Aliment Pharmacol Ther 1996; 10: 787–793.

Mebeverine alters small bowel motility in irritable bowel syndrome

P. R. EVANS*, Y.-T. BAK* & J. E. KELLOW*†
*Departments of * Medicine and † Gastroenterology, Royal North Shore Hospital, Sydney, Australia*

Accepted for publication 12 June 1996

SUMMARY

Background and Aim: Despite its widespread use in irritable bowel syndrome (IBS), limited clinical data exist on the effects of mebeverine hydrochloride on gastrointestinal motility. Human motor activity in the small bowel is more reproducible than that in the large bowel; therefore the aim of this study was to determine in the small bowel the effects of oral mebeverine in both IBS patients and in healthy controls.
Methods: Twelve IBS patients (11 females/ 1 male, 46 ± 13 years old)—predominant constipation (IBS-C, $n = 6$) and predominant diarrhoea (IBS-D, $n = 6$)—and six healthy controls, underwent continuous 48 h ambulant recording of small bowel motor activity. One low energy (400 kcal) and one high energy (800 kcal) standard meal were administered in each consecutive 24-h period. Subjects received, in blinded fashion, placebo tablets in the first 24 h then mebeverine 135 mg q.d.s. in the second 24 h.
Results: Mebeverine had no effect on parameters of small bowel motility in controls. In contrast, in both IBS-C ($P = 0.01$) and IBS-D ($P < 0.05$) patients, phase 2 motility index was increased during mebeverine administration. Also, after mebeverine the proportion of the migrating motor complex cycle occupied by phase 2 was reduced in IBS-D ($P = 0.01$), while phase 2 burst frequency was reduced in IBS-C ($P < 0.05$). For phase 3 motor activity in IBS-C patients, the propagation velocity was decreased ($P < 0.01$), and the duration increased ($P < 0.01$).
Conclusions: These findings suggest that mebeverine, in the initial dosing period, has a normalizing effect in the small bowel in IBS, enhancing contractile activity in a similar fashion to 'prokinetic' agents, as well as producing alterations in motor activity consistent with an 'antispasmodic' effect.

INTRODUCTION

Mebeverine hydrochloride, a derivative of methoxybenzamine, is widely used in the management of irritable bowel syndrome (IBS). Evidence from clinical trials supports its effectiveness in improving symptoms in such patients.[1–3] It has been described as a musculotropic agent, with its site of action postulated to be directly on smooth muscle cells. *In vitro* studies indicate blocking effects on sodium, potassium and calcium channels.[4] It has been proposed that mebeverine reduces excessive contractile activity but that, in contrast to anticholinergic agents, it does not inhibit or affect normal motor activity.[2,5] Den Hertog & Van den Akker[4] demonstrated the effects of mebeverine on guinea-pig taenia caeci smooth muscle cells, of reduced sodium permeability and inhibition of response to alpha 1 receptor stimulation. The latter appeared to involve limitation of the amount of calcium available for mobilization and hence potassium efflux. The effects were limitation of both depolarization and hyperpolarization. This would be expected to both attenuate hypercontractility and prevent excessive relaxation or loss of tone. Indeed, studies of pelvic colonic motility in both healthy subjects[5] and patients with IBS[2] demonstrated the reduction but not abolition of contractile activity following intraluminal[5] and intravenous[2] mebeverine. Connell[2] suggested that the observed effects were more pronounced in those IBS patients with a

Correspondence: Dr J. E. Kellow, Department of Medicine, Royal North Shore Hospital, St. Leonards, NSW 2065, Australia.

greater degree of hypermotility. However, these studies represent only limited clinical data on the effects of mebeverine on human gastrointestinal motility.

