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Effect of a Tricyclic Antidepressant on Small Intestinal Motility in Health and Diarrhea-Predominant Irritable Bowel Syndrome

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Antidepressants are used in irritable bowel syndrome (IBS) and may have effects on the gut independent of improving mood. We have investigated the actions of a tricyclic antidepressant on small intestinal motor function in eight healthy volunteers and in six patients with diarrhea-predominant IBS. Fasting ambulatory motility was recorded from six small intestinal sites for 16–18 hr while on no drug (baseline) and while taking imipramine for five days. Orocecal transit time (OCTT) was measured by lactulose hydrogen breath test, during baseline and imipramine administration. Imipramine did not alter migrating motor complex periodicity, but slowed jejunal phase III propagation velocity in controls from 7.5 ± 1.1 to 3.6 ± 0.5 cm/min ($P < 0.01$) and in IBS from 7.8 ± 0.6 to 4.4 ± 0.5 cm/min ($P < 0.0001$). Phase III duration at each site was increased, and total recorded phase III was greater during imipramine than baseline studies. Imipramine increased the amplitude of phase III contractions. There was no effect of imipramine on non-phase-III motility index or discrete clustered contractions. Imipramine prolonged OCTT from 73 ± 6 min to 97 ± 8 min in controls ($P < 0.05$) and from 61 ± 9 min to 89 ± 8 min in IBS ($P < 0.05$). Although OCTT was shorter in this IBS group, no motility differences were seen between controls and IBS. This demonstration that a tricyclic antidepressant can modify small intestinal motor function in health and in IBS supports the view that these drugs may have therapeutic actions in IBS unrelated to mood improvement.

KEY WORDS: motility; antidepressant; intestine; imipramine; irritable bowel syndrome; transit.

Symptoms in irritable bowel syndrome (IBS) may arise from an interaction of abnormal intestinal motor activity, heightened central perception of gut events, and psychological factors. The high prevalence of psychiatric morbidity in IBS patients attending hospital clinics (1) has led some investigators to regard IBS as an integral part of affective disorder, particularly depression (2–4). Consequently antidepressants have been used in the treatment of IBS. However, in addition to improving any associated mood disorders in IBS, antidepressants may also have more direct actions on the gastrointestinal tract. Tricyclic antidepressants have analgesic properties independent of mood-improving effects (5) and have been of therapeutic use in patients with neuropathic pain (6). It is conceivable that tricyclic agents might similarly modulate visceral affer-

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ent activity from the gastrointestinal tract, leading to altered central perception of gut events.

A further action of such drugs, anticipated from their known pharmacological profile, is the alteration of intestinal motility. Abnormalities of small intestinal motility have been reported in IBS (7–10), although not all investigators have been able to reproduce these (11–13). If such abnormalities are important in IBS, then alteration of intestinal motor activity by tricyclic antidepressants might in turn modify intestinal symptoms. Despite their widespread use in IBS, the effects of tricyclic antidepressants on small intestinal motor function have not been explored. We have previously investigated the action of a selective 5-hydroxytryptamine (5-HT) reuptake inhibitor on small intestinal motor function in health (14). In the current study, we wished to investigate the effect of a commonly used tricyclic antidepressant, imipramine, on small intestinal motor function in health and in IBS. Imipramine is a tertiary amine with which newer antidepressants are compared. It inhibits the neuronal reuptake of 5-HT and norepinephrine and is an antagonist at muscarinic, histamine, and α-adrenergic receptors. When prescribed in depression, imipramine tends to cause constipation. This side effect might be expected to benefit IBS patients whose principal bowel habit is diarrhea. We have studied the effect of imipramine on ambulatory small intestinal motility in diarrhea-predominant IBS patients and in healthy volunteers.

MATERIALS AND METHODS

Subjects. Six patients (median age 34 years, range 24–48 years, three females) with diarrhea-predominant IBS attending a gastroenterology clinic were studied. They all complained of abdominal pain and their predominant bowel habit was frequency and urgency of defecation, with the passage of loose stools three to six times daily. Bowel symptoms in these patients were often severe enough to interfere with their work and social activities. All fulfilled diagnostic criteria for IBS (15). Each patient had a normal full blood count, plasma biochemistry, barium enema, sigmoidoscopy, and rectal biopsy. When considered clinically appropriate, colonoscopy, barium follow-through, jejunal biopsy, and lactose tolerance test were performed and found to be normal.

Eight healthy volunteers (median age 26 years, range 21–32 years, three females) without any gastrointestinal symptoms were studied as controls. No patient or control subject had taken any drugs for at least three weeks before the study. The study was approved by the research ethics committee of the City and Hackney Health District and all participants gave written informed consent.

