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Altered oesophageal motility following the administration of the 5-HT$_1$ agonist, sumatriptan

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SUMMARY

Background: The 5-HT$_1$ agonist sumatriptan, used in the treatment of migraine, can cause chest pain.
Aim: To investigate the effect of a therapeutic dose of sumatriptan (6 mg s.c.) on oesophageal motility.
Methods: In 16 normal healthy subjects aged 19–32 years (9 males), the manometric response of the lower oesophageal sphincter (sleeve sensor), oesophageal body (four sites), stomach and pharynx (to register swallows) to 5 mL water swallows was assessed before and after a subcutaneous injection of either sumatriptan (6 mg) or saline control. Symptoms and ECGs were also monitored.
Results: Sumatriptan 6 mg s.c. altered oesophageal motility in all subjects. This was reflected by a significant increase in the amplitude of oesophageal body contractions (change from pre- to 1 h post-injection: sumatriptan 9.9 (2.8, 17.1) mmHg vs. placebo – 0.8 (– 4.2, 2.6) mmHg, difference 10.8 (4.4, 17.1) mmHg; $P = 0.003$) and a transient increase in lower oesophageal sphincter pressure (change from pre- to 5 min post-injection: sumatriptan 10.9 (5.2, 16.6) mmHg vs. placebo 5.1 (1.8, 8.4) mmHg, difference 5.8 (– 0.7, 12.3) mmHg; $P = 0.08$). Sumatriptan had no effect on the velocity of propagation of oesophageal contractions (change from pre- to 1 h post-injection: sumatriptan – 0.1 (– 0.3, 0.1) cm/s vs. placebo – 0.1 (– 0.3, 0.0) cm/s, difference 0.1 (– 0.1, 0.2) cm/s; $P = 0.40$). One subject experienced chest symptoms following sumatriptan and, although motility was altered, this did not reach pathological levels. No ECG abnormalities were observed.
Conclusion: Sumatriptan (6 mg s.c.) significantly alters oesophageal motor function without affecting the ECG. It is therefore possible that sumatriptan-induced chest symptoms may have an oesophageal origin. The evaluation of similar therapeutic agents for migraine on oesophageal function may be justified.

INTRODUCTION

Sumatriptan, a 5-HT$_1$ agonist used in the treatment of migraine, induces chest symptoms in 3–5% of patients.[1] These chest symptoms have been linked to cardiac abnormalities in several case reports.[2–9] However, in the majority of cases either the temporal relationship between the administration of sumatriptan and the cardiac event was poor, or the subjects had pre-existing cardiovascular disease. Furthermore, several studies have failed to demonstrate electrocardiographic changes following administration of sumatriptan,[10, 11] even when chest symptoms have been experienced.[12, 13] These observations suggest that the heart may not necessarily be the origin of this problem in most cases.

An alternative reason for this side-effect of sumatriptan could be abnormal oesophageal contractility.[14–16] We have previously shown that a supratherapeutic dose of subcutaneous (s.c.) sumatriptan (16 mg) produces pathological changes in oesophageal motility in ≈ 50% of healthy volunteers.[17] These changes tended to be greater in those subjects who experienced sumatriptan-

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induced chest symptoms, when compared with subjects who did not report chest symptoms. Furthermore, all remaining subjects demonstrated some change in oesophageal motility with sumatriptan, although this did not reach pathological levels.

The aim of this study was to investigate the effect of a standard therapeutic dose of sumatriptan (6 mg s.c.) on oesophageal motility. In addition, the effect of this 6 mg dose on oesophageal motility was compared with that obtained in our previous study which used a supra-therapeutic 16 mg dose of sumatriptan.[17]

MATERIALS AND METHODS

Subjects

Sixteen healthy subjects (9 male, 7 female) aged 19–32 years (mean age of 24.9 years) participated in the study. All subjects underwent a physical examination and were excluded if they exhibited any abnormality in the following: haematology, biochemistry, urinalysis or 12-lead electrocardiography (ECG). None of the subjects had taken regular medication in the 4 weeks preceding their recruitment, except for the contraceptive pill. In addition, females were required to provide a negative pregnancy test on each visit to the laboratory. All volunteers drank below the recommended alcohol limit (males, 21 units/week; females, 14 units/week) and smoked less than five cigarettes per day. They were asked to abstain from smoking, alcohol and strenuous exercise in the 24 h prior to each study. Caffeine and over-the-counter medications were prohibited for 48 h before each study. The protocol was approved by South Manchester Medical Research Ethics Committee and the subjects gave written informed consent.

