

Effect of jejunal infusion of bile acids on small bowel transit and fasting jejunal motility in man

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SUMMARY The effect of jejunal infusion of glycochenodeoxycholic acid and glycocholic acid on small bowel transit time, fasting jejunal motility and serum bile acid concentrations was investigated in groups of five to six healthy subjects. Glycochenodeoxycholic acid at a concentration of 15 mmol/l (total amount: 5 mmol) and glycocholic acid 15 mmol/l (total amount: 5 mmol), both with lecithin 2.5 mmol/l, delayed ($p < 0.02$) small bowel transit when compared with a bile acid free infusion [158.3 (12.5) min ν 111.7 (17.6) min and 103.3 (21.8) min ν 70.0 (14.9) min], inhibited ($p < 0.01$ and $p < 0.05$ respectively) the percentage duration of pressure activity of phase 2 [13.1 (1.8)% ν 28.1 (3.4)% and 29.2 (5.5)% ν 34.9 (3.9)%], but did not change duration of migrating motor complex, or of its phases. Glycochenodeoxycholic acid 10 mmol/l (total amount: 3.3 mmol), either with or without lecithin, did not delay small bowel transit significantly [145.0 (13.2) min ν 115.0 (19.5) and 90.0 (11.7) min ν 84.0 (8.3)]. When bile acids were infused, serum bile acid curves were similar to those obtained after a liquid meal and the peak serum bile acid concentration occurred 33.7 (6.6) min before ($p < 0.001$) completion of small bowel transit. These observations suggest a role for endogenous bile acids in the regulation of small gut motility.

Bile acids and bile have been claimed to have stimulatory effects on small intestinal motility and transit, but data are discordant¹⁻³ and no observations are available in man. Dihydroxy bile acids have been shown to inhibit water and electrolyte absorption in the human jejunum⁶ and ileum⁷ and oral intake of chenodeoxycholic acid for dissolution of gall stones gives rise to diarrhoea in a considerable number of patients.⁸⁻⁹ The effect is thought to be because of a direct secretory action of the dihydroxy bile acid on colonic mucosa¹⁰ but an increased ileal flow and rapid small intestinal transit may be contributory factors.¹¹

The present study was designed to clarify whether bile acids affect small bowel motility and transit. Bile acids were administered in physiological amounts and in most experiments lecithin was added to the infused solutions to mimic endogenous input of bile acids which occurs in the physicochemical state of mixed micelles.

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Methods

SUBJECTS

Eighteen healthy subjects (aged 19-32 years, 15 men) entered the study which was approved by the Brent Health District Ethical Committee. Women were studied in the follicular phase of the menstrual cycle.

EXPERIMENTAL DESIGN

Each subject underwent measurement of the small bowel transit time (SBTT) of lactulose during jejunal infusion of saline alone and during infusion of at least one of four solutions containing either glycochenodeoxycholic acid (GCDC) or glycocholic acid (GC) in amounts comparable with an average bile acid pool,^{12,13} as described in Table 1. Throughout this study the concentration of the bile acids infused is expressed in mmol/l and the total amount administered in mmol. Fourteen subjects were infused with one bile acid solution only, four were infused with two bile acid solutions: one with GCDC 10 mmol/l

Table 1 Solutions used during all experiments. Concentrations of infusates are expressed in mmol/l, with total amounts in brackets

- Saline (n=18)
- Saline+GCDC* 10 mmol/l (3.3 mmol) (n=5)
- Saline+GCDC 10 mmol/l (3.3 mmol)+lecithin† 2.5 mmol/l (n=5)
- Saline+GCDC 15 mmol/l (5 mmol)+lecithin 2.5 mmol/l (n=6)
- Saline+GC‡ 15 mmol/l (5 mmol)+lecithin 2.5 mmol/l (n=6)

*Glycochenodeoxycholic acid, as sodium salt, Sigma Chemical Company Ltd, 98% pure; †BDH Chemicals Ltd, 90% pure (chief contaminants: sulphated ash, nitrogen, phosphorus); ‡glycocholic acid, as sodium salt, Sigma Chemical Company Ltd, 99% pure.

One subject was studied during infusions of GCDC 10 mmol/l and GCDC 10 mmol/l+lecithin on separate occasions; three subjects were studied during infusion of GCDC 15 mmol/l+lecithin and GC 15 mmol/l+lecithin on separate occasions.

and GCDC 10 mmol/l+lecithin (L) and three with GCDC 15 mmol/l+L and GC 15 mmol/l+L. Each solution was infused on a separate day in randomised order. To avoid stimulation of endogenous bile acid secretion by feeding, the subjects were studied in the fasted state.

