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EFFECT OF PIRENZEPINE ON POSTOPERATIVE GASTRIC SECRETION

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INDEXING WORDS

pirenzepine hydrochloride; gastric secretion; gastrin

SYNOPSIS

Post surgical stress ulcers of the upper digestive tract, once developed, is difficult to control depending on the primary disease and associated complications. As to the cause of postoperative stress ulcers, decreased defensive factors shch as gastric mucosal blood flow and increased gastric secretions have been pointed out.

Recently, pirenzepine hydrochloride has been shown to be a specific antagonist of muscarinic cholinergic M_1 receptors and a suppressant of gastric acid secretion. Therefore we studied its effect on gastric secretions in postoperative patients.

Twenty one patients admitted for abdominal surgery, excluding gastric surgery, were selected and randomly assigned to the pirenzepine group (10 cases) or control group (11 cases). Since the serum half life of pirenzepine is 10 hours, 20mg of pirenzepine was administered intravenously immediately after the operation and twice daily (9 a.m. and 9 p.m.) from postoperative day 1 until day 7. Gastric secretions and gastric pH were measured preoperatively and daily until day 7.

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In the control group, significant increases in the volume of secretion and significant decreases in gastric pH were observed after the operation. In contrast, the pirenzepine group had a significantly decreased amount of gastric secretion and the gastric pH was higher than those in the control group.

Thus we conclude that pirenzepine decreases gastric secretion and increases gastric pH in postoperative patients. Pirenzepine can be regarded as an effective agent for the control of postoperative gastric hypersecretion and possibly a good prophylactic for postoperative stress ulcers.

INTRODUCTION

Acute ulcers, which develop in the upper digestive tract after surgical operations, are similar to Curling's ulcers in burn patients and Cushing's ulcers in neurosurgery patients, and are classified as "stress ulcers". Once the ulcers develop, it is frequently very difficult to control because of the nature of the underlying disease and its associated complications[2,6]. It has been pointed out that defensive factors such as gastric mucosal blood flow as well as aggressive factors such as augmented secretion of gastric acid are both involved factors of postoperative stress ulcers[11].

Pirenzepine hydrochloride (Gastrozepine®, Boelinger Ingerheim Co., hereinafter as pirenzepine) is a selective antagonist of muscarinic receptors regulating acetylcholine release from the vagal nerve[8,17]. Conventional anticholinergic drugs frequently induce side effects such as increased heart rates, suppression of digestive tract motility, increase in intraocular pressure and disturbances in urination. In this regard, pirenzepine is highly specific to M_1 receptors among all the muscarinic receptors[8]. Hence, it is considered a potent suppressant of gastric acid secretion without increased adverse side effects[3]. Pirenzepine is also known to be an effective drug for the clinical treatment of gastric ulcers, duodenal ulcers and gastritis[15].

In this study, intravenous pirenzepine was examined with special references to its effect on gastric secretion and gastric pH in postoperative patients. The results indicate that gastric secretions, gastric pH and clinical symptoms are indeed ameliorated by the use of this agent.

MATERIALS AND METHODS

1. Patient characteristics

Among the patients operated under general anesthesia in the First Department of Surgery, Kobe University School of Medicine, from March 1990 until February 1993, 21 cases of laparotomy, excluding gastrectomy, were selected. Ten patients were assigned to the pirenzepine group (P group) and the remaining 11 patients to the control group (C group). Patients with history of ulcers, or who are pregnant or suspected of being pregnant, were excluded from the study. Prior to the study, informed consent from each patient was obtained.

As shown in Tab. 1, 21 patients, 10 in P group and 11 in C group were studied. The cases consisted of 10 colon cancer, 6 hepatoma, 4 cholelithiasis and 1 cholangioma. The sex ratio was 13 male versus 8 female and the ages ranged from 30's to 70's with a peak in the 60's. The number of individuals in each weight group increased in the order of 50's, 40's and 60's kg range. According to the American Society of Anesthesiologists' physical status risk ranking, 11 cases were PS1, 9 were PS2 and 1 was PS3. With respect to physical background factors, no significant differences were observed between P group and C group (Tab. 1).

