Enprostil lowers elevated serum gastrin concentrations in patients with pernicious anemia

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P KIRDEIKIS, M MANT, L ZUK, D FISHER, L BYNUM, ABR THOMSON. Enprostil lowers elevated serum gastrin concentrations in patients with pernicious anemia. Can J Gastroenterol 1991;5(3):85-90. A double-blind, randomized, crossover, placebo controlled study of Latin square design was conducted to determine the gastrin-lowering effects of a synthetic orally administered prostaglandin, enprostil, in fasted and fed patients with hypergastrinemia due to pernicious anemia. The study subjects were one male and six female patients between the ages of 39 and 76 years with known pernicious anemia and elevated serum gastrin concentrations. In random order patients received twice daily enprostil 350 µg bid, enprostil 700 µg bid and placebo for one week, with a one week washout between treatment phases. Measurements of serum gastrin were performed in the fasting and postprandial states prior to dosing, at the end of each treatment phase, and at the end of each washout phase. Enprostil 350 µg bid lowered elevated fasting gastrin concentrations, and both doses of enprostil lowered the food-stimulated increases in serum gastrin. When changes in food-stimulated gastrin concentrations were adjusted for pre-meal gastrin concentrations, there was a consistent dose response between placebo, 350 and 700 µg enprostil bid. All patients experienced adverse events while on enprostil, particularly on the higher dose; nausea, vomiting, diarrhea and abdominal pain were reported most frequently. Thus, enprostil reduced basal and food-stimulated gastrin release in seven patients with pernicious anemia. The mechanism of this effect remains to be established, but it is clearly independent of an effect on acid secretion. *(Pour résumé, voir page 86)*

Key Words: *Enprostil, Hypergastrinemia, Prostaglandin,*

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ENPROSTIL IS AN ORALLY ADMINISTERED synthetic prostaglandin analogue with gastric antisecretory and mucosal protective properties which has been shown to be effective in the treatment of duodenal and gastric ulcers (1-6).

Enprostil reduces acid secretion and suppresses the release of gastrin following food stimulation in normal volunteers and in patients with duodenal ulcers (7-9). Enprostil may also reduce basal or food-stimulated gastrin release in patients with antral G cell hyperfunction, Zollinger-Ellison syndrome (10), and pernicious anemia (11). Pernicious anemia is a condition characterized by atrophic gastritis, impaired vitamin B12 absorption and achlorhydria. Due to the loss of both parietal cell function and normal acid-associated reduction in gastrin release, most patients with this disorder have chronically elevated concentrations of serum gastrin.

This study was undertaken to determine the gastrin-lowering effects of enprostil in patients with pernicious anemia.

L'enprostil réduit l'augmentation des taux de gastrine sérique chez les patients atteints d'anémie pernicieuse

RESUME: On a effectué un essai randomisé à double insu avec permutation, contrôlé contre placebo, selon un plan expérimental en carré latin. Il s'agissait de déterminer les propriétés antisécrétoires d'un analogue de synthèse des prostaglandines, l'enprostil, administré à jeun et après un repas, à des patients atteints d'une hypergastrinémie due à une anémie pernicieuse. L'étude portait sur un patient et six patientes âgés de 39 à 76 ans, souffrant d'une anémie pernicieuse connue et ayant des concentrations élevées de gastrine sérique. Les malades ont reçu deux prises journalières de 350µg d'enprostil, de 700µg d'enprostil et d'un placebo pendant une semaine, avec une semaine d'interruption entre les phases de traitement. On a mesuré la gastrine sérique chez le patient à jeun et après les repas avant d'instituer le traitement, au terme de chaque phase de traitement, et à la fin de chaque semaine d'interruption. L'enprostil administré à la dose de 350µg réduisait les taux de concentrations de gastrine mesurés à jeun, et les deux doses réduisaient l'augmentation post-prandiale des taux sériques de gastrine. Quand les variations des taux de gastrine stimulée par la nourriture étaient ajustées par rapport aux concentrations à jeun, on a noté une relation dose-effet constante entre le placebo, 350µg et 700µg d'enprostil. Tous les patients sous enprostil ont ressenti des effets indésirables, surtout à la dose de 700µg: nausées, vomissements, diarrhée et douleurs abdominales ont été le plus fréquemment rapportés. Ainsi, l'enprostil a inhibé la sécrétion de gastrine à jeun et stimulée par la nourriture chez sept patients atteints d'anémie pernicieuse. Le mécanisme de cet effet reste à établir mais le médicament semble agir, de toute évidence, au niveau de la sécrétion d'acide.