The subjects were instructed to limit their meals from lunchtime on the day before each study to those foodstuffs which result in little, or no rise in breath hydrogen (rice and meat). After an overnight fast, all subjects swallowed an assembly of polyvinyl tubes weighted at the end with a double balloon containing 1 ml mercury. The assembly contained one radio-opaque tube to facilitate fluoroscopic localisation. When the assembly entered the duodenum a small amount of air was injected into the terminal balloon to accelerate intubation, until the infusion port, marked by a small radio-opaque plug, was placed 10 cm beyond the duodenojejunal flexure. The balloon was then deflated and the mercury completely aspirated.

In the experiments testing GCDC 10 mmol/l±L (n=10) the tube assembly consisted of two single lumen tubes (external diameter=2 mm), one for infusion and one for balloon inflation. In the 12 experiments testing GCDC 15 mmol/l+L and GC 15 mmol/l+L a three lumen (external diameter=2 mm) tube (Dural Plastics, Australia) was added to measure jejunal intraluminal pressures at 5, 20, and 35 cm beyond the infusion port. The three manometry tubes were continuously perfused with water at 0.15 ml/min by a low compliance pneumohydraulic capillary infusion system (Mui Scientific), permitting a response time of 35 mmHg/sec. The tubes were connected to external pressure transducers (Statham p231D) and signals recorded on a polygraph (Grass, model 7). A further polygraph channel monitored respiration through a pneumatic belt placed round subjects' chest.

When the tube assembly was in place, a cannula was inserted into a forearm vein using local anaesthetic and kept patent with heparinised saline. After one hour's rest in the experiments testing GCDC 10 mmol/l±L, and after appearance of phase 3 of a migrating motor complex (MMC) detected by the three manometry ports in the experiments testing GCDC 15 mmol/l+L and GC 15 mmol/l+L, the study started as described in Figure 1. In one subject who did not have phase 3 MMC after four hours of recording on the first study day, GC and control study were performed starting in phase 2 without waiting for an activity front.

Solutions described above were infused at 3 ml/min using an infusion pump (MHRE Mk4 Flow Inducer, Watson-Marlow Ltd, England) for 80 minutes. Simultaneously saline for the first 30 minutes, and a solution containing lactulose 5 g for the following 50 minutes was infused at 1 ml/min. This quantity of lactulose was approximately equivalent to unabsorbed carbohydrate after an ordinary meal.¹⁴ All infusates were iso-osmotic and pH was adjusted to 7.0 using NaOH.

MEASUREMENT OF BREATH HYDROGEN

Using a modified Haldane Priestley tube, end expiratory breath samples were taken every five minutes from the beginning of the infusion for 150 minutes, or until a sustained hydrogen concentration rise was detected in breath.

Breath hydrogen was measured using an electrochemical detector (GMI, Renfrew, Scotland) with a sensitivity of 2 ppm and an accuracy of ±2%. Small bowel transit time was defined as time elapsed when increase of breath hydrogen of at least 3 ppm above baseline occurred, continuing to rise for at least 30 minutes.

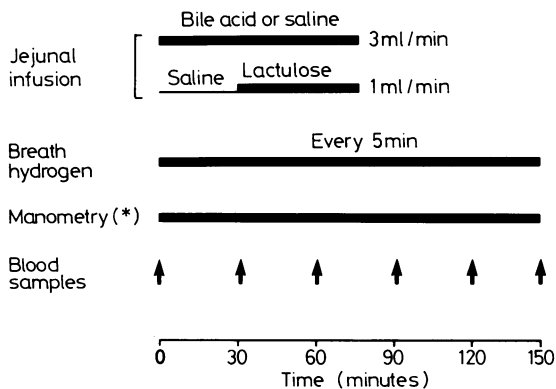


Fig. 1 Diagram illustrating the protocol of all experiments. (*) in the experiments testing glycochenodeoxycholic acid 15 mmol/l+lecithin and glycocholic acid 15 mmol/l+lecithin only (n=12).

MEASUREMENT OF SERUM BILE ACIDS

Blood samples were taken at 0, 30, 60, 90, 120, 150 minutes for measurement of total bile acids in the experiments using GCDC and cholyglycine in the experiments using GC (Fig. 1). Total bile acids were measured by direct spectrophotometry (Enzabile, Nyegaard) using an automatic analyser (Cobas Mira, Roche) with a good reproducibility (CV=4.1%; n=10). Cholyglycine was measured using a specific radioimmunoassay (CG RIA, Abbott Diagnostics), giving a CV of 3.8% (n=10). For total bile acids and cholyglycine, peak incremental response (PIR) and integrated incremental response (IIR=area under the curve taking the basal value as zero) were calculated.

