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Metoclopramide reduces carbohydrate absorption in man

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1 The effect of metoclopramide (20 mg p.o) on the times taken for a radiolabelled liquid starch meal to empty from the stomach and to reach the ileum (230 cm from the mouth), the ileal flow rates and the degree of carbohydrate absorption were studied in five normal male volunteers, intubated with a four lumen intestinal tube.
2 Administration of metoclopramide significantly reduced the time taken for delivery of 50% and 80% of the meal to the ileal aspiration site, but had no significant effect on the half time for gastric emptying.
3 Administration of metoclopramide did not affect the average flow rate or the total postprandial volume, which passed the ileal aspiration site.
4 Administration of metoclopramide reduced carbohydrate absorption in every subject by between 8 and 30%.
5 This study is consistent with the hypothesis that metoclopramide may reduce the degree of absorption in the human small intestine by decreasing the contact time between food and small intestinal epithelium, though it could also act by reducing the area of mucosa in contact with nutrients.

Keywords intestinal absorption transit time flow rate metoclopramide gastric emptying

Introduction

Metoclopramide is known to accelerate transit through the stomach and small intestine in man (James & Hume, 1968) by stimulating propulsive contractions of smooth muscle. Its effect on absorption of nutrients is less well understood. Matuchansky and colleagues (1972) have shown that it induces secretion of fluid and electrolytes in an isolated perfused segment of human jejunum, while we have shown (Holgate & Read, 1983) that the acceleration of transit, induced by metoclopramide in patients with terminal ileostomies is associated with an increase in ileostomy output and a decrease in fat absorption. The aim of the present study was to investigate the effect of metoclopramide on gastrointestinal transit and absorption of a liquid test meal in normal volunteers, and to determine the extent to which a change in small intestinal absorption induced by metoclopramide in normal volunteers could be explained by a decrease in the contact time or exposure of the liquid test meal to the small intestinal epithelium.

Methods

Subjects

Studies were performed on five volunteers (all male, aged 18–24 years) who had no history of serious bowel disease. Each subject signed a consent form fully explaining the nature of the study, and the protocol was approved by the Ethical Subcommittee of the Sheffield Area

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Protocol

After fasting overnight, subjects swallowed a flexible polyvinyl probe (total diameter = 6 mm), consisting of four polyvinyl tubes bonded together; one for ileal infusion, another for aspiration of ileal contents from a point 10 cm below the infusion site, an air line to assist aspiration and a tube terminating in a double-sealed blow-off mercury bag (Read *et al.*, 1984). The probe was allowed to progress down the intestine and was positioned fluoroscopically so that the infusion port was in the ileum, 200 cm from the teeth. The mercury bag and a small (1 cm) length of tubing was then blown off by rapid ingestion of 20 ml of air through one of the tubes, and was eventually passed in the faeces. This ensured that the tube did not progress further down the intestine. The subject again fasted overnight and commenced the experiment on the next day.

Subjects underwent the control study and the metoclopramide study on 2 consecutive days. The latter was always carried out on the last day to avoid any carry-over effect of the drug. Metoclopramide was administered in tablets containing 20 mg of the drug on the evening before the study and again 30–45 min before commencing the infusion. In the control studies identical placebo tablets were administered at the same times. During each study, the subject lay semi-recumbent on a comfortable bed and a solution of 0.9% saline, containing 2.5 μCi/100 ml [^{14}C]-PEG, was infused into the ileum at a rate of 1.0 ml/min. Twenty minutes after the start of the ileal infusion, each subject drank 750 ml of a liquid meal consisting of 60 g rice starch, 15 ml lactulose syrup (Duphalac, Duphar, Weesp, Holland), containing 10 g lactulose, 25 ml peppermint cordial (Cadbury-Schweppes, England), 5 ml of vanilla essence (Boots, Nottingham, England), and labelled with 3.75 g polyethylene glycol and 50 μCi ^{99m}Technetium sulphur colloid. Lactulose, a disaccharide which is not absorbed in the small intestine, was included in order to ensure sufficient flow past the ileal aspiration site for purposes of collection. Ileal contents were continuously aspirated from a point 30 cm below the infusion port. Each 10 min sample was injected into pre-weighed 100 ml conical flasks and stored on ice.