Assuming the same variability as seen in our previous data,[17] this study on 16 healthy subjects had an 80% power of detecting a 20% difference in the amplitude of oesophageal body contractions in any of the recording sites between the sumatriptan 6 mg and placebo treatment groups.

Design and procedure

The study was double-blind, randomized and placebo-controlled with a crossover design, where each subject received either 6 mg s.c. sumatriptan or saline control on two separate occasions. Studies were performed at the same time of day and were separated by between 5 days and 3 weeks.

On the day of the study, subjects attended the Clinical Investigations Laboratory after an overnight fast. A Dent sleeve manometric catheter (Dentsleeve Pty Ltd, Bowden, South Australia 5007; external diameter 4.5 mm) was passed via an anaesthetized nostril and manoeuvred into position such that the sleeve sensor straddled the lower oesophageal sphincter. With the subjects in a supine position and after a 10 min rest period, basal oesophageal motility was recorded for 15 min. During this time, two sequences of six consecutive 5 mL water swallows were performed, each water swallow being separated by at least 20 s and each sequence of six water swallows being separated by 10 min. If the subject swallowed twice, or took a dry swallow during the 20 s interval between water swallows, the water swallow was repeated after a further 20 s. Sumatriptan 6 mg or saline control was then administered subcutaneously to the deltoid region of the arm with an autoinjector. Following injection, further sequences of six water swallows were carried out at 5, 15, 30, 45, 60, 80, 100, 120, 150 and 180 min. 12-lead ECG recordings (Marquette Mac PC; R L Dolby and Co. Ltd, Dunblane, Scotland) preceded each sequence of water swallows and were also taken 10 min before, and 10 and 20 min after injection. Additional 12-lead ECGs were taken if the subject experienced chest symptoms outside the standard recording times. The subjects were prohibited from sleeping during the study and only moved from the recumbent position to void their bladders.[18] All adverse events were noted.

Oesophageal manometry

Manometric recordings were performed using an eight-lumen catheter which incorporated a 6 cm long sleeve sensor at the distal end to monitor the lower oesophageal sphincter pressure. Swallowing was recorded by a side hole in the pharynx, 25 cm above the proximal margin of the sleeve. Oesophageal contractions were measured by side holes located 0, 5, 10 and 15 cm above the proximal margin of the sleeve and gastric pressure by a side hole 1 cm below the distal margin of the sleeve. The oesophageal and pharyngeal side holes were perfused with degassed distilled water at 0.3 mL/min, and the sleeve sensor and gastric side hole at 0.5 mL/min, by a pneumohydraulic capillary infusion system (Arndorfer Medical Specialities Inc., Greendale, Wisconsin, USA). Pressures were sensed by external water-filled pressure transducers connected to an ana-

logue–digital converter (Polygraph HR; Synectics Medical, Stockholm, Sweden) and then displayed and recorded on an IBM-compatible computer using Polygram software (Synectics Medical). The system was calibrated at 0 and 50 mmHg at the beginning of each study and checked again at the end of each study to confirm it was still recording these pressures accurately.

Data measurements

Oesophageal motility. The oesophageal contractions produced by the water swallows were assessed blindly by one observer (JMF), who manually positioned cursors on the computer monitor and then used the software (Polygram 5.06; Synectics Medical, Stockholm, Sweden) to calculate the various parameters. Baselines were automatically set by the computer program. The amplitude was measured (in mmHg) from the baseline to the peak of the oesophageal contraction. The contraction duration was defined as the time interval (in seconds) between the onset of the sharp increase in the oesophageal pressure wave and the return of the pressure to the baseline.[19] The velocity of propagation was calculated (in cm/s) by dividing the time interval between the peaks of the oesophageal contractions into the distance between adjacent side holes (5 cm).[20] Peristaltic contractions were defined as having a velocity > 0 cm/s but ≤ 10 cm/s.[19] Simultaneous contractions were said to occur when the velocity of propagation of contractions between adjacent side holes was > 10 cm/s.[19] Repetitive contractions were defined as contractions with more than one peak, where each peak had an amplitude of at least 10 mmHg and was separated from the previous peak by at least 1 s.[21]

Lower oesophageal sphincter pressure (LOSP). Basal lower oesophageal sphincter pressure was measured visually by placing a 'best-fit' line over the end expiratory pressures recorded in the 1 min period preceding each sequence of six water swallows and referenced to intragastric pressure.[22] The basal lower oesophageal sphincter pressure before each water swallow and the nadir sphincter pressure during sphincter relaxation were also measured and referenced to intragastric pressure, to determine the extent of relaxation of the lower oesophageal sphincter.[23] This was represented as the percentage relaxation, calculated as follows: % relaxation $=$ [(basal pressure – relaxed pressure)/basal pressure] $\times$ 100.

