

Pentagastrin induced motility pattern in the human upper gastrointestinal tract is reversed by proglumide

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SUMMARY The effects of pentagastrin and the putative gastrin antagonist proglumide on interdigestive motility of the upper small bowel were studied in a randomised double blind study in 10 healthy human volunteers. Intraluminal pressures were recorded manometrically in the duodenum and jejunum for five hours. Sixty minutes after starting a pentagastrin infusion (0.15 $\mu\text{g}/\text{kg}/\text{h}$) either placebo or proglumide was infused intravenously. Pentagastrin converted the normal interdigestive motility to irregular motor activity, while proglumide restored the periodic fasted pattern. We conclude that gastrin is a likely candidate involved in the conversion of the fasted to the fed motility pattern in the human upper gut.

In the fasted state, motility of the stomach and small intestine of man is characterised by periodic activity of the interdigestive migrating motor complex (MMC).¹⁻⁴ Immediately after feeding, gastrointestinal motility becomes irregular.⁴ In the conversion of the interdigestive to the digestive motility pattern not only neural mechanisms,⁵ but also gastrointestinal hormones, particularly cholecystokinin (CCK) and gastrin, appear to be involved.⁶⁻⁸ This is illustrated by recent observations, showing that endogenous gastrin interrupts the migrating motor complex in an autotransplanted, denervated fundic pouch.⁹

Proglumide inhibits the CCK stimulated secretion of dispersed pancreas acini,¹⁰ and also the motor response of isolated smooth muscle cells after stimulation by CCK octapeptide.¹¹ These and other findings^{12,13} support the concept of proglumide being an antagonist of CCK and gastrin at the receptor site.

The present study examines the effect of pentagastrin infused at a dose that produces a rise in gastric acid secretion similar to the increased serum gastrin seen after feeding,¹⁴ and its combination with the putative gastrin antagonist proglumide on the interdigestive motility of the human upper gastrointestinal tract.

Methods

SUBJECTS

Ten healthy male volunteers (mean age 25 ± 2 ($\bar{x} \pm \text{SD}$) years) were examined in a double blind, randomised, crossover study after giving informed consent.

Intraluminal pressures were measured manometrically by a triple lumen polyvinyl tube. The inside diameter of the three catheters was 0.8 mm each. The distal side openings of the three catheters were 20 cm apart. Beyond the side openings the catheters were occluded by a stainless steel plug. At their proximal ends the catheters were connected to pressure transducers. Pressure events were recorded via a bridge amplifier (Hellige TF 19) on a direct writing polygraph (Hellige P 31). The pressure transducers and the catheters were continuously perfused by a low compliance pneumohydraulic pump¹⁵ at a rate of 9 ml $\text{H}_2\text{O h}^{-1}$.

Before each experiment the volunteers were fasted for 10 hours. The manometric tube was introduced through the mouth and positioned under radiographic control with its side openings into the duodenum and jejunum. The initial basal registration was continued, until the first activity front of the MMC had passed the duodenum. Then the volunteers received pentagastrin 0.15 $\mu\text{g}/\text{kg}$ bodyweight/h by intravenous infusion for five hours. Sixty minutes after starting the pentagastrin infusion, in addition, either proglumide or the same volume of placebo solution (normal saline) was

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infused for four hours in a double blind fashion. The dose of proglumide was 400 mg as an initial 5 ml bolus followed by an infusion of 500 mg/h.

The order of the experiments (pentagastrin + proglumide or pentagastrin + placebo) was randomised. After the start of the additional infusion (proglumide or placebo), the pressure recordings were continued for four hours. The control experiment with either placebo or proglumide followed within one week. Serum proglumide concentrations were determined by gas chromatography.¹⁶

We evaluated the number of activity fronts of the MMC in the duodenum and jejunum. Differences between the proglumide and placebo experiments were tested for significance by Student's *t* test for paired data.