Study Design. Patients and controls underwent an ambulatory small intestinal motility study and measurement of orocecal transit time (OCTT) while on no medication and while taking imipramine. The IBS patients had their drug-free (baseline) study performed before the imipramine study. Five of the eight controls also had their studies in this order. The remaining three controls underwent imipramine studies first, to investigate whether any drug effect was, in fact, due to study order. A minimum period of three weeks separated imipramine and baseline studies. A placebo was not used since it was anticipated that imipramine's side effects would readily unmask the active drug.

For the studies on imipramine, subjects took oral imipramine as a single bedtime dose for 5 nights before the motility study. The intended daily dose, by the time of the motility study was 100 mg, but side effects of imipramine prevented the initiation of the drug at this dose. Therefore subjects were commenced on 50 mg and were supervised in increasing the dose by 25-mg increments to the desired dose of 100 mg daily. On the morning after the fourth bedtime dose of imipramine, OCTT measurement was performed. The following day, after the fifth dose, the motility study was conducted. A further bedtime dose of imipramine was taken during the motility study. Side effects of sedation, dizziness, and dry mouth prevented two patients and two controls reaching the desired daily dose of 100 mg imipramine. These subjects performed the studies while taking 75 mg daily.

Small Intestinal Motility. Ambulatory small intestinal motility was recorded from six electronic strain-gauge transducers mounted on a nasoenteric catheter, 2.7 mm in diameter and 3 m in length (Gaeltec Ltd, Isle of Skye, UK), as previously described (13). The proximal transducer was sited at the duodenojejunal flexure (site A) and the other five transducers were 15 cm (site B), 30 cm (site C), 50 cm (site D), 70 cm (site E), and 95 cm (site F) distal to the duodenojejunal flexure (Figure 1). Pressure was sampled from each transducer at a rate of 8 Hz and stored in digital form within a portable recorder (7-MPR recorder, Gaeltec Ltd). The recorder's 512 kbyte memory stored the minimum number of points of inflection to accurately reconstruct the pressure record. At the conclusion of each study, data were transferred to a computer for display and analysis.

Recording of small intestinal motility commenced in the afternoon and continued for 16–18 hr, throughout which subjects were fully ambulant. Subjects slept overnight in a comfortable single room, and the recording was concluded during the following morning. Eating was prohibited during the 16- to 18-hr ambulatory study, although small quantities of clear fluids were allowed. Subjects were asked to keep a written record of times of sleeping, awakening, defecation, fluid ingestion, and any IBS or other symptoms. At such times, they also pressed an event button, which inserted a mark on the motility record.

Analysis of Motility. Each motility record was analyzed by an observer who was unaware as to whether it was from a control or IBS subject, or whether it was a baseline or imipramine recording. Phase III of the migrating motor complex (MMC) was recognized as a minimum of 3 min of uninterrupted contractions at the maximum rate for that intestinal site, followed by phase I (Figure 2). Phase I was

