Gastro-oesophageal function in normal subjects after oral administration of ranitidine

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SUMMARY The aim of the study was to investigate gastro-oesophageal function in normal subjects after oral administration of 150 mg ranitidine as a single dose. The study was designed as a double blind crossover investigation. Ten healthy men, aged 26-49 years (median 29 years) joined the study. A series of oesophageal function tests were performed, starting 90 minutes after oral intake of ranitidine or placebo. Gastro-oesophageal sphincter pressure was measured using a perfused catheter system and a continuous pull-through technique. No changes in sphincter pressure could be demonstrated. Peristaltic amplitude in the body of the oesophagus as well as the duration and velocity of the peristalsis were measured after wet swallows (bolus 5 ml of water). We found no changes in these variables. Intragastric pH was measured and was higher after ranitidine than after placebo ($p < 0.005$). Plasma ranitidine concentration did not correlate with intragastric pH. No effect of ranitidine could be demonstrated on the results of a standard acid clearing test. It is concluded that ranitidine, given orally in sufficient doses to suppress gastric acid secretion, does not influence gastro-oesophageal sphincter pressure or peristaltic activity in the oesophagus of normal subjects.

Ranitidine (substituted aminoalkyl furan) is a new potent histamine H_2 -receptor blocker. Comparisons with cimetidine have shown ranitidine to be about six times more potent on a molar basis in the inhibition of gastric acid secretion.¹⁻³ Oral intake of ranitidine is followed by plasma concentrations high enough to inhibit acid secretion eight hours after administration of the drug.

The possible role of ranitidine in the treatment of patients with acid gastro-oesophageal reflux has not yet been fully established. Before such studies are carried out, it is necessary to clarify the influence of ranitidine on the gastro-oesophageal region. So far, only gastro-oesophageal sphincter pressure has been measured after administration of ranitidine and the results are conflicting.^{4,5}

The aim of the present study has been to investigate gastro-oesophageal sphincter pressure, oesophageal motility, and clearing efficiency after

oral intake of ranitidine in a dose which is followed by inhibition of gastric acid secretion.

Methods

SUBJECTS

The subjects were 10 healthy men, aged 26-49 years (median 29 years). They all gave informed consent.

The study was designed as a double blind crossover study. On separate days the fasting volunteer received either ranitidine (150 mg) or placebo as coded tablets in randomised order. The measurements began 1.5 hours after oral intake of the tablet. When the whole study and reading of the curves had been completed, the code was broken and the results allocated to drug or placebo group for statistical evaluation.

The pressure measurements were carried out using a probe consisting of three perfused polyethylene catheters (Clay Adams, PE 160; internal diameter 1.14 mm, external diameter 1.58 mm). One catheter was connected to a cylindrical metal capsule with three side holes at the same level 120° apart.⁶ The diameter of the side holes was the same

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as the internal diameter of the catheter. The capsule was 1.5 cm long and had an external diameter of 2.5 mm. The capsule was sealed off just distal to the side holes and *via* a short length of tubing connected to a metal weight. Open tip catheters were fixed 10 and 15 cm above the capsule. The catheter connected to the metal capsule was used for sphincter pressure measurements and was perfused by means of a capillary infusion system (Intraflo CFS 30; flow 30 ml/h). The open tip catheters were used for measurements of peristalsis; each catheter was perfused by means of a capillary infusion system (Intraflo CFS 03; flow 3 ml/h). External pressure transducers (Siemens Elema 746) were connected and the pressure curves were transcribed on a mingograph (Elema Schonander, EMT 81). The technical characteristics of the pressure measuring system are stated in Table 1.

The pressure probe was introduced transnasally and passed to the stomach and all pressure measurements were carried out with the volunteer in the supine position. Gastro-oesophageal sphincter pressure was measured at end expiration by continuous withdrawal of the probe through the sphincter at a rate of 0.8 cm/s. An electric motor withdrew the probe. Three measurements of the gastro-oesophageal sphincter pressure were carried out during each experiment.

The probe was then positioned with the metal capsule 5 cm oral to the sphincter and thus the open tip catheters 15 and 20 cm oral to the sphincter. After five minutes of rest oesophageal peristalsis was measured in relation to three swallows using a 5 ml bolus of water each time.

The pressure probe was withdrawn and another probe consisting of a pH electrode (Radiometer GK 282 C) and two open tip polyethylene catheters (Clay Adams PE 160) was introduced. The tip of the catheters was fixed just above the pH electrode and 15 cm above, respectively. The pH electrode was connected to a pH-meter (Beckmann Chem-Mate™) and the catheters to pressure registration units as above.

