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Vu, M.K.

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Chapter 6

**THE OSMOTIC LAXATIVE MAGNESIUM SULPHATE ACTIVATE
THE ILEAL BRAKE**

M.K. Vu, M.A.G. Nouwens, I. Biemond, C.B.H.W. Lamers, A.A.M. Masclee

Department of Gastroenterology-Hepatology, Leiden University Medical
Centre, the Netherlands

The osmotic laxative magnesium sulphate activates the ileal brake

M. K. VU, M. A. G. NOUWENS, I. BIEMOND, C. B. H. W. LAMERS & A. A. M. MASCLEE

Department of Gastroenterology–Hepatology, Leiden University Medical Centre, The Netherlands

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SUMMARY

Background: Alterations in gastrointestinal motility and hormone secretion, especially activation of the ileal brake, have been documented in malabsorption.

Aim: To investigate whether artificially-induced accelerated small intestinal transit activates the ileal brake mechanism.

Methods: Eight healthy volunteers (four female, four male; age 21 ± 3 years) participated in four experiments: (a) meal with either oral magnesium sulphate (MgSO_4) or placebo; and (b) fasting with either oral MgSO_4 or placebo. Antroduodenal motility was recorded by perfusion manometry. Duodenocaecal transit time was determined by the lactulose H_2 breath test. Gall-bladder volume was measured by ultrasound at regular intervals, and blood samples were drawn for determi-

nation of cholecystokinin and peptide YY (RIA). Twenty-four hour faecal weight and fat excretion were determined.

Results: MgSO_4 significantly accelerated duodenocaecal transit time and increased faecal fat and weight in all subjects. MgSO_4 significantly delayed the reoccurrence of phase III and affected antroduodenal motility during fasting but not after meal ingestion. Postprandial gall-bladder relaxation and postprandial peptide YY release were significantly increased during the MgSO_4 experiment compared to placebo.

Conclusions: The osmotic laxative MgSO_4 accelerates intestinal transit both in the fasting and fed state. MgSO_4 activates the ileal brake mechanism only in the fed state, with peptide YY release and inhibition of gall-bladder emptying.

INTRODUCTION

Both in humans and dogs, intra-ileal infusion of nutrients delays gastric emptying and small intestinal transit and inhibits exocrine pancreatic secretion.^{1–3} This phenomenon is called the 'ileal brake', a negative feedback response from the distal to the proximal gut. There is evidence suggesting that the ileal brake is hormonally mediated.⁴ Peptide YY is considered a hormonal representative of the ileal brake. Peptide YY is released from the ileo-colonic region in response to intraluminal unabsorbed nutrients.^{5,6} Plasma peptide YY levels are increased in patients with malabsorptive

diseases and in patients with diarrhoea, compared to healthy subjects.^{7,8} Although these findings could be explained by increased loads of unabsorbed nutrients to the distal gut, the increased levels of plasma peptide YY may also be related to, or result from, the underlying disease. The present study was performed to investigate whether artificially induced accelerated transit with reduced intestinal absorption of nutrients *per se* is able to stimulate peptide YY release and activate the ileal brake mechanism.

In healthy subjects, osmotic laxatives accelerate small intestinal transit and reduce the intestinal absorption of fat, protein and carbohydrates following ingestion of a solid meal.⁹ For this reason magnesium sulphate (MgSO_4), an osmotic laxative, was used in the present study. We hypothesized that accelerated small intestinal transit and subsequent reduced intestinal absorption

Correspondence to: Dr A. A. M. Masclee, Department of Gastroenterology–Hepatology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands.
E-mail: A.A.M.Masclee@LUMC.nl

induced by MgSO_4 would stimulate peptide YY release and activate the ileal brake mechanism in healthy subjects. In order to differentiate between the effects of reduced intraluminal nutrient absorption and those of MgSO_4 itself on gastrointestinal motility and secretion, experiments with MgSO_4 were performed both in the fed and fasted state. Antroduodenal and gall-bladder motility and proximal and distal gut hormone secretion were studied.