Motor activity in the human small bowel is more reproducible than that in the large, and although small bowel motor disturbances have previously been documented in IBS,[6,7] very little data are available evaluating the effects of mebeverine on motor activity in this region of the gut. Connell[2] demonstrated only a slight and transient reduction in contractile amplitude via a radiotransmitter positioned in the small intestine; most recently Greenwood & Doolittle noted reduced motility in the jejunum of ferrets after both intravenous and intraluminal mebeverine.[8] Based on these limited *in vitro* and *in vivo* data, we hypothesized that oral mebeverine in human subjects may reduce small bowel contractile activity, particularly (or exclusively) if this was hyperactive, but that the drug would be less likely to affect the qualitative patterns of (fasting) small bowel motility. The aim of this study was therefore to determine, in both IBS patients and healthy subjects, the effects of mebeverine on small bowel motor activity, as assessed using prolonged ambulant manometry during an initial 24-h dosing period.

MATERIALS AND METHODS

Subjects

Twelve patients participated (11 females/1 male, age 46 ± 13 years) with well-documented IBS, who fulfilled the symptom criteria of Drossman *et al.*[9] Patients completed a validated symptom questionnaire[10] which was used to establish the presence of IBS and to subdivide patients into those with predominant constipation (IBS-C, $n = 6$) and those with predominant diarrhoea (IBS-D, $n = 6$). Six asymptomatic healthy controls (4F/2M, 41 ± 17 years) acted as a control group. The protocol was approved by the Medical Research Ethics Committee of the Royal North Shore Hospital and each subject gave informed consent for the procedures.

Experimental protocol

All medications known to affect gastrointestinal motility were ceased at least 48 h prior to the study. Subjects fasted, and following a light breakfast were intubated in the afternoon using a transnasal flexible strain gauge catheter (Gaeltec, Dunvegan, Isle of Skye, UK), with an external diameter of 3 mm and three distal sensors each located 10 cm apart. Fluoroscopy was used to assess catheter movement—a latex balloon on the catheter tip was inflated in the duodenum to advance the catheter so that the three sensors were situated in the distal duodenum and proximal jejunum—the balloon was then deflated. The catheter was connected to a portable solid state 2 Mb digital recorder (Intestinal Data Logger, IDL, Cavendish Automation, Huntington, Cambridge, UK) which had a pressure range of 0–200 mmHg. A sampling frequency of 2 Hz, previously shown to be sufficient for the identification of contractile events,[11] was used. Recording was commenced at 14.00 hours and continued until 17.30 hours on day 3, resulting in two consecutive 24-h recording periods.

During these periods subjects remained in the Motility Unit, although they were encouraged to go about their usual daily activities as normally as possible. Subjects remained awake during the day and evening until $\approx$ 22.00 hours. Two standard meals were administered in each 24-h period: a high energy (800 kcal) meal at 17.30 hours, and a low energy (400 kcal) meal at 07.30 hours. Fasting, except for water (maximum 300 mL) was maintained. Both meals were equivalent in their proportions of protein (17%), carbohydrate (47%) and fat (33%). For the first 24-h period placebo tablets were administered at 16.00 hours, 22.00 hours, 07.00 hours and 12.00 hours. Identical tablets of mebeverine (135 mg) were administered at the same times during the second 24-h period. Subjects were unaware of which period involved administration of the active medication. A standardized diary was kept of symptoms. These were grouped into the following categories: pain; discomfort; bloating, fullness or swelling; nausea or vomiting; borborygmi; character of bowel movements—hard, normal or loose.

Analysis of motility data

Data were initially analysed manually before subsequent analysis by a validated, automated computer program.[12]

Manual analysis. At the end of each subject's study, data was downloaded from the IDL onto a 386SX personal computer (Compaq Deskpro) and was then transferred in analog form (Cavcom, Cavendish Automation Ltd, UK) via an analog-to-digital coverter (MacLab, Analog Digital Instruments, Castle Hill, NSW, Australia) to an Apple Macintosh computer. Data were stored and displayed

using a MacLab Chart program (Analog Digital Instruments). Diary entries were marked on to each subject's recording by one observer who then divided the recording into the two 24-h periods (placebo and active), and coded each period separately according to a random number schedule. The MacLab Chart file on the computer was similarly divided and coded. A second observer then, in a blinded fashion for placebo or active periods, identified and recorded start and end-points for phase 3 and phase 2 of the migrating motor complex (MMC), postprandial patterns, discrete clustered contractions (DCCs) and artifacts in the distal channel, as well as phase 3 start points in the proximal channel (middle channel if absent at the former) for the determination of propagation velocity. The number of bursts and other qualitative events in all channels was noted.