Pathologically abnormal oesophageal motility. Oesophageal motility was arbitrarily defined as pathologically abnormal when $> 15\%$ of the total number of oesophageal contractions exhibited one or more of the following: amplitude > 180 mmHg;[19] duration > 7 s;[24] repetitive contractions with more than two peaks.[19]

Chest symptoms. Chest symptoms were defined as chest pain, discomfort, heaviness, tightness or a feeling of needing to breathe harder. These were said to be associated with abnormal oesophageal motility if the chest symptoms occurred within 2 min of the onset of an oesophageal event.[15]

Statistical analysis

Data was averaged pre-injection, and 1 and 3 h post-injection of sumatriptan and saline control. Paired *t*-test or Wilcoxon's matched-pairs signed-rank tests were used to compare (i) the pre-injection baseline values for sumatriptan 6 mg and placebo groups, and (ii) the change from baseline values following injection of sumatriptan 6 mg and placebo. Differences in the number of subjects exhibiting pathologically abnormal motility after injection of sumatriptan and placebo were compared using the McNemar's test. In addition, the difference between the effect of 6 mg and 16 mg sumatriptan[17] on oesophageal motility was examined. This was done by firstly assessing the change from baseline values following injection of sumatriptan 6 mg and placebo and then calculating the difference in this change between sumatriptan 6 mg and placebo (A); and secondly assessing the same difference between sumatriptan 16 mg and placebo (B). The actual comparison between 6 mg and 16 mg sumatriptan was then made by assessing the difference between A and B. A *P*-value of < 0.05 was taken to be significant. Results are expressed as mean and 95% confidence interval, unless otherwise stated.

RESULTS

Oesophageal motility

Under basal conditions (pre-injection) there was no significant difference in the amplitude ($P = 0.8$), duration ($P = 0.08$) or peristaltic propagation velocity ($P = 0.6$) (Figures 1 and 2) of the oesophageal contractions between the sumatriptan and placebo groups.

Administration of sumatriptan significantly increased the amplitude of oesophageal body contractions compared with placebo ($P < 0.005$) (Figures 1 and 2, Table 1). Following the initial increase in contraction amplitude after sumatriptan administration, it gradually reduced over the 3 h studied, and the difference in mean contraction amplitudes between the sumatriptan and placebo groups appeared to be maintained (Figure 1). The effect of sumatriptan on oesophageal contraction duration was less clear, because although the statistics support a significant increase in duration after sumatriptan injection when compared with placebo (Table 1), visualization of the graphical representation of the data suggests that this is unlikely (Figure 1). This was due to a difference, although not significant ($P = 0.08$), between the two treatments pre-injection. There was no difference in the velocity of propagation of peristalsis between the sumatriptan and placebo groups (Figures 1 and 2, Table 1).

Lower oesophageal sphincter function

Pre-injection, there was no significant difference in the basal lower oesophageal sphincter pressure between the sumatriptan and placebo groups ($P = 0.4$) (Figure 1). Administration of sumatriptan produced an immediate increase in the lower oesophageal sphincter pressure (change from pre- to 5 min post-injection: sumatriptan 10.9 (5.2, 16.6) mmHg vs. placebo 5.1 (1.8, 8.4) mmHg;