TABLE 1
Demographic data

Patient	Sex	Age (years)	Weight (kg)	Height (cm)	Order of treatment administration (drug dose given in µg bid)
1	M	76	99.2	171	Enprostil (350) – Placebo – Enprostil (700)
2	F	53	58.0	166	Placebo – Enprostil (700) – Enprostil (350)
3	F	69	69.0	159	Enprostil (700) – Enprostil (350) – Placebo
4	F	39	49.0	150	Placebo – Enprostil (350) – Enprostil (700)
5	F	39	49.0	152	Enprostil (350) – Enprostil (700) – Placebo
6	F	66	64.0	157	Enprostil (700) – Placebo – Enprostil (350)
7	F	71	56.0	159	Placebo – Enprostil (350) – Enprostil (700)
Mean		59.0	63.5	159	
Standard deviation		15.4	17.4	7.3	
Maximum		39.0	49.0	150	
Minimum		76.0	99.2	171	

Patient 7 withdrew from the study prematurely due to severe gastrointestinal symptoms while taking enprostil 700 µg bid

PATIENTS AND METHODS

Study design: This study was a double-blind, randomized, crossover, placebo controlled study of Latin square design.

Patient population: Seven patients with confirmed diagnoses of pernicious anemia (gastric atrophy, megaloblastic anemia or abnormal Schilling's test and known hypergastrinemia) were enrolled and randomly assigned to oral treatment with enprostil 350 µg bid, enprostil 700 µg bid and placebo for 6.5 days each in a crossover fashion, with a one week washout period between treatment phases. One subject withdrew from the study prematurely due to severe gastrointestinal symptoms (dyspepsia, nausea and vomiting) while taking enprostil 700 µg bid. The other six subjects completed all phases of treatment and testing. Table 1 shows demographic data, indicating that the seven patients ranged in age from 39 to 76 years (mean 59). The order of treatment administration is also shown.

Schedule of visits and assessment procedures: At the baseline visit, a fasting blood sample was obtained for serum gastrin measurement (8). Following a standardized protein-containing meal (Table 2), blood samples were drawn for measurement of food-stimulated gastrin concentrations at 15 and 30 min intervals for the next 3 h. Each patient was then given one of the three study medications and was instructed to take it twice daily for one week. At this time measurements of serum gastrin were repeated. These same measurements were repeated at the end of a one week washout, at the end of the second phase of treatment, at the end of another one week washout, and finally at the end of the third phase of treatment.

Statistical methods: Two different methods were used to calculate treatment effects: the pretreatment serum gastrin concentration minus the corresponding post treatment serum gastrin concentration; or the same as the first method except for the substitution of a change from pre-meal serum gastrin concentration for the corresponding serum gastrin concentration. Method 1 reflects the treatment effects on decreasing both pre- and post meal serum gastrin concentrations. Method 2 reflects the treatment effects on decreasing the elevated serum gastrin concentrations due to the standard meal for post meal analyses.

The analysis of variance models were run using SAS procedure GLM (12). The model statement for the three period pretreatment (baseline) comparison was of the form: model response = PT phase, where PT is a class variable indicating the eight patients, and 'phase' is a class variable indicating three periods.

The model statement for treatment comparisons was of the form: model response = PT phase TRT, where PT and 'phase' are defined as above, and TRT is a class variable with three levels indicating the three statements.

Type III sums of squares were used

for all tests of effects (12). Unfortunately, pretreatment serum gastrin concentrations were not recorded for patient 7 during the first period. To calculate the change from pre- to post treatment serum gastrin concentrations for this patient for the first period, the baseline serum gastrin concentrations during the second period were used for calculation. This was the only extrapolation made for missing data.

Ethical review and informed consent: All patients signed an informed consent form, and the study was reviewed and approved by an Institutional Review Board.