Automated analysis. Start and end points as above, together with the number of bursts and other qualitative events, were then entered into the analysis program (MacMotility, Royal North Shore Hospital Department of Medicine and Connect Developments, Sydney, Australia), which identified contractions and calculated their respective durations, amplitudes and areas under curve (*AUC*). Hence for fasting phase 3 and phase 2 and for postprandial patterns, the following parameters were calculated: motility index (*AUC* per unit time); phase 3 periodicity, duration and propagation velocity; proportion of the MMC cycle occupied by phase 2; postprandial pattern duration; and for phase 2 and postprandial patterns, the proportion occupied by DCCs, and the frequency of bursts, sustained incoordinated phasic activity (SIPA) and in postprandial patterns alone, phase 3-like activity.

The following motor parameter definitions were used: Phase 3, a period with at least 2 min of uninterrupted regular phasic contractions at the maximum frequency for that locus, usually followed by quiescence;[13] Phase 3 periodicity, the time interval between the commencement of consecutive activity fronts; Phase 3 propagation velocity, the distance between proximal and distal recording sensors divided by the time interval between the onset of phase 3 at the two sensors;[14] Phase 3 abnormality, contractile irregularity or disruption, or non-, simultaneous- (> 20 cm/min) or retrograde propagation; Phase 2, a period of irregular and intermittent contractions with three or more contractions within 10 min;[15] Postprandial state, the period from the time of an evident increase in amplitude and/or frequency of contractions after commencement of a meal to the onset of the next phase 3;[16] DCCs, a period longer than 5 min with groups of clustered contractions with/without propagation, with at least 30 s of quiescence before and after each cluster;[17] Burst, a group of irregular uninterrupted contractions (10 contractions/min or more) longer than 2 min, with 50% or more of contractions higher than 20 mmHg without propagation;[18] Sustained incoordinated phasic pressure activity (SIPA), sustained (> 30 min), intense phasic pressure activity occurring in one or more segments of intestine while normal or decreased activity is being recorded simultaneously elsewhere;[18] Phase 3-like activity during fed pattern, regular phasic contractions at the slow-wave frequency lasting longer than 1 min and occurring 5 min or later after intake of a meal,[14] and if lasting longer than 2 min then not propagating through all three channels or not obviously terminating the postprandial pattern.

Statistical analysis

Once data analysis was complete the code was broken to determine which file numbers corresponded to placebo and active periods. Because of the cyclical nature of fasting small bowel motility, prolonged manometric studies produce repeated measurements of motor parameters within individual subjects. To account for non-independence between repeated measures, the data were first normalized by log transformation and then a generalized linear model technique was used to adjust for repeated measures whereby the correct error term was determined for subsequent analysis.[19]

Placebo phase between group comparisons. For a given parameter, repeated measurements for the 24-h placebo period were plotted consecutively along the x-axis with the quantitative value on the y-axis. For an individual subject, a single slope and intercept were then derived and as such was a summary of the repeated measures; these values were then compared between the subject groups. If a difference was present, the intercept and slope were then compared individually using Student's t-test. Depending on the relationships between these values it could be determined whether, on average over the 24 h, a given parameter differed between the groups. For these comparisons, the control group consisted of six healthy subjects plus an additional 19 healthy asympto-

matic subjects (12F/7M, 40±12 years old) studied for a 24-h period using an identical recording technique.