Estimated irradiation from ^{99}Technetium was less than 1 mrad to the whole body, 2–4 mrad to the gonads and 6–8 mrad to the gut. Estimated irradiation to the gut from ^{14}C was 50 mrad.

Measurements of gastric emptying

Gastric emptying of the radiolabelled test meal was measured by counting the radioactivity over the fundus of the stomach for 1 min out of every 5 min using a single crystal scintillation detector, positioned over the area of maximum radioactivity and connected to a scaler rate-meter (Read *et al.*, 1980). This method can yield values for gastric emptying that are as accurate and reproducible as those obtained using the gamma camera, while using only a fraction of the radioactivity (Ostick *et al.*, 1976). Counting continued until counts, corrected for isotope delay, had fallen to less than one third of their original value. A value of the half time for gastric emptying was derived from the graph of count rate *vs* time, taking the count 10 min after starting to eat the meal as the initial or 100% value.

Mouth to ileum transit time

The profile of mouth to ileum transit was determined by measuring the cumulative arrival of ^{99m}Tc at the ileal aspiration site.

Each sample aspirated from the ileum was weighed and the radioactive counts determined by placing each conical flask in turn in a fixed position under the head of the crystal scintillation counter. This procedure was validated by counting increasing volumes of a test solution of radioactive technetium in water in the same way, and indicated that as more solution was added the count rate increased in a linear fashion ($r = 0.99$, $P < 0.001$).

The study was continued until there appeared to be no further delivery of radioactively labelled aspirate, counts having returned to background levels. To ensure complete recovery of the meal, a 400 ml drink of diabetic orange juice (Boots, Nottingham, England) was then given to the subject to flush out the upper small intestinal contents. Orange juice appeared in the ileal aspirate within 20 min and sample collection was continued until there was no further delivery of orange juice or radioactive technetium from the ileum.

Since it was not possible to aspirate all the intestinal contents passing the aspiration site, the count rates for each sample were corrected for the flow rate using the following equation.

Equation 1

$$\text{Total counts} = \frac{SC \times FR \times 10}{SV}$$

where
SC = number of counts in the aspirated sample
FR = calculated ileal flow rate (ml min^{-1}) (see below)
SV = sample volume

Calculated values for the total recovery of radioactivity from the ileal site were greater than 97% of the radioactivity in the original meal in every test carried out.

The cumulative corrected counts were plotted against time on the same graph as the gastric emptying profile, and the times taken for 15, 50 and 80% of the meal to be aspirated from the ileum were estimated.

Measurement of ileal flow rate

Ileal flow rate was determined from the dilution of [^{14}C]-PEG, infused 10 cm above the ileal aspiration site.

Samples of infusate and each aspirate were weighed and 1 ml aliquots of each were pipetted into separate, numbered scintillation bottles, and 9.0 ml of scintillation cocktail (Toluene: Triton × 100; 2:11 + 0.4% w/v ppo) was added to each bottle. The samples were then counted in an automatic β-counter (L.K.B. Wallac, Finland), with an automatic quench correction, after sufficient time had elapsed for counts from ^{99m}Tc to decay to negligible levels. Flow rate was calculated for each ten minute sampling period using standard equations (Phillips & Giller, 1973), and the total volume of fluid passing the ileal aspiration site after ingestion of the meal was calculated from the area under the profile of flow rate.

Estimation of degree of carbohydrate absorption

This was determined by subtracting the calculated ileal recovery of carbohydrate from the amount in the meal.

After removing aliquots for radioactive counting of [^{14}C]-PEG, the samples were pooled in a pre-weighed beaker, and the weight of the pooled aspirate was recorded. A 10 ml aliquot was removed and assayed for unlabelled PEG (Malawer & Powell, 1967) and a value for the total recovery of PEG was determined. The remainder of the pooled aspirate was freeze-dried to constant weight and chemically analysed for carbohydrate by acid hydrolysis followed by incubation with glucose oxidase for 45 min at 37 °C. Solutions were read at 420 nm on a Unicam SP6 spectrophotometer. The same procedure was used to analyse the carbohydrate content of the meal and pilot experiments showed that 97% of the total amount of starch added to the meal could be accounted for using this method. A value for the total recovery of carbohydrate was calculated and the amount of carbohydrate passing the aspiration site was determined using Equation 2.