SUBJECTS AND METHODS

Subjects

Eight healthy volunteers (four men and four women, mean age 21 years, range 18–24 years) participated in this study. None of the subjects had a history of gastrointestinal disease or surgery and none was taking any medication. Informed consent was obtained from each subject and the protocol had been approved by the local ethical committee.

Experimental design

Each subject participated in four experiments performed in random order on separate days. Experiment 1: fasting and MgSO_4 ; 2: fasting and placebo; 3: meal and MgSO_4 ; 4: meal and placebo. The experiments started at 07:45 hours. After an overnight fast of at least 10 h subjects were intubated transnasally with the antroduodenal manometry catheter. Thereafter motility recording was started. An intravenous cannula was inserted into the antecubital vein of one arm for blood sampling. The spontaneous occurrence of a phase III in the duodenum marked the start point for all the experiments and was defined as $t = -30$ min. At $t = -15$ min, 15 g MgSO_4 dissolved in 50 mL water or placebo was ingested. In experiments 1 and 2, at time $t = 0$ min, the volunteers drank a 400-mL liquid meal (banana shake) containing 45 g fat, 35 g protein, 58 g carbohydrates and 780 kCal. In all experiments 6 g lactulose dissolved in 60 mL water was administered intraduodenally at time $t = 0$ min for measurements of small intestinal transit time. Antro-duodeno-jejunal motility was recorded for at least 6 h after MgSO_4 /placebo administration.

Stool collection

At the end of experiments 1 and 2 each subject received a standard evening meal consisting of potatoes, minced

meat, gravy, green beans, apple sauce and fruit cocktail (40 g protein, 42 g fat, 139 g carbohydrates, 1093 kcal). Stool was collected for 24 h (starting at 07:45 hours on the day of the experiment until 07:45 hours the next day) in a pre-weighed plastic bucket. Subjects were instructed to eat rice, cauliflower and chicken breast at dinner the evening before the day of the experiment. During the 24-h period of stool collection they did not consume other caloric items apart from the meal offered. Faecal weight and faecal fat were determined in gram per 24 h according to a previously described method.¹⁰

Antroduodenal manometry

Antroduodenal motility was recorded using a multilumen water perfused polyvinyl catheter (outer diameter 5 mm). The catheter incorporated eight side holes located at 0, 5, 10, 15, 20, 25, 30 and 35 cm from the distal tip. The manometry catheter was passed trans-nasally into the stomach and from there positioned into the duodenum-jejunum under fluoroscopic control. The tip of the catheter was located just distal to the ligament of Treitz so that one or two side hole openings were in the jejunum, three to four side hole openings were in the duodenum and at least two in the antrum. When the correct position had been verified the catheter was taped to the nose. At the end of each experiment the position of the catheter was checked again by fluoroscopy. Each lumen was connected to a pressure transducer and perfused with distilled water by a low compliance pneumo-hydraulic perfusion system (Arndorfer Medical Systems) at a rate of 0.5 mL/min. Outputs from pressure transducers were recorded by a polygraph (Synectics Medical, Stockholm, Sweden), displayed on a monitor and stored on a personal computer for automated and manual analysis.

Small intestinal transit

Small bowel transit time was determined by the lactulose hydrogen breath test after intraduodenal instillation of 6 g lactulose (Legendal, Inpharlam, Amersfoort, The Netherlands), dissolved in 60 mL water at time $t = 0$ min.¹¹ End expiratory breath samples were first collected under fasting conditions at time $t = -30$, and -15 min and every 10 min thereafter and were analysed immediately in a hydrogen breath test unit (Lactoscreen, Hoekloos, The Netherlands).

Duodenocaecal transit time was defined as the time between administration of lactulose and a sustained rise in breath H_2 concentration of at least 10 parts per million (p.p.m.) above basal levels. At our department the mean coefficient of variation for duodenocaecal transit using the lactulose hydrogen breath test with 6 g lactulose is $12 \pm 5\%$.