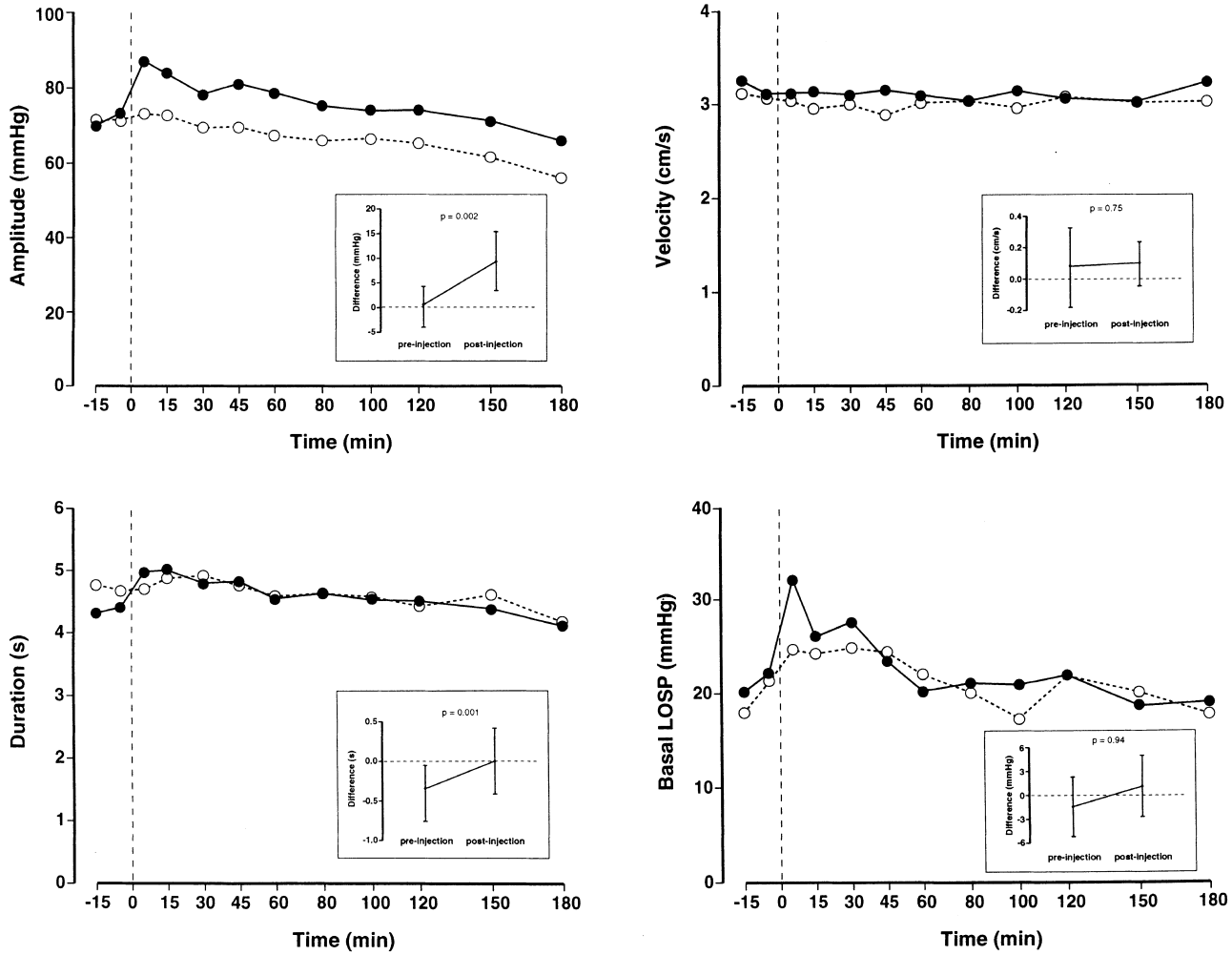

Figure 1. Change in amplitude, duration and velocity of propagation of oesophageal body contractions, and basal lower oesophageal sphincter pressure (LOSP) with respect to time. Results expressed as mean of each series of water swallows. ○ = placebo and ● = sumatriptan 6 mg. Panels show the mean difference (95% CI) between sumatriptan and placebo groups pre- and post-injection.