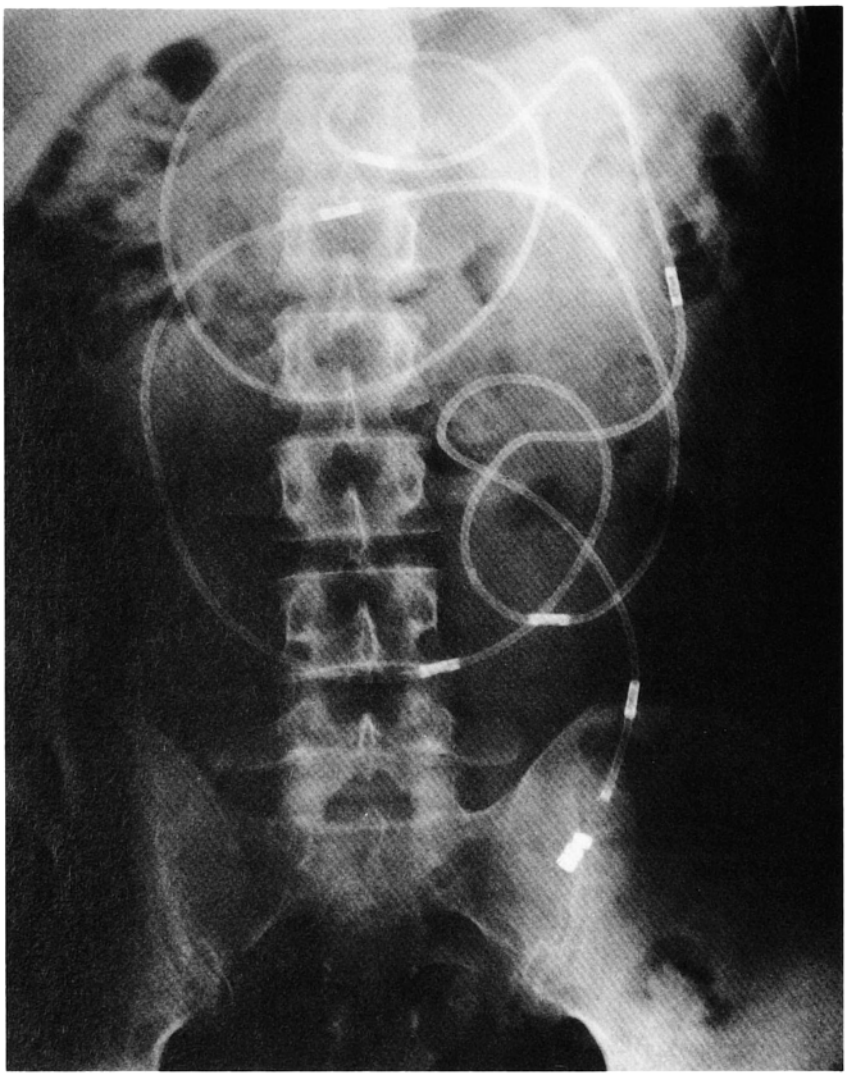

Fig 1. Abdominal radiograph showing motility catheter with six transducers positioned in the small intestine.

defined as motor quiescence with a maximum of three single contractions >15 mm Hg during a 10-min period. Irregular contractile activity was otherwise categorized as phase II. MMC cycle length (periodicity), and the percentage contribution of phases I, II, and III to MMC cycles at the proximal jejunum (site B) was calculated. The propagation velocity, duration, maximum contractile rate, mean contractile amplitude, and extent of distal migration of phase III activity fronts were determined (13). A motility index (MI) for non-phase-III (combined phase I and II) contractile activity in the proximal jejunum (site B), was computed as previously described (13):

$$MI = \frac{\text{mean amplitude of contraction (mm Hg)} \times \text{mean duration (min)} \times \text{no. of contractions}}{\text{time (min)}}$$

Contractions less than 15 mm Hg greater than the current baseline, which might represent respiratory movement, were excluded from calculation of MI. Simultaneous brief contractions occurring at all sensors due to artifacts, such as coughing, were also excluded. Daytime MMC characteristics were compared with nighttime (2300 hr to 0500 hr) MMC characteristics.

Within phase II, the existence of patterns such as discrete clustered contractions (DCCs) was sought (16, 17). DCCs were recognized as rhythmic bursts, each lasting less than 2 min, of 3–10 contractions at the slow-wave frequency for that intestinal site. At least 1 min of motor quiescence preceded and followed each DCC. The pressure record was scrutinized for patterns or changes coinciding with events, including IBS symptoms documented by the subjects. Such motility patterns were con-

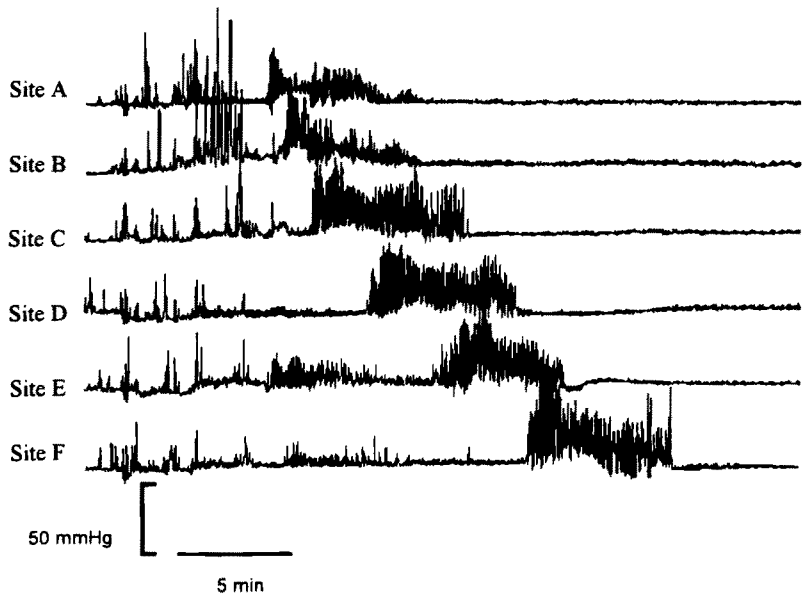

Fig 2. Motility recording from the six small intestinal sites showing a distally propagating phase III activity front, which is preceded by irregular contractile activity of phase II and followed by motor quiescence of phase I. Site A is the duodenojejunal flexure; sites B, C, D, E, and F are 15 cm, 30 cm, 50 cm, 70 cm, and 95 cm distal to site A.

sidered to be temporally associated if they occurred within 2 min of patients' symptoms.