Measurements of gall-bladder volumes

Gall-bladder volumes were measured by real time ultrasonography (Toshiba, 3.75 MHz transducer) at $t = -30, -15, 0, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 330$ and 360 min during experiments 1 and 2 and at $t = -30, -15, 0, 15, 30, 45, 60, 90, 120, 180, 240, 300,$ and 360 min during experiments 3 and 4. Gall-bladder volumes were calculated by the sum of cylinders method using a computerized system.^{12, 13} In this method the longitudinal image of the gall-bladder is divided into series of equal height, with diameter perpendicular to the longitudinal axis of the gall-bladder image. The uncorrected volume is the sum of volumes of these separate cylinders. To correct for the displacement of the longitudinal image of the gall-bladder from the central axis, a correction factor is calculated from the longitudinal and transversal scans of the gall-bladder. Gall-bladder volume is calculated by multiplication of the uncorrected volume with the square of the correction factor; the mean of two measurements was used for analysis. The assumptions and the mathematical formula used to calculate gall-bladder volume have been described and validated previously.^{12, 13} Fasting gall-bladder volumes were expressed in millilitres. Gall-bladder emptying was calculated as a percentage of fasting gall-bladder volume.

Hormone assays

Blood samples for measurement of plasma pancreatic polypeptide, cholecystokinin and peptide YY were drawn at time $t = -0, -15, 0, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 330$ and 360 min during experiments 1 and 2 and at $t = -30, -15, 0, 15, 30, 45, 60, 90, 120, 180, 240, 300,$ and 360 min during experiments 3 and 4. The blood samples were collected in ice-chilled tubes containing EDTA. The samples were centrifuged at a rate of 3000 r.p.m. for 10 min at a temperature of 4°C . Plasma cholecystokinin was measured by a sensitive and specific radio-

immunoassay.¹⁴ This antibody binds to all cholecystokinin peptides including sulphated cholecystokinin octapeptide, but not gastrin. The detection limit of the assay is 0.1 pM plasma. Plasma peptide YY was measured by radioimmunoassay. Peptide YY antiserum was generated in rabbits by intracutaneous injections of synthetic human peptide YY (BACHEM AG, Bubendorf, Switzerland). Peptide YY was labelled with ^{125}I iodine using chloramine T. There is no cross-reactivity with pancreatic polypeptide or VIP; the detection limit is 10 pM plasma. Both peptide YY¹⁻³⁶ and peptide YY³⁻³⁶ bind to the antibody in dilutions up to 25 000.

Analysis of motility recording

Motility patterns from antroduodenal manometry were analysed both visually and by computer. The individual tracings were processed by special software (Polygram, Synectics Medical, Stockholm, Sweden) for adjusting baselines and extracting respiratory artefacts. However, the computer program does not recognize simultaneous pressure events as artefacts. Therefore, remaining artefacts due to increments in intra-abdominal pressure were identified visually and excluded from the analysis. Duodenal phases of the migrating motor complex (MMC) were defined as follows: phase I, no more than two contractions every 10 min for at least 5 min and preceded by phase III; phase II: irregular contractile activity at a frequency of more than two every 10 min and amplitude above 12 mmHg; phase III: regular contractile activity at a frequency of 10–12 contractions per min for at least 2 min. Phase III activity had to be propagated over at least two recording sites. Antral phase III activity was defined as rhythmic contractile activity at maximum frequency (three contractions/min) for at least 1 min in temporal relationship with duodenal phase III activity.¹⁵ Duration of the MMC cycle was taken as the interval between the end of phase III in the duodenum until the end of the next phase III cycle.

The postprandial period was defined as the time interval between the end of the meal and the occurrence of the first duodenal phase III propagated over at least two channels. Only pressure waves with an amplitude ≥ 10 mmHg and duration ≥ 1.5 s were considered as true contractions. The motility indices in the antrum and duodenum were calculated as the area under the contraction curves and expressed in mmHg.sec. In experiments 1 and 2, antral and duodenal motility

indices were calculated for the first three postprandial hourly intervals. For experiments 3 and 4, antral and duodenal motility indices were calculated during the last 30 min of phase II of the first MMC cycle and of the following MMC cycles.

