Actions of the 5-hydroxytryptamine 1 receptor agonist sumatriptan on interdigestive gastrointestinal motility in man

J Tack, B Coulie, A Wilmer, T Peeters, J Janssens

Abstract

Background—Pharmacological studies of the enteric nervous system have shown the presence of several subtypes of 5-hydroxytryptamine (5HT) receptor, which might be involved in control of the migrating motor complex.

Aims—To study the effect of sumatriptan, an agonist of enteric neuronal 5HT1P receptors, on interdigestive motility in man.

Subjects and methods—In 12 healthy subjects, interdigestive motility was recorded manometrically in the upper gastrointestinal tract. In seven subjects blood samples were drawn every 15 minutes for radioimmunoassay of motilin and somatostatin. After two phase 3s of the migrating motor complex, 6 mg of sumatriptan was administered subcutaneously. Recording continued until two more phase 3s had occurred.

Results—Sumatriptan induced a premature phase 3 in the jejunum after a median of 10 (8) minutes. The duration of the migrating motor complex cycle was shortened at the expense of phase 2. After sumatriptan, plasma somatostatin concentrations were reduced and gastric phase 3s were suppressed, although median motilin concentrations and the occurrence of plasma motilin peaks were not affected. Phase 3s of the migrating motor complex preceding sumatriptan were associated with motilin peaks, while phase 3s after sumatriptan were not. Furthermore, pretreatment with sumatriptan prevented the induction of a gastric phase 3 by the motilin agonist erythromycin.

Conclusions—Administration of the 5HT1P receptor agonist sumatriptan induces a premature intestinal phase 3, suppresses gastric phase 3s, prevents induction of a gastric phase 3 by erythromycin, and reduces plasma somatostatin concentrations.

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Keywords: migrating motor complex; motilin; somatostatin; erythromycin; enteric nervous system

Evidence has accumulated that enteric neuronal 5-hydroxytryptamine (5HT) receptors are involved in regulation of the MMC in animals and in man.8–11 In vitro studies in the guinea pig showed that 5HT1 receptors, 5HT3 receptors, 5HT4 receptors, and 5HTP receptors are present on myenteric neurones in the stomach and in the small intestine.8–11 Using the selective 5HT3 receptor antagonist ondansetron, we showed that 5HT3 receptors are involved in the initiation of gastric phase 3 motor activity in man.12 Lack of suitable ligands precluded a similar study for 5HT1 receptors and for 5HT4 receptors. Recently, however, we showed that sumatriptan, a 5HT1 receptor agonist which is used in the treatment of migraine in man,13 is an agonist of 5HT1P receptors on myenteric neurones in the stomach.14

We have also shown that administration of sumatriptan in man causes a notable delay in gastric emptying of both solids and liquids.15 The present study was undertaken to investigate the effect of sumatriptan on interdigestive gastrointestinal motility and on gastrointestinal hormones in man. We recorded gastrointestinal motor activity in healthy volunteers before and after the administration of sumatriptan. Simultaneously, plasma immunoreactive motilin and somatostatin concentrations were monitored and, finally, the effect of a low dose of the motilin agonist erythromycin16 on gastrointestinal motor activity in the presence of sumatriptan was also studied.

In the treatment of migraine, sumatriptan 6 mg is administered subcutaneously, with a bioavailability of 96%. After subcutaneous administration, a plasma peak is reached after 10 minutes, and the mean plasma half life is about two hours.17 Sumatriptan does not cross the blood–brain barrier.18 In the present study, we used the dose and route of administration of sumatriptan which is applied in the acute treatment of migraine.

Materials and methods

STUDY SUBJECTS

Twelve healthy volunteers (two women and 10 men; mean age 25.9 (2.8) years) participated in the sumatriptan study. None of the subjects had symptoms or a history of gastrointestinal disease or drug allergies, and none were taking any medication. The control group consisted of 22 sex and age matched healthy volunteers. Informed consent was obtained from each participant. The protocol was approved by the Ethics Committee of the University Hospital.
RECORDING TECHNIQUE

