Differential regional effects of octreotide on human gastrointestinal motor function

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Abstract

The effects of octreotide on regional motor function in the human gut are unclear. In a randomised, blinded study the effects of octreotide (50 μg, subcutaneously, three times daily) and placebo on gastric, small bowel, and colonic transit, and colonic motility and tone were assessed in 12 healthy volunteers whose colon had been cleansed. Octreotide accelerated initial gastric emptying ($p=0·05$), inhibited small bowel transit ($p<0·01$), and reduced ileocolonic bolus transfers ($p<0·05$). Colonic transit was unaltered by octreotide; the postprandial colonic tonic response was inhibited ($p<0·05$ *v* placebo), whereas colonic phasic pressure activity was increased by octreotide ($p<0·05$ *v* placebo). These data support the use of octreotide in diarrhoeal states but not in diseases that cause small bowel stasis and bacterial overgrowth. Simultaneous measurements of colonic transit, tone, and phasic contractility are valid in studying the effects of pharmacological changes and may be applicable to the study of the human colon in health and disease.

(*Gut* 1995; **36:** 743–748)

Keywords: somatostatin, motility, colon, small bowel, tone, transit.

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Accepted for publication
9 September 1994

The cyclised somatostatin analogue, octreotide, has been proposed as a potential treatment for several gastrointestinal disturbances,[1] including dumping syndromes, portal hypertension, bleeding oesophageal varices, and several diarrhoeal diseases such as those induced by neuroendocrine tumours (such as carcinoid syndrome), small bowel fistulae, ileostomy, and short bowel syndrome, and the diarrhoea associated with acquired immune deficiency syndrome and diabetes mellitus.[2] Octreotide has been suggested as a potential treatment in patients with diarrhoea-predominant irritable bowel syndrome in view of the inhibition of orocaecal transit in healthy subjects.[3] Recent studies also suggest that it may have a role in suppressing visceral hypersensitivity in functional gastrointestinal disease.[4] While its application in these diarrhoeal disorders has received much attention, somatostatin is known to induce reproducibly a propagated activity front, similar to a migrating motor complex, in the small intestine.[5–10] Thus, Soudah *et al* proposed its use in intestinal scleroderma,[11] in which there is evidence of stasis and bacterial overgrowth.

In view of these diverse indications proposed from clinical studies, ranging from severe stasis with bacterial overgrowth to severe diarrhoeas of diverse aetiologies, we undertook a study to examine in detail the regional effects of octreotide on motor function in the human gastrointestinal tract. In a previous study, we reported the effects of 50 μg subcutaneous octreotide on gastroduodenojejunal motility in health and disease.[12] In this study, we wished to assess specifically colonic motor function in greater detail in view of the recent observation that carcinoid patients show significant changes in colon function,[13] and although octreotide is frequently used in the treatment for this form of diarrhoea, its mechanism of action in these patients is unclear.

To test the hypothesis that octreotide inhibits motor function throughout the gut, and specifically colonic contractility, we evaluated its effects on gastric emptying, small bowel transit, ileocolonic transfer of solid residue, regional colonic transit, and postprandial tonic and phasic pressure activity in the colon of healthy subjects.