RESULTS

Efficacy: There was no statistically significant difference in fasting or post meal gastrin concentrations at baseline, at the two washout periods, or with placebo (Tables 3,4). Enprostil 350 µg bid was associated with a decline in the mean value of fasting basal gastrin concentrations, whereas both doses of enprostil prevented the meal-stimulated increase in gastrin concentrations. The values for food-stimulated gastrin concentrations in the enprostil-treated group were lower than the values obtained at baseline, during the two washout periods, or with placebo.

Table 5 shows the mean change in serum gastrin concentrations, representing the difference between concentrations measured at baseline or after washout, and concentrations measured following a week of therapy with one of the study drugs. Treatment had no statistically significant influence on pre-meal values, but post meal values showed greater changes with the two active treatment groups (enprostil 350 and 700 µg bid) compared to placebo. This treatment effect was statistically significant. It is noteworthy that the magnitude of change following treatment with enprostil 350 µg bid was greater than that following treatment with 700 µg bid.

There was no statistically significant difference between basal values and the two washout values, thereby verifying the validity of washout values as being representative of the baseline state (Table 6).

Table 7 displays the mean changes from pretreatment to post treatment gastrin concentrations for each of the individual time points at which blood sampling was performed. This analysis again shows a statistically significant treatment effect at 0.25, 0.75, 1.25 and 1.75 h. There was also a significant

TABLE 2
Composition of the standardized meal

Meal	Weight (g)	CHO (g)	Protein (g)	Fat (g)	Fluid (mL)
Breakfast A					
Orange muffin*	1	30.7	2.0	9.5	—
Butter/margarine	5	—	4.0	—	—
Scrambled egg	48	0.4	6.2	5.5	—
Bacon (crisp)	10	0.2	2.4	6.2	—
Orange juice	—	15.0	—	—	140
Water or herbal tea	—	—	—	—	160
Total		46.3	14.6	21.2	300
Breakfast B					
Whole wheat toast	46	21.6	4.8	1.4	—
Butter/margarine	16	—	—	12.8	—
Bacon (crisp)	20	0.4	4.8	12.4	—
Jam **or**	10	7.0	—	—	—
Jam and	4	2.8	—	—	—
sugar	4	4.0	—	—	—
Orange juice	—	16.0	—	—	100
Water or herbal tea	—	—	—	—	200
Total		51.8	9.6	26.6	300

Orange muffin mix was pre-measured. CHO Carbohydrates

TABLE 3
Fasting pre-meal total serum gastrin concentrations (ng/L)

		Measured concentrations						From baseline/washout		
Patient	Sequence*	Baseline	WO_1	WO_2	Placebo	E_{350}	E_{700}	Placebo†	E_{350}‡	E_{700}§
1	Enprostil (350) – Placebo – Enprostil (700)	1464	1792	803	1140	1596	1414	652	–132	–611
2	Placebo – Enprostil (700) – Enprostil (350)	400	428	556	172	192	340	228	364	88
3	Enprostil (700) – Enprostil (300) – Placebo	1024	900	952	1328	1024	1920	–376	–124	–896
4	Placebo – Enprostil (350) – Enprostil (700)	808	948	780	1692	636	732	–884	312	48
5	Enprostil (350) – Enprostil (700) – Placebo	2584	2280	1780	1384	1044	2492	396	1540	–212
6	Enprostil (700) – Placebo – Enprostil (350)	432	724	1184	892	352	180	–168	832	252
7	Placebo – Enprostil (350) – Enprostil (700)	¶	936	466	958	616	**	–221	320	††
	Mean	1118.7	1144.0	931.6	1080.9	780.0	1178.7	–24.9	444.6	–221.8
	Standard deviation	819.8	650.7	443.7	484.2	478.1	919.8	513.3	583.9	447.1
	Standard error	334.7	246.0	167.7	183.0	180.7	375.5	194.0	220.7	182.5
	Minimum	400	428	466	172	192	180	–884	–132	–896
	Maximum	2584	2280	1780	1692	1596	2492	652	1540	252

*Drug doses are given in µg bid. †Baseline or washout value minus placebo value. ‡Baseline or washout value minus E_{350} value. §Baseline or washout value minus E_{700} value. ¶Missing data. **Patient terminated early. ††Using washout 1 serum gastrin for missing baseline serum gastrin level. E_{350} Enprostil 350 µg bid; E_{700} Enprostil 700 µg bid; WO_1 First washout; WO_2 Second washout*

TABLE 4
Post meal average total serum gastrin concentrations (ng/L)