Placebo to active phase within-group comparisons. In this instance repeated measurements for the entire 48 h were plotted consecutively along the *x*-axis with the quantitative value on the *y*-axis. Slope and intercept values were then compared for the subject groups against zero using the *F* test. If a difference was present, the intercept and slope were then compared individually using Student's *t*-test. Depending on whether the slope differed from zero it could be determined whether a given parameter significantly changed over the two recording periods.

Quantitative fed motor parameters—which involved single measurements from each subject—and symptoms, were compared between patients and controls using the Mann–Whitney *U*-test. The placebo and active periods were compared using the Wilcoxon Signed Rank test. For the phase 2 qualitative parameters (other than DCCs), because the most frequent observation of these events was zero, the number of events in the 24-h period was divided by the total duration of phase 2 activity in that 24-h period, giving an 'average' frequency of events (number per h). Similarly, the total number of phase 3 abnormalities was divided by the total number of MMC cycles.

In patients, rates of small bowel motor abnormality for phase 2, phase 3 and postprandial patterns were compared between the placebo and active phases using the χ^2 or Fisher's Exact test. For this purpose, a patient was considered to be abnormal in phase 3, phase 2, postprandial (low energy) and/or postprandial (high energy) if one or more quantitative or qualitative parameters fell outside the control range. In the case of the quantitative fasting parameters, a single estimate for each subject was derived by taking the median value of those for all the MMC cycles in that 24-h period. *P*-values from multiple hypothesis tests were interpreted according to the method of Hochberg & Benjamini,[20] a more powerful modification of the Bonferroni procedure. Standard *P*-values are reported together with, if necessary, an indication of significance after accounting for the number of statistical tests performed.

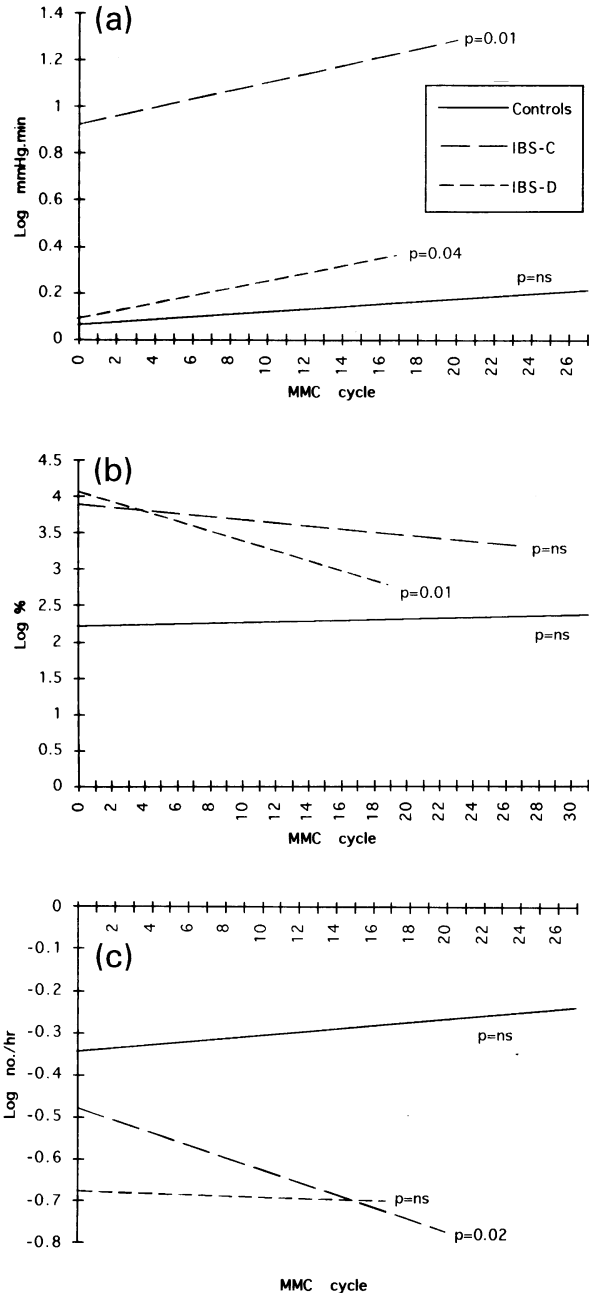

Figure 1. Effects of mebeverine on phase 2 motor parameters: (a) phase 2 motility index: change over consecutive 24 h (placebo to active drug) periods—note increase in motility index in IBS patients but not controls; (b) proportion of MMC cycle occupied by phase 2: change over consecutive 24-h periods—note reduction in IBS predominant diarrhoea; (c) phase 2 burst frequency: change over consecutive 24-h periods.