Recordings of antroduodenoejunal intraluminal pressures were performed using an eight lumen polyvinyl catheter (outer diameter 6 mm) with a latex bag at its end that could be filled with mercury. The probe was introduced via the mouth and positioned under fluoroscopic control in such a way that the most distal of the three proximal sensors, which were 3 cm apart, was located in the antrum at the level of the pylorus or just distal to it. The three other sensors were located in the horizontal part of the duodenum and in the proximal jejunum, respectively at 17, 42, and 67 cm distal to the antrypyloric recording sites. The two remaining catheters were used for filling and emptying the mercury bag. This catheter assembly allowed at least one recording orifice to be kept in the distal antrum during the entire experiment and thus the migrating motor complex was adequately monitored simultaneously in the distal antrum, the duodenum, and the upper jejunum. The recording catheters were continuously perfused with water by means of a low compliance pneumohydraulic infusion pump (Arndorfer Medical Specialities Inc., Greendale, Wisconsin, USA) at a flow rate of 0.4 ml/min, and were connected to external pressure transducers (Siemens Elema 746; Siemens, Iselin, New Jersey, USA). Pressures were recorded on a polygraph (Elema Mingograph 82, Siemens) using a paper speed of 5 mm/s.

STUDY DESIGN

Following an overnight fast of at least 12 hours, the recording probe was introduced as described above and secured to the subject’s chin with adhesive tape. In 12 volunteers, gastrointestinal motility was recorded until the passage of two phase 3s of the MMC. Ten minutes after the second phase 3 passed at the most distal recording site, 6 mg of sumatriptan (Imitrex, the second phase 3 passed at the most distal part of the MMC. Ten minutes after the administration of sumatriptan, 40 mg of erythromycin lactobionate (Abbott Labs), dissolved in 100 ml normal saline, was infused over 20 minutes via a second intravenous line. Motor activity was continuously recorded until the passage of a phase 3.

The control group for the study of the effect of sumatriptan on the MMC consisted of 16 volunteers in whom motor activity was recorded with the same technique until four phase 3s had occurred. The control group for the study of the interaction between sumatriptan and erythromycin consisted of six volunteers in whom motor activity was recorded with the same technique; the same dose of erythromycin was administered 15 minutes after the passage of a spontaneous phase 3.

ANALYSIS

Analysis of the recordings of gastroduodenoejunal motor activity was performed by two of the authors (JT and AW) independently. Visual inspection allowed continuous identification of the most distal antral recording site as the catheter that recorded up to three pressure waves per minute (antral waves) just proximal to the catheter that recorded up to 12 contractions per minute (duodenal waves) or to the catheter that exhibited a mixture of antral and duodenal waves. The different phases of the migrating motor complex were identified as described previously.21 22 Whenever possible, the propagation velocity of phase 3 was assessed from the gastric to the duodenal sensor and from the first to the second jejunal sensor.

Plasma motilin and somatostatin concentrations were determined by radioimmunoassay as previously described.17 18 To determine whether sumatriptan affects basal concentrations of somatostatin or motilin, all concentrations of each hormone before sumatriptan were compared against all concentrations of each hormone after sumatriptan. In addition, the average hormone concentrations for each MMC cycle were assessed for possible differences between each other. In addition, the maximum motilin concentration before sumatriptan was compared with the maximum motilin concentration after sumatriptan. The motilin concentration associated with phase 3 was defined as the motilin concentration measured during phase 3 at its segment of onset or just prior to the onset of phase 3 if no sample was taken during the phase 3.16 17 To test whether motilin peaks were present at the onset of a phase 3, the motilin concentrations associated with each phase 3 were compared with the average of all motilin concentrations over the whole recording time and to the average motilin concentrations of each MMC cycle preceding (or following) the phase 3.

The two tailed paired t test was used to determine significant differences between cycle lengths, the velocity of propagation, and the duration of the phase 3. A one population model with repeated measurements on categorical data for time and treatment main effect (Catmod procedure, SAS software) was used to determine whether there was a significant difference between the number of phase 3s of MMC starting in the stomach before and after sumatriptan. The unpaired t test was used to compare the number of phase 3s originating in the stomach in the control group versus the sumatriptan group. Data on hormone concentrations were analysed by analysis of variance, or Student’s paired t test. All values are presented as median (SEM). Differences were considered to be significant at the 5% level.

RESULTS

EFFECT OF SUMATRIPTAN ON THE DIFFERENT PHASES OF THE MIGRATING MOTOR COMPLEX

In all 12 volunteers, two phase 3s before and two phase 3s after the administration of sumatriptan were readily identified. In all volunteers, sumatriptan caused a premature...
The duration of the MMC cycle length from 84 (10.6) minutes (first MMC cycle) and after (second and third MMC cycles) (p=0.002). The duration of phase 2 of the MMC cycle was not significantly different from the control (p=0.88).