Statistical analysis

Data are expressed as mean \pm S.E.M. Differences in plasma cholecystokinin and peptide YY concentrations, gall-bladder volumes and postprandial antral and duodenal motility indices within and between groups were analysed for statistical significance using multiple analysis of variance (MANOVA). When this indicated a probability of less than 0.05 for the null hypothesis, Student–Newman–Keuls analyses were performed to determine which values between or within subjects differ significantly. The remaining interdigestive, digestive, small intestinal transit, faecal weight, fat excretion and integrated values of cholecystokinin and peptide YY data were analysed by the Wilcoxon signed rank test or when appropriate by the two-tailed Student's *t*-test for paired results. Pearson's correlation was used to correlate the percentage of gall-bladder and plasma cholecystokinin level. The significant level was set at $P < 0.05$.

RESULTS

MgSO₄ in the fasting state

Duodenocaecal transit time. Three out of the eight studied subjects had watery diarrhoea within 3 h after the administration of MgSO₄. The duodenocaecal transit time was significantly ($P < 0.05$) shorter in the MgSO₄ (40 ± 6 min) compared to the placebo experiment (65 ± 8 min).

Antroduodenal motility. Twenty-nine and 24 complete MMC cycles were observed during the MgSO₄ and placebo experiment, respectively, in eight subjects during 50 h of recording after the administration of MgSO₄/placebo. The mean duration of the MMC cycles in the MgSO₄ experiment (158 ± 20 min) was significantly ($P < 0.05$) prolonged compared to placebo (104 ± 8 min) due to a significantly longer phase II (142 ± 18 min in the MgSO₄ and 83 ± 9 min in the placebo experiment). On further analysis, this prolongation of the MMC cycle length and of phase II was only

Table 1. Characteristics of MMC cycles (mean \pm S.E.M., min) in eight healthy volunteers during experiments in the fasting state

	First MMC	Following MMC
Placebo		
MMC cycle length	99 ± 13	101 ± 9
Phase I	8 ± 2	15 ± 4
Phase II	86 ± 12	81 ± 15
Phase III	5 ± 1	5 ± 1
MgSO ₄		
Duration (min)	$211 \pm 37^*$	$137 \pm 32^\dagger$
Phase I (min)	10 ± 3	14 ± 3
Phase II (min)	$197 \pm 34^*$	$119 \pm 31^\dagger$
Phase III (min)	4 ± 1	4 ± 1

* $P < 0.05$ compared to placebo; $^\dagger P < 0.05$ compared to the first MMC cycle.

present in the first MMC cycle after the occurrence of the spontaneous phase III. No significant differences in the duration of the remaining MMC cycles and phase I, II, and III were found between the placebo and MgSO₄ experiment (Table 1). In addition, the duration of the first MMC cycle was significantly ($P < 0.05$) longer compared to the remaining MMC cycles during the MgSO₄ experiment (Table 1).

The antral motility index calculated during the last 30 min of phase II of the first MMC cycle was significantly lower in the MgSO₄ compared to the placebo experiment (Table 2). This lower antral motility indices in the MgSO₄ experiment was due to a decrease in number as well as amplitude of individual contractions (Table 2). The mean antral motility index of phase II of the remaining MMC cycles was not significantly different between the MgSO₄ and placebo experiments. Duodenal motility indices during the last 30 min of phase II were not significantly different between the MgSO₄ and the placebo experiments in either the first MMC cycle or the remaining MMC cycles (data not shown).

Gall-bladder emptying. Basal gall-bladder volumes were not significantly different between the placebo (16.9 ± 2.9 mL) compared to the MgSO₄ experiment (17.1 ± 2.5 mL). No significant changes in gall-bladder volume compared to basal values were observed after the administration of MgSO₄ or placebo.

Plasma cholecystokinin. Basal plasma cholecystokinin levels were not significantly different between the MgSO₄ and the placebo experiment (0.8 ± 0.2 pM vs.