Orocecal Transit Time. Orocecal transit time (OCTT) was measured after an overnight fast and a chlorhexidine gluconate mouth rinse to eradicate hydrogen-producing buccal flora. End-expiratory breath samples were collected before ingestion of 20 ml (13.4 g) lactulose and at 10-min intervals thereafter. Each breath sample was analyzed using a hydrogen monitor (GMI Medical Ltd, Renfrew, UK). OCTT was defined as the time interval between ingestion of lactulose and a sustained rise (>10 ppm above baseline) in breath hydrogen.

Statistical Methods. Data are expressed as mean ± SEM. Analysis of variance and Student's *t* tests for paired and unpaired data were used to assess statistical significance. To determine the association of patients' symptoms with motility patterns, recordings were divided into 5-min time epochs, and each epoch was categorized as a specific motility phase. Chi-squared test with Yates correction was then used to assess occurrence of symptoms during motility phases.

RESULTS

In the eight control subjects, 99 complete MMCs were recorded during the baseline study and 109 complete MMCs were recorded on imipramine. In the six IBS patients, the numbers of complete MMCs recorded during baseline and imipramine studies were 63 and 81, respectively. The volume of clear fluid ingested over each 16- to 18-hr study was 440 ± 40 ml in controls and 470 ± 50 ml in IBS during baseline. While on imipramine, the volumes ingested were 630 ± 50 ml in controls and 590 ± 65 ml in the IBS patients.

MMC Cycle Characteristics. During baseline recording, the overall MMC periodicity was similar in controls and IBS (Table 1). In both groups, daytime MMC periodicities were greater than their respective nocturnal periodicities. Despite a tendency to decrease MMC periodicity, imipramine had no statistically significant effect on overall, diurnal, or nocturnal MMC periodicities in the control and IBS groups. While awake, the periodicity of MMC cycles in which fluids were consumed did not differ from cycles during which subjects were strictly fasted.

TABLE 1. MMC PERIODICITY RECORDED IN PROXIMAL JEJUNUM (SITE B) IN CONTROLS AND IBS WHILE ON NO DRUG (BASELINE) AND ON IMIPRAMINE*

	MMC periodicity (min)		
	Overall	*Diurnal*	*Nocturnal*
Baseline			
Controls	74 ± 5	79 ± 10	70 ± 6
IBS	76 ± 7	88 ± 13	64 ± 5
Imipramine			
Controls	65 ± 3	71 ± 4	58 ± 3
IBS	68 ± 5	71 ± 9	62 ± 5

*Values are mean ± SEM.

TABLE 2. PERCENTAGE DURATION OF PHASES I, II, AND III WITHIN MMC CYCLES RECORDED AT PROXIMAL JEJUNUM (SITE B)*

	Phase I (%)	*Phase II (%)*	*Phase III (%)*
Baseline			
Day			
Controls	14 ± 4	78 ± 4	8 ± 1
IBS	13 ± 4	82 ± 4	6 ± 1
Night			
Controls	73 ± 5	17 ± 3	10 ± 1
IBS	75 ± 5	15 ± 3	10 ± 1
Imipramine			
Day			
Controls	12 ± 3	76 ± 7	13 ± 3†
IBS	11 ± 3	78 ± 7	11 ± 3†
Night			
Controls	70 ± 6	13 ± 4	16 ± 3†
IBS	74 ± 7	15 ± 4	12 ± 1†

*Values are mean ± SEM.
†Baseline vs imipramine, $P < 0.05$.

The proportion of MMC cycles occupied by phases I, II, and III did not differ between control and IBS subjects (Table 2). Phase II was the predominant pattern by day, and phase I occupied most of the MMC cycle at night ($P < 0.01$). This circadian variation (9) was unchanged by imipramine. However, by day and by night, the relative contribution of phase III to MMC cycles was increased by imipramine.