Table 1. Background factors of patients

		Pirenzepine group	Control group	Total	Statistical significance
	Number of cases	10	11	21	
Disease	Colon cancer	4	6	10	N. S.
	Hepatoma	3	3	6	
	Cholelithiasis	2	2	4	
	Cholangioma	1	0	1	
Sex	Male	6	7	13	N. S.
	Female	4	4	8	
Age (yr)	30 – 39	1	1	2	N. S.
	40 – 49	1	2	3	
	50 – 59	3	3	6	
	60 – 69	4	5	9	
	70 – 74	1	0	1	
Body weight (kg)	40 – 50	3	3	6	N. S.
	50 – 60	5	4	9	
	60 – 70	1	4	5	
	70 –	1	0	1	
ASA risk	PS 1	5	6	11	N. S.
	PS 2	5	4	9	
	PS 3	0	1	1	
Operation time (hr)	~3	2	2	4	N. S.
	3~5	4	5	9	
	5~	4	4	8	

N.S. : no significancy

2.Method

Patients in P group received a single intravenous injection of pirenzepine (20mg) in the recovery room just after operation. From postoperative day 1 until day 7, 20mg of IV pirenzepine was administered twice daily (9 a.m. and 9p.m.). Drug administration was discontinued if the adverse side effects were clinically serious or inappropriate. During this period, all medications that affect gastric motility or function and other antiulcer drugs were withheld.

3. Analysis (Tab. 2)

1) Blood pressure, heart rate, respiration rate and body temperature were measured before the operation, before the first dose of pirenzepine, and then once daily before 9 a.m. until the end of the study.

2) Preoperative examination of gastric secretion and pentagastrin (6 $\mu g/kg$) stimulated gastric secretion were examined according to the standards set forth by the Commission for Assay Method of Gastric Secretion, the Japanese Society of Gastroenterology. Gastric secretion volume and gastric acid output were measured.

3) Gastric secretion volume and pH

Immediately after the operation, gastric juices were collected and the volume and pH were measured. From postoperative day 1 until day 3, gastric secretion and its pH were measured daily for 1 hour, starting at 10 a.m. pH was determined with a pH meter.

4) Serum gastrin concentration

Fasting serum gastrin levels were measured by radioimmunoassay before operation and 3 days after the operation.

5) Clinical observation

Each patient was examined for abdominal distention, pyrosis, nausea, emesis and eructation on the day of the operation prior to surgey, before the first administration of pirenzepine and once daily before the morning dose.

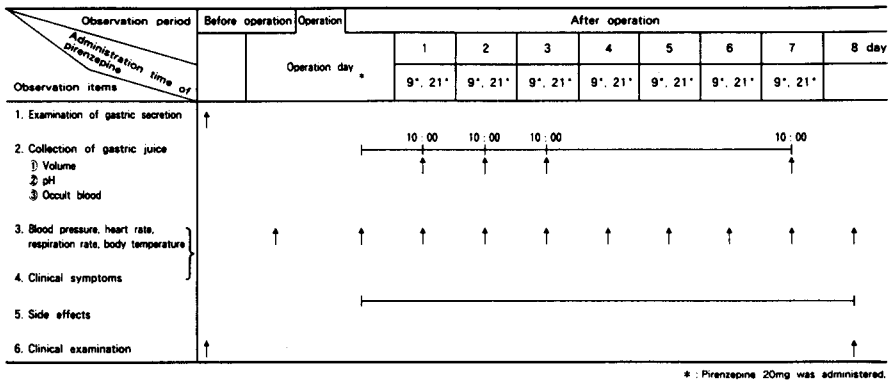
6) Side effects

When any side effects were suspected, the symptoms, time of appearance, treatments and progress were recorded.

7) Clinical examination

Prior to starting and after the final administration of pirenzepine, CBC and SMAC 20 were obtained.

Table 2. Observation designs



4. Statistics

Background factors were examined by the X^2 test. Each value was expressed as mean ± SEM. The data on gastric secretion and blood gastrin levels are analyzed by the Student's test. P value of < 0.05 was considered significant.

RESULTS

1. General observation

There were no remarkable abnormal changes on blood pressure, heart rate, respiration rate or body temperature of all 21 patients.

Analysis of gastric juices, carried out soon after admission, showed no significant differences between the two groups in the volume of secretion, whether basal or pentagastrin (6 μg/kg) stimulated (Tab. 3).

Table 3. Examination of gastric secretion at admission

		Pirenzepine group (n = 10)	Control group (n = 11)	Statistical significance
Basal secretion	Volume (ml/hr)	24.5 ± 6.2	20.6 ± 5.6	N. S.
	Basal acid output (mEq/hr)	1.36 ± 0.40	1.50 ± 0.34	N. S.
Stimulated secretion*	Volume (ml/hr)	80.2 ± 12.7	76.5 ± 13.7	N. S.
	Maximum acid output (mEq/hr)	7.81 ± 2.03	6.42 ± 1.85	N. S.

mean ± SEM * Stimulation with pentagastrin (6 μg/kg)
N.S. : no significancy

2. Changes in postoperative gastric secretion

In C group, gastric secretion volume was 25.0 ± 5.5 ml/hr before operation and significantly increased to 58.6 ± 9.4 ml/hr on postoperative day 1 ($P < 0.01$). The volume gradually decreased thereafter, but still significantly increased on day 3 and returned to baseline (23.7 ± 6.0ml/hr) on day 7.

