Influence of sumatriptan on gastric fundus tone and on the perception of gastric distension in man

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Abstract

Background—In animals, activation of 5-HT, like receptors causes a relaxation of the gastric fundus through the activation of intrinsic inhibitory neurones.

Aims—To investigate the effect of sumatriptan, an agonist at enteric neuronal 5-HT, receptors, on fasting fundus tone and sensitivity to gastric distension in man.

Methods—A gastric barostat was used to study the effect of placebo and sumatriptan, 6 mg subcutaneously, on basal fundic tone in healthy subjects. In addition, stepwise isobaric and isovolumetric gastric distensions were performed and perception was measured before and after the administration of placebo and sumatriptan.

Results—Placebo had no significant effects on gastric tone and on perception. Sumatriptan induced an immediate relaxation of the gastric fundus, reflected by an intragastric volume increase of 209 (39) ml (p<0.0005). After sumatriptan, intragastric pressures at the thresholds for perception or discomfort were not significantly altered. However, the intragastric volumes and the corresponding calculated wall tensions at perception and discomfort thresholds were significantly increased.

Conclusions—Administration of the 5-HT, receptor agonist sumatriptan induces a relaxation of the gastric fundus in man, allowing larger intragastric volumes before thresholds for perception or discomfort are reached. The effects of sumatriptan on the gastric fundus may have therapeutic potential in the treatment of patients with functional dyspepsia.

Keywords: sumatriptan; 5-HT; receptors; gastric barostat; visceral sensitivity; enteric nervous system.

During fasting, gastric fundus tone in the dog is maintained by a vagally mediated cholinergic input.1 After a meal, a receptive relaxation of the fundus occurs, which is mediated via a vago-vagal reflex pathway, and which activates non-adrenergic non-cholinergic neurones in the gastric wall.2,3 In the mouse and in the guinea pig, involvement of 5-hydroxytryptamine (5-HT) receptors on intrinsic neurones in the vagally mediated gastric relaxation has been shown.4 More recently, it was shown that 5-HT induced relaxations of the guinea pig stomach are mediated via the release of nitric oxide through activation of a 5-HT, like receptor.5 In man, the effect of 5-HT on gastric fundus tone has not been studied directly. Several subtypes of 5-HT receptors are known.6 Of these, 5-HT1A, 5-HT1D, and 5-HT3 receptors have been identified in the myenteric plexus of the guinea pig stomach.7 Selective antagonism of 5-HT1 receptors by ondansetron or alosetron does not influence interdigestive and postprandial fundus tone in man.8,9 Lack of suitable ligands precluded a similar study for 5-HT1P receptors. Recently, however, we showed that sumatriptan, a 5-HT1P receptor agonist which is used in the treatment of migraine in man,10 is an agonist at 5-HT1P receptors on nitrergic myenteric neurones in the stomach.11

The present study was undertaken to test the hypothesis that sumatriptan is able to induce a relaxation of the gastric fundus in man. An electronic barostat was used to register variations in gastric fundus tone in healthy volunteers before and after the administration of placebo or sumatriptan. The effects of placebo and sumatriptan on gastric compliance and on the perception of gastric distension were also assessed.

Materials and methods

STUDY SUBJECTS
Fifty eight healthy volunteers (36 men and 22 women; aged 19–30 years; mean age 23.4 (0.4) years) participated in this study. None of the subjects had symptoms or a history of gastrointestinal disease or drug allergies, nor were they taking any medication. Informed consent was obtained from each participant. The protocol was approved by the Ethics Committee of the University Hospital.

RECORDING TECHNIQUE
Following an overnight fast of at least 12 hours, a double lumen polyvinyl tube (Salem sump tube 14 Ch, Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1200 ml capacity; 17 cm maximal diameter) finely folded, was introduced through the mouth and secured to the subject’s chin with adhesive tape. The position of the bag in the gastric fundus was checked fluoroscopically.

The polyvinyl tube was then connected to a computer driven programmable volume displacement barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). The barostat device can deliver volume ramps or pressure

Abbreviations used in this paper: 5-HT, 5-hydroxytryptamine; MDP, minimal distending pressure; MI, motility index.
steps at different rates, while simultaneously monitoring pressure and volume at a sampling rate of eight samples per second. To unfold the intragastric bag, it was inflated with a fixed volume of 500 ml of air for two minutes with the study subject in a recumbent position, and again deflated completely. After a 10 minute equilibration period, the subjects were positioned in a comfortable sitting position with the knees slightly bent (80°) in a bed, specifically designed for that purpose.

