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Inter-digestive and post-prandial antro-pyloro-duodenal motor activity in humans: effect of 5-hydroxytryptamine 1 receptor agonism

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SUMMARY

Background: Little is known about the effect of 5-hydroxytryptamine 1 (5-HT_1) receptor agonism on the co-ordinated motor activity of the gastric antrum, pylorus and duodenum under fasting and fed conditions.
Aim: To evaluate the effect of sumatriptan, a 5-HT_1 agonist, on fasting and fed antro-pyloro-duodenal motility.
Methods: In study 1, antro-pyloro-duodenal motility was recorded for two phase IIIs of the migrating motor complex and then, following either a subcutaneous injection of sumatriptan 6 mg or saline control, for at least one additional phase III in 11 healthy volunteers (21–36 years). In study 2, the post-prandial motility was recorded for 3 h after either a subcutaneous injection of sumatriptan 6 mg or saline control in 10 healthy volunteers (18–36 years).
Results: Sumatriptan prolonged the migrating motor complex cycle ($P = 0.009$) by increasing the duration of phase II ($P = 0.02$) but not phases I and III. Post-prandially, sumatriptan reduced the activity index ($P = 0.017$) by reducing the frequency of co-ordinated motor activity involving the antrum and/or the duodenum ($P < 0.05$).
Conclusion: 5-HT_1 receptor agonism increases the periodicity of the migrating motor complex and reduces the occurrence of post-prandial co-ordinated motor activity involving the gastric antrum, pylorus and duodenum.

INTRODUCTION

5-Hydroxytryptamine (5-HT), acting through 5-HT_1, 5-HT_3 and 5-HT_4 receptors, plays a significant role in the control of gastrointestinal motility, sensation and secretion.[1–3] Furthermore, recent observations that plasma 5-HT concentrations are elevated in female patients with diarrhoea-predominant irritable bowel syndrome[4, 5] and in functional dyspepsia,[6] especially in those exhibiting post-prandial symptoms,[5, 6] provide support for its involvement in the motor and sensory dysfunction associated with these conditions.

Over the last decade, 5-HT receptors have been targeted in the development of pharmacological compounds for the treatment of these disorders. Partial agonism of the 5-HT_4 receptor, using for example tegaserod, has been shown to improve abdominal pain, bloating, stool frequency and consistency in patients with constipation-predominant irritable bowel syndrome.[7, 8] It has also been shown to decrease sensitivity to rectal distension,[9] increase the gastric emptying rate[10] and accelerate small and large bowel transit.[10, 11] In addition, recent preliminary data have suggested a tendency for tegaserod to improve symptoms in patients with functional dyspepsia.[12] Antagonism of the 5-HT_3 receptor using alosetron, on the other hand, relieves pain, normalizes bowel frequency and reduces bowel urgency,[13] as well as reducing visceral sensation by relaxing the colon[14] and retarding small[15] and large[15, 16] bowel transit, in patients with diarrhoea-predominant irritable bowel syndrome. In addition, alosetron has recently been reported to reduce

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symptoms in patients with functional dyspepsia,[17] an effect which appears to be independent of changes in gastric emptying[17] or gastric volume.[18] Both tegaserod and alosetron have now been approved by the Food and Drug Administration for use in irritable bowel syndrome of the appropriate sub-type.

Another potential therapeutic approach to the treatment of functional dyspepsia, which has still to be established, is 5-HT_1 receptor agonism. Tack's group have reported that the 5-HT_1 receptor agonist, sumatriptan, normalizes meal-induced gastric relaxation and improves early satiety in functional dyspeptic patients with impaired post-prandial accommodation.[19] This improvement in dyspeptic symptomatology appears to occur despite the fact that sumatriptan is known to delay gastric emptying of both liquids[20] and solids,[20, 21] a phenomenon related in part to a reduction of fundic tone,[22] although, until the present study, its effect on the motor activity of the gastric antrum, pylorus and duodenum, which are also involved in the control of gastric emptying,[23] was unknown. Other studies, however, have failed to reproduce these beneficial effects of sumatriptan on dyspeptic symptoms,[24] and in healthy volunteers have suggested that it shortens the migrating motor complex (MMC) cycle length by inducing premature jejunal phase III-like activity and reducing the length of phase II.[25] No data, however, currently exist on the effect of 5-HT_1 receptor agonism on the pattern, frequency and amplitude of contractions occurring in the antro-pyloro-duodenal region during the different phases of the MMC.

The aim of this study was to assess the effect of 5-HT_1 receptor agonism, using sumatriptan, on the antro-pyloro-duodenal motility under both fasting (study 1) and fed (study 2) conditions in healthy volunteers.