In contrast, gastric secretion volume of P group patients was 25.7 ± 7.2 ml/hr before the operation and stayed in the range of 17.3–20.4 ml/hr throughout the postoperative period. Gastric secretion of this group on days 1–3 was significantly less than those of C group ($P < 0.01$ on day 1 and $P < 0.05$ on days 2, 3) (Fig. 1).

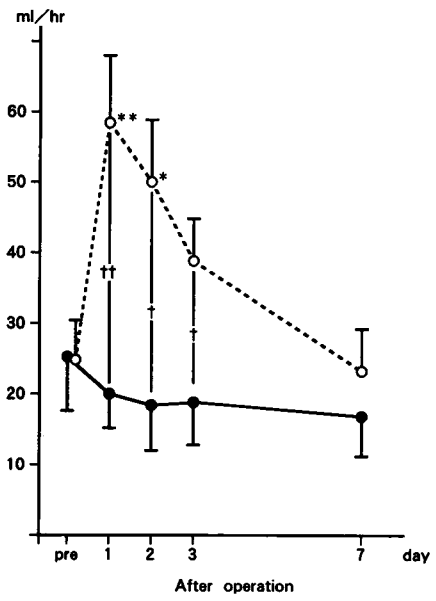


Fig. 1 Changes of the gastric secretion volume.
O·····O : control group (n = 11),
●——● : pirenzepine group (n = 10), mean ± SEM. **($P < 0.01$) and *($P < 0.05$) showed significant differences compared with the initial value. ++ ($P < 0.01$) and + ($P < 0.05$) showed significant differences compared with each other.

3. Postoperative changes in gastric pH

In C group, pH of gastric juices were 3.7 ± 0.5 before operation. One day after operation, it lowered significantly to 2.1 ± 0.5. The low pHs were also observed on days 2 and 3, and then returned to baseline (3.5 ± 0.6).

Gastric pH in P group was 3.5 ± 0.5 before operation and stayed in the range of 4.1–4.6 after operation. The pH values on days 1 and 2 were significantly higher than those obtained in C group ($P < 0.01$ on day 1 and $P < 0.05$ on day 2) (Fig. 2).

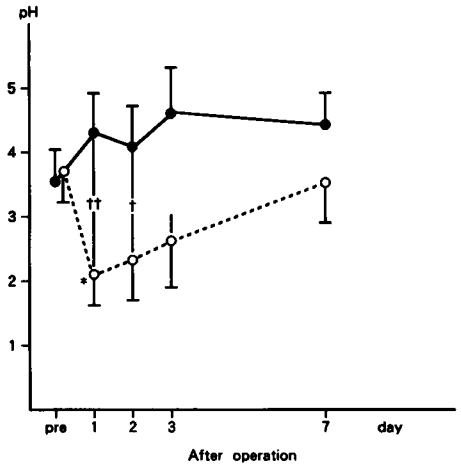


Fig. 2 Changes of pH in gastric juice. O·····O : control group (n = 11), ●——● : pirenzepine group (n = 10), mean ± SEM. *($P < 0.05$) showed a significant difference compared with the initial value. ++ ($P < 0.01$) and + ($P < 0.05$) showed significant differences compared with each other.

4. Changes in blood gastrin level

Preoperative blood gastrin concentration was 98.2 ± 10.7 pg/ml in C group and 105.4 ± 11.6 pg/ml in P group. Three days after operation, the concentration in each group was slightly decreased, 75.7 ± 9.2 pg/ml in C group and 78.5 ± 10.3 pg/ml in P group. No significant difference was detected (Fig. 3).

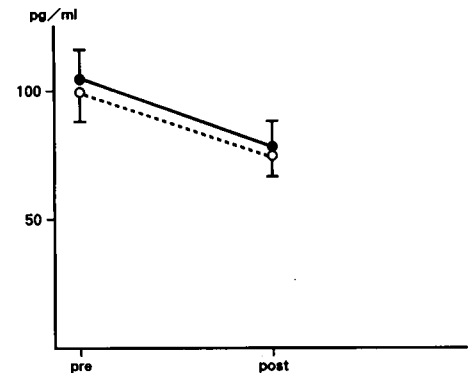


Fig. 3 Changes of serum gastrin level. O·····O : control group (n = 11), ●——● : pirenzepine group (n = 10), mean ± SEM. Pre means preoperation and post means three days after operation. There were no significant differences in these data.