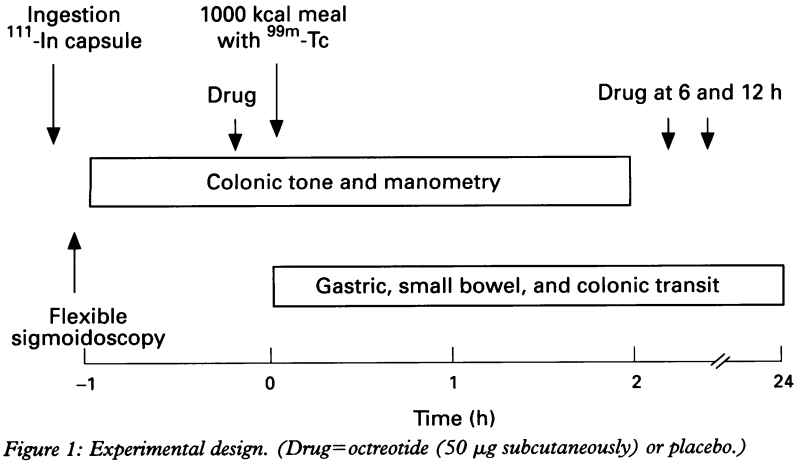

Figure 1: Experimental design. (Drug=octreotide (50 μg subcutaneously) or placebo.)

Methods

HEALTHY CONTROLS

We studied 12 healthy control subjects, whose ages ranged from 20 to 54 years (mean: 34 years; four women and eight men). All women participating in the study who were of childbearing potential had a negative plasma (βHCG) pregnancy test within 48 hours of the study. The research protocol was approved by the Mayo Institutional Review Board and all participants provided written informed

TABLE I *Effect of octreotide on gastric emptying*

	Lag time (min)	*Post-lag fractional emptying rate (%min^{-1})*	*β*	*κ×10^{-4}*
Placebo (n=6)	92 (21)	0·28 (0·04)	2·15 (0·34)	44 (6)
Octreotide (n=6)	40 (17)	0·46 (0·25)	1·26 (0·21)	89 (45)
p Value (placebo *v* octreotide)	0·09	>0·1	0·048	>0·1

Data show mean (SEM).

consent. All subjects received 1·5 l of an oral colonic lavage solution (OLS, Abbott Laboratories, Chicago, IL) on the evening before the study.

GASTROINTESTINAL TRANSIT STUDY

We quantitated gastric, small bowel, and regional colonic transit by means of a validated scintigraphic method[14–17] that utilises a delayed release capsule containing ^{111}In-radiolabelled Amberlite-IR 120 ion exchange pellets (Sigma Chemical Co, St Louis, MO) to assess colonic transit, and ^{99m}Tc radiolabelled pellets (Amberlite 410, Sigma Chemical Co, St Louis, MO) in an egg meal to assess gastric and small bowel transit. The preparation, conduct, and analysis of these studies have been previously published.[14–17]

COLONIC TONE AND PHASIC PRESSURE ACTIVITY

After placement of a soft tipped guidewire (Microvasive, Hobbs Medical Inc, Stafford Springs, CT) into the transverse colon via colonoscopy, a combined barostat-manometric assembly was inserted into the descending colon so that the tip of the multilumen tube was located at the splenic flexure in all subjects. The barostat balloon was 10 cm in length, and the method used for measuring and calculating tone in the colon followed the studies previously reported.[18–20] Manometric side holes were located 2 cm proximal, as well as 2, 7, and 12 cm distal to the barostat balloon. Briefly, an infinitely compliant bag was inflated with air and kept under a constant operating pressure throughout the studies; changes in the volume within this bag were used as estimates of changes in colonic tone. The barostat tracing was separated (by means of a computer program (Modified VAX LAB Program, DEC, Boston, MA) into a baseline volume which reflects tone, and phasic pressure events which typically coincide with manometric phasic pressure activity. The phasic pressure profiles recorded by the three manometric side holes were averaged and used to estimate the phasic pressure activity in the left colon in the fasting and postprandial periods.

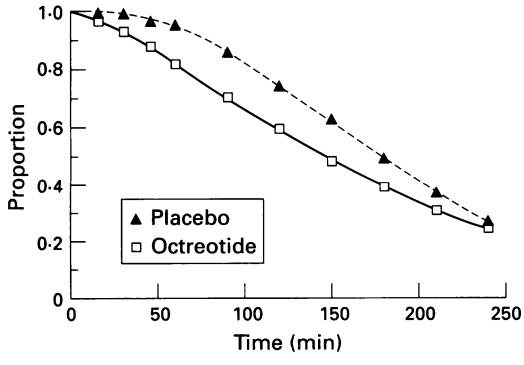

Figure 2: Effect of octreotide on gastric emptying. The calculated medians for the octreotide and placebo groups have been plotted. Note the acceleration of the initial phase of gastric emptying with octreotide.