MATERIALS AND METHODS

Subjects

Eleven healthy volunteers (eight males, three females), aged 21–36 years (mean age, 25.1 years), participated in study 1, and 10 healthy volunteers (eight males, two females), aged 18–36 years (mean age, 22.9 years), participated in study 2. All subjects underwent a routine clinical examination and electrocardiogram, and were excluded if they had any history of gastrointestinal disease or surgery (except appendicectomy and herniorrhaphy), diabetes mellitus, alcoholism, collagen vascular disease, neurological disorders or electrocardiographic abnormalities.

Subjects who had participated in another study within the past 3 months or who had taken regular medication during the past month (with the exception or oral contraceptives) were excluded. All females provided a negative pregnancy test prior to entering the study. Subjects who smoked more than 10 cigarettes per day, drank more than the recommended units of alcohol (females, > 14 units; males, > 21 units) per week or had a body mass index over 30 kg/m^2 were excluded. In addition, subjects were asked to abstain from smoking, alcohol and strenuous exercise for 24 h prior to the study. Caffeine and over-the-counter medications were prohibited for 48 h prior to each study. The protocol was approved by the South Manchester Local Research Ethics Committee and the subjects gave written informed consent.

Study design and procedure

Both studies were randomized, double-blind, placebo-controlled and two-way cross-over in design, where each subject received either 6 mg of subcutaneous sumatriptan or saline control on two separate occasions. For both studies, subjects were assessed at the same time of the day, and there were at least 5 days but no more than 21 days between the sumatriptan and control arms of the studies.

Study 1. After an overnight fast, a manometric catheter was passed transnasally and positioned across the pylorus by dual-point transmucosal potential difference (TMPD) measurements, as described previously.[26, 27] Fasting pressures were recorded for two complete phase IIIs of the MMC and, 5 min after the second phase III, a subcutaneous injection of either sumatriptan 6 mg or normal saline was administered to the deltoid region of the arm using an auto-injector. Pressure recordings were then continued until at least one additional phase III had passed.

Study 2. As for study 1, the manometric catheter was positioned following an overnight fast, as described above. Five minutes after the end of phase III of the MMC, subjects were given a standard meal consisting of a one-egg omelette and two slices of bread [31.2 g carbohydrate, 6.25 g protein, 5.8 g fat, 124 kcal (468 kJ)] which was consumed within 10 min.

Immediately after the meal, a subcutaneous injection of either sumatriptan 6 mg or saline control was administered to the deltoid region of the arm by auto-injector, and fed pressure activity was recorded for a further 3 h.

Manometric technique

The manometric technique was similar to that described previously.[26, 27] Pressures were measured with an eight-lumen perfused catheter (Dentsleeve plc, Adelaide, South Australia), which incorporated a 4.5-cm-long stiffened sleeve sensor in parallel with three side-holes (1.5 cm apart) proximal and four side-holes (3 cm apart) distal to the sleeve. The side-holes at each end of the sleeve recorded the intraluminal pressure and TMPD simultaneously. Each lumen was connected to a pressure transducer and perfused with degassed distilled water, with the exception of those at either side of the sleeve, which were perfused with normal saline from two separate reservoirs from that used for water perfusion, via a low-compliance pneumohydraulic capillary perfusion system (Arndorfer Medical Specialties Inc., Wisconsin, USA). All channels were perfused at 0.2 mL/min, except for the sleeve which was perfused at 0.4 mL/min. Signals acquired by the pressure transducers were converted by an analogue–digital converter (Polygraph, Synectics Medical, Stockholm, Sweden). The equipment was calibrated at 0 and 50 mmHg before and re-checked after each study. The TMPD was measured using a technique described previously, [26] and the sleeve was said to be correctly positioned across the pylorus TMPD gradient if the antral TMPD was − 20 mV or less and the duodenal TMPD was − 15 mV or more, with a difference between the two of at least 15 mV.[26] Using these criteria, the catheter was correctly positioned for 88% ± 6% (mean ± s.d.) of the total recording time during the experimental period.