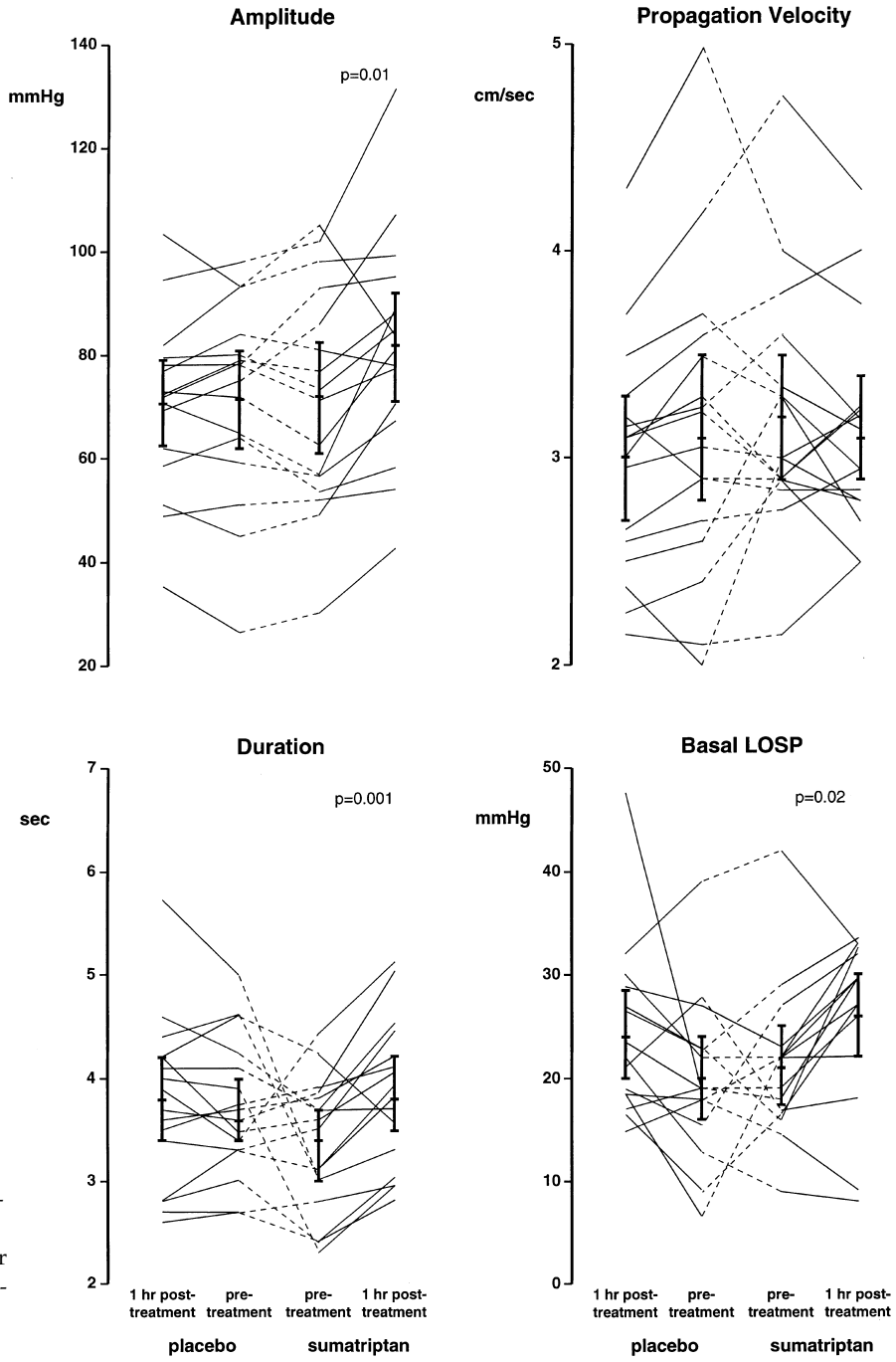

Figure 2. Line diagrams showing individual data points for amplitude, duration and velocity of propagation of oesophageal body contractions, and basal lower oesophageal sphincter pressure (LOSP) pre- and 1 h post-treatment. Bold arrow bars represent the mean and 95% CI.

difference 5.8 (– 0.7, 12.3) mmHg, $P = 0.08$). However, this elevation in basal sphincter pressure was not sustained beyond a mean of 64.3 (38.5, 90.1) min post-injection (Figure 1), resulting in no overall difference between the sumatriptan and placebo groups (Table 1). The percentage relaxation of the lower oesophageal sphincter was significantly greater after sumatriptan when compared with placebo injection (change from pre- to post-injection: sumatriptan 4.0 (0.8, 7.2)% vs. placebo – 7.1 (– 16.3, 2.1)%; $P = 0.03$).

Pathologically abnormal motility

Although all subjects exhibited some change in oesophageal motor function after sumatriptan administra-

Table 1. Effect of 6 mg sumatriptan s.c. on oesophageal motility

	Placebo	Sumatriptan
Change pre- to 1 h post-injection		
Amplitude (mmHg)	– 0.8 (– 4.2, 2.6)	9.9 (2.8, 17.1)
Mean difference from placebo		10.8 (4.4, 17.1)*
Duration (s)	0.1 (– 0.2, 0.3)	0.5 (0.2, 0.7)
Mean difference from placebo		0.4 (0.2, 0.7)*
Propagation velocity (cm/s)	– 0.1 (– 0.3, 0)	– 0.1 (– 0.3, 0.1)
Mean difference from placebo		0.1 (– 0.1, 0.2)
LOSP (mmHg)	4.3 (– 0.6, 9.3)	4.7 (1.1, 8.4)
Mean difference from placebo		0.4 (– 4.1, 4.8)
Change pre- to 3 h post-injection		
Amplitude (mmHg)	– 4.5 (– 8.0, – 0.9)	4.8 (– 1.2, 10.9)
Mean difference from placebo		9.3 (4.0, 14.5)†
Duration (s)	– 0.1 (– 0.3, 0.1)	0.3 (0.1, 0.5)
Mean difference from placebo		0.4 (0.2, 0.5)‡
Propagation velocity (cm/s)	– 0.1 (– 0.3, 0)	– 0.1 (– 0.2, 0.1)
Mean difference from placebo		0 (– 0.2, 0.2)
LOSP (mmHg)	2.1 (– 2.7, 6.8)	1.9 (– 1.6, 5.4)
Mean difference from placebo		– 0.2 (– 4.3, 4.0)