EXPERIMENTAL DESIGN (FIG 1)

After bowel preparation on the preceding evening and an overnight fast, subjects ingested the methacrylate coated capsule containing ^{111}In pellets and underwent partial colonoscopy without sedation. The combined barostat-manometry assembly was introduced into the descending colon under fluoroscopic control. Subjects were then transferred to a gamma camera laboratory and placed in a chair with the back at an angle of 30° to the horizontal. When the methacrylate coated capsule was shown to have emptied from the stomach on the gamma camera image (that is, below markers placed on the anterior superior iliac spines and to the right of the midline), barostat and manometry recordings were obtained for 40 minutes in the fasting period. Octreotide, 50 μg, or an equal volume of saline (0·5 ml) was administered subcutaneously and colonic recordings were then obtained for a further 10 minutes. Subjects next ingested a 1000 kcal meal which included 300 kcal of egg (radiolabelled with ^{99m}Tc pellets), brown bread, and a chocolate malt (protein 15%, carbohydrate 35%, and fat 50%). After the meal was ingested, regular monitoring of gastrointestinal transit was obtained with a dual headed gamma camera, continuous recordings of colonic motility were obtained by multilumen manometry and the barostat balloon, and blood samples to measure gut hormones were obtained at 10 minute intervals during the first two hours postprandially.

DATA ANALYSIS

The transit profiles were summarised by the following parameters, as in previous studies from our group[14–17 21] and others.[22] We evaluated gastric emptying by the lag time (defined as the time for 10% of the isotope to empty from the stomach,[14 21] post-lag gastric fractional emptying rate, and by power exponential analysis $[Prop_t = a_0 * \{-\kappa t\}^{\beta}]$.[21] Briefly, $prop_t$ is the proportion remaining in the stomach at time t, a_0 is the proportion at time 0, β describes the shape of the initial part of the curve, and κ is an expression of the rate constant of the emptying curve. Small bowel transit time (expressed as the time for 10% of isotope to reach the colon, minus time for the same proportion to empty from the stomach, or t10%), proximal colonic emptying rate, and colonic geometric centre (weighted average of counts in five regions of interest: ascending, transverse, descending, sigmoid/rectum, and stool) at two, eight, and 24 hours were also measured. Ileocolonic transit and ascending

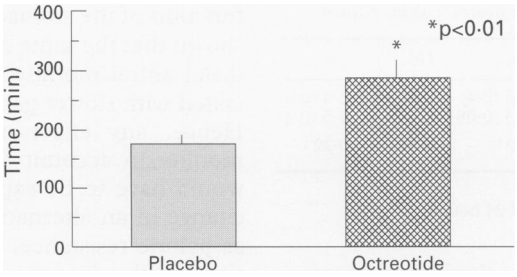

Figure 3: Effect of octreotide and placebo on small bowel transit time in the two groups of healthy subjects. Note the marked prolongation in t10% for small bowel transit.

colon emptying were plotted for 11 of the 12 participants, since in one patient taking octreotide, the methacrylate coated capsule did not dissolve until it reached the distal transverse colon. Ileocolonic bolus transfers were defined by a rate of flow $\geq 10\%$ of ^{111}In over 15 minutes, as in previous studies.[14 23]

Colonic tone was calculated by the baseline volume of the barostat balloon. Since the baseline volume depends on the dimensions, shape, as well as the elasticity and muscular function of the viscus, which differ between individuals, we calculated the percentage change in volume relative to the fasting period, thereby normalising for interindividual differences before octreotide or placebo. Colonic manometric phasic pressure activity was averaged for the three tracings, 2, 7, and 12 cm distal to the barostat balloon and expressed as a motility index:

[MI=(Σ amplitude×no of contractions+1)] per hour.

