

EFFECT OF VERAPAMIL ON GASTRIC ACID SECRETION AND ULCERATION BY PYLORIC - LIGATION AND ASPIRIN IN ALBINO RATS

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Summary : Verapamil at doses 5, 10, 20 and 40 mg/kg, intraperitoneally (ip) and 40 mg/kg, orally reduced incidence of ulceration by Pyloric - ligation. Similarly verapamil inhibited aspirin - induced ulceration at a dose 40 mg/kg, orally and ip. Effect of verapamil on gastric acid secretion was also studied. At low dose it increased acid secretion significantly (5 mg/kg, ip) and at high dose (40 mg kg, ip and orally) it significantly decreased volume of secretion. This indicates that reduction of acid secretion contributes little to the antiulcer activity of verapamil because antiulcer effect was seen even at doses which did not decrease acid secretion.

Key words : verapamil gastric ulcer pyloric-ligation aspirin acid-secretion

INTRODUCTION

Calcium is important in stimulus - secretion coupling and smooth muscle contraction. Calcium-channel blockers, which act by reducing transmembrane calcium - influx, may modify these two functions in various organs and may have diverse pharmacological actions. However, only cardiovascular actions of these drugs are studied well. Present communication deals with effect of verapamil on gastric acid secretion and ulceration.

There are a few reports on gastric anti-secretory action of Verapamil (1, 2), which are equivocal. Oegle et al (2) have reported antiulcer activity of Verapamil in rats subjected to stress. We have studied effect of verapamil on gastric acid secretion and also on ulceration induced by pyloricligation and aspirin.

MATERIAL AND METHODS

Albino rats weighing 150-200 gm were chosen for the study. Rats were fasted for 24 hr and water was allowed upto one hr, before experiments or sacrificing. Weight and sex matched controls were taken for each treatment group. Care was taken to avoid coprophagy.

Verapamil (Isoptin) was dissolved in normal saline before administration. Controls were treated with normal saline. Aspirin was administered as suspension in 2% gum acacia by gavage.

(I) Methods for producing ulcers :

(a) Modified method of Shay et al (3) was used. Rats were pretreated with a single dose of Verapamil, 5; 10; 20 and 40 mg/kg, ip and 40 mg/kg, orally, daily for three days. Controls received a

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comparable volume of saline by appropriate route. On the third day, half an hour after saline or drug treatment pylorus was ligated under light ether anaesthesia. Four hours later, rats were sacrificed by ether over dosing and stomach was dissected out after ligating its cardiac end.

(b) Modified method of Hemmati et al (4) was used for aspirin-induced ulceration: Rats were pre-treated with a single dose of Verapamil 40 mg/kg, ip and 20 and 40 mg/kg, orally daily for three days. Controls received saline. A single dose of aspirin 200 mg/kg orally was given daily half an hour after saline or drug treatment for three days. Food was withheld for two hours after aspirin treatment. On the third day, four hours after aspirin administration, rats were sacrificed by ether overdosing and stomach was dissected out.

Grading of ulcers - Stomach was cut-open along greater curvature and the contents were collected, then mucosa was washed under slow running tap water. Ulcers were examined by a magnifying lens. The examiner involved in grading of ulcers was unaware of the treatments. Modified method of Wilhelmi and Menasse - Gdynia (5) was used to grade severity of ulcers: Grade I—Pin-point ulcers, Grade II—Ulcers less than 1 mm. in diameter, Grade III—Ulcers more than 1 but less than 2 mm. in diameter and Grade IV—Ulcers more than 2 mm. in diameter. A mean of the ulcer grade was calculated for each group.

(II) Estimation of gastric acid secretion in pylorus - ligated rats: Secretions from stomach were collected individually in centrifuge tube and volume was noted. After centrifugation, 0.1 ml of clear supernatant was taken for acid estimation. Free and total acid was estimated by titration method described by Hawke et al (6). The acid present was expressed as mEq/l per hr per 100 gm body weight.