In the sumatriptan group, the first phase 3 of the MMC cycle started from the stomach in 8/12 subjects and the second phase 3 in 5/12 (not significantly different from the control group). The third phase 3 of the MMC cycle, the first after sumatriptan, started at the level of the stomach in 0/12 subjects and the fourth phase 3 in 1/9. In total, 54% (13/24) of the spontaneously occurring phase 3s before the administration of sumatriptan started in the stomach, versus 5% (1/21) after the administration of sumatriptan (p=0.005 in comparison with phase 3s occurring before sumatriptan; p<0.001 in comparison with the control group).

**PLASMA MOTILIN CONCENTRATIONS**

An average of 25.4 (1.6) samples (14.3 (1.4) before and 11.1 (1.0) after sumatriptan) were taken in each of the seven volunteers. In these subjects, 9/14 phase 3s before sumatriptan had a gastric origin. For technical reasons, the collecting of plasma samples was stopped prematurely on some occasions. Thus, after sumatriptan, plasma samples continued to be available in all volunteers for the first phase 3 and in 4/7 volunteers for the second phase 3. Of these, none originated in the stomach.

Table 2 presents data on motilin plasma concentrations before and after sumatriptan. Sumatriptan did not affect basal and peak motilin concentrations: there were no significant differences between the median of all motilin concentrations before and after sumatriptan and between the peak motilin concentrations: there were no significant differences between the median of all motilin concentrations before and after sumatriptan.

The average motilin concentration for the whole MMC cycle was not different before (first MMC cycle) and after (second and third MMC cycle) sumatriptan. The motilin values associated with the phase 3s before sumatriptan (376 (32) pg/ml) were significantly different from the median motilin values over the whole recording time (p=0.0009) and from the median motilin concentrations of the first MMC cycle (p=0.01). In contrast, the motilin values associated with the phase 3s after sumatriptan (213 (23) pg/ml) were not significantly different from the median motilin values over the whole recording time (p=0.08) and from the median motilin concentrations of the second and third MMC cycles (p=0.2).

These data show that administration of sumatriptan did not change basal motilin concentrations and did not inhibit normal cyclic increases of plasma motilin concentrations. As illustrated in fig 2, plasma motilin peaks before sumatriptan were associated with the occurrence of gastric phase 3 activity. After sumatriptan, plasma motilin peaks continued to

**RESULTS**

The results are expressed as median (SEM).

**Table 1** Characteristics of MMC activity before and after administration of sumatriptan in 12 healthy volunteers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Sumatriptan</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMC cycle duration (minutes)</td>
<td>84.0 (10.6)</td>
<td>34.0 (6.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Phase 1 duration (minutes)</td>
<td>20.5 (4.8)</td>
<td>17.5 (5.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Phase 2 duration (minutes)</td>
<td>61.7 (8.2)</td>
<td>13.0 (2.2)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Phase 3 duration (minutes)</td>
<td>5.2 (0.7)</td>
<td>5.0 (0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Phase 3 propagation velocity (cm/min)</td>
<td>5.9 (1.1)</td>
<td>5.1 (1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Phase 3, percentage gastric onset</td>
<td>54% (13/24)</td>
<td>5% (1/21)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Results are expressed as median (SEM). The duration of the different phases of the MMC were measured during the cycle preceding the administration of sumatriptan and the first cycle after the administration of sumatriptan at the most distal jejunal channel; the propagation velocity of phase 3 was measured at the jejunal level.

**Table 2** Plasma concentrations of gastrointestinal hormones (in pg/ml) before and after administration of sumatriptan in seven healthy volunteers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Sumatriptan</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median motilin concentration</td>
<td>309 (38)</td>
<td>317 (42)</td>
<td>NS</td>
</tr>
<tr>
<td>Peak motilin concentration</td>
<td>393 (46)</td>
<td>403 (49)</td>
<td>NS</td>
</tr>
<tr>
<td>Median motilin concentration during MMC cycle</td>
<td>326 (42)</td>
<td>316 (44)</td>
<td>NS</td>
</tr>
<tr>
<td>Motilin concentration associated with phase 3</td>
<td>376 (32)*</td>
<td>213 (23)</td>
<td>0.009</td>
</tr>
<tr>
<td>Median somatostatin concentration</td>
<td>7.5 (0.9)</td>
<td>5.6 (0.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Median somatostatin concentration during MMC cycle</td>
<td>6.8 (2.2)</td>
<td>5.3 (1.7)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Results are expressed as median (SEM). Median hormone concentrations before and after sumatriptan were calculated from respectively 14.3 (1.4) and 11.1 (1.0) samples per subject. The median hormone concentrations during the MMC cycle before and after sumatriptan were calculated from respectively 7.1 (0.8) and 6.4 (1.8) samples per subject. *Significantly different from the motilin level during the MMC cycle before sumatriptan.