Patient	Sequence*	Measured concentrations						From baseline/washout		
		Baseline	WO_1	WO_2	Placebo	E_{350}	E_{700}	Placebo†	E_{350}‡	E_{700}§
1	Enprostil (350) – Placebo – Enprostil (700)	1911.4	1829.1	1734.9	2038.3	1516.6	1337.3	–209.2	394.8	397.6
2	Placebo – Enprostil (700) – Enprostil (350)	690.3	860.0	781.4	570.9	352.0	274.3	119.4	429.1	585.7
3	Enprostil (700) – Enprostil (300) – Placebo	1927.4	2528.6	1924.0	1845.1	1629.1	1861.7	78.9	899.4	65.7
4	Placebo – Enprostil (350) – Enprostil (700)	1594.9	1436.6	1329.1	1771.4	1200.0	982.3	–176.6	236.6	346.9
5	Enprostil (350) – Enprostil (700) – Placebo	2826.3	1947.4	2451.4	1954.9	961.1	2004.0	496.7	1865.1	–56.6
6	Enprostil (700) – Placebo – Enprostil (350)	680.6	958.3	804.6	984.6	452.0	174.9	–26.3	352.6	505.7
7	Placebo – Enprostil (350) – Enprostil (700)	¶	1312.0	1321.1	1536.0	749.7	**	–224.01	562.3	††
	Mean	1605.2	1553.1	1478.1	1528.7	980.1	1105.8	8.4	677.1	307.5
	Standard deviation	822.3	590.1	605.2	549.8	497.4	775.2	255.8	564.9	252.0
	Standard error	335.7	223.0	228.8	207.8	188.0	316.5	96.7	213.5	102.9
	Minimum	680.6	860.0	781.4	570.9	352.0	174.9	–224.0	236.6	–56.6
	Maximum	2526.3	2528.6	2451.4	2038.3	1629.1	2004.0	496.7	1865.1	585.7

**Drug doses are given in µg bid. †Baseline or washout value minus placebo value. ‡Baseline or washout value minus E_{350} value. §Baseline or washout value minus E_{700} value. ¶Missing data. **Patient terminated early. ††Using washout 1 serum gastrin for missing baseline serum gastrin level. E_{350} Enprostil 350 µg bid; E_{700} Enprostil 700 µg bid; WO_1 First washout; WO_2 Second washout*

TABLE 5
Mean change in serum gastrin levels

	Pre-meal	Post meal
Placebo	–24.9 (513.3	8.4 (255.8)
Enprostil 350 µg bid	444.6 (583.9)	677.1 (564.9)
Enprostil 700 µg bid	–221.8 (447.1)	307.5 (252.0)
P	0.12	0.05

Change was calculated as pretreatment serum gastrin minus post treatment serum gastrin. P value was calculated from analysis of variance testing for equality of pretreatment minus post treatment differences

TABLE 6
Mean serum gastrin levels: Basal and post washout (ng/L)

	Pre-meal	Post meal
Basal	1118.7 (819.8)	1605.1 (822.3)
Washout 1	1144.0 (650.7)	1553.1 (590.1)
Washout 2	931.6 (443.7)	1478.0 (605.2)
P	0.48	0.78

P value was calculated using analysis of variance for washout validation

treatment effect on the peak post meal change in gastrin concentrations. Again, changes following treatment with enprostil 350 µg bid were greater than those recorded following treatment with 700 µg bid. However, this is not the case when changes from pre-meal gastrin concentrations are examined at each of the individual post meal time points. The changes from pre-meal to post meal gastrin concentrations show a consistent numeric dose response, with greater changes following enprostil 700 versus 350 µg bid.

Safety: Five of the six subjects completing the study reported complaints following treatment with 350 µg bid enprostil, and all subjects reported complaints with 700 µg bid. Gastrointestinal symptoms predominated with nausea, vomiting, diarrhea and abdominal pain appearing most frequently. These symptoms were occasionally rated by the patients as severe more often during treatment at 700 µg bid than during treatment at 350 µg bid. Patient 7 dropped out of the study prematurely because of severe gastrointestinal symptoms while taking enprostil 700 µg bid.