Statistical analysis - The data obtained was analysed by Students 't' test.

RESULTS

I. Effect of Verapamil on gastric - ulceration induced by:

(a) Pyloric - ligation: Verapamil inhibited ulceration at all doses (5, 10, 20 and 40 mg/kg, ip and 40 mg/kg, orally). Except at dose of 5 mg/kg, ip, the inhibition of ulceration was statistically significant.

The antiulcer effect, was maximum at a dose 10 mg/kg, ip, and higher doses did not increase the antiulcer effect (Table I).

TABLE I: Effect of Verapamil on gastric-ulceration by pyloric-ligation.

| Doses | No. of rats | Mean ulcer grade with SEM |
|----------------------------|-------------|---------------------------|
| 1. Control (Saline) | 7 | 2.14±0.67 |
| Verapamil 40 mg/kg, orally | 7 | 0.57±0.20* |
| 2. Control (Saline) | 13 | 1.61±0.55 |
| Verapamil 5 mg/kg, ip | 6 | 1.33±0.84 |
| Verapamil 10 mg/kg, ip | 8 | 0.00±0.00** |
| Verapamil 20 mg/kg, ip | 9 | 0.45±0.13* |
| Verapamil 40 mg/kg, ip | 9 | 0.44±0.14* |

* P<0.05 ** P<0.01

(b) Aspirin - Verapamil 40 mg/kg, ip and orally significantly inhibited ulceration by aspirin. At dose 20 mg/kg orally the antiulcer effect was statistically insignificant (Table II).

TABLE II: Effect of Verapamil on aspirin-induced ulceration.

| Doses | No. of rats | Mean ulcer grade with SEM |
|-----------------------------|-------------|---------------------------|
| 1. Control (Saline), orally | 9 | 3.66±0.23 |
| Verapamil 20 mg/kg, orally | 9 | 3.30±0.43 |
| Verapamil 40 mg/kg, orally | 11 | 2.54±0.45* |
| 2. Control (Saline), ip | 8 | 3.85±0.16 |
| Verapamil 40 mg/kg, ip | 8 | 1.85±0.58** |

*P<0.05 **P<0.01

II. Effect of Verapamil on Gastric acid secretion :

Verapamil increased volume of secretions, free and total acid secretion at doses 5; 10 & 20 mg/kg, ip (statistically significant at dose 5 mg/kg, ip). Verapamil at dose 40 mg/kg, orally and ip, reduced volume of secretions, total and free acid secretion. However, statistically significant reduction in volume of secretions was noted at a dose of 40 mg/kg by oral and ip routes. Reduction of free acid secretion was statistically significant only at 40 mg/kg, ip dose of Verapamil. Thus, verapamil significantly increased acid secretion at low and reduced at high doses respectively (Table III).

TABLE III : Effect of Verapamil on gastric-acid secretion.

| Doses | No. of rats | Volume of secretions per 100 gm body weight | Free acid in mEq/l per hr per 100 gm body weight | Total acid in mEq/l per hr per 100 gm body weight |
|-----------------------------|-------------|---|--|---|
| 1. Control (Saline), ip | 9 | 1.97±0.17 | 9.85±3.38 | 17.55±3.49 |
| Verapamil 5 mg/kg, ip | 6 | 3.17±0.25* | 16.00±0.84* | 24.64±1.96* |
| Verapamil 10 mg/kg, ip | 8 | 2.77±0.47 | 12.8 ±1.48 | 18.48±1.76 |
| Verapamil 20 mg/kg, ip | 8 | 2.60±0.43 | 10.83±3.27 | 17.80±3.61 |
| Verapamil 40 mg/kg, ip | 6 | 0.91±0.34* | 1.37±1.20* | 10.04±4.26 |
| 2. Control (Saline), orally | 6 | 2.92±0.20 | 8.73±2.11 | 18.24±1.06 |
| Verapamil 40 mg/kg, ip | 6 | 2.23±0.23* | 16.72±1.41 | 14.61±3.49 |