ANALYSIS OF PRESSURE RECORDS

After Kerlin and Phillips,¹⁵ phase 1 was defined as quiescence, phase 2 as intermittent activity and phase 3 as three minutes or more of uninterrupted rhythmic contractions, followed by quiescence. Migration required the recording of phase 3 activity successively from all three recording ports. Migrating motor complexes were defined as starting at the end of a migrated phase 3 and terminating at the end of the next one. All pressure tracings were blindly measured by one of the authors. Tracings were quantitatively analysed with respect to duration of MMC and its phases, and with respect to percentage duration of pressure activity during phase 2. The latter variable was calculated for each experiment as

a whole and divided into 30 min epochs. In addition tracings were qualitatively analysed for presence of specific patterns of contractions, defined according to Summers *et al.*¹⁶

Calculations of percentage duration of pressure activity during phase 2 were carried out twice (n=21), giving a CV of 3.5%.

STATISTICAL ANALYSIS

Results, expressed as mean (SE), were analysed using Student's *t* test.

Results

SMALL BOWEL TRANSIT TIME

Solutions containing GCDC 15 mmol/l and GC 15 mmol/l significantly prolonged SBTT [158.3 (12.5) v 111.7 (17.6) and 103.3 (21.8) v 70.0 (14.9), $p < 0.02$]. Solutions containing GCDC 10 mmol/l either with or without lecithin had a less consistent effect on SBTT [145.0 (13.2) v 115.0 (19.5) and 90.0 (11.7) v 84.0 (8.3), $p = \text{ns}$] (Fig. 2).

MOTILITY

Duration of MMC and of its phases was not altered significantly by infusions of GCDC 15 mmol/l and GC 15 mmol/l GC (Fig. 3). Infusion with GCDC 15 mmol/l produced decreased pressure activity during phase 2 and this reduction appeared to be more marked than that due to GC 15 mmol/l, when compared with saline [Fig. 4; 13.1 (1.8)% v 28.1

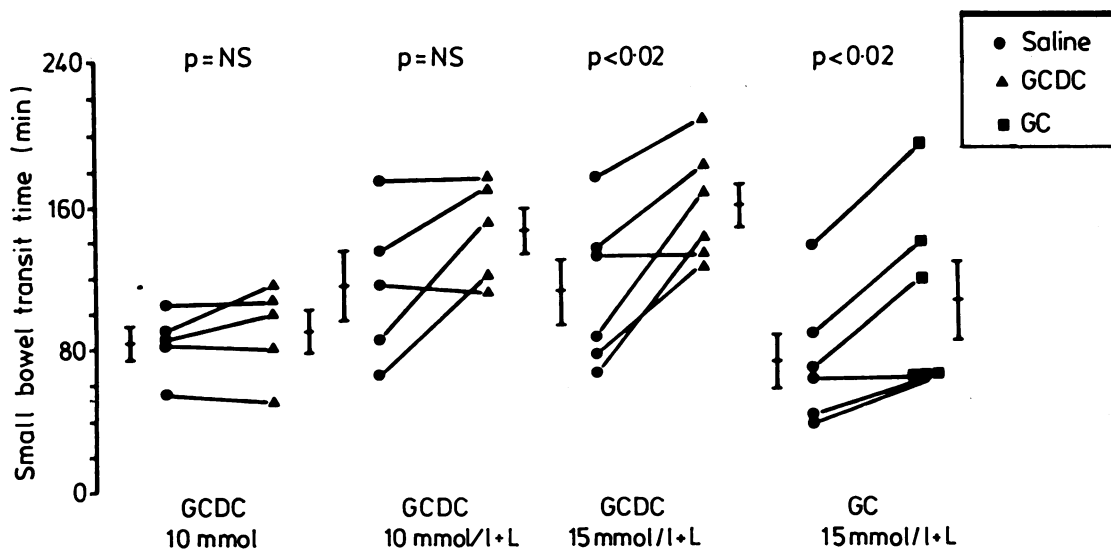


Fig. 2 Small bowel transit time of lactulose when the jejunum of healthy volunteers was infused with saline (●), GCDC (▲) or GC (■). Individual values and means (SE). GCDC=glycochenodeoxycholic acid, GC=glycocholic acid, L=lecithin.