Table 2. Antral motility characteristics during the last 30 min of phase II of the first MMC cycle and of the remaining MMC cycles in eight healthy subjects during experiments in the fasting state

	Antrum		Duodenum	
	Placebo	MgSO ₄	Placebo	MgSO ₄
First MMC				
Number of contractions	37 ± 10	17 ± 3*	109 ± 46	46 ± 12
Amplitude (mmHg)	72 ± 8	49 ± 4*	26 ± 1	27 ± 4
Motility index (mmHg.sec)	7750 ± 1342	2104 ± 806*	3857 ± 1097	2058 ± 604
Following MMC				
Number of contractions	21 ± 2	29 ± 6	46 ± 6	50 ± 11
Amplitude (mmHg)	98 ± 11	51 ± 6	29 ± 3	25 ± 3
Motility index (mmHg.sec)	5876 ± 1231	3407 ± 1146	2223 ± 511	1797 ± 535

* $P < 0.05$ compared to placebo.

Table 3. Postprandial antral and duodenal motility index (mean ± S.E.M., mmHg.sec) for the first three hourly intervals and for the total fed period after meal ingestion in eight healthy subjects

Motility indices	Placebo	MgSO ₄
Antrum 0–60 min	105 ± 37	149 ± 60
Antrum 60–120 min	303 ± 128	331 ± 85
Antrum 120–180 min	1012 ± 189	748 ± 299
Antrum, total fed period	1001 ± 138	1425 ± 201
Duodenum 0–60 min	2601 ± 737	2606 ± 1062
Duodenum 60–120 min	1687 ± 436	1752 ± 919
Duodenum 120–180 min	2130 ± 895	1614 ± 451
Duodenum, total fed period	2415 ± 601	2560 ± 847

* $P < 0.05$ compared to placebo.

0.7 ± 0.1 pM, respectively; Figure 1A). Plasma cholecystokinin levels at $t = 15$ and $t = 30$ min during the MgSO₄ experiment were slightly higher compared to basal values and compared to the placebo experiment but this difference did not reach significance (Figure 1A). The integrated incremental plasma cholecystokinin secretion was not significantly different between the MgSO₄ (29 ± 84 pM.360 min) compared to the placebo experiment (–13 ± 17 pM.360 min).

Plasma peptide YY. Basal plasma peptide YY levels were not significantly different between the MgSO₄ and the placebo experiment (19.2 ± 1.9 pM vs. 18.2 ± 2.0 pM, respectively; Figure 2A). No significant changes in plasma peptide YY levels compared to basal values were observed during either the MgSO₄ or the placebo experiment (Figure 2A). The integrated incremental

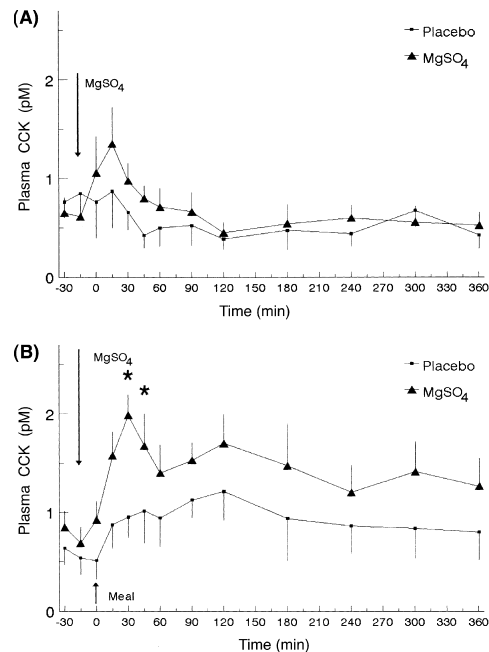


Figure 1. (A) Plasma cholecystokinin levels in the fasting state during the MgSO₄ (triangles) and the placebo experiment (squares). (B) Basal and postprandial plasma cholecystokinin levels during the MgSO₄ (triangles) and the placebo experiment (squares). * $P < 0.05$ compared to placebo.

plasma peptide YY secretion was also not significantly different between the MgSO₄ (56 ± 23 pM.360 min) and the placebo experiment (35 ± 30 pM.360 min).