Results

The results are given in Figures 1 and 2. Pentagastrin 0.15 µg/kg bodyweight/h interrupted the normal interdigestive motility pattern of the upper intestine (Fig. 1). During pentagastrin infusion the number of activity fronts in the duodenum and jejunum was reduced to 0.4 ± 0.2 ($\bar{x} \pm \text{SEM}/4$ h). Irregular contractions prevailed (Fig. 3).

Infusion of proglumide in addition to pentagastrin restored the normal periodic interdigestive motor activity (Fig. 2). The mean period of the MMC was approximately two hours. The number of activity fronts of the MMC increased to $2.0 \pm 0.5/4$ h ($\bar{x} \pm \text{SEM}/4$ h) in the duodenum ($p < 0.02$ compared

with pentagastrin + placebo), and to $1.7 \pm 0.4/4$ h in the jejunum ($p < 0.01$).

Serum proglumide concentrations were determined 30 minutes and 240 minutes after the start of the proglumide infusion. After 30 minutes proglumide infusion serum concentrations ranged from 0.58 µg/ml to 28.26 (median 3.8), they were less than 2 µg/ml in seven subjects. Two hundred and forty minutes after the beginning of the proglumide infusion serum concentrations ranged from 0.58 µg/ml to 39.2 µg/ml (median 5.4), they were less than 2 µg/ml in seven subjects. There was no clear relationship between the serum proglumide concentrations 30 or 240 minutes after starting the proglumide infusion and the number of activity fronts of the MMC.

Discussion

In the interruption of cyclic interdigestive motility after feeding not only neural mechanisms, but also gastrointestinal hormones appear to be involved. Endogenous gastrin⁹ and exogenous administration of CCK⁸ have been found to convert the fasted to the fed motility pattern which is characterised by apparently irregular contractile activity.

The present study shows that the administration of pentagastrin in a dose which stimulates gastric acid secretion to a similar extent as the postprandial gastrin rise interrupts the regular periodic interdigestive motility in the upper gastrointestinal tract. Activity fronts of the MMC are absent or their number clearly reduced. The motility pattern

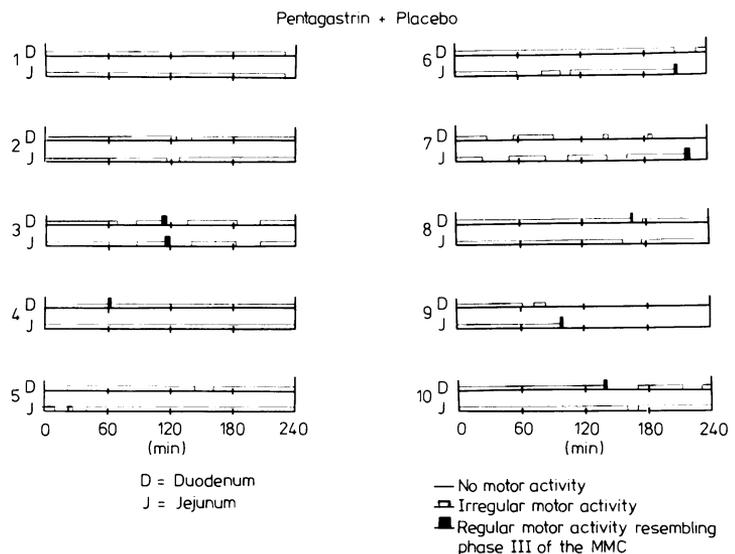


Fig. 1 Effect of pentagastrin (0.15 µg/kg/h) on interdigestive motility of the duodenum (D) and jejunum (J) in 10 healthy volunteers.