Analysis of manometric data

Under fasting conditions, the periodicity of the MMC cycle was measured as the time interval between the start of two successive phase IIIs, where phase III was defined as at least 2 min of regular contractile activity at a frequency of 3/min in the antrum and 10–12/min in the duodenum.[26] The velocity of propagation of each phase III was calculated by dividing the time from the start of phase III activity at one side-hole to that at a successive side-hole into the distance between these side-holes. The fed manometric records were divided into three 1-h periods, with time 0 being the start of the subcutaneous injection. A phasic contraction was said to occur if there was an increase in pressure of 10 mmHg or more (to allow for pressure changes due to respiration) that lasted between 15 and 25 s in the antrum and 4 and 10 s in the duodenum.[26–29] Each of the three post-prandial periods, together with phase II of the MMC under fasting conditions, was analysed to yield values for: (i) the number of pressure waves greater than 10 mmHg; (ii) the mean amplitude of pressure peaks; and (iii) the activity index (i.e. area under the curve calculated by integration of the curve). In addition, antral and duodenal pressure waves were judged to be associated in time (i.e. co-ordinated) if the onset of the pressure wave in one channel occurred within 5 s of the onset of a pressure wave recorded in an immediately adjacent channel.[26, 27] Co-ordinated events were subdivided as follows: (i) antro-pyloric co-ordination — pressure waves in two or more antral sites and the sleeve sensor but no duodenal sites; (ii) pyloro-duodenal co-ordination — pressure waves in two or more duodenal sites and the sleeve sensor but no antral sites; (iii) duodenal co-ordination — pressure waves in two or more duodenal sites but no antral or sleeve sensor sites; (iv) antro-pyloro-duodenal co-ordination — pressure waves in antral, sleeve sensor and duodenal recording sites. Pressure waves recorded by the sleeve sensor in the absence of any discernible pressure wave in the adjacent antral and duodenal side-holes were classified as isolated pyloric pressure waves (IPPWs).[26, 27, 30] As IPPWs are known to occur following both inter-digestive phase III activity and nutrient ingestion,[26, 27, 30–33] these were recorded under both conditions. Lastly, the mean basal pyloric pressure was calculated as the difference between the basal pressure recorded by the sleeve and that recorded by the distal antral side-hole for each post-prandial hour and for phases I and II of the MMC.[26, 27, 30]

Statistical analysis

Wilcoxon's matched-pairs signed-rank test was used to compare the changes from pre- to post-injection under fasting conditions and the post-prandial data for the sumatriptan 6 mg and placebo groups. The analysis

was based on subjects with data for all periods, and a test for any carry-over effect was included. Results are expressed as the median and range or interquartile range (IQR) unless otherwise stated. Bonferroni's correction was applied for multiple comparisons, and a P value of < 0.05 was taken as significant.

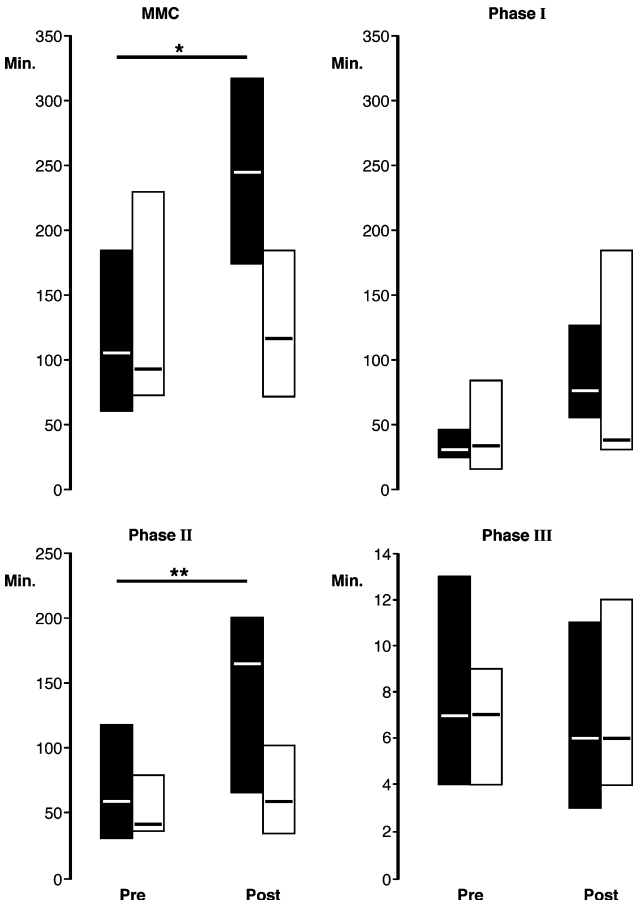

Figure 1. Duration (min) of migrating motor complex (MMC) cycle, phase I, phase II and phase III, pre- and post-administration of sumatriptan 6 mg (filled bars) and saline control (open bars). Results are expressed as the median and interquartile range. Comparison of pre- and post-injection difference between sumatriptan and saline control, where $^{*}P < 0.01$ and $^{**}P = 0.02$.

