Rat Forestomach Ulcer Induced by Drinking Glucose Solution as an Experimental Model of Gastroesophageal Ulcer of Swine

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(Received for publication July 20, 1979)

Abstract. Forestomach ulcer of rat which resembles with swine gastroesophageal ulcer developed in 100% of starved rats reared with glucose solution for 5 days. This incidence rate was much higher than that observed in water given rats. Examining the difference of ulcer incidences between 2 groups, the enhancement of gastric secretion attended by a large amount of drinking may be a causative factor. In that gastric expansion due to drinking a large amount of glucose solution may cause to stimulate gastric secretion. Forestomach mucosa may be attacked more vigorously by the increased secretion of gastric acid and pepsin. This causative process of the ulcer development may be similar to that of the swine ulcer. Antiulcerogenic test of following 5 substances on the forestomach ulcer was also performed; pepstatin, NaHCO_3 , carboxy-methylcellulose, sodium polyacrylate (PAS) and sodium alginate (AGS). Among them pepstatin (an antipeptic), PAS (a thickening agent) and AGS (a thickening agent or anti-heartburn agent) were evaluated to be effective prophylactic agents. Now we are in contemplation to examine their effectiveness on the naturally occurring or experimentally induced swine ulcer.

In a previous report we described the forestomach ulcer developed in about 50% of rats by starvation for a week. This injury seemed to resemble the naturally occurring gastroesophageal ulcer of swine in the pathogenesis [3]. Recently, we found that the identical forestomach ulcer could be produced in all rats which were deprived of feed and allowed to drink 20% glucose solution for 5 days. In the present investigation we studied on the gastric secretion, a possible causative factor, during the ulcer production by glucose ingestion. Antiulcerogenic activity of some agents was also studied using this model system.

Materials and Methods

Male Wistar rats, weighing 200–220 g, were used after 24 hr starvation. During the study they were housed in the individual plastic cages with wire

mesh of a large net to prevent coprophagy. The volume of water or other solutions drunk during the experiment was recorded every day. After the experiments, animal was killed by gassing with chloloform in a box.

1) Ulcer production

Thirty rats were divided into 4 groups. They were deprived of feed during the experiment for 5 days; Group I, Ten rats were allowed to drink water during the experiment ad libitum. Group II, Five rats were forcedly given 10 ml water, 5 times a day, by gavage. Group III, Ten rats were allowed to drink glucose solution (20%) ad libitum. Group IV, Five rats were restrictedly given glucose solution (50%) 20 ml per day.

After 5-day experimental period, the stomach was removed, cut along with the greater curvature and stuck on the hard paper with pins. The stomach mucosa was examined under a ten times magnification.

2) Antiulcerogenic test

The antiulcerogenic properties of sodium poly-

Fig. 1. Forestomach ulcer in starved rat produced by ad libitum drinking 20% glucose solution for 5 days.

acrylate (PAS, Nippon Kayaku Co. Ltd.), sodium alginate (AGS, Tokyo Kasei Co. Ltd.), carboxy methyl cellulose (CMC, Tokyo Kasei Co. Ltd.), pepstatin (Sanraku Ocean Co. Ltd.) and NaHCO_3 were tested. These substances were put into the glucose solution (20%) with various concentrations. Fifty rats grouped, starved for 24 hr and then allowed to drink the test solutions for 5 days.

3) Determination of acidity and peptic activity of stomach content

Fifty rats were grouped in 5 and used after 24 hr starvation. Drinking solutions for each group were water, glucose solution (20%), glucose solutions mixed with PAS (0.5%), AGS (0.5%) and CMC (1%). Animals were allowed to drink from 5:00 p.m. and gassed next day at 9:00 a.m., and the stomachs were removed after ligations of distal end of the oesophagus and proximal end of the duodenum. The stomach content and rinsing water of mucosa were put together into a measuring flask and filled exactly up to 30 ml. Solution in the flask was centrifuged and 0.5 ml of supernate was served for the measurement of peptic activity [4]. The result was expressed as the weight of bovine crystalline pepsin. The remainder of the fluid was titrated with 0.02N NaOH to pH 7.0 using an automatic titrator. The cases of the rats having consumed

the test solution less than 50 ml during the experimental period or those having much feces in the stomach, were discarded.

Results

1) Experimental production of the forestomach ulcer

The forestomach ulcer induced by the intake of glucose solution was shown in Fig. 1. As shown in the picture, all lesions were located in the forestomach portion. No change was observed in the glandular portion of the stomach. The results of the comparative study of the ulcer formation (Table 1) indicates that the injury developed in 100% of the animals in Group II and Group III. On the other hand, such a high incidence of the ulceration was not found in the animals of Group I or IV. The rats of Group III consumed a large amount of glucose solution, while those of Group I did water poorly.