Results expressed as mean (95% CI). LOSP = lower oesophageal sphincter pressure.
*$P = 0.003$; †$P = 0.002$; ‡$P = 0.001$.

tion, only four exhibited pathologically abnormal motility. One subject exhibited long duration contractions before placebo treatment, and long duration and repetitive contractions after placebo treatment; but no abnormal activity during either the pre- or post-sumatriptan treatment periods. A further subject had long duration contractions post-placebo injection and normal activity pre-placebo and pre- and post-sumatriptan treatment. Two subjects exhibited abnormally long duration contractions post-sumatriptan injection.

Adverse events

Ten of the 16 (63%) subjects reported adverse events following administration of placebo and 15 (94%) following sumatriptan. The most commonly reported events after placebo injection were headaches (5 subjects), tingling (4 subjects) and heaviness (2 subjects) in various regions of the body, occurring on average 35 min (range 1–123 min) after injection and lasting 140 min (range 2–360 min). The most common side-effects induced by sumatriptan were bodily heaviness (4 subjects) and warmth (4 subjects), throat tightness (2 subjects), drowsiness (2 subjects), tingling (2 subjects), nausea (2 subjects) and headache (2 subjects) which began a mean of 6 min (range 1–46 min) after injection and lasted for 54 min (range 2–185 min).

Chest discomfort was experienced by one subject (female), 19 min after administration of sumatriptan; it continued intermittently for 166 min. No subject experienced chest discomfort after injection of placebo.

Relationship of chest discomfort to motility

Although the one subject who reported chest discomfort did exhibit an increase in both the amplitude and duration of their oesophageal body contractions, these did not reach pathologically abnormal levels.

Electrocardiogram

No ECG abnormalities were observed in any of the subjects either in the presence or absence of chest symptoms.

Comparison between 6 mg and 16 mg sumatriptan

The increase in oesophageal body contraction amplitude was significantly greater after 16 mg sumatriptan compared with the 6 mg dose (mean difference between sumatriptan and placebo in the change from pre- to post-injection: 6 mg, 8.7 (2.1, 15.2) mmHg vs. 16 mg, 19.3 (11.9, 26.7) mmHg; $P = 0.04$) (Figure 3). A similar difference between the two doses of sumatriptan was