**STUDY DESIGN**
The study consisted of two separate protocols. In the first protocol, the acute effects of placebo (subcutaneous saline) (n=10) or sumatriptan (n=11) on basal volume were studied in 21 subjects (13 men and eight women, age range 19–30 years). After a 30 minute accommodation period, minimal intragastric distending pressure (MDP) was first determined as the lowest pressure level that provided an intrabag volume of 30 ml or more. This pressure level equilibrates the intra-abdominal pressure. With the subjects in sitting position, MDP, determined by increasing intrabag pressure by 1 mm Hg every three minutes, was 6.7 (0.4) mm Hg. During the study, a fixed intrabag pressure of 2 mm Hg above MDP was set, and the intrabag volume at this pressure was recorded during 45 minutes after which placebo or sumatriptan (Imitrex, Glaxo Wellcome, Belgium) 6 mg was administered subcutaneously. The recording of the intrabag volume at MDP + 2 mm Hg continued for another 45 minutes.

In the second protocol, after a 30 minute accommodation period, a sequence of stepwise isobaric or isovolumetric distensions were performed. The MDP was again defined as the lowest pressure level that provided an intrabag volume of 30 ml or more. Subsequently, the pressure level was set at MDP + 2 mm Hg during 30 minutes, with administration of sumatriptan 6 mg or placebo subcutaneously after 15 minutes. Afterwards, graded distensions were repeated. Subjects were instructed to score their perception of upper abdominal sensations induced by each distending stimulus at the end of every distending step, using a graphic rating scale that combined verbal descriptors on a scale graded from 0 to 6.12 Pressure–volume and pressure–perception curves were obtained from the stepwise distensions. Different curve models (including linear, parabolic, sigmoid, hyperbolic, and power exponential models) were evaluated for goodness of fit of the individual pressure, volume, and pressure–perception curves. A linear regression model provided the best fit (median r²=94.1%).

To evaluate the effect of sumatriptan on basal intragastric volume, the average volumes calculated over a 45 minute period before and after administration of the drug were compared using the paired Student’s t test. Previously, we observed that phasic fundus contractions, reflected in the MI, are not related to antral contractile activity (unpublished observations).
To evaluate the effect of sumatriptan on gastric compliance and perception of gastric distension, the intercepts and slopes, obtained by linear regression analysis of pressure–volume curves and distension–perception curves, were compared by Student’s *t* test.

To evaluate the effect of sumatriptan on perception and discomfort thresholds, the number of subjects that reported perception or discomfort at a given intragastric volume or pressure, were compared before and after drug administration using a logistic regression procedure with stratification, implying exact conditional inference. In addition, the perception and discomfort thresholds before and after sumatriptan were compared using the paired Student’s *t* test. The relation between changes in perception and changes in gastric tone was analysed by linear regression analysis of the gastric relaxation and the increase in perception thresholds after drug administration in the second protocol. Differences were considered to be significant at the 5% level.

**Results**

**Influence of Placebo on Gastric Fundus Tone and on the Perception of Gastric Distension**

The effect of placebo on fundic tone was assessed in ten volunteers, in whom the MDP was 7.7 (0.5) mm Hg. The average intragastric volume at MDP + 2 mm Hg, as measured by the barostat during the basal 45 minute period was 236 (34) ml. After the administration of placebo, the average intragastric volume remained unchanged (220 (32) ml, NS). Phasic contractile activity of the proximal stomach, assessed by calculating MI, was also not altered by administration of placebo (MI 36.1 (4.3) versus 39.9 (3.4) ml × sec; NS).

Administration of placebo in ten healthy subjects had no significant influence on the pressure level inducing threshold perception (10.7 (0.6) versus 11.5 (0.7) mm Hg, NS) or discomfort (19.1 (1.1) versus 18.1 (1.1) mm Hg, NS) during isobaric distensions. The slope (50 (4) versus 50 (4.8) ml/mm Hg, NS) and the y intercept (146 (50) versus 119 (35) ml, NS) of the pressure–volume curve, obtained after linear model fitting, were also not altered. Likewise, administration of placebo in seven healthy subjects had no significant influence on the volumes inducing threshold perception (291 (53) versus 277 (33) ml, NS) or discomfort (700 (63) versus 682 (38) ml, NS) during isovolumetric distensions.