Table 1 *Technical characteristics of perfused pressure measurement systems*

	Natural frequency (Hz)	Degree of damping	Pressure rise dp/dt (mmHg/s)	Compliance (μ l/100 mmHg)
Intraflo CFS 03 with catheter	16.8	0.163	35	2.33
Intraflo CFS 30 with catheter	16.8	0.24	1010	0.825

Pressure transducer: Siemens-Eléma 746; catheter: 110 cm Clay Adams PE 160.

Intragastric pH was measured and the probe was withdrawn and positioned with the electrode 5 cm oral to the sphincter by means of manometric characteristics. An acid clearing test⁷ was then performed. Fifteen ml 0.1M HCl was instilled through the oral catheter and the volunteer swallowed every half minute until oesophageal pH was above 5.

Blood samples for measurement of plasma ranitidine concentration were taken by the end of the experiment (120–150 minutes after intake of the tablet).

VARIABLES AND DEFINITIONS

The gastro-oesophageal sphincter pressure is defined as the maximal pressure in sphincter less gastric fundic pressure (mmHg).

Peak peristaltic pressure less mean oesophageal pressure 15 cm oral to the gastro-oesophageal sphincter was calculated as the peristaltic amplitude (mmHg). Duration of the peristaltic pressure was measured from the beginning of the rise in pressure until the pressure had returned to basal level, expressed in seconds.

The velocity of the peristaltic pressure wave was calculated from the maximal peristaltic pressure registered by the orally placed open tip catheter to the maximal pressure registered by the other open tip catheter expressed in cm/s. The acid clearing efficiency is expressed as the number of swallows needed to bring pH above 5.

STATISTICS

Wilcoxon's test for paired comparisons was used. Spearman's rho was used for test of correlation between intragastric pH and plasma ranitidine. P values less than 0.05 were regarded as significant.

Results

The results are stated in Table 2. Comparing the results obtained after ranitidine with those after placebo no significant differences could be found except with regard to intragastric pH. No correlation was found between intragastric pH and plasma ranitidine concentration (rho: 0.4182; $p > 0.1$).

Discussion

We found that oral intake of ranitidine is followed by a rise in intragastric pH, while no change could be shown in gastro-oesophageal sphincter pressure, oesophageal peristalsis, or acid clearing efficiency in normal subjects.

We chose a dose of ranitidine which is recom-

Table 2 Gastro-oesophageal function and plasma ranitidine concentration in 10 healthy subjects after oral administration of 150 mg ranitidine or placebo tablets

	Plasma concentration (ng/ml)	Sphincter pressure (mmHg)	Peristaltic amplitude (mmHg)	Wave duration (s)	Peristaltic velocity (cm/s)	Intragastric pH	Acid clearing (swallows)
Placebo	0 (0-9)	13 (3-27)	74 (19-118)	4.0 (2.6-8.4)	3.6 (2.6-5.6)	1.0 (0.2-2.0)	13 (5-33)
Ranitidine	245 (102-720)	13 (5-28)	65 (18-143)	4.0 (2.6-6.0)	3.8 (1.8-6.3)	2.6* (0.8-6.1)	17 (8-42)

Results given in median and range. * Significant difference, $p < 0.005$.

mended for the treatment of patients with duodenal ulcer⁸ and we administered the drug orally. It is well documented that this dose of ranitidine is followed by a rise in intragastric pH and a reduction of the volume and acidity of gastric acid secretion,^{1 2 8 9} both in patients with duodenal ulcer and normal subjects.

Intravenous bolus injection of ranitidine has been shown to increase gastro-oesophageal sphincter pressure in normal subjects.⁵ This effect was blocked by atropine, so the effect was thought to be mediated *via* the cholinergic nervous system. Plasma ranitidine concentration was not measured in that study, so the result might be explained by excessive high peak values of ranitidine.

The effect of continuous infusion of ranitidine on sphincter pressure has been investigated recently⁴ and no change in sphincter pressure was found. Furthermore, the effect of oral ranitidine in a dose of 100 mg on sphincter pressure was studied, and, as with the results of the present investigation, no change was found.⁴

The effect of continuous infusion of cimetidine on sphincter pressure has been investigated, and no change was found in one study,¹⁰ while in the other an increase in sphincter pressure was followed by a decrease.¹¹ Oral intake of cimetidine does not change sphincter pressure.¹² Changes in intragastric milieu are followed by changes in gastro-oesophageal sphincter pressure¹³ and of the competence of the gastro-oesophageal region.¹⁴ Thus we would have expected a rise in intragastric pH after ranitidine to be followed by an increase in sphincter pressure.

This study is the first to elucidate the possible effect of ranitidine on oesophageal motility. The peristaltic amplitude, velocity, and duration was not found to be influenced by ranitidine and, furthermore, the acid clearing efficiency was unchanged.

The studies mentioned have all been carried out using normal volunteers for the investigations. It is possible that treatment with ranitidine of patients with incompetent gastro-oesophageal sphincter is

followed by a slight increase in pressure, as is treatment with cimetidine.^{15 16}

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