Phase III Characteristics. The propagation velocity of phase III decreased with aboral progression, and this was similar in the control and IBS groups. However, phase III propagation velocity was slower between each pair of adjacent sensors while on imipramine compared to baseline (Figure 3). Thus, in the proximal jejunum, imipramine slowed the propagation velocity in controls from 7.5 ± 1.1 cm/min to 3.6 ± 0.5 cm/min ($P < 0.01$) and in IBS from 7.8 ± 0.6 to 4.4 ± 0.5 cm/min ($P < 0.0001$). In the ileum, phase III propagation velocities in controls were not significantly different during baseline (3.0 ± 0.4 cm/min) and imipramine recordings (2.5 ± 0.3 cm/min). However, ileal propagation velocities in the IBS patients were significantly slowed from 3.6 ± 0.3 to 2.0 ± 0.2 cm/min by imipramine ($P < 0.0001$).

The duration of phase III at each successive intestinal site increased as MMC cycles progressed aborally. This pattern was seen equally in controls and IBS (Figure 4). Imipramine increased the duration of phase III in both controls and IBS. The prolongation of MMC duration by imipramine was more marked proximally than distally in both groups.

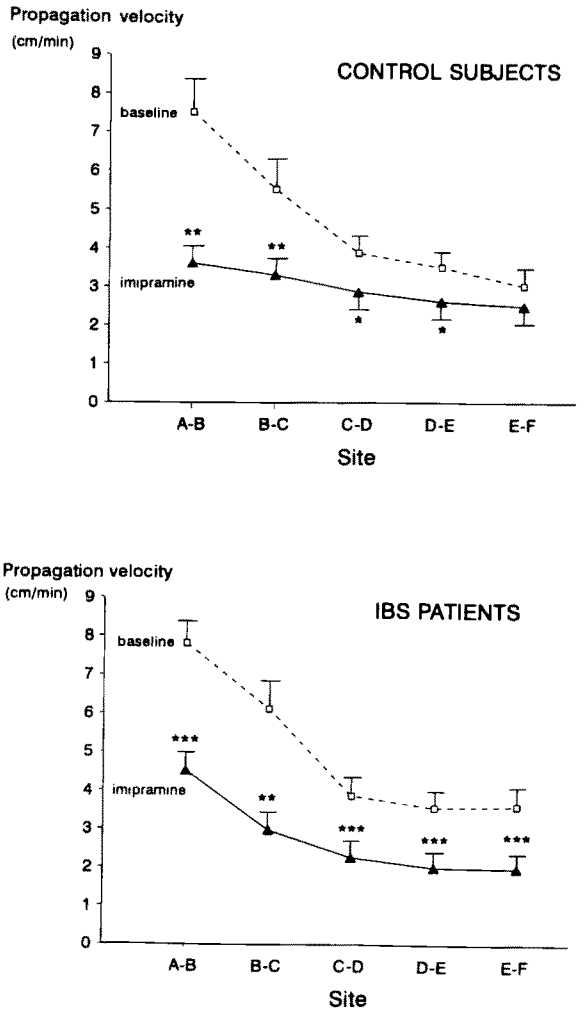

Fig 3. Propagation velocity of phase III between adjacent pairs of sensors in controls (upper panel) and in IBS patients (lower panel) during baseline (-□-) and imipramine (-▲-) studies. Site A is the duodenojejunal flexure; sites B, C, D, E, and F are 15 cm, 30 cm, 50 cm, 70 cm, and 95 cm distal to site A. *$P < 0.05$ imipramine vs baseline velocity; **$P < 0.01$ imipramine vs baseline velocity; ***$P < 0.0001$ imipramine vs baseline velocity.

The maximum rate of contraction at each site decreased with distal propagation of phase III, in both controls and IBS patients (Table 3). Imipramine had no effect on the maximum contractile rates, and the gradient of decreasing maximal contractile rate was preserved. The mean amplitude of contraction within phase III was similar in controls and IBS during the baseline recording (Table 4). In both groups, phase III amplitude increased with aboral progression, so that contractile amplitude at site F was greater than in the proximal jejunum ($P < 0.01$). This difference was maintained while on imip-