RESULTS

Fasting conditions

In all but one volunteer, two phase IIIs before and at least one phase III after subcutaneous injection of either sumatriptan or saline control were recorded. In the remaining volunteer, despite recording in excess of 350 min post-sumatriptan injection, a third phase III was not recorded.

Sumatriptan significantly prolonged the cycle length of the MMC [median (IQR): change from pre- to post-injection, sumatriptan 136 min (112–160 min) vs. control −22 min (− 80 to 45 min); $P = 0.009$], and this was associated with a significant increase in duration of phase II [105 min (35–118 min) vs. −18 min (− 80 to 22 min); $P < 0.02$], but no significant changes in the duration of phase I [46 min (31–118 min) vs. 4 min (− 14 – 100 min)] or III [1 min (1–2 min) vs. 1 min (0–3 min)] (Figure 1).

Sumatriptan did not influence the number of phase IIIs with either an antral or duodenal origin [phase IIIs with antral origin: pre- and post-sumatriptan injection, 7/11 vs. 4/10 ($P = 0.24$); pre- and post-saline injection, 6/11 vs. 5/11 ($P = 0.812$)] or the velocity of their propagation (Table 1). Similarly, sumatriptan did not significantly change the activity index, pattern of co-ordination or amplitude of contractions during phase II, the numbers of IPPWs during phase I or the pyloric tone during phases I and II of the MMC compared with control conditions (Table 2).

Fed conditions

Sumatriptan significantly reduced the activity index in the antrum and duodenum during the first post-prandial hour ($P = 0.017$), and tended to reduce the

Table 1. Velocity of propagation of the antral and duodenal components of phase III of the migrating motor complex (cm/s)

	Sumatriptan 6 mg			Placebo		
	Pre-injection	Post-injection	Δ	Pre-injection	Post-injection	Δ
Antral	5.7 (5.1–6.2)	5.9 (5.3–6.3)	0.5 (0.2–0.9)	6.2 (5.6–6.8)	5.5 (5.0–6.1)	0.6 (0.3–1.2)
Duodenal	4.2 (3.5–6.1)	4.4 (3.4–6.0)	0.3 (0.1–0.7)	4.0 (3.0–5.8)	3.8 (3.3–5.3)	0.3 (0.1–0.6)

Results expressed as median (interquartile range). Δ = difference post- minus pre-injection.

Table 2. Motor activity during phase I and II of the migrating motor complex (/h)

	Sumatriptan 6 mg			Placebo		
	Pre-injection	Post-injection	Δ	Pre-injection	Post-injection	Δ
Phase II						
Activity index (mmHg)						
Antral	380 (103–1143)	160 (63–1027)	− 104 (− 500 to 12)	192 (46–697)	253 (53–434)	− 22 (− 240 to 288)
Pyloric	197 (99–281)	184 (95–207)	− 4 (− 80 to 95)	136 (73–339)	198 (87–328)	45 (− 82 to 198)
Duodenal	148 (82–1163)	152 (82–3573)	− 83 (− 280 to 362)	203 (69–952)	157 (65–725)	10 (− 300 to 342)
Co-ordinated activity (no.)						
Total	52 (23–118)	25 (14–59)	− 16 (− 75 to 10)	44 (27–103)	38 (16–62)	2 (− 50 to 30)
AP	1 (0–6)	1 (0–3)	0 (− 2 to 0)	0 (0–11)	0 (0–4)	0 (− 7 to 10)
APD	36 (11–47)	10 (3–18)	0 (− 40 to 10)	30 (19–58)	18 (8–29)	− 10 (− 30 to 30)
PD	14 (5–26)	8 (2–18)	0 (− 5 to 33)	5 (1–9)	11 (6–20)	2 (− 8 to 12)
D	0 (0–12)	1 (0–3)	1 (− 2 to 10)	7 (2–9)	1 (0–6)	− 1 (− 10 to 8)
Amplitude (mmHg)						
Antral	32 (22–45)	23 (15–39)	− 7 (− 10 to 2)	47 (22–57)	43 (28–69)	− 4 (− 15 to 18)
Pyloric	31 (26–42)	29 (20–37)	− 8 (− 12 to 2)	29 (27–50)	26 (19–39)	− 8 (− 15 to − 3)
Duodenal	23 (20–29)	18 (16–26)	− 3 (− 8 to − 1)	23 (18–26)	23 (20–26)	2 (− 6 to 6)
Pyloric tone (mmHg)	1.8 (1.5–2.8)	1.6 (0.6–2.4)	− 0.4 (− 0.8 to 0.3)	1.5 (0.8–2.1)	1.2 (0.4–1.6)	− 0.3 (− 0.4 to 0.9)
Phase I						
IPPWs	30 (2–98)	54 (8–146)	5 (− 25 to 105)	14 (0–40)	23 (6–38)	1 (− 3 to 24)
Pyloric tone (mmHg)	1.1 (0.7–2.1)	1.6 (0.5–2.4)	0.4 (− 0.1 to 0.5)	1.3 (0.8–1.8)	1.1 (0.3–1.9)	− 0.2 (− 0.4 to 0.5)