Table 1. Forestomach ulcer production with starvation and various drinking waters

	Water		Glucose solution	
	Group I	Group II	Group III*	Group IV**
No. of rats used	10	5	10	5
No. of rats with forestomach ulcer	6	5	10	3
Ulcer incidence	60%	100%	100%	60%
Daily intake of fluid (ml/day/head)	14.6 ± 10.5	50	78.3 ± 19.2	20

Mean ± SD

* 20% glucose solution was given ad libitum.

** 50% glucose solution was given 20 ml per day.

Table 2. Antiulcerogenic examination of several substances on the forestomach ulcer

	20% glucose solution (control)	20% glucose solution									
		PAS		AGS		CMC		Pepstatin		NaHCO ₃	
		0.5%	0.1%	0.5%	0.1%	2%	0.5%	5 mg%	1 mg%	1%	0.2%
No. of rats used	10	5	5	5	5	5	5	5	5	5	5
No. of rats with forestomach ulcer	10	0	3	0	1	1	4	0	1	2	3
Ulcer incidence	100%	0	60%	0	20%	20%	80%	0	20%	40%	60%
Daily intake of fluid (ml/day/head)	72.3 ± 23.2	87.0 ± 26.4		84.3 ± 24.1		79.0 ± 20.3		69.5 ± 19.4		10.0* ± 6.1	60.5 ± 18.5

Mean ± SD

* P < 0.05 (compared with control group).

2) Antiulcerogenic study

The results of the antiulcerogenic study on the forestomach ulcer induced by intake of glucose solution were shown in Table 2. All the substances except for NaHCO₃ displayed a high effectiveness with dose dependency. In the NaHCO₃ groups, rats consumed 0.2% antacid solution well (more than 50 ml a day) giving a limited effect of antiulcerogenicity, but those given 1% solution drunk poorly and showed without any significant protection.

3) Analysis of stomach content

The effect of ingestion of test solutions

on the total amount of gastric acid and pepsin in stomach contents were analysed. The result was summarized in Table 3. The outputs of acid and pepsin in glucose given rats were much higher than in water given ones. The suppressive effect of casein digestion could be observed to a varying degree in the stomach contents of PAS and AGS given animals. CMC did not display an antipeptic activity. Differences in acid amount between groups administered 3 kinds of thickening agents were not significant statistically.

Discussion

In the previous report, we may conclude

Table 3. Effect of ingestion of water and glucose solution (20%) with or without test substances on gastric secretion in starved rat

	Water	20% glucose solution			
		Without drug (control)	0.5% PAS	0.5% AGS	2% CMC
Acidity (μ Eq/stomach)	43.6** $\pm$ 14.2	215.9 $\pm$ 38.4	238.6 $\pm$ 55.8	236.9 $\pm$ 40.5	230.1 $\pm$ 40.2
Pepsin content (mg/stomach)	7.9** $\pm$ 1.4	23.7 $\pm$ 4.0	14.0* $\pm$ 3.2	14.3* $\pm$ 2.3	20.9 $\pm$ 4.9
Volume of intake (ml/day/head)	15.4** $\pm$ 10.3	55.5 $\pm$ 15.3	71.0 $\pm$ 14.5	68.3 $\pm$ 20.0	65.2 $\pm$ 16.2
No. of rat used	9	10	10	9	9

Mean $\pm$ SD

* $P < 0.05$ (compared with control group).

** $P < 0.01$ (compared with control group).

the rat forestomach ulcer induced by a long term starvation may be an analogous pathological change to GE ulcer of swine according to the macro- and micro-scopical findings, and the etiological standpoint [3]. As shown in Fig. 1, similar forestomach ulcer with that of the previous paper [3] could be developed in 100% of the starved rats which had given 20% glucose solution ad libitum within a relatively short period (5 days). They consumed the solution more than 50 ml a day. On the other hand, the rat given plain water drunk less than 20 ml a day and only 60% of rats were seized with the ulcer. Even if a similar amount of glucose was given but the volume of the solution was restricted, the ulcer incidence was relatively low. Besides, being forcedly administered plain water 50 ml a day per os a high incidence of ulcer production was found. On these evidences a high consumption of a mobile fluid seems to be a key factor for the ulcer production with a high incidence, and glucose may play a role for the increase in water consumption.

There are many reports which indicate

stomach expansion stimulates gastric secretion through releasing endogenous gastrin or stimulating neural activity in various experimental animals [1, 2, 5]. In the present study we could also find the enhancement of gastric acid and pepsin secretion in rat which consumed a large amount of solution. Therefore, raising of ulcer incidence by high fluid consumption might be due to increase gastric secretion caused by the stomach expansion.