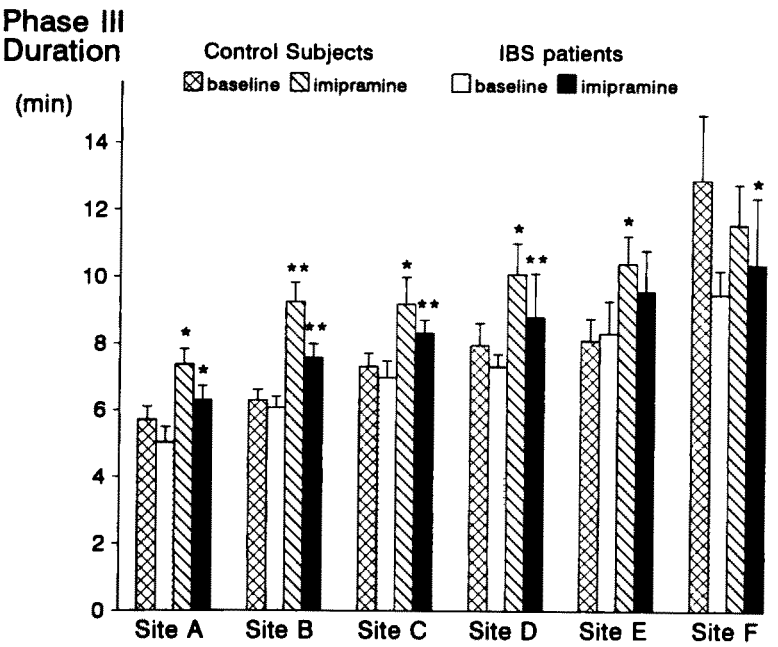

Fig 4. Duration of phase III recorded at each site in control subjects and in IBS patients during baseline and imipramine studies. Site A is the duodenojejunal flexure. Sites B, C, D, E, and F are 15 cm, 30 cm, 50 cm, 70 cm, and 95 cm distal to site A. *$P < 0.05$ imipramine vs baseline; **$P < 0.01$ imipramine vs baseline.

ramine. Imipramine increased the contractile amplitude within phase III at all sites ($P < 0.01$).

Imipramine had no effect on the degree of propagation of phase III activity fronts. In the control group during the baseline recording, 28% of phase III fronts recorded at site A and seen to propagate to at least the next two sensors (site C), failed to reach site F. While on imipramine, this proportion was 24%. In the IBS patients during the baseline recording, 25% of phase III fronts at site A propagating to at least site C, failed to reach site F. While on imipramine, this percentage was unchanged at 27%. Imipramine did not influence the number of MMCs starting distally. In the control group, the proportion of phase IIIs originating at a site distal to site B (and traversing at least two adjacent sensors) was 9% and 11% during baseline and imipramine recordings, respectively. In the IBS patients, the corresponding figures for distally commencing MMCs during baseline and imipramine recordings were 12% and 9%.

Phase II Features. In the control group, the motility index (MI) for combined phase I and II was 4.9 ± 2.4 by day. At night it was 1.1 ± 0.4 ($P < 0.05$), reflecting the diminished amount of phase II at night. In the IBS patients, MI during the day (3.0 ± 0.8) was also greater than at night (0.4 ± 0.8) ($P < 0.05$), but these values were not different to those of

TABLE 3. MAXIMUM CONTRACTILE RATE AT EACH RECORDING SITE IN CONTROLS AND IBS DURING BASELINE AND IMIPRAMINE RECORDINGS*

	Contractions (/min)					
	Site A	*Site B*	*Site C*	*Site D*	*Site E*	*Site F*
Baseline						
Controls	11.1 ± 0.3	10.8 ± 0.2	10.7 ± 0.2	10.6 ± 0.2	10.2 ± 0.3	9.8 ± 0.2
IBS	11.3 ± 0.2	11.0 ± 0.2	10.7 ± 0.2	10.5 ± 0.2	10.3 ± 0.3	10.0 ± 0.2
Imipramine						
Controls	11.0 ± 0.2	10.9 ± 0.3	10.7 ± 0.1	10.4 ± 0.1	10.2 ± 0.2	10.0 ± 0.2
IBS	11.1 ± 0.2	10.9 ± 0.3	10.6 ± 0.1	10.4 ± 0.1	10.4 ± 0.2	9.9 ± 0.2

*Values are mean ± SEM.

TABLE 4. AMPLITUDE OF CONTRACTION WITHIN PHASE III AT EACH RECORDING SITE IN CONTROLS AND IBS DURING BASELINE AND IMIPRAMINE RECORDINGS*

	Amplitude (mm Hg)					
	Site A	*Site B*	*Site C*	*Site D*	*Site E*	*Site F*
Baseline						
Controls	28.5 ± 1.2	25.7 ± 0.9	30.3 ± 1.6	29.1 ± 1.5	32.4 ± 2.2	36.9 ± 2.1
IBS	29.8 ± 1.2	29.0 ± 0.9	30.1 ± 3.1	32.8 ± 2.5	31.0 ± 1.9	39.8 ± 3.2
Imipramine						
Controls	31.8 ± 1.4	31.1 ± 2.1	33.9 ± 4.0	38.5 ± 3.8	38.8 ± 3.2	46.4 ± 4.8
IBS	32.6 ± 1.9	34.0 ± 2.1	33.7 ± 3.1	36.3 ± 2.7	37.0 ± 3.6	49.0 ± 4.5

*Values are mean ± SEM.

the control group. Imipramine did not influence MI in either controls (2.8 ± 0.4 by day, 1.4 ± 0.5 by night) or in IBS patients (2.9 ± 0.4 by day, 1.4 ± 0.8 by night). In both groups the circadian variation was preserved on imipramine ($P < 0.05$).