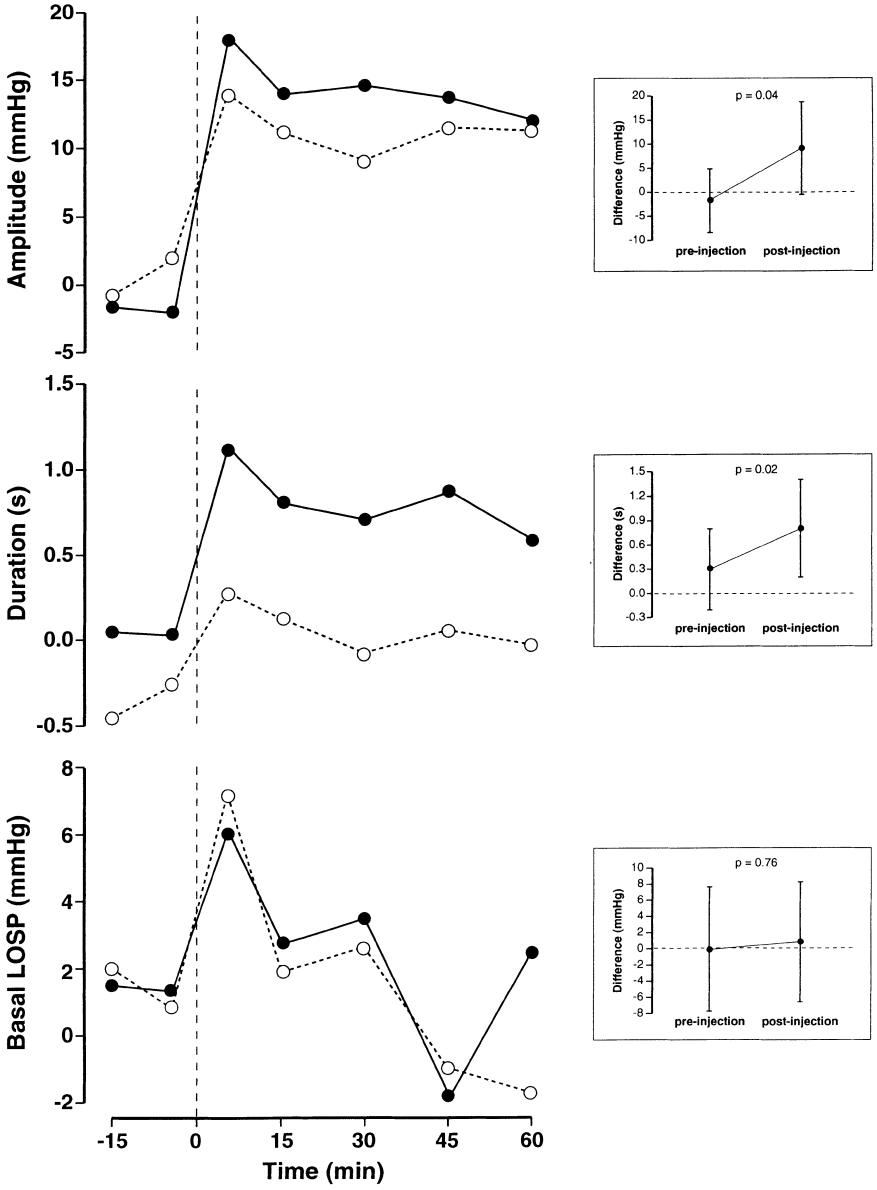

Figure 3. Difference between 6 mg and 16 mg sumatriptan in oesophageal body contraction amplitude and duration, and lower oesophageal sphincter pressure (LOSP). Results expressed as the mean difference between sumatriptan and placebo before and after injection of both 6 mg (○) and 16 mg (●) sumatriptan. Panels show the mean difference (95% CI) between the differences in sumatriptan 6 mg with placebo and sumatriptan 16 mg with corresponding placebo, pre- and post-injection.

observed for the duration of contractions (6 mg, 0.20 (– 0.14, 0.54) s vs. 16 mg, 0.74 (0.46, 1.02) s; $P = 0.02$) (Figure 3). However, there was no significant difference in basal lower oesophageal sphincter pressure between the two doses of sumatriptan (6 mg, 0.4 (– 3.7, 4.5) mmHg vs. 16 mg, 1.3 (– 2.7, 5.3) mmHg; $P = 0.76$) (Figure 3).

DISCUSSION

The results of this study show that a standard therapeutic dose (6 mg s.c.) of sumatriptan alters oesophageal motor function without electrocardiographic effects. As with a supratherapeutic dose (16 mg s.c.),[17] a standard dose significantly increases the amplitude of oesophageal body contractions and transiently increases lower oesophageal sphincter pressure, but has no effect on the velocity of propagation of oesophageal body contractions. In contrast with our previous study, however, a standard dose of sumatriptan appears to have little or no effect on the duration of oesophageal body contractions.

In normal healthy subjects, there is little evidence of a cardiovascular cause for sumatriptan-induced chest pain.[10–13] This is supported by our present and previous[17] observations, which have shown that even

in those subjects who did experience the characteristic chest symptoms associated with sumatriptan administration (5 subjects in the previous and 1 subject in the present study) none of them exhibited any abnormalities in their electrocardiogram. In patients with atherosclerotic arteries, however, sumatriptan should not be used, as it appears to have a more potent vasoconstrictive action on the coronary arteries than in normal healthy subjects.[25] This has been attributed to a reduction in the production of the vasodilator nitric oxide from the damaged arterial endothelial lining.[25]

All subjects in the present study showed some change in oesophageal motor function after sumatriptan administration, with two subjects exhibiting such large increases in the duration of their contractions that they could be classed as pathologically abnormal. However, neither of these subjects reported chest pain and a similar incidence of abnormally long duration contractions was observed post-placebo administration. Only one subject experienced chest symptoms and although they did demonstrate an increase in both the amplitude and duration of their oesophageal body contractions, these increases did not reach pathologically abnormal levels. This apparent lack of association between the degree of change in motility and the occurrence of chest discomfort might be explained by inter-subject variation in oesophageal visceral sensitivity. These differences could result in some individuals perceiving even small changes in motility as painful whilst others may not even notice abnormal contractility. Hypersensitivity of the oesophagus has been noted in patients with non-cardiac chest pain[26–30] and similarly may help to explain why such patients are much more likely to experience chest pain after edrophonium administration than normal healthy volunteers, even though the change in oesophageal motility induced by edrophonium is similar in both groups of subjects.[31] Furthermore, we have recently observed that sumatriptan can also increase oesophageal sensitivity and reduce oesophageal compliance which may lead to a triggering or amplification of perception of any change in oesophageal contractility in susceptible subjects.[32]