STATISTICAL ANALYSIS

Student's *t* test (two tailed) was used to compare summaries of transit in the octreotide and placebo treated group. When parameters did not show a Gaussian distribution, a Wilcoxon rank sum test was used. The occurrence of ileocolonic bolus transfers in the two treatment groups was compared by χ^2 test. Data in this paper are expressed as mean (SEM).

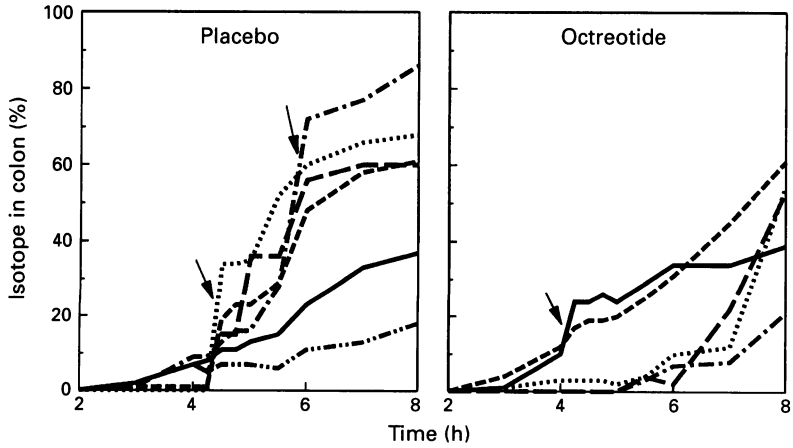

Figure 4: Plots of ileocolonic transit in each healthy subject in the placebo and octreotide groups. The y axis indicates the percentage of isotope in the colon. Examples of bolus transfers are indicated by the arrows. Note that only one subject receiving octreotide showed a rate of flow ≥10% in 15 minute periods (=boluses), whereas the placebo group showed five bolus transfers.

Results

GASTROINTESTINAL TRANSIT

Octreotide resulted in a faster initial emptying from the stomach (Table I) as shown by the lag time ($p=0{\cdot}09$) and by estimates of β, the initial shape of the gastric emptying curve ($p=0{\cdot}048$). Figure 2 shows gastric emptying plots derived from the median data for the two groups. Note the difference in the shape of the initial part of the gastric emptying curve; in contrast, the remainder of the curves look similar. Thus, the post-lag fractional gastric emptying rate and κ were not significantly different in the two groups (Table I).

Octreotide prolonged small bowel transit time (Fig 3). There was also a reduction in the number of bolus transfers (Fig 4) across the ileocolonic junction in subjects treated with octreotide (five bolus transfers in the placebo group, while only one of the octreotide treated subjects had a bolus transfer; $p<0{\cdot}05$ by Pearson's χ^2 analysis).

Ascending colon emptying rate, as well as the geometric centre (weighted average of counts in the colon) at two, eight, and 24 hours (estimates of total colonic transit) were similar in the two treatment groups (Table II). Figure 5 shows the profiles of ascending colon transit corrected for the time of onset of colonic transit, identified by appearance of 100% of the ^{111}In counts in the ascending colon. Two subjects given placebo seemed to have very rapid emptying of the isotope from the ascending colon; however, the remainder of the subjects had very similar profiles of ascending colon emptying characterised by linear phases and plateaux. The geometric centres at two, eight, and 24 hours were similar in the two groups, suggesting no overall effect of octreotide on transit through the prepared colon.

COLONIC MOTOR FUNCTION

Representative examples of tracings of colonic motility are shown in Figure 6(A) (placebo) and (B) (octreotide).