DISCUSSION

Oral enprostil at doses of 350 and 700 µg bid was effective in lowering food-stimulated gastrin concentrations in seven patients with pernicious anemia, whereas the 350 µg bid dose was also associated with a lowering of the elevated fasting gastrin concentration (Tables 2-6). When pretreatment minus post treatment food-stimulated gastrin concentrations were compared following treatment with placebo, 350 or 700 µg bid, a statistically significant treatment effect was present. Numerically, the magnitude of the difference between pre- and post treatment values was greater with 350 versus 700 µg bid, indicating apparent lack of a dose response effect. However, a statistically significant treatment effect was also seen when individual post meal time points were compared with respect to the change from pre- to post treatment measurements. Again, values tended to be greater for the pre- to post treatment change following 350 versus 700 µg bid. Indeed, a consistent dose response was seen when changes from pre-meal to post meal values were compared between the three treatment groups. The apparent inconsistency in dose response can be explained by the flat dose response between 350 and 700 µg bid, suggesting that gastrin suppression may be nearly maximal at the lower dose of enprostil.

Adverse events are mild and infre-

TABLE 7
Mean change in serum gastrin level

	Placebo	Enprostil 350 μg bid	Enprostil 700 μg bid	P
Premeal	−24.9 (513.3)	444.6 (583.9)	−221.8 (447.1)	0.12
0.25 h	135.4 (501.6)	812.6 (844.4)	443.0 (308.8)	0.03
0.75 h	22.3 (399.4)	720.0 (556.3)	541.3 (199.3)	0.03
1.25 h	−39.4 (285.4)	746.9 (580.5)	355.5 (222.5)	0.02
1.75 h	7.1 (171.3)	662.3 (466.3)	327.3 (251.2)	0.02
2.25 h	−122.0 (272.8)	678.0 (696.8)	192.7 (423.6)	0.07
2.75 h	102.9 (307.0)	532.3 (544.0)	166.7 (465.0)	0.32
3.25 h	−47.4 (199.5)	588.0 (473.3)	126.0 (614.1)	0.14
Peak	273.4 (304.9)	994.3 (723.5)	682.0 (76.1)	0.03
Change from premeal				
0.25 h	160.3 (672.7)	368.0 (746.6)	664.8 (570.4)	0.43
0.75 h	47.1 (576.4)	275.4 (514.2)	763.2 (546.6)	0.15
1.25 h	−14.6 (577.7)	302.3 (550.7)	577.3 (417.4)	0.20
1.75 h	32.0 (485.7)	217.7 (444.3)	549.2 (254.3)	0.14
2.25 h	−97.1 (558.4)	233.4 (515.8)	414.5 (300.5)	0.24
2.75 h	127.7 (434.5)	87.7 (397.9)	388.5 (478.3)	0.48
3.25 h	−22.6 (442.3)	143.4 (421.2)	347.8 (596.0)	0.52
Peak	298.3 (545.6)	549.7 (639.1)	903.8 (506.9)	0.20

Change was calculated as pretreatment serum gastrin minus post treatment serum gastrin. 'Peak' denotes peak during post meal period. P value was calculated from analysis of variance testing for equality of pretreatment minus post treatment differences

quent in patients with gastric or duodenal ulcers treated with enprostil (1,2). Thus, it was surprising that all patients in this study developed side effects from the enprostil; adverse events ranged from mild to severe (severe enough for one patient to withdraw from the study). The mechanism of this high rate of adverse effects is unclear, since it was not clearly associated with the higher versus the lower dose of enprostil, nor was there any clear association between prevalence or severity of side effects and baseline gastrin concentrations (400 to 2584 pg/mL) (Table 3).

It is possible but unproven whether the absorption and metabolism of enprostil differs in patients with achlorhydria compared with individuals with normal or increased amounts of gastric acid associated with peptic ulcer disease. Alternatively, in the presence of prolonged hypergastrinemia, there may be hyperplasia of gastric D or enterochromaffin-like cells (14,15), and the administration of enprostil could possibly alter the release of these or other peptides (such as pancreatic polypeptide [16]), which in turn might possibly result in the adverse events reported in these patients. The above suggestions are speculative. Nonetheless, careful clinical observation would be appropriate if it were ever clinically indicated to administer enprostil to patients with pernicious anemia.