Equation 2

$$CHO_{Unabs} = \frac{PEG_M}{PEG_R} \times CHO_R$$

where
CHO_{Unabs} = amount of unabsorbed carbohydrate
PEG_M = amount of PEG in the meal
PEG_R = amount of PEG recovered
CHO_R = amount of carbohydrate aspirated

Subtraction of this amount from the amount of carbohydrate in the meal, analysed in the same way, yielded a value for carbohydrate absorption.

Statistical analysis

The degree of statistical significance between paired data was determined using Student's paired *t*-test.

Gastric emptying

Administration of metoclopramide did not significantly reduce the half time for gastric emptying (Table 1).

Mouth to ileum transit time

Under control conditions, the meal appeared at the ileal aspiration site within 10 min of ingestion, 15% of the meal had passed the ileal site by 0.5 h, 50% by 1.5 h and 80% by 3 h (Figure 1). Administration of metoclopramide significantly reduced the time taken for 50% and 80% of the meal to reach the ileal aspiration site (Table 1).

Ileal flow rate

In control studies, the average flow rate past the ileal aspiration site rose rapidly to reach a plateau at about 20 min after ingesting the meal, remaining at this level for the next 90 min before gradually declining (Figure 2). After administration of metoclopramide, the flow rate rose to a peak within 30 min after ingestion of the meal. Thereafter, it fell to reach basal levels at around 4 h after the meal. However, metoclopramide did not significantly affect the

Table 1 Effect of metoclopramide administration on the transit of a liquid carbohydrate meal through the stomach and small intestine, the ileal flow rate and volume and the degree of carbohydrate absorption in five healthy volunteers.

	Control (n = 5)	*Metoclopramide* (n = 5)
Gastric emptying $t_{½}$ (h)	0.8 ± 0.2	0.6 ± 0.1
Delivery of the meal to the ileal aspiration site (h)		
15%	0.5 ± 0.3	0.5 ± 0.3
50%	1.5 ± 0.2	1.1 ± 0.3[a]
80%	3.0 ± 0.3	1.8 ± 0.2[c]
Mean flow rate during first 3 h of study (ml min^{-1})	6.6 ± 1.0	6.2 ± 1.4
Postprandial ileal volume (ml)	1176 ± 176	1144 ± 275
Absorption of carbohydrate (%)	66.7 ± 4.5	49.8 ± 5.9[b]

Data is expressed as mean ± s.e. mean
Superscripts refer to the degree of statistical significance compared with paired controls (n = 5).

a, $P < 0.05$, b, $P < 0.01$, c, $P < 0.001$

average ileal flow rate, or the total volume of the meal passing the ileal site (Table 1).

Absorption of carbohydrate

Under control conditions, between 50 and 81% of the carbohydrate in the test meal was absorbed by the time it reached the ileal aspiration site (Table 1). Administration of metoclopramide significantly reduced carbohydrate absorption in every subject to between 29 and 62% (Table 1) of that in the test meal. This represented a reduction in absorption of between 8 and 30%.

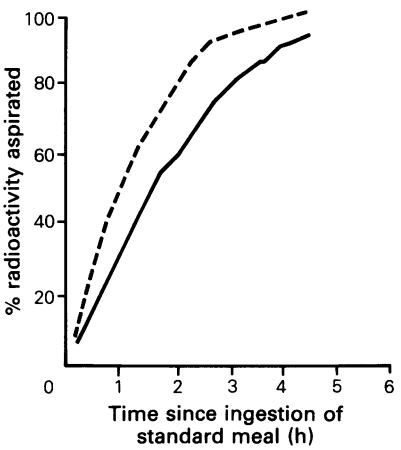

Figure 1 The average profile for the delivery of the radioactive marker in the test meal to the ileum under control conditions (—) and after administration of metoclopramide (---). The data has been corrected for non recovery of ileal fluid.