The effect of sumatriptan 6 mg on the amplitude of oesophageal contractions was still seen up to 3 h after administration. As the half-life of sumatriptan is $\approx$ 2 h[33] this would suggest that even lower doses of the drug (below 6 mg) might be capable of altering oesophageal motility and thus cause chest symptoms. However, the incidence of chest symptoms at lower doses of sumatriptan has not been evaluated. In contrast, the effect of sumatriptan 6 mg on lower oesophageal sphincter pressure was not maintained for nearly as long ($\approx$ 1 h). A similar transient increase in lower oesophageal sphincter pressure has been noted in healthy subjects following, for example, pentagastrin[34] and gastrin[35] administration and could suggest that this short-lived response is a characteristic of the lower oesophageal sphincter. Indeed, *in vitro* studies have suggested that the smooth muscle of the oesophageal body and lower oesophageal sphincter do possess different sensitivities to various compounds.[36] Alternatively, the transient rise in the lower oesophageal sphincter pressure may be a reflex response of the sphincter to the gastric relaxation which is also known to occur after sumatriptan administration.[37, 38] This is supported by the observation that distension of the stomach with air increases lower oesophageal sphincter pressure in normal healthy volunteers.[39]

Comparison of the therapeutic with previous supratherapeutic[17] dose data, show that the 16 mg dose of sumatriptan has a significantly greater effect on both the amplitude and duration of oesophageal contractions than the 6 mg dose. However, it is interesting to note that there was no difference between the 6 mg and 16 mg dose on lower oesophageal sphincter pressure. It is unclear whether this might reflect a maximal effect of the 6 mg dose or represents a dose-independent reflex response of the sphincter to relaxation of the proximal stomach.

The mechanisms underlying sumatriptan-induced motility changes are unknown. Sumatriptan is a selective agonist for 5-HT_1 receptors, having little or no activity at other 5-HT receptor subtypes (5-HT_{2-7}). It has highest affinity for human recombinant 5-HT_{1B} (formally known as 5-$HT_{1D\beta}$), 5-HT_{1D} (formally known as 5-$HT_{1D\alpha}$) and 5-HT_{1F} receptors, and weaker affinity for 5-HT_{1A} and 5-HT_{1E} receptors.[40] The distribution of these receptors and in particular, their role in gastrointestinal function however, remain largely unidentified.

Sumatriptan is a vasoconstrictor agent and studies on isolated blood vessels have indicated that this effect is mediated via activation of 5-HT_{1B} receptors on vascular smooth muscle.[41] Hence a potential mechanism for the oesophageal effects seen in the present study could be via a local action on 5-HT_1 receptors to cause contraction of human oesophageal smooth muscle. However, even at high concentrations, sumatriptan appears to have no contractile effects in human isolated

oesophagus (Houghton *et al.*, data held on file by Glaxo Wellcome). Alternatively, sumatriptan could be acting at prejunctional 5-HT_1 receptors on enteric or sensory nerve terminals in the oesophagus to modulate neurotransmitter release: prejunctional inhibitory 5-HT_1 receptors have been described in peripheral tissues.[42] However, preliminary experiments in electrically stimulated human isolated oesophagus could not reveal such an action for sumatriptan (Houghton *et al.*, data held on file by Glaxo Wellcome).

A further possible mechanism could involve a central action of sumatriptan. Autoradiographic studies in human brain have shown sumatriptan-sensitive 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptor binding in brain stem nuclei such as the nucleus of the solitary tract.[43] Activation of these central receptors could theoretically modulate efferent motor nerves and hence affect oesophageal smooth muscle contraction. However, pre-clinical data indicate that sumatriptan only poorly penetrates the blood brain barrier,[44] making a central mechanism less likely.

In conclusion, a therapeutic (6 mg s.c.) dose of sumatriptan alters oesophageal motility without affecting the ECG, supporting an oesophageal rather than cardiac cause for sumatriptan-induced chest pain. A number of related drugs with varying affinities for the different 5-HT_1 receptors are being developed for treatment of migraine. Investigation of the possible effects of these agents on oesophageal function might help to determine the mechanism of action of sumatriptan on the oesophagus and ascertain whether this is a possible idiosyncratic or class effect.

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