*P<0.05

DISCUSSION

Mechanism of ulcerogenesis by pyloricligation and aspirin may be different. In the classic model of Shay et al (3) accumulation of acid is the major gastric insult, while gastric ulceration by aspirin has a rather complex mechanism, Aspirin may irritate gastric mucosa and damage submucosal capillaries. In the pylorus - ligated rats, a dose of aspirin results in blood loss and necrosis. Besides, inhibition of systemic and or local prostaglandin synthesis may have effect on acid and mucus secretion. Prostaglandins of E series reduce secretion of acid while increase that of cytoprotective

mucus in stomach. After an extensive review of literature we have come across few reports on antiulcer activity of Verapamil. In rats restrained 4°C for one hour, Verapamil dosedependently (1, 2 and 4 mg/kg, ip) prevented gastric ulceration (2). In a preliminary study Verapamil 15 mg/kg orally protected rats against duodenal ulceration induced by cysteamine (7). In our study Verapamil conferred protection against ulceration by pyloric - ligation 10 mg/kg and above, had significant antiulcer activity. The higher doses did not increase the degree of protection. In another model, Verapamil 40 mg/kg ip and orally significantly prevented ulceration caused by aspirin. Thus, our study confirms the reported antiulcer activity of Verapamil and further adds that it also prevents ulceration by aspirin.

Verapamil has an equivocal effect on gastric acid secretion. In animal studies in vitro, it reduced histamine and pentagastrin stimulated secretions from guinea-pig duodinic mucosa (8) and isolated whole stomach of mouse (9). In vivo, Verapamil in doses, 1; 2 and 4 mg/kg, ip (2) and 20 and 40 mg/kg ip (1), reduced volume of secretions and total acid secretion in pylorus - ligated rats.

Many in vitro studies are in agreement that Verapamil lowers gastric secretion stimulated by cholinomimetic drugs. However, effect of Verapamil on histamine or pentagastrin stimulated acid secretion is controversial. Clinical reports are also equivocal. Verapamil reduced gastrin or pentagastrin stimulated secretion in man (8, 10). However, other workers did not find effect of Verapamil on acid secretion stimulated by histamine (10) or pentagastrin (11) or by bethanechol (10).

In our study low doses of verapamil increased acid secretion which was significant at dose 5 mg/kg, ip. Only at a high dose 40 mg/kg by oral and ip routes verapamil inhibited acid secretion. The cause of increased acid secretion at low doses is not

clear and needs to be studied. The antisecretory dose of verapamil (40 mg/kg, ip and oral) in our study is comparable to the doses (20 and 40 mg/kg, ip) in the study of Barge et al (1). While Oegle et al (2) reported antisecretory effect at low doses (1, 2 and 4 mg/kg, ip). But the authors have studied effect of verapamil on bethanechol-stimulated secretion which may explain the difference in doses. However, due to dearth of studies on effect of verapamil on acid secretion it is difficult to comment more on our findings.

In our study, reduction of acid secretion by Verapamil does not seem to be contributing much to the antiulcer activity of the drug because the antiulcer effect was also present at doses which did not reduce acid secretion.

Although accumulation of acid secretion is thought to be the major gastric insult, it is also reported that total acid neutralisation in pylorus - ligated rats fails to prevent ulceration (12). Cimetidine also prevents ulceration at non-acid inhibiting doses (13, 14). Oegle et al (2) have shown that verapamil has a membrane stabilising effect on gastric mast cells and prevents their degranulation and release of histamine. Disodium cromoglycate a mast cell membrane stabiliser is also reported to have antiulcer activity in rats (15).

Antiulcer drugs either decrease acid secretion or increase mucosal resistance. Therefore, it would be interesting to study effects of Verapamil on gastric mucus secretion, epithelial mitosis and ulcer healing.

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