RELEVANCE OF MALE HORMONAL STATUS WITH ANTIULCER EFFECT OF CIMETIDINE IN PYLORUS LIGATED RATS

S. S. RAO AND A. Q. SAIFI

Department of Pharmacology,
Gandhi Medical College, Bhopal - 462 001

(Received on November 6, 1986)

Summary : Ulcer formation after pylorus ligation was assessed in control, testosterone treated and castrated male rats after cimetidine treatment The stomach was studied for incidence of ulcers and its contents analysed for pH, volume, total acidity, free acidity, pepsin and mucin activity. Testosterone and cimetidine when used used alone protected from ulceration while when used in combination the degree of protection was decreased. Castration *per se* ead no effect on ulcer index but potentiated cimetidine induced gastric ulcer protection.

Key words : gastric ulcer, castration, testosterone, cimetidine

INTRODUCTION

Cimetidine has been observed to occupy androgen bin ing sites in c toplasmic preparations of kidney of mature swiss albino male rats (5). Such a blocking effect is believed to result in a relatively greater exposure to oestrogen that normally circulates in male plasma, leading to gynaecomastia (7) If cimetidine does occupy androgen receptors, one may wonder if testosterone can occupy histamine–2 receptors in stomach. To investigate this we studied the effect of testosterone alone and in combination with cimetidine on pylorus ligated gastric ulcers in normal and castrated male albino rats. Gastric mucosal barrier may participate in back diffusion of hydrogen ions and in mucosal resistance of acid peptic ulceration (4). We also investigated if there is any concomitant biochemical effect on gastric mucosal barrier.

MATERIAL AND METHODS

Male albino rats (Swiss) weighing 150-250 g were divided in groups of 10 each. Group I (Control) received normal saline; Group II, III and IV received testosterone propionate (0.5; 1 and 2 *mg/kg*, im) respectively; groups V, VI and VII were treated with cimetidine (10, 20 and 40 *mg/kg*, orally); groups VIII and IX received cimetidine (20 and 40 *mg/kg*, orally) after 2 days treatment with testosterone propionate 1 *mg/kg*, im; group X, XI and XII were castrated under either anaesthesia; after 15 days, group X served as control (treated with normal saline), groups XI and XII received cimetidine (20 and 40 *mg/kg*, orally) respectively.

Testosterone propionate was injected im for 2 consecutive days and cimetidine given for 5 days orally.

At the end of the treatment gastric ulcer was produced by the method of Shay *et al.*, as modified by Tish (6). The stomach was removed, its contents were collected and pH as well as Volume were recorded. The total and free acidity were determined by titration, using 0.01 N sodium hydroxide and phenolphthalein as an indicator and the results expressed as *mEq/l* of total acid. To study the effect of dugs on mucosal barrier, peptic activity was determined in terms of tyrosine *mg/mol/l* as per Winzer (9) and mucin in terms of glucoronic acid *mg*/100 *mg* as per Discha (3). The scoring by the two methods was done seperately by two independent observers (1 and 8). There was no appreciable difference between the two scores by the two methods. The results were tabulated after pooling data obtained by the two observers. Statistical analysis was done by Student's 't'-test.

RESULTS

The results are shown in Table I. In the doses studied testosterone increased gastric juice volume (49%, 62% and 101.40%), free and total acidity (90%, 98%, 43% and 78%, 74%, 5 %) and decreased ulcer index (32%, 65% and 81%). Testosterone increased pH (73%) in 0.5 *mg/kg* dose.

Cimetidine decreased gastric juice volume (30%, 49% and 51%), free and total acidity (40%, 36%, 30% and 52%, 52%, 58%); ulcer index (48%, 62% and 87%) with marked increase in pH (50%, 111% and 119%).

The reduction in ulcer index was 65% after 1 *mg/kg* of testosterone alone as compared to 62% and 87% after 20 and 40 *mg/kg* of cimetidine. Pretreatment with testosterone reduced the ulcer index in response to cimetidine, the reduction in ulcer index being 23% and 62% after the two above doses of cimetidine. Besides modifying the ulcer index pretreatment with testosterone also affected the volume of gastric juice. Cimetidine alone descreased the volume by 50% and 52%; testosterone increased it by 62% while after pretreatment with testosterone cimetidine decreased it by 49% and 63%; Thus preventing the enhancement of the volume by testosterone. Similarly in respect of pH it was observed that cimetidine increased pH by 111% and 119%, testosterone had no effect on it while cimetidine increased it to only 76% and 51% in rats pretreated with testosterone.

Castration *per se* had no effect on ulcer index and pH but increased volume of gastric juice as well as total and free acidity. Cimetidine decreased ulcer index (77% and 98%), and increased pH and gastric volume in castrated rats.

Cimetidine alone and in combination with testosterone (1 *mg/kg*) had no significant effect on tryosine and Glucoronic acid activities in normal as well as in castrated rats.