**Effect of Sumatriptan on Gastric Fundus Tone**

The effect of sumatriptan on fundic tone was assessed in 11 volunteers, in whom the MDP was 6.5 (0.5) mm Hg. The average intragastric volume at MDP + 2 mm Hg, as measured by the barostat during the basal 45 minute period was 229 (25) ml. In all volunteers, subcutaneous administration of sumatriptan caused an immediate relaxation of the gastric fundus, reflected by an increase in the balloon volume within five minutes after administration (fig 1). The maximum increase in balloon volume was 209 (39) ml (p=0.0004), and this occurred 10–15 minutes after the administration of sumatriptan. The intragastric volume remained significantly increased until the end of the measuring period (fig 2). The mean balloon volume averaged over 45 minutes increased from 229 (25) ml to 335 (34) ml after sumatriptan (p=0.002).

The effect of sumatriptan on phasic contractile activity of the fundus was assessed by calculating MI. In all volunteers, sumatriptan caused a significant inhibition of phasic contractions, expressed as a significant decrease of the MI (44.4 (4.9) versus 24.8 (3) ml × sec; p<0.001).

**Effect of Sumatriptan on Isobaric Gastric Distensions**

Both before and after the administration of sumatriptan, distensions of the stomach with progressively higher set pressures produced progressively larger intragastric volumes. At the same distending pressures, intragastric volumes after sumatriptan were significantly larger than the corresponding volumes prior to drug administration (fig 3). The slope of the pressure–volume curves, obtained after linear model fitting, was not altered by sumatriptan (51.4 (4.7) versus 54.3 (6.4) ml/mm Hg, NS). The y intercept of the pressure–volume curves...
was significantly increased after sumatriptan (191 (37) versus 275 (38) ml, p=0.01). This shift of the pressure–volume curve towards higher volumes probably reflects the sumatriptan induced relaxation of the gastric fundus.

Sumatriptan did not change the average perception score at the same distending pressures (fig 4A). After linear model fitting, both the slope and the y intercept of the individual pressure–perception curves were unaltered (respectively 0.33 (0.06) versus 0.32 (0.07) per mm Hg, and 0.8 (0.4) versus 1.0 (0.9) mm Hg, NS). Also, sumatriptan did not change the pressure level inducing threshold perception (11 (0.8) versus 12.7 (1.3) mm Hg, NS) or discomfort (17 (1) versus 17.9 (1.2) mm Hg, NS). This was confirmed by logistic regression analysis of pressure–perception curves and pressure–discomfort curves before and after sumatriptan (both NS). However, the corresponding volumes at the threshold for perception (403 (52) versus 513 (61) ml, p<0.001) and at the threshold for discomfort (489 (43) ml, p=0.0001), and at the same pressures (10.5 (0.6) versus 11.8 (1) mm Hg, NS) after sumatriptan. Likewise, sumatriptan caused a significant increase of the volume inducing discomfort (716 (46)

**EFFECT OF SUMATRIPTAN ON ISOVOLUMETRIC GASTRIC DISTENSIONS**

Both before and after the administration of sumatriptan, distensions of the stomach with progressively larger volumes produced progressively larger intragastric pressures. After linear model fitting, both the slope and the y intercept of the individual volume–pressure curves were not significantly altered (respectively 1.4 (0.1) versus 1.2 (0.2) mm Hg/100 ml and 5.7 (0.6) versus 5.3 (0.6) mm Hg, NS).

Sumatriptan significantly decreased the average perception score at the same distending volumes (fig 4B). The slope of the volume–perception curves, obtained after linear model fitting, was not altered by sumatriptan (0.7 (0.1) versus 0.6 (0.1) per 100 ml, NS). The y intercept of the volume–perception curves was significantly higher after sumatriptan (124 (32) versus 286 (35) ml, p<0.001). In addition, sumatriptan caused a significant increase of the volume inducing first perception (300 (31) versus 443 (127) ml, p=0.008). The increase in the volume inducing discomfort did not reach significance (814 (51) versus 929 (78) ml, NS). Logistic regression analysis of both volume–perception curves and volume–discomfort curves showed a significant shift towards higher volumes after sumatriptan (p<0.001 and p<0.03 respectively) (fig 5). The corresponding pressures at the threshold for perception (9.5 (0.9) versus 10.2 (1.2) mm Hg, NS) and at the threshold for discomfort (17.8 (1.8) versus 16.7 (1.7) mm Hg, NS) were not significantly altered by sumatriptan.