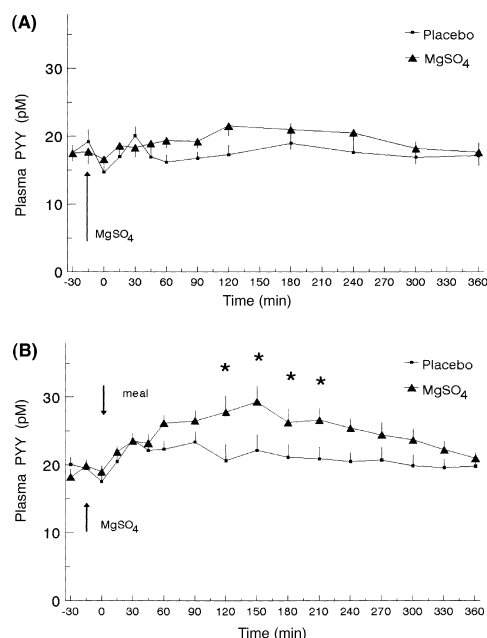


Figure 2. (A) Plasma peptide YY levels in the fasting state during the MgSO_4 (triangles) and the placebo experiment (squares). (B) Basal and postprandial plasma peptide YY levels during the MgSO_4 (triangles) and the placebo experiment (squares). * $P < 0.05$ compared to placebo.

MgSO₄ in the fed state

Duodenocaecal transit time and faecal parameters. MgSO_4 induced diarrhoea and significantly ($P < 0.05$) accelerated duodenocaecal transit time in all subjects compared to placebo. The mean duodenocaecal transit time was 31 ± 3 min after MgSO_4 administration compared to 54 ± 7 min with placebo. The 24 h faecal weight and fat excretion were significantly ($P < 0.05$) increased after the administration of MgSO_4 compared to placebo (395 ± 45 g per 24 h and 10.8 ± 1.4 g per 24 h vs. 128 ± 12 g per 24 h and 4.7 ± 0.6 g per 24 h, respectively).

Antroduodenal motility. The duration of the fed pattern was not significantly different between the placebo and MgSO_4 experiment (307 ± 31 min vs. 271 ± 46 min, respectively). In both experiments antral motor activity was significantly ($P < 0.01$) lower during the first two

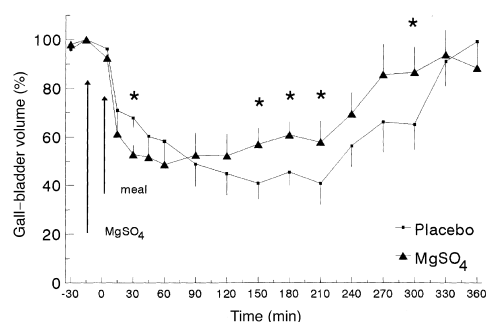


Figure 3. Percentage of postprandial gall-bladder emptying during the MgSO_4 (triangles) and the placebo experiment (squares). * $P < 0.05$ compared to placebo.

compared to the third postprandial hour (Table 1). Antral and duodenal motility indexes for the first three hourly intervals were not significantly different between the placebo and the MgSO_4 experiment (Table 1).

After the transition from a digestive into an interdigestive motility pattern, 10 complete MMC cycles in the placebo experiment and 13 complete MMC cycles in the MgSO_4 experiment were registered. The duration of MMC cycles was not significantly different between the placebo and MgSO_4 experiment (143 ± 12 min vs. 120 ± 17 min, respectively).

Gall-bladder emptying. Basal gall-bladder volumes were not significantly different between the placebo (17.8 ± 3.1 mL) and MgSO_4 experiment (17.1 ± 2.9 mL). In both the experiments gall-bladder volumes significantly ($P < 0.01$) decreased after meal ingestion and remained significantly decreased until $t = 300$ min in the placebo and until $t = 240$ min in the MgSO_4 experiment (Figure 3). Gall-bladder emptying at $t = 30$ min was significantly ($P < 0.05$) greater during the MgSO_4 compared to the placebo experiment. Gall-bladder emptying was significantly ($r = 0.55$; $P = 0.04$) correlated with plasma cholecystokinin levels from $t = 0$ to $t = 30$ min. In contrast, postprandial gall-bladder contraction between $t = 150$ and $t = 240$ min was significantly ($P < 0.05$) reduced in the MgSO_4 compared to the placebo experiment. In both experiments gall-bladder volumes had returned to basal levels at time $t = 360$ min.