Colonic tonic motility

The fasting baseline barostat volumes in the two groups were not significantly different, and after the meal both groups showed a gastrocolonic response which was significantly increased in the placebo group ($p<0{\cdot}05$) and was less marked, although still showing a trend toward significance ($p=0{\cdot}09$) in the octreotide group (Fig 7). The magnitude of the tonic response to the meal is best summarised by the fractional decrease in the balloon volume after the meal, and was significantly lower in the octreotide group 13 (5)% compared with the placebo group 28 (4)% ($p<0{\cdot}05$).

Colonic motility measured by manometry

The fasting colonic phasic pressure activity measured by manometry was similar in the octreotide and placebo groups. Postprandially,

TABLE II *Effect of octreotide on overall colonic transit*

	GC_2	GC_8	GC_{24}
Placebo (n=6)	2·0 (0·4)	2·8 (0·6)	3·4 (0·6)
Octreotide (n=6)	1·3 (0·08)	2·5 (0·4)	4·3 (0·4)
p Value (placebo *v* octreotide)	0·21	0·69	0·22

Data show mean (SEM).
GC=geometric centre at 2, 8, and 24 hours.

both groups showed a significant increase in the motility index (Fig 8). However, the increment in phasic pressure activity in the octreotide group showed a trend to being greater than in the placebo group (p=0·09).

Discussion

This study has shown the regional effects of octreotide on the motor function of the stomach, small intestine, and colon. The predominant effects seem to be on initial emptying from the stomach and on small bowel transit. Important but opposite effects on colonic tone and phasic pressure activity were noted. The effects of octreotide on gastric emptying of solids are unclear. O'Donnell *et al*[3] showed prolongation of orocaecal transit time, but whether this prolongation was the result of impaired gastric or small bowel transit was unknown. There is some evidence that somatostatin[24] and octreotide[25] inhibit gastric emptying, and in a previous perfusion study of the jejunum, transit time over a 30 cm segment was prolonged by octreotide.[26] Previous reports did not, however, clearly evaluate octreotide's effect on transit of solid residue through the entire small bowel.

A novel finding in our study was a significant difference in the shape of the initial part of the gastric emptying of solids (β factor), consistent with quicker initial emptying with octreotide compared with placebo. However, no effect was shown on the subsequent rate of gastric emptying. These observations on gastric emptying may be, at least partly, explained by the inhibitory effects of the somatostatin analogue on gastric secretion. Thus, since the total intragastric volume (standard meal plus endogenous secretion) was probably smaller in the subjects taking octreotide, the more rapid initial emptying rate may reflect either the reduced volume load or a change in the motor function of the stomach. Previous studies have shown that the same dose of octreotide inhibits distal antral motility,[12] which is usually associated with slower gastric emptying of solids.[21] Hence, any effect of octreotide on gastric motility to account for accelerated emptying would have to be explained on the basis of a change in an alternative motor function, such as pyloric resistance, fundic tone, or a reduction in the intestinal resistance to flow by induction of a migrating motor like complex.[12] Shortening of the lag phase is typically seen after vagotomy,[27] presumably as a result of the abolition of the stomach's accommodation and inhibition of fundic tone,[28] or after stimulation of highly propulsive gastric contractions by erythromycin.[29] Further studies of these motor functions will be necessary to demonstrate conclusively the mechanism whereby octreotide reduces the lag phase for solid emptying.

The similarity in the second phase of gastric emptying in the two groups may suggest that since the gastric volume load was likely smaller with octreotide, the latter may actually have slowed gastric emptying during this period. The precise or relative contributions of volume load and emptying rate cannot be resolved by our methodology, but alternative approaches, such as magnetic resonance imaging, may be more useful.[30]