RESULTS

In the basal (placebo) period the interdigestive phase 2 motility index was higher in IBS-C patients (intercept 0.647, slope 0.067) compared to controls (intercept 0.068, slope 0.004; $P = 0.0009$). There was also a tendency for phase 3-like activity in the postprandial pattern to be more frequent in IBS patients as a whole

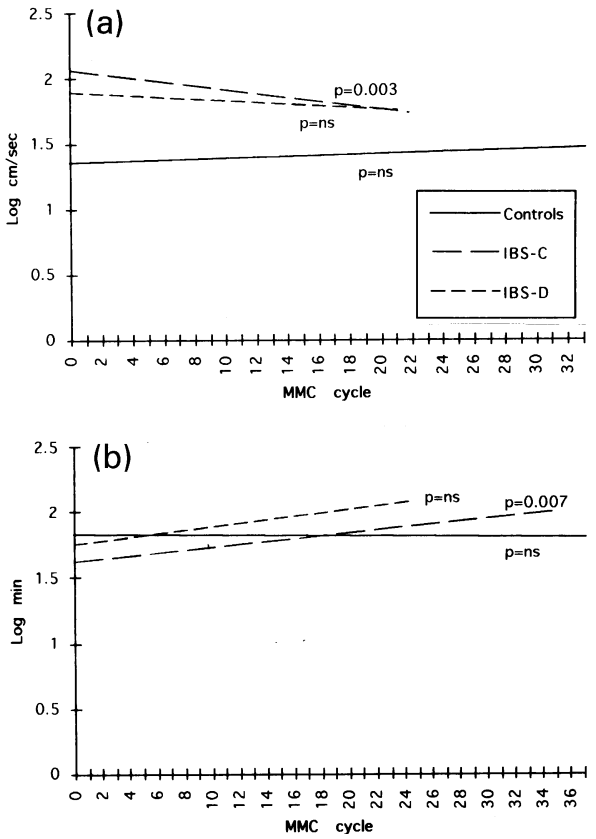

Figure 2. Effect of mebeverine on phase 3 motor parameters: (a) phase 3 propagation velocity: change over consecutive 24-h periods—note reduction in IBS predominant constipation; (b) phase 3 duration: change over consecutive 24-h periods—note increase in IBS predominant constipation.

when compared to controls, for both the high energy ($P = 0.04$) and low energy ($P = 0.04$) meal.

When compared to the placebo period, mebeverine had no significant effects on interdigestive small bowel motor parameters in controls. In patients, in contrast, mebeverine resulted in alterations in both phase 2 and phase 3 motor activity. Thus a higher phase 2 motility index was observed in both IBS-C and IBS-D (Figure 1a). The proportion of the MMC cycle occupied by phase 2 was reduced in IBS-D (Figure 1b), while the frequency of phase 2 burst activity was reduced in IBS-C following mebeverine (Figure 1c). For phase 3 motor activity, mebeverine was associated with lower phase 3 propagation velocity, and increased phase 3 duration, in IBS-C (Figure 2). Phase 3 duration also increased after mebeverine in IBS-D ($P = 0.02$), and phase 3 periodicity was reduced in IBS-C ($P = 0.04$); these did not remain statistically significant after correction.

Mebeverine had no significant effects on postprandial small bowel motor parameters in either controls or in IBS patients. There were also no significant effects on the rates of small bowel motor abnormality, either interdigestive or postprandial, in IBS. Symptom reporting did not differ between the placebo and active phases of the study.

