The effect of intravenous infusions of prostaglandins E_2 and $F_{2\alpha}$ on human gastric function

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SUMMARY The effect of intravenous infusions of prostaglandins E_2 and $F_{2\alpha}$ at various dose levels on basal, or on maximally or submaximally pentagastrin-stimulated acid secretion, was studied in 40 male subjects. Intraluminal antral pressures were also measured. Prostaglandin $F_{2\alpha}$ ($0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$) transiently, but significantly, inhibited submaximal acid output and increased the frequency of antral contractions. Prostaglandin E_2 ($0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$) inhibited basal acid secretion.

Robert, Nezamis, and Phillips (1967) have shown that intravenously administered prostaglandins E_1 and A_1 (PGE_1 and PGA_1), but not $\text{PGF}_{2\alpha}$, inhibit histamine- and food-stimulated acid secretion of canine denervated oxyntic cell pouches. Some of these results have been subsequently confirmed in laboratory animals and in man, but $\text{PGF}_{2\alpha}$ has not been further studied (Main, 1969; Classen, Koch, Deyhle, Weidenhiller, and Demling, 1971; Nezamis, Robert, and Stowe, 1971; Koch, Demling, and Classen, 1972).

$\text{PGF}_{2\alpha}$ is suitable for further investigation because it raises human cardiac sphincter pressure without affecting plasma gastrin (Dilawari, Newman, Poleo, and Misiewicz, 1975), has few undesirable cardiovascular side effects (Hollenberg, Walker, and McCormick, 1968), and does not influence lipolysis (Steinberg, Vaughan, Nestel, Strand, and Bergström, 1964; Weeks, Chandra Sekhar, and Ducharme, 1969). PGE_2 is suitable for study because it occurs naturally in human gastric mucosa (Bennett, Stamford, and Unger, 1973). It inhibits gastric acid secretion in animals, but has not been extensively studied in man and its role in gastric function has not been fully elucidated (Robert *et al.*, 1967). We have studied in human subjects the effects of intravenous infusions of these prostaglandins on basal or pentagastrin-stimulated acid output. Since PGs have powerful

effects on smooth muscle tone, we have also investigated their effects on antral motility.

Patients and Methods

Forty men with peptic ulcer, x-ray negative dyspepsia, or with no gastrointestinal complaints were studied. Each subject gave his informed consent to the test.

A no. 14 Salem sump tube was placed under fluoroscopic control in the most dependent part of the stomach. Gastric secretion was collected by continuous suction in 10-min periods. The 10-min collections were titrated to pH 7.4 with 0.1 N Na OH. In 22 studies the tube was modified by the addition of two or three open-ended polythene tubes 1 mm in diameter, which were constantly perfused with water at 5 ml h^{-1} and connected to pressure-sensitive transducers. The tube assembly was positioned under fluoroscopic control so that the pressure sensors were in the antrum whilst the sump tube was in the most dependent part of the stomach. Antral pressure waves were recorded on a multi-channel pen-writer (Devices).

Each subject received a continuous intravenous infusion from a constant-infusion syringe pump. The syringe contained either 0.15 M saline, pentagastrin, or the PG. Pentagastrin and PG were given simultaneously from separate syringes.

BASAL STUDIES (BASAL + PG)

The effect of $\text{PGF}_{2\alpha}$ or PGE_2 on basal secretion was studied in 12 subjects. After six consecutive 10-min aspiration periods during which intravenous saline was given, the infusion was changed either to $\text{PGF}_{2\alpha}$ $0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$ (five subjects) or PGE_2

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Study	Subjects (n)	Dose ($\mu\text{g/kg/min}$)		Variable Measured		Results	
		Penta- gastrin	Prosta- glandin	Acid Output	Antral Motility	Acid Output	Antral Motility
Basal + $\text{PGF}_{2\alpha}$	5	—	0.8	+	3/5	No effect	Increased number of contractions
Pentagastrin + $\text{PGF}_{2\alpha}$	10	0.01	0.5	+	7/10	No effect	Pentagastrin increased number of antral contractions.
Pentagastrin + $\text{PGF}_{2\alpha}$	7	0.01	0.8	+	7/7	Inhibition in 7/7	$\text{PGF}_{2\alpha}$ had no effect.
Pentagastrin + $\text{PGF}_{2\alpha}$	4	0.1	0.8	+	—	No effect	—
Basal + PGE_2	3	—	0.04	+	2/3	No effect	No effect
Basal + PGE_2	4	—	0.08	+	3/4	Inhibition in 4/4	No effect
Pentagastrin + PGE_2	3	0.1	0.04	+	—	Inhibition in 2/3	—
Pentagastrin + PGE_2	4	0.1	0.08	+	—	Inhibition in 4/4	—

Table Summary of studies

(seven subjects: three at $0.04 \mu\text{g kg}^{-1} \text{min}^{-1}$ and four at $0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$) and gastric juice aspirated for six additional 10 min periods.

PENTAGASTRIN-PG STUDIES

In 28 subjects the effect of $\text{PGF}_{2\alpha}$ or PGE_2 on pentagastrin-stimulated gastric secretion was measured. After a 30-min basal collection, pentagastrin was infused intravenously at either a submaximal dose of $0.01 \mu\text{g kg}^{-1} \text{min}^{-1}$ (17 subjects) or at the maximal dose of $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$ (11 subjects). After five or six collection periods when a plateau of secretion was attained, PG was administered and the pentagastrin infusion continued. Twenty-one subjects received $\text{PGF}_{2\alpha}$ (10 at $0.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ and 11 at $0.8 \mu\text{g kg}^{-1} \text{min}^{-1}$), while seven received PGE_2 (three at $0.04 \mu\text{g kg}^{-1} \text{min}^{-1}$ and four at $0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$). The pentagastrin and PG infusions were continued for six collection periods in most studies and in all with $0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$ of PGE_2 .