The overall inhibition in the small bowel transit of solid residue measured accurately by the scintigraphic method clarifies the observations of previous studies evaluating orocaecal transit time which was appreciably delayed by octreotide in both health[31 32] and in disease states.[3] Our results have also been confirmed in a preliminary report by Vecht *et al*.[33] These specific observations on small bowel transit are important because of the previous suggestion that octreotide might be used to stimulate propulsive activity fronts and, hopefully, accelerate transit through the small intestine of patients who have intestinal involvement by progressive systemic sclerosis.[10] Our data show the importance of not trying to predict transit times on the basis of manometric recordings. Peeters *et al* have shown in the dog that octreotide induced phase III like interdigestive activity, while reducing the intermittent pressure activity of phase II.[34] The slowing of small bowel transit may result from the inhibition of phase II contractile activity reported in dogs[34] or of the fed motor pattern reported in healthy subjects.[33] We have also previously shown that octreotide (50 μg subcutaneously) invariably induces a migrating motor complex or activity front in the small intestine in functional or organic dysmotilities[12]; however, this form of motor stimulation is not necessarily associated with acceleration of overall small bowel transit. Thus, for example, it is known that morphine, a μ-opioid agonist, frequently stimulates phase III like activity fonts in the small intestine,[35] but it is well known that such agonists delay small bowel transit.[36 37] Our observations suggest that octreotide significantly prolongs small bowel transit time in healthy subjects to levels

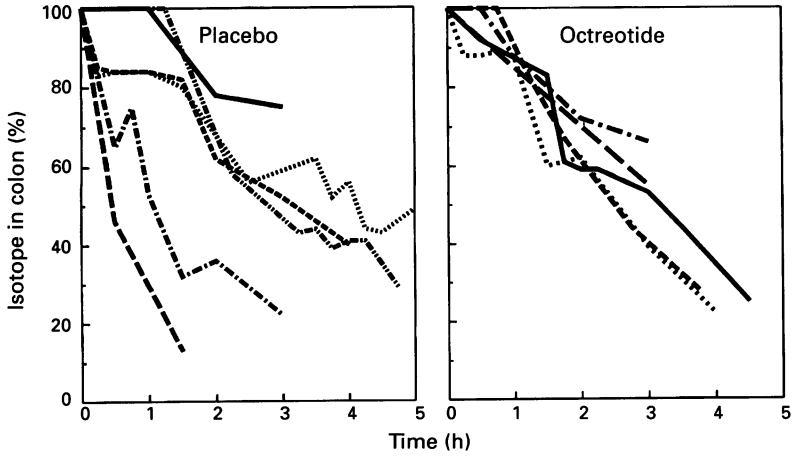

Figure 5: Ascending colon emptying curves in the placebo and octreotide groups. The y axis indicates the percentage of isotope in the ascending colon. Note the overall similarity in the rates of emptying. Time 0 indicates the time when all ^{111}In isotope was located in the ascending colon.