In the controls, 13 ± 5% of diurnal phase II activity at the duodenojejunal flexure was occupied by DCCs during the baseline recording (Figure 5). In the IBS patients, a similar proportion, 15 ± 4%, of diurnal phase II was occupied by DCCs during baseline. Imipramine had no effect on the proportion of diurnal phase II occupied by DCCs. While on imipramine the proportion of phase II occupied by DCCs was 11 ± 6% in controls, and 13 ± 7% in IBS.

Symptoms. During the baseline recording, four IBS patients reported a total of 10 episodes of their typical abdominal pain. Four of the 10 episodes occurred during the propagation of a phase III front at one of the intestinal sites. One pain episode was documented within 2 min of a series of DCCs at sites A and B, and five occurred while nonspecific phase II activity was being recorded at all six sites. During the imipramine study, eight pain episodes occurred in three patients. Two episodes occurred in association with a phase III front, one was coincident with DCC activity at sites A and B, and five occurred during nonspecific phase II activity at all sites. One of the controls experienced pain during the baseline study, and this single episode occurred during nonspecific phase II activity at all sites. When the duration of each motility phase and the proportion of time for which different phases could be seen at any of the sensors were taken into consideration, there was no correlation between pain episodes and motility patterns.

Orocecal Transit Time. Baseline OCTT in the control group was 73 ± 6 min. Imipramine prolonged the OCTT in the controls to 97 ± 8 min ($P < 0.05$). Baseline OCTT in the IBS patients was shorter at 61 ± 9 min than in the control group ($P < 0.05$). OCTT in the IBS patients was similarly increased by imipramine to 89 ± 8 min ($P < 0.05$).

Study Order. The significant effects that imipramine had on propagation velocity, amplitude, and

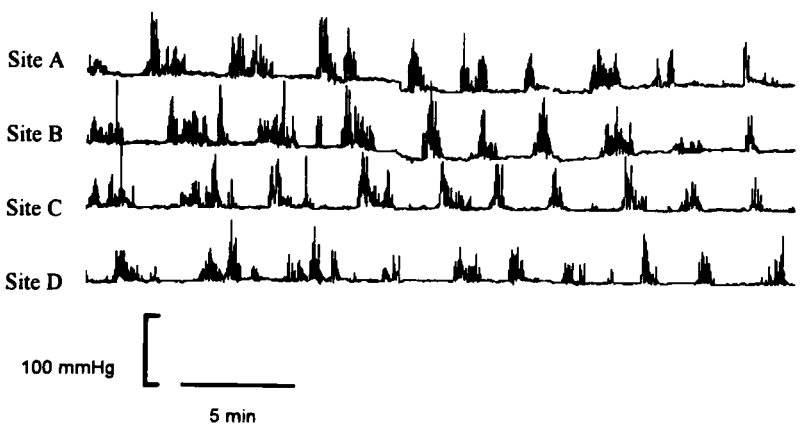

Fig 5. Discrete clustered contractions occurring at the four most proximal sensors in a control subject. Site A is the duodenojejunal flexure; sites B, C, and D are 15 cm, 30 cm, and 50 cm distal to site A.

duration of phase III and OCTT were seen to a similar extent in subjects who underwent the first motility study on imipramine and subjects who underwent their first study while drug-free.

DISCUSSION

This study has shown that the tricyclic antidepressant imipramine has some specific actions on prolonged ambulatory small intestinal motility in health and in diarrhea-predominant IBS. Imipramine slowed the propagation velocity of phase III activity fronts, and this was most evident in the proximal jejunum. There was an accompanying increase in the duration of time for which the more slowly travelling phase IIIs were recorded at each sensor. Since the periodicity of MMC cycling was not prolonged by imipramine, the percentage contribution of phase III to MMC cycles was increased. Thus, the total recorded phase III activity was greater while on imipramine. The mean amplitude of contraction within phase III was also increased by imipramine, although the drug did not affect MI for non-phase-III activity. These actions of imipramine were similar in controls and IBS. In contrast to other studies (7–10), we were not able to detect differences of small intestinal motility between controls and IBS (13). OCTT was, however, decreased in this group of diarrhea-predominant IBS, as previously observed (18). Imipramine prolonged OCTT in both controls and IBS. Although a slowing of small intestinal transit might be expected to accompany more slowly propagating MMCs, we did not distinguish whether the drug was delaying gastric emptying or slowing small intestinal transit or both.