TABLE I : Effect of cimetidine on gastric juice analysis in testosterone treated and castrated male albino rats. Values are means (±SEM) from 10 rats in each group

Drug and dose mg/kg		*Volune*	*pH*	*ACIDITY MEq/l*		*Tyrosine activity*	*Glucoronic acid*	*Ulcer*	*Index*
				Total	*Free*	*μ/mol/l*	*mg/100 ml*	*Shrimali*	*Bhargav*
1. Control P. O. Saline		11.4±2 3	2.6±0.43	61.2±16.3	31 5±5.8	36 6±6.5	195 6±18 2	1.9	20
2. Testosterone, im	0.5	17.5±0.24*	4.5±0.2*	110±2.2**	60.0±1 2*	39 2±1 6	164.06±3.64	1 25	20
	1	18.5±1 3*	2.5±0.1	107.5±6 29**	62.5±3 53*	20 74±05*	168 08±1.55	0 65*	10 6*
	2	23±2 2*	2.5±1.1	95±8.5*	45.62±2.4*	27 42±2 6*	161.48±2.5*	0 35*	7 5*
3. Cimetidine, orally	10	7.9±1 4*	4.15±0.14*	28.5±72*	18 5±5,1*	39.1±2.4	155.00±7.1	0.85*	17.50*
	20	5.7±2.4*	5.5±0.5*	26.5±9.8*	19.9±1.38*	40.3±0.6	154.0±3.02	0.65*	12.5*
	40	5.5±0.5*	5.7±0.3*	24.5±1.8*	21.5±0.5*	33.3±3.5	168.3±2.20	0.13*	5*
4. Testosterone, 1 mg.+ cimetidine	20	6.77±0.23*	4.4±0.32*	26.89±0.62*	30.4±2.5	26.2±0.92	140.3±9.2	0.5*	8*
	40	9.4±0.17*	3.77+0.24*	25.2+2.5*	28.4+1.6	16.98+9.66	142.8+6.3	0.25*	4*
5. Castrated		20±2.4*	2.0±05	110±112*	72±6.5*	26.86±4.6	196.42±12.5	1.8	30
6. Castration + 20 Cimetidine		29±0.85*	5.0±0.14*	130±13.2*	90.2±11.2	39.76±3.5	255.14×13.5	0.35*	7.5*
	40	25±3.5*	5.4±0.5*	145±3.3	105±10.5*	58.71±8.5	178±16.5	0.15*	0*

*P<0.01, **P<0.001 Comparison with respect to 1 and 2, 3, 5; 2 and 3 with 4 and 6

Testosterone decreased tyrosine activity in 1 & 2 *mg/kg* doses and glucoronic acid only in 2 *mg/kg* dose.

DISCUSSION

The gastric ulcer protection by cimetidine was assessed in control, testosterone treated i. e. in presence of additional testosterone and castrated rats i.e. in absence (95%) of testosterone. Cimetidine decreased gastric juice volume, free and total acidity, increased pH and protected the rats from gastric ulcer formation (48%, 6 % and 88%). Testosterone *per se* decreased ulcer index in doses of 0.5, 1.0 and 2 *mg/kg* (32%, 65% and 81%). Testosterone has also been reported to protect stress induced ulcer in doses of 8 *mg/kg* (2). Presence of high levels of testosterone (in testosterone treated rats) antagonised the ulcer protection activity of cimetidine as evident from less reduction in ulcer index (Cimetidine 61% and 87%, Testosterone 65%, cimetidine in testosterone treated rats 23% and 61%). Castration *per se* had no effect on ulcer index but cimetidine produced much greater gastric ulcer protection in castrated rats (77% and 97%). It seems this is related to antiandrogenic property of cimetidine (5) in view of the observation that excess of testosterone antagonised ulcer protecting ability of cimetidine in testosterone treated rats while in castrated rats where there was little testosterone to antagonise cimetidine, it exerted much greater protection against ulceration.

REFERENCES

1 Bhargava, K. P , M. Dass, G. P. Gupta and M. B. Gupta. Study of central neurotransmitters in stress induced gastric ulceration in rats. *Br. J. Pharmac.*, **68** : 765-772, 1980

2. Dinesh Chandra, S. S. Gupta and A W Bhagwat. Effect of testorterone and meprobamate on the gastric acidity and peptic ulceration. *Ind. J. Med. Res.*, **59** : 609-613, 1971.

3. Discha, Z. New colour reactions for determination of sugar in Polysaccride. In method of biochemical analysis by click II New york, 342, 1985

4. James, E. and Mcguigan. Peptic ulcer in Harrison's Principles of internal medicine edited by Peterasoed ect. Macgraw Hill international Book Co. Singapore XEd, 1697-1712, 1982.

5. Funder, J. W. and J. E. Mercer. Cimetidine a H2 receptor antagonist occupies androgen receptor. *J. Clin. Endocrinol. Metab.*, **48** : 189-191, 1979.

6. Shay, H. S A. Kamarow and S. S. Fele. A simple method for the uniform production of gastric ulceration in the rats. *Gastroenterology*, **5** : 504-508, 1976.

7. Stephen, J., M. D. Winters and L. James. Cimetidine is an antiandrogen in the rat. *Gastroenterology*, **76** : 504-508, 1976.

8. Thullie, J., P. Bessin, F. Gefroy and J. J. Godfroid. Whimic et pharmacologic de la clofezome. *Chimtherapy*, **3** : 53-67, 1968.

9 Winzer, R. J. Method of biochemical analysis, New York II 210, 1955.