AP, antro-pyloric co-ordinated events; APD, antro-pyloro-duodenal co-ordinated events; D, duodenal co-ordinated events; PD, pyloro-duodenal co-ordinated events; IPPWs, isolated pyloric pressure waves.
Results expressed as median (interquartile range). Δ = difference post- minus pre-injection.

activity index in the pylorus during the first hour ($P = 0.06$) and in the duodenum during the second hour ($P = 0.09$), compared with control conditions. By the third hour, there were no differences in activity index between the two groups (Figure 2). This was associated with a significant reduction in the number of contractions during the first and second hours ($P < 0.05$) (Figure 2), a reduction in the number of co-ordinated motor events, particularly during the first hour ($P < 0.05$) (Figure 3), but no change in the amplitude of contractions or number of IPPWs induced by meal ingestion (Figures 2 and 3). Likewise, the pyloric tone was unaffected by the administration of sumatriptan [sumatriptan: first hour, 2.1 mmHg (1.6–2.9 mmHg); second hour, 1.6 mmHg (0.9–1.9 mmHg); third hour, 1.8 mmHg (1.3–2.4 mmHg); placebo: first hour, 1.9 mmHg (1.4–2.8 mmHg); second hour, 1.5 mmHg (1.0–2.1 mmHg); third hour, 1.8 mmHg (1.2–2.1 mmHg)].

No carry-over effect was observed for any parameter assessed in this study.

Adverse events

Table 3 lists the number of subjects reporting various adverse events. Under fasting conditions, nine of 11 subjects reported adverse events following the administration of sumatriptan 6 mg, which occurred 4–15 min after administration and lasted between 6 and 15 min. One subject reported chest pain, but this was not associated with a change in the electrocardiogram. Only one subject reported an adverse event following the administration of placebo, which was headache and was reported 12 min after the injection and lasted 22 min. Similarly, under fed conditions, nine of 10 subjects reported adverse events following sumatriptan administration, compared with only two subjects following placebo administration. These occurred 3–8 min after the administration of sumatriptan and lasted between 2 and 16 min. One subject reported headache and another nausea 5–12 min after the administration of placebo, which lasted between 3 and 32 min.