The mechanism of the effect of enprostil on serum gastrin concentrations is unknown. Fasting serum gastrin concentrations are elevated in patients with pernicious anemia, likely due to the loss of acid-induced inhibition of gastrin release. Food is a physiological stimulus of acid secretion in healthy subjects as well as in acid-secreting persons with duodenal ulcers and non-acid-secreting patients with pernicious anemia.

Enprostil reduces acid secretion in volunteers as well as in duodenal ulcer and Zollinger-Ellison patients, but has no effect on acid secretion in the achlorhydric patient with pernicious anemia. Rather, the effect of enprostil on serum gastrin concentration is likely mediated at the level of gastrin synthesis or release.

In conclusion, enprostil effectively lowered elevated basal and food-stimulated serum gastrin concentrations in seven patients with pernicious anemia. The optimal dose appeared to be 350 μg enprostil bid, but such therapy may be limited by frequent and moderately severe adverse effects.

REFERENCES

1. Navert H, Thomson ABR, Archambault A, et al. Treatment of gastric ulcer with enprostil. Am J Med 1986;81:75-9.
2. Thomson ABR, Navert H, Halvorsen L, et al. Treatment of duodenal ulcer with enprostil, a synthetic prostaglandin E_2 analogue. Am J Med 1986;81:59-63.
3. Thomson ABR, McCullough HN, Kirdeikis P, et al. Twenty-four hour intragastric measurements in twenty healthy subjects: Effect of enisoprost, a novel and potent antisecretory and antipeptic synthetic E_1 prostaglandin. Aliment Pharmacol Ther 1988;2:325-36.
4. Thomson ABR. Introduction: Protective and therapeutic effects of gastrointestinal prostaglandins. Enprostil: A new modality. Am J Med 1988;81:1.
5. Bright-Asare P. Treatment of duodenal ulcer with enprostil, a prostaglandin E_2 analogue. Am J Med 1986;81 (Suppl 2A):64-8.
6. Winters L. Comparison of enprostil and cimetidine in active duodenal ulcer disease. Am J Med 1986;81(Suppl 2A):69-74.
7. Thomas FJ, Koss MA, Hogan DL, Isenberg JI. Enprostil, a synthetic prostaglandin E_2 analogue, inhibits meal-stimulated gastric acid secretion and gastrin release in patients with duodenal ulcer. Am J Med 1986;81(Suppl 2A):44-9.
8. Mahachai V, Walker K, Sevelius H, Thomson ABR. Antisecretory and serum gastrin lowering effect of enprostil in patients with duodenal ulcer disease. Gastroenterology 1985;89:555-61.
9. Deakin M, Ramage J, Paul A, Gray SP, Billings J, Williams JG. Effect of enprostil, a synthetic prostaglandin E_2 on 24 hour intragastric acidity, nocturnal acid and pepsin secretion. Gut 1986;27:1054-7.
10. Crobach LFSJ, Jansen JBMJ, Lamers CBHW. Effect of enprostil on basal and post-prandial serum gastrin levels in patients with antral G-cell hyperfunction, Zollinger-Ellison syndrome and normal subjects. Gut 1987;28:A1282.
11. Buchanan N, Laferla G, Hearns J, Buchanan KD, Crean GP, McColl KEL. Effect of a single oral dose of

enprostil on gastric secretion and gastrin release. Am J Med 1986;81(Suppl 2A):40-3.
12. Cary: SAS Institute Inc, 1985:77-92.
13. Borch K, Renvall H, Liedberg G. Gastric endocrine cell hyperplasia nd carcinoid tumors in pernicious anemia. Gastroenterology 1985;88:638-48.
14. Jewell LD, Yacoub W, Salkie ML, et al. Enprostil reduces G-cell hyperplasia and hypergastrinemia in duodenal ulcer. Clin Ther 1987;9:281-95.
15. Sherbaniuk R, Jewell LD, Yacoub W, et al. Synergistic interaction between an H_2-receptor antagonist and enprostil on 24-hour intragastric pH, serum gastrin concentrations, and tissue immunoperoxidase staining for gastrin, somatostatin, and serotonin in a patient with metastatic gastrinoma. Clin Ther 1986;8:667-88.
16. Peterson W, Feldman M, Taylor I, Bremar M. The effect of 15(R)-15-methyl prostaglandin E_2 on meal-stimulated gastric aid secretion, serum gastrin and pancreatic polypeptide in duodenal ulcer patients. Dig Dis Sci 1979;24:381-4.