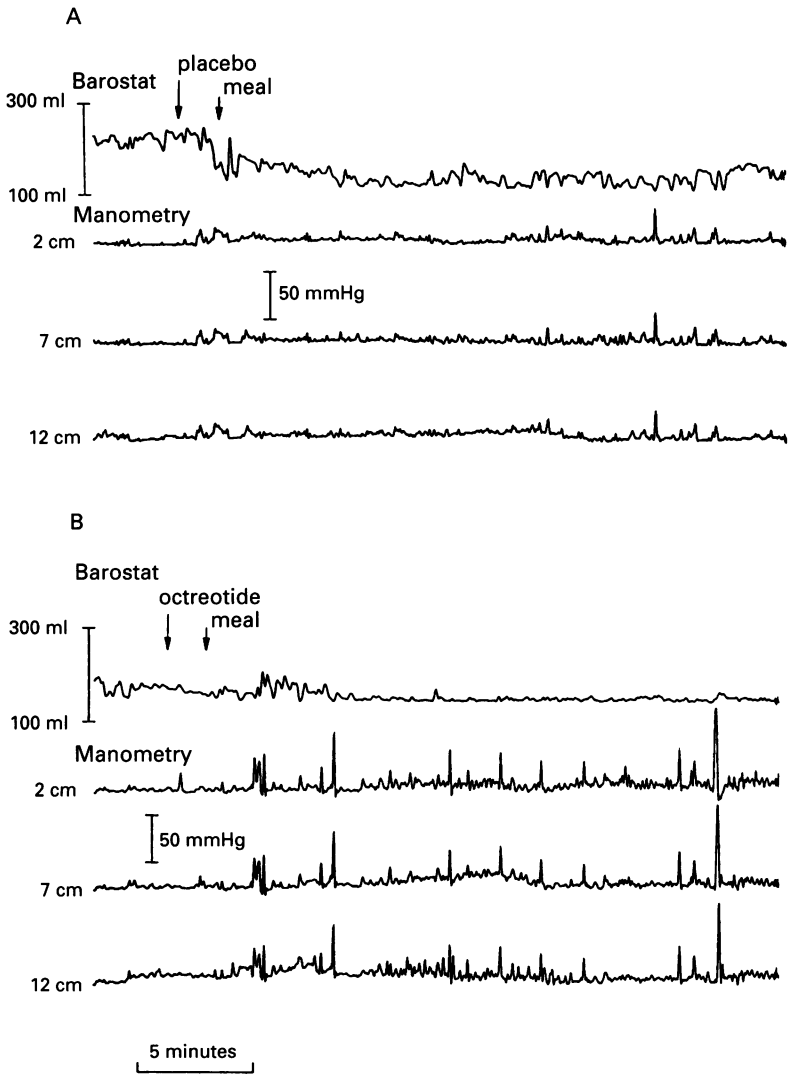

Figure 6: Examples of tracings during fasting and postprandially showing colonic tone and manometry in the placebo (A) and octreotide (B) groups. Note the inhibition of the postprandial tonic increase (reduction in volume) with octreotide.

observed in patients with myopathic pseudo-obstruction[23] studied using identical methods in our laboratory. The use of octreotide in disorders associated with small bowel stasis requires further detailed study of its effects on objective and subjective parameters in disease states, as well as placebo controlled rather than open trials.[10]

The pattern of delayed overall small bowel transit in the octreotide treated patients is associated with a reduction in the number of bolus transfers[14] across the ileocaecal junction. In the one patient receiving octreotide who showed a bolus transfer, its magnitude (15%) was identical to the mean magnitude of the transfers in the placebo group (14%). Thus, although the pattern of motor mechanisms that result in bolus transfers across the ileocaecal junction is unclear,[38] octreotide seems to inhibit this propulsive event in most individuals and this may contribute further to the overall retardation of small bowel transit. The presumably reduced pancreaticobiliary and intestinal secretion in the presence of octreotide may result in a lower ileal volume load and, hence, a lower contractile response by the distal ileum with the attendant reduction in the size of bolus transfers.

We were unable to show any change in overall colonic transit or in the emptying rate of the ascending region of the prepared colon.

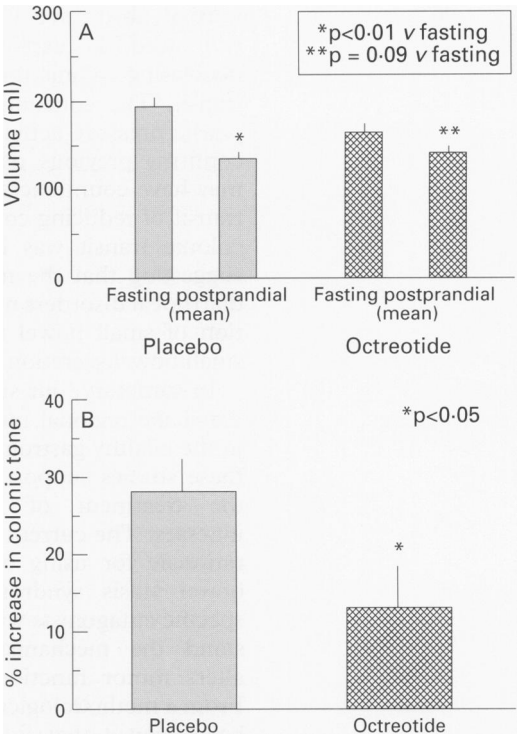

Figure 7: (A) Summary of colonic tone measured as baseline barostat volumes. Note the similarity of fasting baseline barostat volume and the decrease in volume (=increase in tone) observed in both groups postprandially ($p<0·05$ for placebo, $p=0·09$ for octreotide). (B) Although the absolute volumes measured postprandially in the two groups are similar, the increase in tone (fractional decrease in volume) was significantly greater with placebo than with octreotide.