Discussion

This study has shown that administration of metoclopramide to normal human volunteers reduced the time taken for a liquid carbohydrate meal to reach the ileum and reduced carbohydrate absorption. The results support and extend our previous study in which administration of metoclopramide to ileostomists accelerated the transit of a solid meal to the terminal ileum and reduced the absorption of fluid and lipid. In both cases the half time for gastric emptying was not significantly reduced by metoclopramide suggesting that the dominant influence of the drug was on transit time through the small intestine.

The observation that absorption of carbohydrate was less complete in this study than in the previous study may be explained in three ways; (i) the transit time of a liquid meal through the small intestine is faster than that of a solid meal (Read, 1984), (ii) lactulose would retain fluid in the lumen, further accelerating transit, (iii) aspiration from a point in the small intestine 230 cm from the teeth eliminated the distal

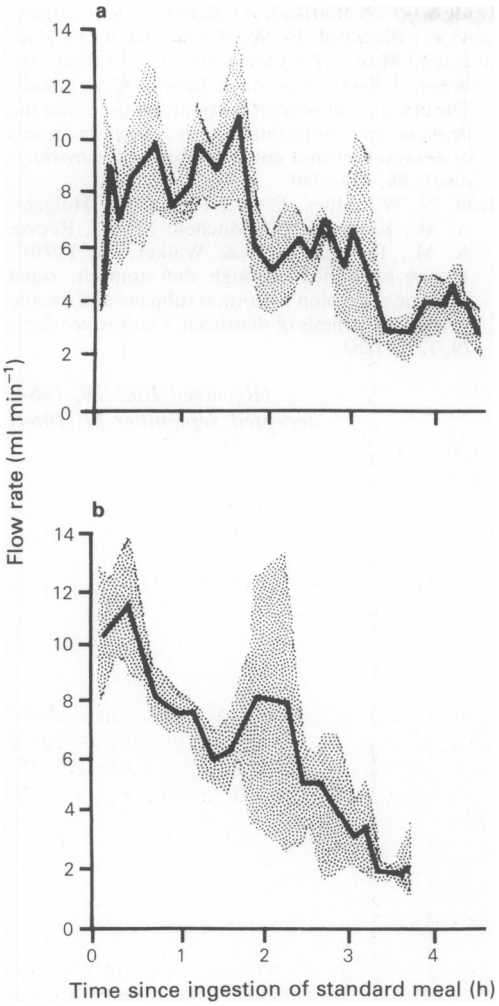

Figure 2 Graphs showing the average profile (± s.d.) of the postprandial ileal flow rate, calculated every 10 min under control conditions (a) and after administration of metoclopramide (b) (n = 5).

ileum as an important site for further digestion and absorption (Hurst, 1913). In support of the latter, ileostomy fluid and electrolyte outputs in patients with ileal resection are greater than in patients with an intact terminal ileum (Hill *et al.*, 1974). As absorption in the small intestine is exponentially related to transit time (Johansson, 1975), then the greater effect of metoclopramide on carbohydrate absorption in this study compared with our previous study could well be explained if absorption of carbohydrate under control conditions is on the steep part of the curve.

Although both studies support the suggestion that administration of metoclopramide reduced absorption by reducing contact time between nutrients and absorptive epithelium, there are other possibilities. The observation that transit time to the ileum was accelerated without any significant change in flow rate suggests that capacity of the intestine was reduced. This confirms the results of previous studies, in which reductions in transit time through perfused segments of canine or human small intestine were associated with reductions in luminal volume and diameter but no significant changes in flow rate (Tinker & Cox, 1969; Matuchansky *et al.*, 1972). Reductions in luminal volume and diameter would decrease the cross sectional area of small intestinal epithelium exposed to the luminal contents, and could well contribute to the reduction in glucose absorption observed in our studies. Glucose absorption could also be reduced as a result of a decrease in the transport of glucose across the epithelium or impairment of starch digestion. To our knowledge there is no published data to support these suggestions and we were unable to demonstrate any significant effect of metoclopramide on absorption of glucose across everted sacs of rat jejunum (Redfern & Read, unpublished data).

In conclusion, these studies lend weight to the proposal that agents, such as metoclopramide, that are thought to act predominantly on gastrointestinal motility, may also reduce absorption of food from the intestine.

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