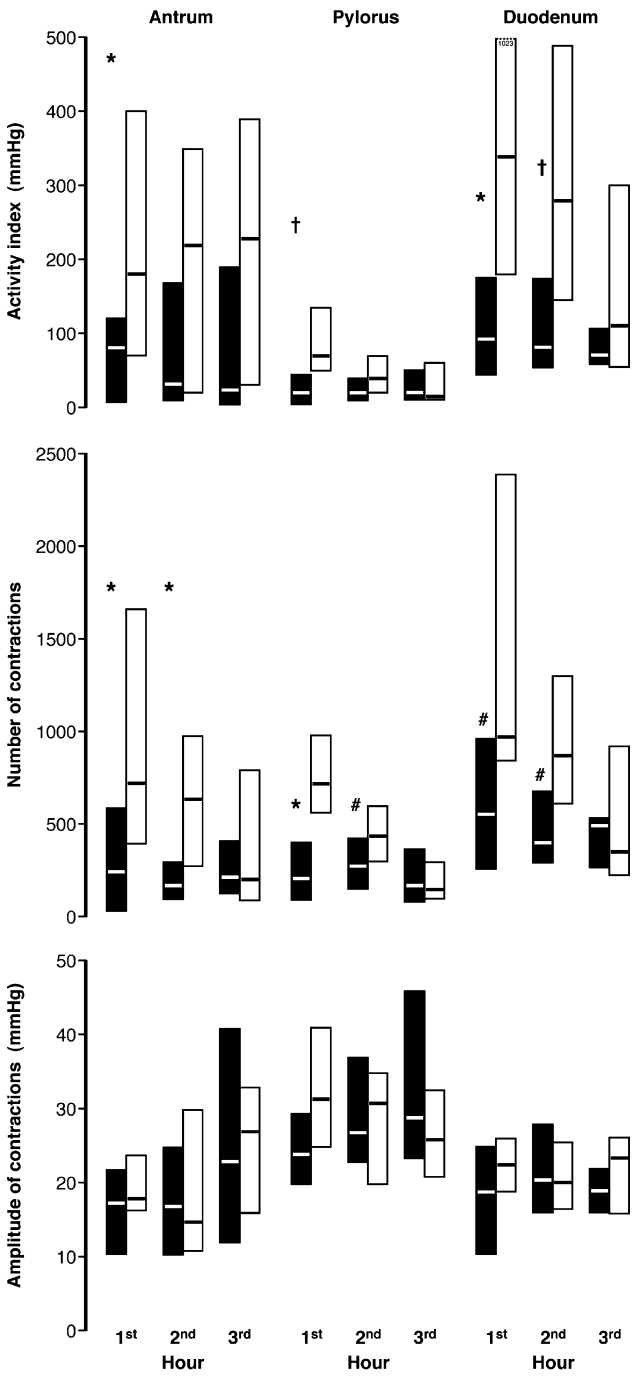

Figure 2. Activity index (mmHg), number of contractions and amplitude of contractions (mmHg) during the first, second and third post-prandial hour following administration of sumatriptan 6 mg (filled bars) and saline control (open bars). Results are expressed as the median and interquartile range over the three antral channels, the pyloric channel and four duodenal channels. $^{*}P < 0.02$, $^{\#}P < 0.05$ and $\dagger P < 0.09$ compared with saline control.

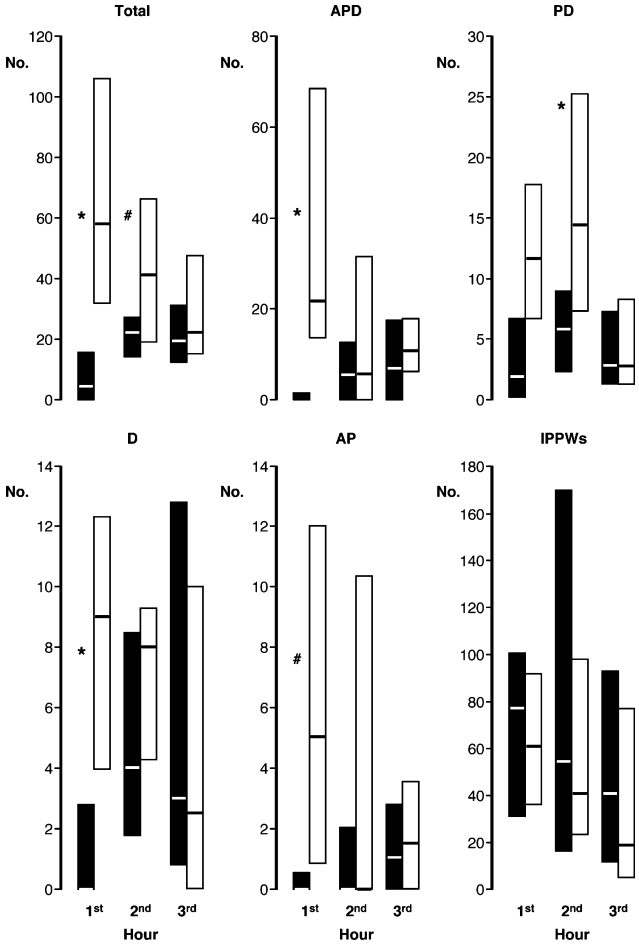

Figure 3. Number of total, antro-pyloro-duodenal (APD), pyloro-duodenal (PD), duodenal (D) and antro-pyloric (AP) co-ordinated motor events, together with isolated pyloric pressure waves (IPPWs), during the first, second and third post-prandial hour following the administration of sumatriptan 6 mg (filled bars) or saline control (open bars). Results are expressed as the median and interquartile range. $^{*}P < 0.01$ and $^{\#}P < 0.05$ compared with saline control.

DISCUSSION

This study has shown for the first time that 5-HT_1 receptor agonism using sumatriptan substantially increases the periodicity of the MMC in the antrum and duodenum by prolonging phase II. The duration and velocity of propagation of phase III were unchanged. Following meal ingestion, sumatriptan reduced the activity index of the antro-pyloro-duodenal motor region for up to 2 h, and this was associated with a reduction in the frequency rather than the amplitude of contractility. This reduction in contraction frequency reflected a decrease in the occurrence of co-ordinated

Table 3. Number of subjects reporting adverse events following the administration of sumatriptan 6 mg or placebo under fasting and fed conditions

	Fasting		Fed	
	Sumatriptan	Placebo	Sumatriptan	Placebo
Light-headedness	6	0	2	0
Tingling/pain in forehead	5	0	4	0
Tingling/pain in back of neck	4	0	6	0
Pins and needles	4	0	4	0
Legs feeling heavy	3	0	3	0
Headache	0	1	0	1
Chest pain	1	0	0	0
Nausea	0	0	0	1

phasic activity involving both the antrum and/or the duodenum.