We were impressed by the rapidity with which the ascending colon and the remainder of the colon emptied in comparison with transit profiles in our previous studies[15 17] which were performed with the colon unprepared. Preparation of the colon results in an increase in colonic motor activity measured manometrically.[39] Future studies will need to appraise whether octreotide significantly alters transit in the unprepared colon.

The effects of octreotide on colonic motor function are intriguing. Octreotide caused a reduction in the tonic response to a standardised meal. It is possible that beneficial therapeutic effects of octreotide in patients with carcinoid diarrhoea who have increased postprandial colonic tone[13] are to restore normal colonic tone and facilitate greater storage in the colon, thereby enhancing its

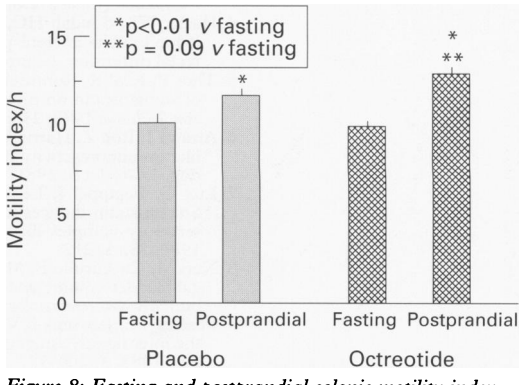

Figure 8: Fasting and postprandial colonic motility index. Note the similar fasting value in the two groups and the greater increment postprandially in the octreotide group.

normal absorptive functions. Future studies will need to explore the hypothesis that decreasing colonic tone retards overall colonic transit. The concomitant increase in colonic phasic pressure activity induced by octreotide confirms previous data in the rectum,[4] and may have counteracted the potential effect on transit of reducing colonic tone. Thus, overall colonic transit was unaltered by octreotide, suggesting that the major beneficial effect in diarrhoeal disorders may be due to the retardation of small bowel transit and inhibition of small bowel secretion.[26]

In summary, our study has characterised in detail the regional motor effects of octreotide in the healthy gastrointestinal tract. Data from these studies support the use of octreotide in the treatment of diarrhoea predominant illnesses. The current studies do not provide a rationale for using octreotide to treat small bowel stasis syndromes. Approaches using specific antagonists will be necessary to understand the mechanisms whereby octreotide alters motor function in the whole animal. From a methodological standpoint, our studies have proved that it is feasible to study the colon's motor function using simultaneous measurements of transit, tone, and phasic contractility. This approach seems to be advantageous as it provides a means of assessing simultaneously the functional significance of contractile activity, and may allow a clearer understanding of the processes that result in colonic propulsion in health, pharmacological perturbations, and disease.

This study has been presented in part at the Annual Meeting of the American Gastroenterological Association, New Orleans, Louisiana, 15–18 May 1994, and appears in abstract form in *Gastroenterology* (April 1994).

This study was supported in part by the Mayo General Clinical Research Center Grant #RR00585 from National Institutes of Health. Doctor Camilleri was supported by an American Gastroenterological Association/SmithKline Beecham Award for Clinical Research and by an unrestricted grant from Glaxo Inc. Doctor von der Ohe was supported by grant Oh54/1-2 from Deutsche Forschungsgemeinschaft. We wish to thank the director and staff of the Mayo General Clinical Research Center for support, Messrs R B Hanson and R L Tucker for technical assistance and Mrs C L Stanislav for preparing the submitted manuscript.

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