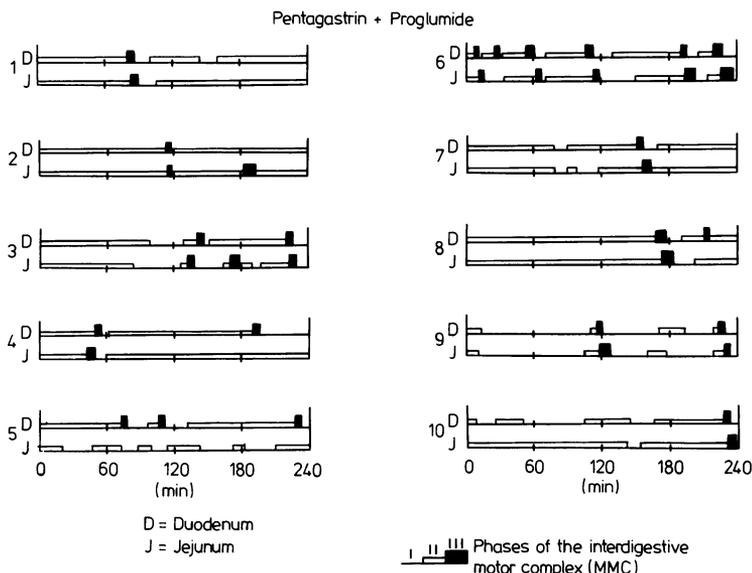


Fig. 2 Effect of pentagastrin (0.15 µg/kg/h) and proglumide (400 mg as a bolus followed by 500 mg/h) on interdigestive motility of the duodenum (D), and jejunum (J) in 10 healthy volunteers.

brought about by pentagastrin administration is characterised by irregular motor activity. These findings lend support to the idea that the serum gastrin rise after feeding is involved in the conversion of the interdigestive to the digestive motility pattern in the upper gut.^{6 7 9}

Additional infusion of proglumide restores the interdigestive motility pattern which has a mean period between activity fronts of the MMC of approximately two hours. These findings support

the hypothesis of proglumide being a gastrin- and CCK-receptor antagonist.¹⁰⁻¹³

Proglumide and pentagastrin have direct actions on the gastrointestinal smooth muscle cell^{11 17 18} in that they appear to act on CCK and gastrin receptors. In these observations pentagastrin and gastrin were shown to increase myoelectrical and motor activity of the stomach, while proglumide inhibited myoelectric and motor activity in the isolated stomach and ileum.¹⁸ It is unlikely that

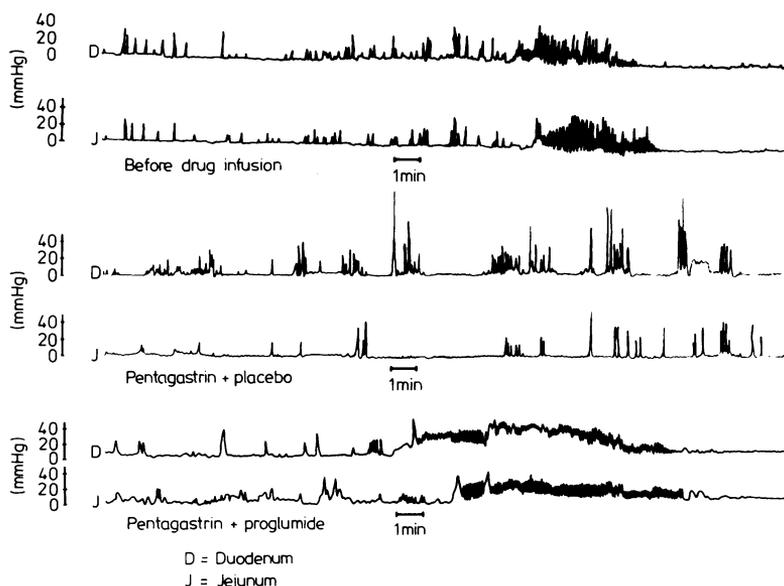


Fig. 3 Interdigestive motility of the duodenum (D) and jejunum (J) before and during pentagastrin + placebo and pentagastrin + proglumide infusion.

changes in gastric acid secretion play a major role in the motor effects of pentagastrin and proglumide, as (a) in animal experiments pentagastrin alters small intestinal motility even if gastric secretions are diverted from the duodenum⁷ and (b) proglumide has only weak actions on gastric acid secretion.¹⁹

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