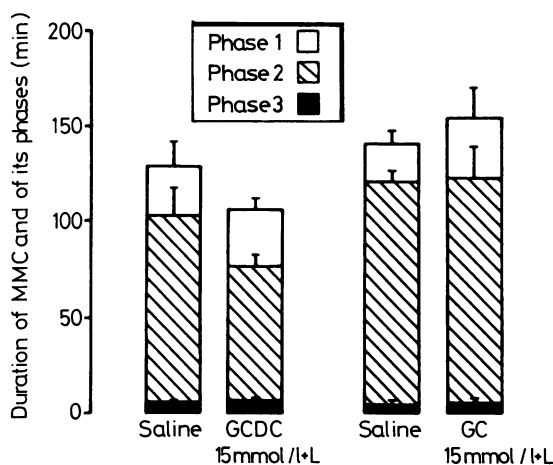


Fig. 3 Duration of migrating motor complex (MMC) and of its phases when the jejunum of healthy volunteers was infused with saline, GCDC 15 mmol/l+L or GC 15 mmol/l+L. [means (SE)]. GCDC=glycochenodeoxycholic acid, GC=glycocholic acid, L=lecithin.

(3.4%), $p < 0.01$ and 29.2 (5.5)% v 34.9 (3.9)%, $p < 0.05$ respectively]. Dividing the analysis of phase 2 pressure activity in 30 min epochs, it is apparent that inhibition of activity by GCDC (Fig. 5) was not immediate and persisted in all subjects after the infusion ended ($p < 0.05$). When 30 min epochs were sampled for the GC studies, a lower mean pressure activity of phase 2 was seen along the whole of the GC experiment compared to saline, but the difference failed to reach statistical significance in any of the epochs. Qualitative analysis of pressure records showed runs of discrete clustered contractions in three subjects during saline infusion (occupying 7.6% to 18.5% of total duration of phase 2), in no subject during GCDC infusion and in two subjects during GC infusion (occupying 11.7% and 15.3% of phase 2).

SERUM BILE ACIDS

Compared with saline, total bile acid and cholyglycine IIR and PIR were significantly ($p < 0.05$) higher after all solutions containing bile acids (Table 2). Considering all the 22 infusions of bile acids together, the peak serum bile acid concentration occurred 33.7 (6.6) minutes before ($p < 0.001$) the rise in breath hydrogen. In particular peak serum bile acid concentration preceded the arrival of lactulose in the caecum in 17 of the 22 infusions.

Discussion

Bile acids are generally considered to have a stimulatory effect on gut motility and transit. The present

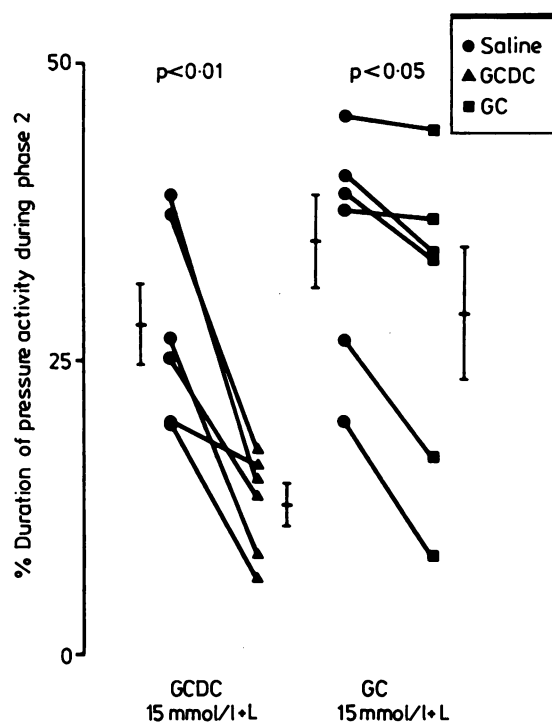


Fig. 4 Percentage duration of pressure activity of phase 2 of migrating motor complex when the jejunum of healthy volunteers was infused with saline (●), GCDC 15 mmol/l+L (▲) or GC 15 mmol/l+L (■). Individual values and means (SE). GCDC=glycochenodeoxycholic acid, GC=glycocholic acid, L=lecithin.