In the present study an examination of antiulcerogenic properties of 3 thickening agents, NaHCO_3 , an antacid, and pepstatin, a potent antipeptic [6], was performed on the ulcer. Except for NaHCO_3 which the animal consumed rarely in high concentration, all the substances inhibited decidedly the ulcer production without lessening water consumption. PAS and AGS inhibited peptic activity to some extent, while they did not affect on gastric acid in the stomach content. CMC inhibited the ulcer production, but displayed neither antacidic nor antipeptic activity. Therefore, the main antiulcerogenic properties of the 3

thickening agents may be due to a physical protection on the gastric mucosa by their viscous nature.

In a previous report we described the forestomach injury induced by a long term starvation seemed to resemble the naturally occurring gastroesophageal ulcer of swine, and pointed out the availability of that ulcer as a pathological model of the swine ulcer [3]. PAS has been reported to have a preventive effect on the swine ulcer at 0.2% in the ration in the field trials [7]. In the present study we confirmed an apparent antiulcerogenic effect of this agent of 0.2–0.5% in the drinking water. These evidences may support that the forestomach ulcer in rat is usable in screening test for development of antiulcerogenic agent to the swine ulcer. The other agents which were found to show the preventive effect in the present study are now in contemplation to examine their effectiveness on the naturally occurring or experimentally induced swine ulcer.

Acknowledgments. The authors are indebted to Dr. T. Hayama, Professor of Tokyo University of Agriculture and Technology, for the kindness in correcting the manuscript.

This work was supported by a Grant-in-Aid for

the Scientific Research from the Ministry of Education, Science and Culture of Japan.

References

- [1] Code, C. F., and Watkinson, G. (1955). Importance of vagal innervation in the regulatory effect of acid in the duodenum on gastric secretion of acid. *J. Physiol. (Lond.)* **130**, 233–252.
- [2] Grossman, M. I. (1962). Secretion of acid and pepsin in response to distension of vagally innervated fundic gland area in dogs. *Gastroenterology* **42**, 718–721.
- [3] Kokue, E., Nakamura, T., and Hayama, T. (1977). Forestomach lesions induced by starvation in rat; Its similarity with gastroesophageal ulcer of swine. *Jpn. J. Vet. Sci.* **39**, 337–341.
- [4] Kunitz, M. (1947). Crystalline soybean trypsin inhibitor. II. General properties. *J. Gen. Physiol.* **38**, 291–310.
- [5] Redford, M., and Schofield, B. (1965). The effect of local anesthesia of the pyloric antral mucosa on an acid inhibition of gastrin-mediated acid secretion. *J. Physiol. (Lond.)* **180**, 304–320.
- [6] Umezawa, H., Aoyagi, T., Morishima, H., Matsuzaki, M., Hamada, M., and Takeuchi, T. (1970). Pepstatin, a new pepsin inhibitor produced by actinomycetes. *J. Antibiotics* **23**, 259–262.
- [7] Yamaguchi, M. (1978). Gastric ulcer in swine. *J. Jpn. Vet. Med. Assoc.* **31**, 327–333 (in Japanese).

要 約

ラットの前胃部潰瘍について—ブタの胃食道部潰瘍の実験モデルとしての有用性: 小久江栄一・榎林陽一 (東京農工大学農学部獣医学科)——絶食ラットにグルコース溶液を5日間与えると100%の発生率で前胃部に潰瘍病変が生じた。この発生率は水を与えた群に見られたものに比して有意に高かった。発生率の差は前群における多量の飲水にとまなう胃液分泌の亢進がその原因と考えられた。すなわち絶食ラットの飲水量をグルコース溶液と水と比較すると前者ははるかに多量であり、その結果胃の拡張が生じ多量の胃酸とペプシンが前胃部を侵襲し高率の発生がおこると考えられた。この発生の因果関係はブタの胃食道部潰瘍のそれと同質のものと推察された。本病変に対するペプスタチン、重炭酸ソーダ、カルボキシメチルセルローズ、ポリアクリル酸ソーダ、アルギン酸ソーダの予防効果を試験した。その結果、抗ペプシン薬のペプスタチン、増粘剤のポリアクリル酸ソーダ、増粘剤で“むねやけ”の一般治療薬として使用されているアルギン酸ソーダが有効な予防薬であると判定された。我々は現在これら3つの物質について、養豚場における自然発生のブタの胃潰瘍、また実験的に作製したそれに対する予防効果を試験中である。