Our observation that sumatriptan prolongs the MMC cycle length in the antrum and duodenum is in contrast with a previous report by Tack *et al.*, who suggested that the cycle length was considerably shortened by the induction of premature phase III-like activity in the jejunum and that gastric phase III activity was suppressed.[25] The apparent lack of gastric and duodenal phase III activity following sumatriptan administration in the study by Tack *et al.*, however, could be related to the fact that the manometric recording was terminated approximately 120 min following the administration of sumatriptan.[25] In our study, antro-duodenal phase III activity did not return until approximately 240 min after administration, a time which far exceeds the post-sumatriptan recording period in the study by Tack *et al.*[25] Unfortunately, we did not record the jejunal activity in the present study and so are unable to comment on whether premature jejunal phase III-like activity occurred in our subjects. Premature phase III-like activity has been shown to occur in response to a number of agents, including somatostatin[34] and erythromycin,[35] as well as to intraduodenal infusion of acid,[31] fat[32] and dextrose,[30] and even to stress.[33, 36] Stress has been suggested to not only induce premature phase III-like activity in distal regions of the duodenum and jejunum, but also to inhibit motility in more proximal regions of the duodenum and antrum,[33, 36] an observation similar to that reported in the study by Tack *et al.*[25] This could lead to the speculation that stress might be a confounding factor in the study by Tack *et al.*, as there was no placebo injection in the comparator group and thus no control for the potential stress associated with injections.[25] Distal movement of the catheter in the study by Tack *et al.*, especially during phase III (the location of the catheter was only checked fluoroscopically at the beginning of the study), may also have led to a reduced ability to record antral motor activity,[25] especially given that the distance between the side-holes was 3 cm, a configuration which has been shown to be less reliable at recording antral motility than our 1.5 cm spacing.[37] In addition, any distal movement of the catheter during phase III activity would have made it more likely that any phase III-like activity occurring in more distal regions of the duodenum and jejunum would have been recorded. Further studies are required in which antral, pyloric, duodenal and jejunal motility should be recorded simultaneously, using an appropriately TMPD-positioned catheter assembly, for prolonged periods of time (> 4 h) following subcutaneous injections of sumatriptan and saline control, to clarify these inconsistencies. Finally, our study adds to previous data on the effect of sumatriptan on the periodicity of the MMC[25] by reporting on the pattern of antro-pyloro-duodenal co-ordination, amplitude of contractions and activity index during phase II, the presence of IPPWs during phase I, and the basal pyloric tone during phases I and II of the MMC; none of these were significantly affected by the administration of sumatriptan.

Post-prandially, sumatriptan significantly reduced the occurrence of co-ordinated motor activity involving the antrum, pylorus and duodenum. However, it appeared to have no effect on the amplitude of contractions still occurring in these three regions, the pyloric tone or IPPW activity. Gastric emptying of solids is characterized by an initial lag period in which the solid is redistributed between the proximal and distal regions of the stomach, followed by a linear emptying period.[27, 38, 39] The duration of the lag phase has been suggested to be inversely related to the amount of antral motor activity.[38] Thus, the reduction in co-ordinated motor activity involving the antrum, seen following

sumatriptan administration in the present study, together with its known relaxing effect on the gastric fundus,[22] probably accounts for the prolongation of the lag phase and the concomitant delay in the emptying of solids.[21] In addition, the reduction in co-ordinated activity involving the antrum and pylorus may be expected to reduce the breakdown of the food to suitably sized particles to transverse the pylorus, whilst the reduction in co-ordinated motor activity involving the duodenum might be expected to still further delay gastric emptying by decreasing the duodenal clearance of emptied gastric chyme. It could be argued that the reduction in co-ordinated activity involving the antrum, seen following sumatriptan administration, might just represent a decreased likelihood of the pressure sensors to be able to register a rise in pressure due to there being less solid present in the antrum because of increased fundic retention of the food. Antral contractions would be more able to displace small rather than large quantities of food, making the contractions less likely to be registered as pressure rises. This, however, does not appear to be the case as the amplitudes of contractions still occurring in the antrum during the first post-prandial hour following sumatriptan administration (i.e. during the expected lag period when there is increased fundic retention of the solids) were of a similar value to those occurring in subsequent hours and following placebo.