Plasma cholecystokinin. Basal plasma cholecystokinin levels were not significantly different between the placebo (0.7 ± 0.1 pM) and MgSO_4 experiment (0.7 ± 0.2 pM; Figure 1B). Plasma cholecystokinin levels increased significantly over basal, starting from $t = 15$ min after meal ingestion and continuing until $t = 210$ min in the placebo and until $t = 240$ min in the MgSO_4 experiment. Plasma cholecystokinin levels during the first hour after meal ingestion were significantly higher in the MgSO_4 experiment compared to placebo (Figure 1B). The integrated incremental plasma cholecystokinin secretion during the total 6 h postprandial period was also significantly ($P < 0.01$) higher in the MgSO_4 (202 ± 69 pM) compared to the placebo experiment (95 ± 43 pM).

Plasma peptide YY. Basal plasma peptide YY levels were not significantly different between the placebo (19.5 ± 1.3 pM) and MgSO_4 experiment (19.9 ± 0.9 pM; Figure 2B). Plasma peptide YY levels increased significantly ($P < 0.05$) over basal starting from $t = 60$ min after meal ingestion until $t = 240$ min in the MgSO_4 experiment while no significant changes in plasma peptide YY levels were found in the placebo experiment. Plasma peptide YY concentrations from $t = 120$ min until $t = 240$ min were significantly ($P < 0.05$) higher in the MgSO_4 compared to the placebo experiment (Figure 2B). The integrated incremental plasma peptide YY secretion during the total 6 h postprandial period was significantly ($P < 0.01$) increased in the MgSO_4 (1667 ± 395 pM) compared to the placebo experiment (545 ± 125 pM).

DISCUSSION

This study shows that oral magnesium sulphate significantly accelerates small intestinal transit both in the fasting and fed state. During the interdigestive state, MgSO_4 significantly modulates antroduodenal motility without changes in intestinal hormone secretion. On the other hand, postprandial antroduodenal motility remains unaffected after the administration of MgSO_4 . When given in combination with a fatty meal, MgSO_4 induced diarrhoea in all healthy subjects with a significantly higher faecal weight and faecal fat excretion compared to placebo. Postprandial plasma levels of the distal gut hormone peptide YY were significantly increased in parallel with an increase in

gall-bladder volume (relaxation) after the administration of MgSO_4 .

It is apparent from the results that alterations in antroduodenal motility were present only in the early phase after the administration of MgSO_4 during the fasting state. MgSO_4 significantly increased the duration of the first MMC cycle by increasing the length of phase II and thus delaying the reoccurrence of phase III motor activity. In addition, the antroduodenal motility index of phase II of the first MMC cycle was significantly decreased. No significant differences in the remaining MMC cycles were found between the MgSO_4 and the placebo experiment. The exact mechanism(s) underlying these time-related changes is not obvious. MgSO_4 may affect antroduodenal motility through different mechanisms: increased intraluminal secretion; stimulation of cholecystokinin release; increased nitric oxide (NO) release; or a combination.^{1-4, 16-18} In the present study, plasma cholecystokinin levels during the first hour after MgSO_4 administration were slightly, although not significantly, increased compared to placebo. It has been shown that cholecystokinin interrupts the MMC cycle and induces a fed-like motor pattern.¹⁹ Thus, the prolonged phase II found in the present study could have resulted from cholecystokinin. The role of nitric oxide as a mediator of the laxative action of MgSO_4 has been recently recognized; MgSO_4 increases nitric oxide synthase activity.^{16, 18} Both in humans and animals, an increase of NO facilitates a postprandial-like motor pattern while NO synthase inhibitor induces a fasting-like motor pattern.²⁰ We did not measure NO but the congruency between motility changes found in the present study and reported changes induced by NO suggests that NO might be involved in delaying the reoccurrence of phase III and increasing the duration of the MMC cycle.

