Inhibition of meal stimulated gastric acid secretion by an octapeptide somatostatin analogue SMS 201-995

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SUMMARY A dose response study of the effect of an octapeptide somatostatin analogue, SMS 201-995, on meal stimulated gastric acid secretion was carried out in 12 healthy volunteers. Infusion of SMS 201-995 in a dose of 50 pmol/kg/h almost completely abolished the acid response to the meal. Pl-gastrin was significantly decreased during infusion of 10 pmol/kg/h of SMS 201-995 and insulin was significantly inhibited during infusion of 50 pmol/kg/h. SMS 201-995 in a dose of 50 pmol/kg/h inhibited basal and submaximal pentagastrin stimulated acid secretion by 77% and 84% respectively ($p < 0.01$). On a molar basis SMS 201-995 is substantially more potent than natural somatostatin in inhibiting gastric acid secretion.

Several studies in man have shown that exogenously administered somatostatin (a tetradecapeptide) is a potent inhibitor of gastric acid secretion^{1,2} and may participate in the physiological control of acid secretion.³ This concept is supported by the localisation of somatostatin producing D-cells in the gastric epithelium.⁴

SMS 201-995 is a cyclic bridged octapeptide analogue of somatostatin (Fig. 1), which in animals was found to be 20 times more potent than somatostatin in growth hormone suppression and three and 11 times more potent than somatostatin with respect to inhibition of insulin and glucagon release, respectively. Plasma half life after intravenous infusion is approximately 45 minutes.⁵

The present study was undertaken to study the effect of SMS 201-995 on gastric acid secretion in normal human subjects and to find the lowest dosage of SMS 201-995, which results in inhibition of acid secretion. In addition we studied the effect on insulin and gastrin release.

Methods

SUBJECTS

Twelve healthy volunteers, eight men and four women, median age 34 (range 23-50) were studied.

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All gave informed consent. The study was approved by the regional ethical committee.

EXPERIMENTAL PROCEDURES

In each subject meal stimulated acid secretion was studied on three separate days. After an overnight fast a Levin tube with a thin welded polyvinyl tube was placed in the stomach under fluoroscopic control and the stomach was emptied. The gastric acid secretion was measured by automatic intragastric titration, using a modification of the method described by Fordtran and Walsh.⁶ A peristaltic pump was used to mix the stomach content and to aspirate and reinfuse samples to and from a titration chamber in which a pH-probe was placed. The pH-probe was connected with an autotitrator (Radiometer, Copenhagen) which maintained a constant pH of 5.5 in the stomach by infusion of 0.5 M NaHCO₃ to the titration chamber. The cumulative volume of bicarbonate used was recorded on a pen writer. The number of millimoles of sodium bicarbo-

Somatostatin

H-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

SMS 201-995

H-(D-Phe)-Cys-Phe-(D-Trp)-Lys-Thr-Cys-Thiol, acetate

Fig. 1 Amino acid sequence of natural somatostatin and of SMS 201-995.

nate required per hour to maintain pH at 5.5 is equal to the amount of acid secreted (expressed as mmol HCl per hour).

The test meal, 300 ml of a 10% peptone solution (Peptone Orthane, Orthane Kemiske Fabrik, Kastrup, Denmark) with pH 5.5 was instilled into the stomach, and infused constantly at a rate of 200 ml/hour via the polyvinyl tube to maintain an approximately constant volume of the test meal in the stomach during the study.

On the first day each subject was studied for three hours during intravenous infusion of physiological saline, in order to record the time course of test meal stimulated acid secretion. On separate days each subject was studied for three hours during intravenous infusion of different doses of SMS 201-995. The somatostatin analogue was diluted with 0.9% saline containing 1% human albumin. Meal stimulated acid production was measured during infusion of SMS 201-995 in doses of 100, 200, and 400 pmol/kg/h in 12 subjects. Five of the subjects furthermore had infusions of 10 and 50 pmol/kg/h in order to estimate the lowest doses with acid inhibitory effect.