Imipramine inhibits reuptake of 5-HT and norepinephrine, thereby increasing the availability of these neurotransmitters. It also antagonizes muscarinic, histamine, and α-adrenergic receptors. An increase in 5-HT availability would be expected to stimulate small intestinal contractile activity (19–21), and we have demonstrated that selectively inhibiting 5-HT reuptake leads to faster phase III propagation velocity, shortened MMC periodicity, and shorter OCTT (14).

An increase in the availability of synaptic norepinephrine by imipramine might be offset by the drug's ability to block α-adrenergic receptors. In general, adrenergic stimulation leads to intestinal relaxation. Stimulation of α_1 receptors decreases duodenal motility and slows OCTT (22). Activation of presynaptic α_2 receptors inhibits the release of excitatory neurotransmitters and may suppress human small intestinal MMCs (23). Stimulation of intestinal smooth muscle β receptors prolongs OCTT (24, 25). In view of imipramine's antagonist and indirect agonist actions at these different adrenoceptors it is difficult to predict the effect of imipramine on motility via adrenergic pathways.

Imipramine also has prominent antimuscarinic effects that may account for some of the observed effects on small intestinal motility. Intravenously administered antimuscarinic drugs can abolish duodenojejunal contractions (26, 27) and yet can also stimulate phase III-like activity (28) even when small intestinal transit time is prolonged (29). Oral atropine prolongs MMC periodicity (30), but its effect on MMC propagation velocity has not been previously investigated. The effects of histamine receptor blockade on human intestinal motility is unknown, so whether this property of imipramine contributes to the observed effects can not be deduced.

Therefore, a drug with mixed pharmacological actions such as imipramine will have varied and opposing actions on motility. For example, 5-HT reuptake inhibition would tend to shorten MMC periodicity, while muscarinic blockade might tend to lengthen it. Furthermore, imipramine's effect on motility may occur at various sites—intestinal smooth muscle, enteric nervous system, autonomic ganglia, spinal cord, and brain. A direct action on smooth muscle is supported by work showing that desipramine, a metabolite of imipramine, relaxes intestinal smooth muscle *in vitro* (31). On the other hand, enteric neurons resemble central neurons in their response to 5-HT reuptake inhibition (32). These peripheral sites of action do not exclude possible actions of imipramine on higher centers controlling gut motility. However, it is unlikely that the motility effects are due to alteration of mood, since this usually occurs after two weeks, whereas amine reuptake inhibition and receptor blockade occur within hours of drug administration. A sedative effect of imipramine, producing sleeplike motility with decreased propagation velocity (33) and a tendency to shorter MMC cycles, is also unlikely to solely explain the observed effects, since daytime phase II duration and MI were not reduced as during sleep.

In this study we have shown that imipramine alters ambulatory small intestinal motility and OCTT and that this occurs to a similar extent in health and in diarrhea-predominant IBS. The only

previous study documenting a motility effect of antidepressants in IBS showed that desipramine decreased the number of slow contractions during rectosigmoid manometry (34). Whether our demonstration that imipramine modifies small intestinal motility is related to any possible therapeutic action in IBS is unknown, particularly since we have been unable to detect any motility differences in these IBS patients (13). However, this demonstration that a tricyclic antidepressant can modify human small intestinal motor function *in vivo* supports the view that such drugs may have therapeutic effects in IBS even when depression is absent (35). Uncontrolled (2, 36) and controlled trials (34, 37–41) of tricyclic antidepressants have reported success in treating IBS, although these studies, in common with all therapeutic trials in IBS, are open to criticism (42). Any beneficial effect of tricyclic drugs in IBS may be due to improvement of an associated affective disorder or a peripheral action independent of mood, or both. Interestingly, in one study of psychotropic medication (fluphenazine and nortriptyline), psychiatrically normal IBS patients responded more readily than IBS patients with psychoneurotic illness (43).

The current study was not designed to assess any changes in abdominal symptoms but has shown that tricyclic antidepressants such as imipramine do modify small intestinal motility in healthy subjects and diarrhea-predominant IBS. When prescribed in IBS, these drugs should not be viewed solely as mood-improving, but as having multiple actions at different sites along the brain–gut axis.

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