In contrast to the interdigestive state, when MgSO_4 was combined with a meal, it did not affect the postprandial antroduodenal motor pattern. The duration of the fed pattern and antroduodenal motility indices was similar in the placebo and the MgSO_4 experiment. The mechanisms responsible for the variable effects of MgSO_4 during the interdigestive and digestive states are unknown. However, our results are in agreement with those of a previous study reporting that oral administration of MgSO_4 modulates interdigestive motor pattern while digestive motility remains unaffected.²¹

The most striking effects induced by MgSO_4 after ingestion of a meal were observed with respect to intestinal gut hormone secretion. Postprandial release of the proximal gut hormone cholecystokinin was significantly increased after the administration of MgSO_4 compared to placebo. Because cholecystokinin release was only slightly increased by MgSO_4 during fasting, this finding suggests that the presence of intraluminal nutrients is the factor responsible for the significant increase in postprandial plasma cholecystokinin levels. It is conceivable that, due to an accelerated small intestinal transit induced by MgSO_4 , intraluminal nutrients are brought into contact with a larger area of the upper small bowel, permitting a greater number of cholecystokinin releasing cells to be activated, resulting in increased cholecystokinin release. For instance, postprandial plasma cholecystokinin concentrations are increased in patients with dumping syndrome who have accelerated small intestinal transit in addition to accelerated gastric emptying.²²

The same pattern was observed for the distal gut hormone peptide YY. After ingestion of the fatty meal, postprandial plasma levels of the distal gut hormone peptide YY were significantly higher after the administration of MgSO_4 compared to placebo. The fact that MgSO_4 itself did not stimulate peptide YY release during the fasting state indicates that changes in plasma levels of peptide YY after the administration of MgSO_4 in combination with a fatty meal are nutrient-related. Since peptide YY is released from the distal gut, the increased levels of plasma peptide YY suggests that nutrients were not completely absorbed but have reached the distal gut and stimulated peptide YY release.⁶ This is supported by the fact that all subjects had diarrhoea with increased faecal weight and that the faecal fat excretion was significantly increased after the administration of MgSO_4 .

Concerning gall-bladder motility, no significant changes in gall-bladder volume were observed after the administration of MgSO_4 during the interdigestive state. This finding is consistent with the insignificant changes in fasting plasma cholecystokinin levels. Our results, however, contrast with those found by Inoue *et al.* who documented that oral MgSO_4 induces gall-bladder contraction and increases cholecystokinin release.¹⁷ It is possible that MgSO_4 induced cholecystokinin release and subsequent gall-bladder contraction is a dose-dependent response. We have used 15 g MgSO_4 instead

of 25 g used by Inoue *et al.*; it has been reported in a previous study that only high dose intraduodenal MgSO_4 is able to increase bilirubin output.²³ Postprandial gall-bladder emptying in the MgSO_4 experiment, on the other hand, showed significant differences compared to placebo in two regards: an increase in gall-bladder emptying during the early phase and a decrease in gall-bladder emptying during the late phase. The latter was observed in parallel with an increase in plasma peptide YY levels. It could be suggested, based on this finding, that peptide YY is involved in stimulating gall-bladder relaxation in the late postprandial phase. This idea is in line with the hypothesis that unabsorbed nutrients in the distal small intestine stimulate the release of peptide YY which in turn exerts an inhibitory feedback on gall-bladder contraction. The observation that administration of peptide YY increases gall-bladder volume is evidence supporting this concept.²⁴ However, we cannot exclude the possibility that other distal gut hormones might also be involved.

In summary, oral MgSO_4 accelerates small intestinal transit, induces diarrhoea and increases faecal fat excretion in healthy subjects after ingestion of a meal. The increase in plasma peptide YY levels and gall-bladder relaxation in the late postprandial phase can be considered as evidence which indicates that MgSO_4 activates the ileal brake mechanism.

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