 11, 12, 15 and 21). There is no experimental evidence except for clinical observations, that oral administration of corticoids cause gastric ulcers. In the present experiment oral administration of prednisolone, a potent corticoid in optimum doses, induces acute gastric ulcers in the starved rats, which is observed for the first time. The causative factors for corticoid ulceration may be several, such as diminution of mucous secretion, decreased tissue resistance, histamine release or vascular dilatation (4, 6, 5, 11, 12, 14, 8, 15, 18 and 7). The inhibition of steroid induced ulcers by

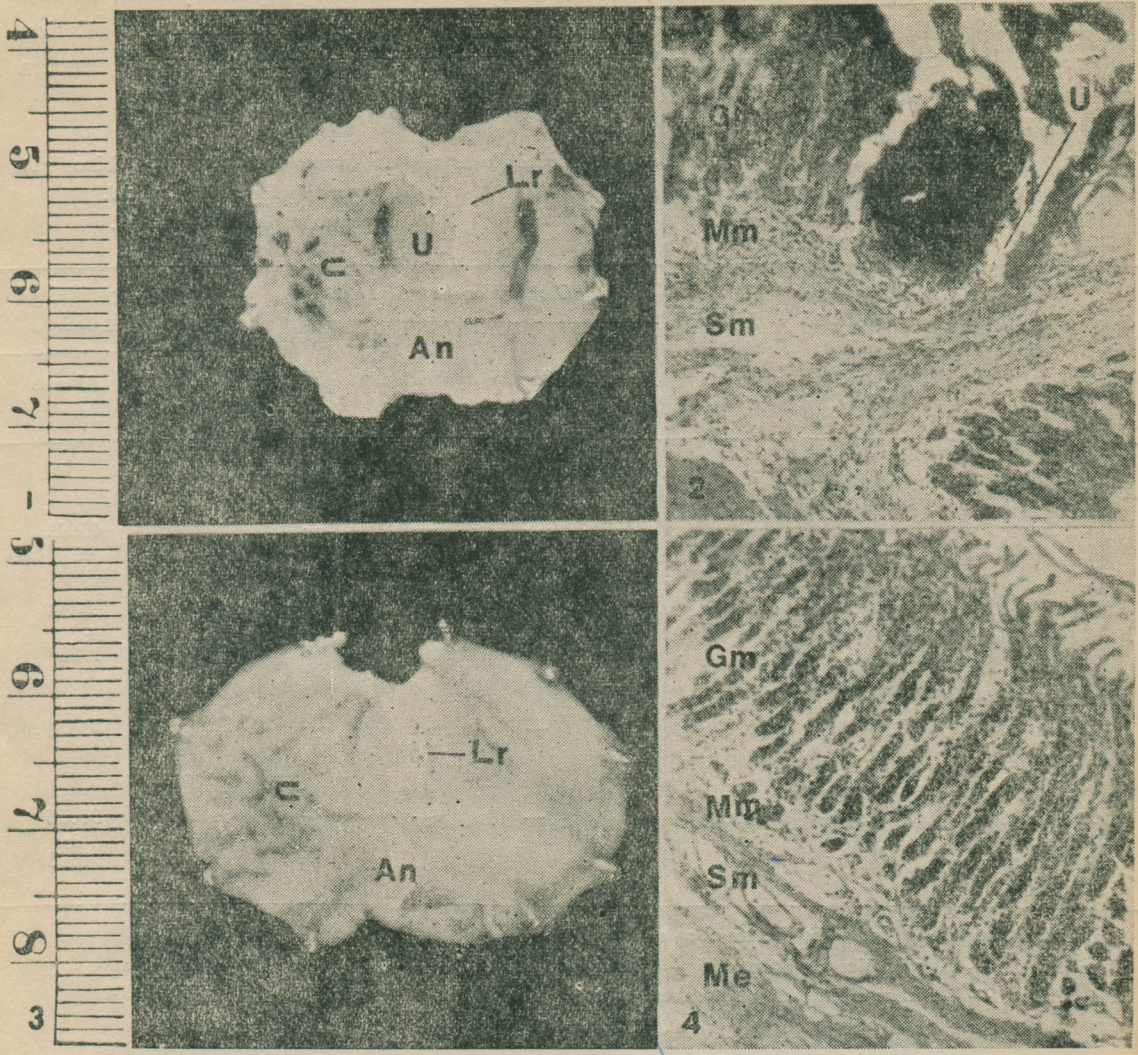

Fig. 1: Haemorrhagic ulcerated corpus region of the stomach of starved forestomachectomized rat with oral feeding of prednisolone.

Fig. 2: Section of the ulcerated region of the corpus with complete erosion of gastric mucosa with coagulative necrosis X 120.

Fig. 3: Complete inhibition of steroid ulcers in the corpus of the starved forestomachectomized rat treated with prednisolone and phenobarbital.

Fig. 4: Section of corpus of the above rat showing normal gastric mucosa X 120.

ABBREVIATIONS

An	=	Antrum	C	=	Corpus
Lr	=	Limiting ridge	Gm	=	Gastric mucosa
Me	=	Muscularis externa	Mm	=	Muscularis mucosa
Sm	=	Sub mucosa	U	=	Ulcerated region

Phenobarbital treatment, as observed for the first time may be due to their insensitization of gastric mucosa to corticoid ulcerogenic action probably through neuro-humoral pathway which is being investigated further. No doubt, this is a preliminary observation which may have a therapeutic value. It is also suggested that forestomachectomized rats are useful and can be successfully employed in ulcerogenic experiments due to their good survival value.

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