DISCUSSION

The present study has demonstrated that following an initial 24-h dosing period of mebeverine, an increase in interdigestive phase 2 motility index occurs in both constipation- and diarrhoea-predominant subgroups of IBS. In contrast, in healthy subjects mebeverine appears to have no significant effect on small bowel motility. Relevant to this differential effect, phase 2 motility index was higher in IBS-constipation when compared to controls during the placebo (basal) period; this finding therefore raises the possibility that mebeverine may influence contractile activity in an intestine already 'primed' or sensitized to display altered motor activity. Although the functional significance or correlation of increased phase 2 contractile activity remains unclear, the increase in this parameter seen after the administration of mebeverine in IBS has some similarity to that observed in healthy subjects following cisapride,[21] and thus may reflect a stimulatory or 'prokinetic' effect. At the same time, however, mebeverine reduced the phase 2 burst activity in the IBS-constipation group—a regulatory or 'normalizing' effect of mebeverine on gut motility has been suggested previously.[2] The reduction, in IBS-diarrhoea, in the proportion of the migrating motor complex cycle occupied by phase 2 may also represent such a phenomenon.

It was notable that mebeverine also influenced interdigestive phase 3 motor parameters. This was apparent again in the IBS-constipation group, where a reduced phase 3 propagation velocity and increased phase 3 duration were observed. There was also a tendency for the latter effect to be present in IBS-diarrhoea, however, and the phase 3 changes thus may not be specific to the constipation subgroup. The cellular mechanisms of action of mebeverine appear to be complex[4] and the effects on small bowel motility observed in this study suggest that the drug not only alters smooth muscle responsiveness. An effect on neural structures, most likely of the myenteric plexus, appears possible, par-

ticularly given the observed changes in fasting phase 3 parameters discussed above.

It is of interest that none of the effects of mebeverine seen in IBS patients were observed in healthy control subjects. The visceral hyperalgaesia hypothesis[22] proposes that the pathogenesis of IBS involves enteric afferent neural dysfunction or sensitization. Such alterations in neural activity, which might include changes in neural synaptic responsiveness, could be conducive to modification from mebeverine. It is feasible that the lack of effect of mebeverine on postprandial small intestinal motor activity, in both IBS patients and controls, relates to a state of maximal stimulation whereby the enteric neuromuscular apparatus is refractory to the effects of mebeverine, at least at serum concentrations achieved with routine clinical oral dosing. The reduction in postprandial rectosigmoid motility seen in the study by Daly *et al.*,[5] where an apparent selective reduction in multiple channel, and not single channel, contractions occurred, may have reflected higher cellular concentrations of mebeverine achieved from intraluminal instillation. Alternatively, the gastrocolic motor reflex may be more responsive to mebeverine than the small intestinal motor response to the direct stimulatory effect of intraluminal nutrients.

The ambulant recording and analysis technique which we employed enabled the double-blind, placebo-controlled sequential study design; in this regard it is important to note that, during a 48-h recording period in healthy subjects, parameters of small bowel motility differ little between the first and second 24-h periods.[12] Certainly, the alterations we observed in the current study have not been observed in healthy subjects in the absence of medication. Our experimental design also employed a standardized protocol of recording to avoid introducing any bias due to the effects of different diet, etc. We acknowledge, however, that as motor alterations in IBS appear to be more prominent in out-patient recordings,[7] and as we did not observe some of the previously documented motor alterations in these in-patient ambulant recordings, the effects of mebeverine in everyday clinical settings may be different.

In conclusion, this study has demonstrated that mebeverine can influence small bowel motor activity in IBS patients, and has produced some insights into its possible modes of action. The alterations in motor parameters observed raise the possibility that mebeverine, in oral doses, can induce 'prokinetic' as well as 'antispasmodic' effects in the small intestine. Further studies are required, including an evaluation of the effects of mebeverine in patients studied in an out-patient environment, to attempt to define these effects more extensively. Assessment of the effects of the drug on intestinal transit in particular, in order to define the net functional significance of the contractile alterations, would also appear to be indicated.