DISCUSSION

It is generally accepted that stress ulcers are induced initially by local microcirculatory disturbance in the gastric mucosa, which subsequently results in the failure in defensive mechanisms and disturbances in gastric acid secretion[11,16]. In the process, gastric acid is especially regarded as the main accelerator of ulcer formation, as has been proverbially said, "no acid, no ulcer"[9].

Postoperative stress ulcers can develop after any kind of operation. Despite vigorous perioperative management, it is frequently difficult to prevent and control postoperative stress ulcers, especially in patients with extensive hemorrhage[2,6]. Its incidence appears to be 1-3% in general[2]. However, the rate may vary depending on the original disease. Although medical technology and surgical technique are indeed improved recently, the number of cases to which surgery is applicable has increased. As a consequence, postoperative morbidity has increased and cases of stress ulcers also increased[2]. In our department, the incidence of stress ulcers in patients who were subjected to surgery due to liver, gall bladder or pancreatic diseases, was 2.3% before 1980, but doubly increased to 4.7% after 1981[10].

In most cases stress ulcers develop within 10 days after operation[2]. Beil et al.[18] reported that 74% of stress ulcers were observed within 10 days after operation and Nagahata et al.[6] 85%. Prognosis of patients with postoperative stress ulcers is also poor. Mortality was reported to be 62% by Beil et al.[18], 58% by Fogelman et al.[4] According to Kumagai et al.[10], the mortality rate of stress ulcers in patients who has undergone surgery of the liver, gall bladder or pancreas, was 42%. Therefore prevention of postoperative stress ulcers is essential[6].

Increased gastric acid secretion can be considered to be a cause of postoperative stress ulcers. Although this idea was supported by several reports, only a handful of studies has been reported on the effect of pirenzepine on stress ulcers.

Pirenzepine is an antagonist to muscarinic receptors in the vagus nerve. It is highly specific for M_1 receptors[8,17] and acts as a suppressant of gastric acid secretion. The half life of pirenzepine in the blood has been reported to be 10 hours after intravenous injection[5]. In addition to the suppression of gastric acid secretion, pirenzepine has also been reported to have antigastrin activity[14], suppressive

effect on pepsin secretion[12] and activating effects on both blood flow in the gastric mucosa and secretion of gastric mucus[16].

In the present study, significant differences in gastric pH were observed between P and C groups. Pre and postoperative gastric pH was essentially unchanged in the P group, whereas the pH in C group decreased significantly.

Differences between the two are most obvious in terms of gastric secretion. Postoperative examination on days 1-3 revealed volumes in P group to be significantly less than that of C group on each corresponding day.

With respect to serum gastrin, postoperative concentration was slightly lower than that of the preoperative one in both P and C group, and the differences between before and after the operation was not significant. Since postoperative gastrin level was measured on the third postoperative day, most of the serum gastrin may have been eliminated through the kidneys during post surgical diuresis.

Recently, relationship between pulmonary complications and gastric pH during ventilator assisted patients has attracted much attention. Comparing famotidine and pirenzepine, Takezawa et al.[13] reported that gastric pH was lower and bacteria count in gastric juice was less in the pirenzepine group. They also stated that bacteria in gastric juice increased at pH of 5 or above. In our study, pHs of gastric juice were 4.1-4.6 during pirenzepine administration and was essentially the same as those reported by Takezawa et al[13].

CONCLUSION

Pirenzepine was administered to patients with laparotomy under general anesthesia, excluding gastrectomy, and postoperative changes of gastric secretion, gastric pH and serum gastrin level were measured. The conclusions obtaind are as follows :

1) Postoperative gastric secretion in the control group increased significantly on postoperative days 1 and 2, whereas the secretion in the pirenzepine group was significantly suppressed on days 1-3.

2) Postoperative gastric pH in the control group was significantly lower on days 1-3 when compared with that before operation. Whereas the pH in the pirenzepine group was significantly higher than that of the control group on days 1 and 2, and stayed in the range of 4.1-4.6 until day 7.

3) The serum gastrin level showed a tendency toward a slight decrease after opration. However, no significant differances were observed between the pirenzepine group and the control group.

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