Phase 3 with jejunal onset after a median interval of 10 (8.2) minutes (fig 1). Table 1 summarises the effects of sumatriptan on different phases of the MMC. Sumatriptan shortened MMC cycle length from 84 (10.6) minutes before administration to 34 (6.5) minutes for the first cycle after sumatriptan (p=0.001) and 51.5 (6.8) minutes for the median of the first and second cycles after sumatriptan (p=0.002). The duration of phase 1 of the MMC cycle was not affected by sumatriptan. In contrast, the duration of phase 2 of the MMC cycle was significantly shortened after sumatriptan. The duration of phase 3 of the MMC cycle, as well as the propagation velocity of the phase 3s at the jejunal level, were not affected by sumatriptan. Due to a lack of gastric and duodenal phase 3s after sumatriptan (see below), it was not possible to compare the duration of phase 3 at the gastric and duodenal level and the propagation velocity from stomach to duodenum before and after administration of the drug.
Sumatriptan and interdigestive motility

Figure 2 Typical changes of interdigestive motility and its relation to motilin plasma concentrations in a healthy volunteer. The seven lower traces depict schematic representations (flat line = phase 1; tinted bars = phase 2; black bars = phase 3) of the different phases of the MMC in the stomach and the upper small intestine. A1, A2, A3, A4, antral recording sites; D1, duodenal recording site; J1, J2, jejunal recording sites. Two spontaneous activity fronts occur, the first of gastric origin and the second of duodenal origin. Administration of sumatriptan induces a premature jejunal activity front. The upper trace depicts motilin plasma concentrations throughout the study. The spontaneously occurring activity front is accompanied by a plasma motilin peak (x). The sumatriptan induced premature activity front is not accompanied by a plasma motilin peak. After administration of sumatriptan, a plasma motilin peak (xx) is not accompanied by phase 3 activity.

PLASMA SOMATOSTATIN CONCENTRATIONS

Somatostatin concentrations were determined on the same samples from which motilin concentrations were measured. Table 2 presents data regarding plasma somatostatin concentrations before and after sumatriptan. Although somatostatin concentrations varied with the MMC cycle, and maximal concentrations were reached during the occurrence of a phase 3, these differences did not reach statistical significance. Sumatriptan significantly decreased basal somatostatin concentrations (7.5 (0.9) versus 5.6 (0.8) pg/ml; p=0.006) (fig 3). The average somatostatin concentrations for the first MMC cycle were significantly higher than the average somatostatin concentrations during the second MMC cycle or during both the second and the third MMC cycles (p=0.03 for both). The average somatostatin concentration for the whole MMC cycle before sumatriptan was significantly higher than the average somatostatin concentration for the whole MMC cycle after sumatriptan (table 2).

Figure 3 Plasma somatostatin concentrations in seven healthy volunteers at 15 minute intervals before and after sumatriptan 6 mg subcutaneously. The activity front preceding the administration of sumatriptan (at time 15 minutes) is accompanied by a plasma somatostatin peak. After its administration, low plasma somatostatin concentrations are observed, and the sumatriptan induced premature activity front (on average at time 10 minutes) is not accompanied by a plasma peak.

Discussion

The present study has shown that administration of the 5HT1 receptor agonist sumatriptan in the interdigestive state in man induces a premature phase 3 of MMC with jejunal onset and suppresses phase 3 motor activity in the stomach. The MMC cycle length was significantly shortened by the administration of sumatriptan, at the expense of phase 2. Of all the phase 3s recorded preceding the administration of sumatriptan, 54% started in the stomach. After administration of sumatriptan, only 5% of phase 3s were observed to start in the stomach, a highly significant decrease. Except for the site of initiation, no differences in the duration and velocity of migration of the phase 3s were observed before and after sumatriptan.