ACKNOWLEDGEMENT

The support of Janssen-Cilag (Aust) Pty. Ltd. is gratefully acknowledged.

REFERENCES

1 Tasman-Jones C. Mebeverine in patients with the irritable colon syndrome: double blind study. NZ Med J 1973; 77: 232–5.
2 Connell AM. Physiological and clinical assessment of the effect of the musculotropic agent mebeverine on the human colon. Br Med J 1965; ii: 848–51.
3 Baume P. Mebeverine, an effective agent in the irritable colon syndrome. Aust NZ J Med 1972; 2: 34–6.
4 Den Hertog A, Van den Akker J. Modification of alpha1-receptor-operated channels by mebeverine in smooth muscle cells of guinea-pig taenia caeci. Eur J Pharmacol 1987; 138: 367–74.
5 Daly J, Bergin A, Sun WM, Read NW. Effect of food and anticholinergic drugs on the pattern of rectosigmoid contractions. Gut 1993; 34: 799–802.
6 Kellow JE, Phillips SF, Miller LJ, *et al.* Dysmotility of the small intestine in irritable bowel syndrome. Gut 1988; 29: 1236–43.
7 Kellow JE, Gill RC, Wingate DL. Prolonged ambulant recordings of small bowel motility demonstrate abnormalities in the irritable bowel syndrome. Gastroenterology 1990; 98: 1208–18.
8 Greenwood B, Doolittle T. Effect of mebeverine hydrochloride on jejunal motility and epithelial transport in the anesthetized ferret. Gastroenterology 1990; 98: A354(Abstract).
9 Drossman DA, Thompson WG, Talley NJ, *et al.* Identification of sub-groups of functional gastrointestinal disorders. Gastroenterol Int 1990; 3: 159–72.
10 Talley NJ, Phillips SF, Melton JI, *et al.* A patient questionnaire to identify bowel disease. Ann Intern Med 1989; 111: 671–4.
11 Lindberg G, Iwarzon M, StSl P, *et al.* Digital ambulatory monitoring of small bowel motility. Scand J Gastroenterol 1990; 25: 216–24.
12 Evans PR, Bak Y, Kellow JE. Ambulatory small bowel manometry in health—comparison of consecutive twenty-four hour recording periods. J Amb Monitoring, in press.
13 Thompson DG, Wingate DL, Archer L, *et al.* Normal patterns of human upper small bowel motor activity recorded by prolonged radiotelemetry. Gut 1980; 21: 500–6.

14 Husebye E, Skar V, Aalen OO, *et al*. Digital ambulatory manometry of the small intestine in healthy adults. Dig Dis Sci 1990; 35: 1057–65.
15 Remington M, Malagelada J, Zinsmeister A, *et al*. Abnormalities in gastrointestinal motor activity in patients with short bowels: effect of a synthetic opiate. Gastroenterology 1983; 85: 625–36.
16 Kellow JE, Borody TJ, Phillips SF, *et al*. Human interdigestive motility: variations in patterns from oesophagus to colon. Gastroenterology 1986; 91: 386–95.
17 Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. Gastroenterology 1987; 92: 1885–93.
18 Malagelada J, Camilleri M, Stanghellini V. Manometric diagnosis of gastrointestinal motility disorders. New York: Thieme Inc., 1986.
19 SAS/STAT User's Guide, Release 6.03 edn. Cary, NC: SAS Institute Inc., 1988.
20 Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. Stat Med 1990; 9: 811–8.
21 Benson MJ, Castillo FD, Deeks JJ, *et al*. Assessment by prolonged ambulatory manometry of the effect of oral cisapride on proximal small bowel interdigestive motility. Dig Dis Sci 1992; 37: 1569–75.
22 Mayer EA, Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. Gastroenterology 1994; 107: 271–93.