**EFFECT OF SUMATRIPTAN ON PERCEPTION AND DISCOMFORT THRESHOLDS**

Pooling of the responses to isobaric and isovolumetric distensions (20 subjects; 13 men and seven women) confirmed that the threshold for perception was reached at higher volumes (367 (37) versus 489 (43) ml, p=0.00001), but at the same pressures (10.5 (0.6) versus 11.8 (1) mm Hg, NS) after sumatriptan. Likewise, sumatriptan caused a significant increase of the volume (716 (46)
animal studies that observed 5-HT induced relaxations of the stomach, through the activation of intrinsic inhibitory neurones. Several subtypes of 5-HT receptors are known. Of these, 5-HT₁₆, 5-HT₁₇, and 5-HT₇ receptors have been identified in the enteric nervous system of the stomach. Selective antagonism of 5-HT₁ receptors did not influence interdigestive and postprandial fundus tone in man³ and sumatriptan has little or no affinity at 5-HT₇ receptors. In the myenteric plexus of the stomach, presynaptic 5-HT₁₆ receptors mediate the inhibition of transmitter release from cholinergic nerve endings. Activation of a presynaptic 5-HT₁₆ receptor on cholinergic motor neurones would result in decreased acetylcholine release. However, sumatriptan is only a weak agonist at 5-HT₁₆ receptors. Moreover, in man, it was reported that atropine (6 µg/kg/h) did not change fasting gastric tone. These observations seem to argue against activation of enteric neuronal 5-HT₁₆ receptors underlying the effects of sumatriptan on gastric fundus tone in man.

In the guinea pig, the 5-HT induced gastric relaxation seems to be mediated via the release of nitric oxide through activation of a 5-HT₃ like receptor. In in vitro studies in the guinea pig, we showed that sumatriptan is an agonist at 5-HT₃ receptors on enteric neurones. 5-HT₃ receptors are mainly present on nitrergic neurones in the myenteric plexus of the guinea pig stomach, where they mediate a prolonged depolarisation in response to the application of 5-HT. Animal studies that observed 5-HT induced relaxations of the stomach, through the activation of intrinsic inhibitory neurones, are in agreement with the hypothesis that the 5-HT₃ receptor is located on inhibitory motor neurones. Antagonists at this receptor include the prokinetic benzamides such as cisapride or cispamide. It has indeed been shown that cisapride, an antagonist at the 5-HT₃ receptor, is able to inhibit 5-HT induced relaxation of the guinea pig stomach. Using gastric barostat studies in cats in vivo, we were able to confirm that the sumatriptan induced relaxation of the gastric fundus is mediated via the release of nitric oxide. Thus, we hypothesise that the effects of sumatriptan on gastric fundus tone in man might reflect the activation of enteric neuronal 5-HT₃ receptors on intrinsic nitrergic neurones.

In the present study, we also showed that sumatriptan causes a significant increase in the volumes needed to reach the thresholds for perception or discomfort. In contrast, the pressures at the thresholds for perception or discomfort are not altered by sumatriptan. Visceral sensations are modulated at different levels of the brain/gut axis and, theoretically, sumatriptan could be acting at each of these levels. It seems less likely that sumatriptan alters perception at a central level, since it penetrates poorly the blood–brain barrier. Sumatriptan may alter the perception of gastric distension because of its effect on gastric tone, or because it has an antinociceptive effect on the afferent sensory pathway. Recently,
Notivol et al showed that gastric tone is a major determinant of the sensitivity to gastric distension.27 We observed that the sumatriptan induced decrease in gastric tone is accompanied by higher intragastric volumes and higher calculated wall tensions at the thresholds for perception and discomfort during gastric distension. In a recent study, the use of a tensostat showed that perception of gastric distension before and during glucagon induced gastric relaxation was determined by gastric wall tension.28 The present study, which used a barostat, does not allow a clear separation of the effects on tone from the effects on perception. However, the significant relation between the sumatriptan induced gastric relaxation and the increase in intragastric volumes needed to induce perception or discomfort suggests that the decrease in tone is the principal effect of sumatriptan, and that higher volume thresholds are most likely occurring secondary to the sumatriptan induced relaxation.

The current study may have important implications for the treatment of patients with functional dyspepsia. Recent studies showed that the accommodation of the gastric fundus to a meal, measured by a barostat, is impaired in a subgroup of patients with functional dyspepsia,23–25 and that this is associated with a high prevalence of early satiety and weight loss.25 In these patients, administration of the 5-HT₁ receptor agonist sumatriptan in man induces an immediate and selective gastric relaxation was determined by gastric wall tension.23

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