After the meal stimulation studies the effect on basal and pentagastrin stimulated acid secretion of the lowest dose of SMS 201-995 which resulted in maximal acid inhibition was studied. The subjects were studied on two separate days in randomised order. In one study basal acid secretion was collected one hour (0–60) followed by intravenous infusion of a submaximal dose of 150 ng/kg/h of pentagastrin for two hours (60–180). The other study was conducted

Fig. 2 Meal stimulated gastric acid secretion during infusion of SMS 201-995 measured by intragastric titration. Median and interquartile range.

Fig. 3 Median plasma SMS 201-995 concentrations during infusion of increasing doses of SMS 201-995.

similarly except that SMS 201-995 in a dose of 50 pmol/kg/h was infused intravenously throughout the study (0–180). Gastric secretion was collected in 15 minutes periods and titrated to pH 7.0 with an autotitrator (Radiometer, Copenhagen).

For analysis of SMS 201-995, gastrin and insulin blood samples were drawn from a cubital vein every 15 minutes throughout the study.

SMS 201-995 plasma concentrations were measured by a radioimmunoassay with a specific antiserum directed against SMS 201-995 sequence

Fig. 4 Median plasma gastrin concentrations during infusion of SMS 201-995.

4–6.⁷ Concentrations of gastrin and insulin in plasma were measured radioimmunochemically.*

Results are given as median and interquartile ranges. Percentage differences are given as the median value of the 12 individually percentage differences and were assessed by Wilcoxon's test for pair differences.

Results

The amount of gastric acid secreted during meal stimulation (mmol/180 min) during increasing doses of SMS 201-995 is shown in Figure 2 and corresponding plasma concentrations of SMS 201-995 in Figure 3. A non-significant 40% reduction in acid secretion ($p>0.10$) was seen after infusion of 10 pmol/kg/h. After 50 pmol/kg/h acid output was reduced 90% ($p<0.05$). Plasma gastrin concentration was significantly decreased during infusion of 50 and 100 pmol/kg/h ($p<0.01$) (Fig. 4). Plasma insulin concentrations decreased significantly after 50 and 100 pmol/kg/h, but insignificantly after 10 pmol/kg/h ($p>0.10$) (Fig. 5). Basal acid secretion was inhibited by 77% ($p<0.01$) and penta-gastrin-stimulated acid secretion by 84% ($p<0.01$) (Fig. 6). No side effects were observed during infusion of SMS 201-995.

Discussion

The mechanism by which SMS 201-995 inhibits meal stimulated gastric acid secretion may partly be via inhibition of gastrin release, as plasma gastrin concentrations decreased with increasing concentra-

Fig. 5 Median plasma insulin concentrations during infusion of SMS 201-995.

Fig. 6 Basal- and pentagastrin (150 ng/kg/h) stimulated gastric acid secretion without and during infusion of SMS 201-995 50 pmol/kg/h. Median and interquartile range.

tions of SMS 201-995. The observed reduction in plasma gastrin concentrations indicates, however, that an action directly on the parietal cells must be likely, a concept supported by parietal cell receptor studies⁹ and by the pentagastrin study. In a previous study in our laboratory a significant inhibition of meal stimulated gastric acid secretion was found after natural somatostatin in doses of 60 pmol/kg/h, whereas a complete inhibition was obtained with a dose of 500 pmol/kg/h.³ As SMS 201-995 significantly inhibited gastric acid secretion completely in a dose of 50 pmol/kg/h this somatostatin analogue seems to be substantially more potent than natural somatostatin in inhibiting gastric acid secretion. Besides its potent acid inhibitory effect somatostatin also reduces splanchnic blood flow.¹⁰ These properties have been the reasons for the use of somatostatin in upper gastrointestinal bleeding, where outcome was improved in three or four controlled studies.^{11–14} The highly active somatostatin analogue, SMS 201-995, with a half-life substantially longer than natural somatostatin, thus may be a potential drug in the treatment of upper gastrointestinal bleeding.

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