Several agents are able to induce a premature phase 3 in the interdigestive state in man. Erythromycin and motilin are able to induce a phase 3 which starts in the stomach,16 19 20 Somatostatin and metenkephalin elicit a phase 3 which starts in the small bowel.19 21 It has already been shown that sumatriptan is able to influence endocrine secretion in man.22 By measuring plasma somatostatin concentrations before and after administration of sumatriptan, we ruled out release of somatostatin as a mechanism by which sumatriptan might induce a premature jejunal phase 3. Although a release of metenkephalin cannot be entirely discarded
as a putative mechanism of action, there are several observations which support the hypothesis that sumatriptan is acting on enteric neuronal 5HT receptors for a premature intestinal phase 3 in man. The fact that sumatriptan poorly penetrates the blood–brain barrier argues against a central action.15

Evidence has accumulated that enteric neuronal 5HT receptors are involved in regulation of the small intestinal MMC in animals. Administration of 5HT, or its precursor 5-hydroxytryptophan, decreases MMC periodicity in animals,87 whereas administration of neutral 5HT receptor antagonists increases MMC periodicity.7 Furthermore, selective destruction of enteric serotonergic neurones disrupts the MMC in rats.8 The serotonergic effects on MMC periodicity are not altered by sectioning the extrinsic nerve supply to the gut.9 In man, the effect of 5HT on the migrating motor complex has not been studied directly. Selective antagonism of 5HT7 receptors suppresses gastric phase 3s in man.10 Administration of a selective 5HT reuptake inhibitor reduced MMC periodicity and increased the propagation velocity of the phase 3 in the jejunum.11 Thus, our observation that sumatriptan induces a premature jejunal phase 3 in man is consistent with animal studies which showed shortened intestinal MMC cycles after administration of 5HT or its analogues.6 8 It is also consistent with the finding that administration of a selective 5HT reuptake inhibitor in man reduced MMC periodicity in the jejunum.12 The latter study showed the involvement of enteric neuronal 5HT receptors in the control of the intestinal MMC in man; the present study implies that sumatriptan is an agonist of these receptors.

Several subtypes of 5HT receptor are known.9 Of these, 5HT1A, 5HT1B, 5HT1D, and 5HT3 receptors have been identified in the enteric nervous system.8–11 The therapeutic effect of sumatriptan in migraine is attributed to its action at 5HT1D receptors, but this 5HT receptor subtype has never been found in the gut. Sumatriptan has little or no affinity at 5HT2 and 5HT4 receptors, but may act as an agonist of 5HT3 receptors.9 In vitro studies in the guinea pig, we showed that sumatriptan is also an agonist of postsynaptic 5HT1D receptors on enteric neurones.11 Furthermore, sumatriptan did not mimic the 5HT3 receptor mediated fast depolarising response or the 5HT1A receptor mediated hyperpolarising response to 5HT.11 The effects of sumatriptan on intestinal motility in man might thus reflect activation of enteric neuronal 5HT1D receptors. Postsynaptic 5HT1D receptors mediate a long lasting depolarisation in a subset of myenteric neurones.11 Presynaptic 5HT1D receptors have been shown to inhibit the release of acetylcholine in the small intestine.12–14 If our observations are indeed attributable to activation of 5HT1D receptors in man, it is unclear whether these are located presynaptically or postsynaptically. Unfortunately, the lack of selective and safe 5HT ligands precludes a more detailed pharmacological study in man at present.

Sumatriptan also suppressed phase 3 motor activity in the stomach. Before administration of sumatriptan, the majority of the phase 3s originated in the stomach, and were associated with a plasma motilin peak. After sumatriptan, phase 3s originated in the small intestine, and were not associated with a plasma motilin peak. Several observations support the hypothesis that, in man, the gastrointestinal peptide motilin is involved in the induction of gastric phase 3.15–18 The serotonergic effect of sumatriptan in the interdigestive state in man induces a premature phase 3 with jejunal onset. Several studies have shown the involvement of enteric neuronal 5HT receptors in the control of the intestinal MMC, both in animals and in man. The present study implies that sumatriptan is an agonist of these receptors. Sumatriptan also suppressed phase 3 motor activity in the stomach, without suppression of the occurrence of plasma motilin peaks. Thus, it seems that sumatriptan inhibits the action rather than the release of motilin. This is further supported by the finding that sumatriptan prevented the induction of a premature gastric phase 3 of the MMC by...
the motilin agonist erythromycin. Finally, we also observed that sumatriptan suppresses plasma somatostatin concentrations. The mechanism underlying the effect of sumatriptan on interdigestive motility and plasma concentrations of gastrointestinal hormones is unclear. Based on our in vitro studies, we hypothesise that sumatriptan is acting at enteric neuronal 5HT1P receptors to cause these effects. Confirmation of this hypothesis awaits the availability of suitable ligands.

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