study suggests that the subject is probably more complicated than previously thought. Glycochenodeoxycholic acid and GC, the two main forms of primary bile acids present in human bile,¹⁷ when infused in the jejunum of healthy man did not stimulate motility. On the contrary, at a concentration of 15 mmol/l (total amount of 5 mmol) they appeared to decrease jejunal intraluminal pressures and delay SBTT. In contrast with previous animal studies,^{4,5} bile acids were infused in the present study at a physiological rate^{12,18} and concentration,¹⁹ comparable with the postprandial state. The serum bile acid curves, which were similar to those obtained after a 440 kcal liquid meal²⁰ support this contention. The effect on SBTT appeared to be dependent on the bile acid concentration and/or rate of infusion, because GCDC 10 mmol/l did not produce significant slowing of transit. Although it cannot be excluded that delay in breath hydrogen rise was due to an effect of bile acids entering the large bowel on hydrogen production, this possibility is unlikely as we have shown bile acids to have an inhibitory effect on small

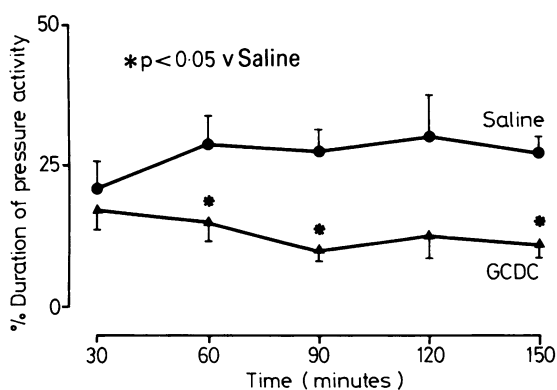


Fig. 5 Percentage duration of pressure activity of phase 2 of migrating motor complex when the jejunum of healthy volunteers was infused with saline (●) or GCDC 15 mmol/l + L (▲) [means (SE)]. Analysis in 30 min epochs. GCDC=glycochenodeoxycholic acid, L=lecithin.

intestinal transit also using a dye dilution technique (unpublished data).

The reason why bile acids slowed SBTT and inhibited motility is unknown. A few observations, however, shed some light on the possible mechanism. First, in the GCDC 15 mmol/l experiments where inhibition of motility was more marked, it was clear (Fig. 5) that decrease in intraluminal pressure activity was delayed with respect to the start of the GCDC infusion. Second, unpublished work in our laboratory investigating the effect of ileal infusion of GCDC on the jejunum and the ileum, showed a pattern of inhibition of jejunal motility similar to the one observed in the present study and a strikingly immediate inhibition in motility in the ileum exposed to the infused GCDC. These observations lead us to the hypothesis that the inhibitory responses recorded in the present study are mediated through bile acid

Table 2 Serum bile acid concentrations during all experiments: means (SE)

	Fasting ($\mu\text{mol/l}$)	PIR ($\mu\text{mol/l}$)	IIR ($\mu\text{mol/l-h}$)
GCDC 10 mmol/l	1.8 (0.5)	5.2 (1.6)*	150.6 (53.7)*
saline	1.6 (0.4)	0.4 (0.4)	-6.3 (16.8)
GCDC 10 mmol/l+L	1.6 (0.2)	6.0 (1.3)*	163.7 (39.9)*
saline	2.3 (0.6)	1.5 (0.5)	13.0 (15.0)
GCDC 15 mmol/l+L	2.3 (0.2)	9.7 (4.5)*	219.6 (100.6)*
saline	3.2 (0.3)	0.4 (0.3)	-19.6 (8.2)
GC 15 mmol/l+L	0.10 (0.07)	4.4 (1.5)*	104.9 (29.7)*
saline	0.11 (0.03)	0.2 (0.1)	3.9 (2.4)

* = different from control ($p < 0.05$). GCDC=glycochenodeoxycholic acid. GC=glycocholic acid. L=lecithin.

specific chemoreceptors located in the ileum. The inhibition of motility may favour absorption of bile acids and minimise their escape into the large bowel. This hypothesis is supported by the fact that peak serum bile acid concentration occurred during most infusions containing bile acids before lactulose reached the caecum, suggesting that transit might have been in some way dependent on absorption of bile acids.

The presence of lecithin has been shown to abolish the inhibitory effect of dihydroxy bile acids on water and electrolyte absorption from the human jejunum, probably by decreasing the concentration of bile acids in monomeric form.⁶ In the present study most of the experiments were done with lecithin added to the infused bile acids, to avoid unphysiological jejunal secretion and mimic endogenous input. Because GCDC was infused in monomeric form only at a concentration (10 mmol/l) ineffective on SBTT, our experiments could not clarify whether the effect of bile acids on small bowel motility and transit is influenced by their physicochemical state.

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