The stimulation of pyloric activity, in particular IPPWs, is also thought to be another important regulator of gastric emptying,[26, 27, 30–32] as IPPWs are associated with the cessation of transpyloric flow[40] and delayed gastric emptying.[27, 41] It was therefore a little surprising to see no change in IPPW activity and, indeed, a significant reduction in pyloric activity overall following sumatriptan administration. These observations might be considered to be more consistent with an acceleration of gastric emptying, but support previous suggestions from the Adelaide group that the fundus, antrum and pylorus all interact to control gastric emptying and have a capacity to compensate for each others' alterations, so that changes in the overall rate of emptying are minimized.[42–45]

The precise mechanisms underlying these sumatriptan-induced motility changes are incompletely understood. Sumatriptan is a selective agonist for 5-HT_1 receptors, having little or no activity at other 5-HT receptor sub-types (5-HT_{2-7}). It has highest affinity for human recombinant 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors, and weak affinity for 5-HT_{1A} and 5-HT_{1E} receptors.[46] There is increasing evidence for the presence of 5-HT_1 receptors on the nitrergic motor neurones of the vagal inhibitory pathways,[47] and, as sumatriptan poorly penetrates the blood–brain barrier,[48, 49] it would seem likely that it is via the activation of these receptors that it mediates its effect on the antro-pyloro-duodenal motility and gastric emptying. This is supported by an *in vivo* cat model study in which it was shown that the nitric oxide synthase inhibitor, N^{ω}-nitro-L-arginine methyl ester, antagonized sumatriptan's effect on gastric relaxation.[22] In addition, the specific nitric oxide synthase inhibitor, N^{G}-monomethyl-L-arginine, has been shown to shorten the MMC cycle length in the antro-duodenal region in humans, and not to alter the site of origin, duration or velocity of propagation of phase III activity.[50] Conversely, the nitric oxide donor, nitroglycerin, has been found to delay gastric emptying of a 25% glucose liquid meal, which was shown to be associated with increased retention of the meal in the proximal stomach, and to reduce antral co-ordinated motor activity and pyloric activity in humans.[45] Interestingly, in the latter study, IPPW activity was also reduced, as it was in another study in which glyceryl trinitrite was shown to inhibit duodenal triglyceride-induced IPPWs.[51] The lack of effect of sumatriptan on pyloric tone and IPPW activity in the present study (although we did observe a reduction in overall pyloric activity) was probably because our meal was less rich in nutrients, thereby inducing less pyloric tone and IPPWs for sumatriptan to inhibit. Thus, the effects of sumatriptan on both the inter-digestive and digestive antro-pyloro-duodenal motility in the present study are consistent with the latter observations, suggesting modulation via the nitrergic inhibitory pathways. Lastly, it has recently been shown that sumatriptan's relaxing effect on the canine fundus can be fully reversed by both GR-127935, a non-selective 5-$HT_{1D/B}$ receptor antagonist, and SB-216641 hydrochloride, a selective 5-HT_{1B} receptor antagonist, but not BRL-15572 hydrochloride, a selective 5-HT_{1D} receptor antagonist, suggesting that it may be the 5-HT_{1B} receptors on the enteric inhibitory motor neurones which play an important role in modulating gastro-pyloro-duodenal motility and gastric emptying.[52] Interestingly, the vasoconstrictor effects of sumatriptan on the coronary arteries are also thought to be mediated via activation of the 5-HT_{1B} receptors on the vascular smooth muscle.[53]

The question of whether 5-HT_1 receptor agonism might be a useful approach to the treatment of certain gastrointestinal motility disorders, such as functional dyspepsia, still remains to be elucidated. Boeckxstaens *et al.*[24] were unable to reproduce the findings of Tack *et al.*[19] of a beneficial effect of sumatriptan on dyspeptic symptoms. In addition, our observations that the co-ordinated motor activity involving the antrum, pylorus and duodenum is reduced provide further evidence that some of the physiological changes observed with 5-HT_1 receptor agonism may not be beneficial to these patients. These uncertainties, together with the known stimulatory effect of sumatriptan on oesophageal motility,[54, 55] its promotion of gastro-oesophageal reflux,[56, 57] its enhancement of oesophageal visceral sensation,[58] its vasoconstrictive effect on the coronary arteries[59] and its unpleasant side-effect profile (e.g. chest pain), might make it an unlikely contender as a potential therapeutic agent in the treatment of gastrointestinal motility disorders.

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