The pressure records were analysed by counting the number of antral contractions in each 10-min period and dividing by 10. The various studies are summarized in the table.

Student's paired *t* test was used for statistical analysis of the results. In the basal + PG studies the mean of the six basal periods was compared with each of the 10-min periods of PG infusion. In the pentagastrin + PG studies, the last three 10-min periods of the pentagastrin plateau were averaged and compared with output during each 10-min period of pentagastrin + PG.

Results

All subjects tolerated the test well and apart from transient erythema at the site of the intravenous infusion which occurred in all the PGE_2 and in half of the $\text{PGF}_{2\alpha}$ studies, there were no unwanted effects.

Fig 1 Frequency of antral contraction before and during intravenous $\text{PGF}_{2\alpha}$

PROSTAGLANDIN $F_{2\alpha}$

Basal + $\text{PGF}_{2\alpha}$

$\text{PGF}_{2\alpha}$ had no effect on basal gastric acid secretion. Increased frequency of antral contractions was recorded in the three subjects in whom it was measured (fig 1).

Pentagastrin + $\text{PGF}_{2\alpha}$

$\text{PGF}_{2\alpha}$ at $0.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ had no effect on submaximally pentagastrin-stimulated gastric secretion. In contrast, $\text{PGF}_{2\alpha}$ at $0.8 \mu\text{g kg}^{-1} \text{min}^{-1}$ profoundly, but transiently, inhibited submaximally stimulated, acid output by decreasing the volume but not the H^+ concentration (fig 2, see table). Raising the level of pentagastrin to the maximal dose of $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$ prevented the inhibitory action of $\text{PGF}_{2\alpha}$.

As previously reported (Misiewicz, Holdstock, and Waller, 1967; Kwong, Brown, Whittaker, and Duthie, 1971), pentagastrin increased the frequency of antral contractions, but $\text{PGF}_{2\alpha}$ had no effect on the stimulated antral motility.

Fig 2 Effect of intravenous $\text{PGF}_{2\alpha}$ $0.8 \mu\text{g kg}^{-1} \text{min}^{-1}$ on acid output stimulated by intravenous pentagastrin ($0.01 \mu\text{g kg}^{-1} \text{min}^{-1}$): individual responses in seven subjects

Fig 3 Effect of one-hour intravenous infusion of PGE_2 $0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$ on basal acid output in four subjects

PROSTAGLANDIN E_2

Basal + PGE_2

PGE_2 significantly inhibited acid output and volume, but not H^+ concentration when given at the rate of $0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$ (fig 3, see table). PGE_2 at $0.04 \mu\text{g kg}^{-1} \text{min}^{-1}$ was ineffective. There was no effect on antral motility at either dose level.

Pentagastrin + PGE_2

PGE_2 infused at the rate of $0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$

Fig 4 Effect of one-hour intravenous infusion of PGE_2 $0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$ on acid output stimulated by intravenous pentagastrin ($0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$) in four subjects

significantly decreased maximally pentagastrin-stimulated acid output (fig 4, see table). Two of three subjects studied at $0.04 \mu\text{g kg}^{-1} \text{min}^{-1}$ of PGE_2 showed a clear inhibition of acid output, but results were not analysed statistically because of the small numbers.

Discussion

The study shows that intravenous PGE_2 significantly decreases basal gastric acid secretion. Gastric acid output stimulated by infusion of $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$ of pentagastrin was also significantly inhibited by PGE_2 at the dose of $0.08 \mu\text{g kg}^{-1} \text{min}^{-1}$. This inhibition was slow and gradual in onset and accounted for only about 30% of the maximally stimulated plateau. It is possible therefore that all, or part, of the observed decrease in acid output was due to 'fade', which is known to occur during prolonged infusions of pentagastrin. The question could be resolved by retesting the same subjects with a two-h infusion of pentagastrin alone, but this was not feasible in this study. $\text{PGF}_{2\alpha}$ transiently inhibits gastric secretion submaximally stimulated by pentagastrin. The inhibitory effect was on the volume of gastric juice; the concentration of H^+ did not change.

The mechanism of inhibition of gastric secretion by PGs is controversial. Koch *et al* (1972) have suggested that PGs have a primary effect on mucosal blood supply. On the other hand Jacobson (1970), Wilson and Levine (1972) and Main and Whittle

(1972a and b) concluded that PGs affect primarily the intracellular mechanisms which control gastric acid secretion. Evidence in favour of the latter hypothesis is more convincing. Studies in dogs in which acid secretion and ^{14}C aniline clearance have been simultaneously measured suggest that the blood-flow changes are secondary to changes in secretion rates (Main and Whittle, 1972b) and experiments on isolated frog gastric mucosa have shown PGs to be capable of inhibiting acid secretion in the absence of vascular supply to the mucosa (Way and Durbin, 1969). Clearance techniques are not at present applicable to man despite recent progress in this direction (Bickel, Witten, and Killian, 1972), and the mechanism in man remains conjectural. PGE_2 and $\text{F}_{2\alpha}$ at dose levels used in this study do not affect plasma gastrin levels (Dilawari *et al*, 1975).

The profound, but transient, inhibition of gastric acid secretion by $\text{PGF}_{2\alpha}$ is of interest and emphasizes the species differences in responses to this prostaglandin: a phenomenon previously noted in studies of cardiovascular effects in cats and dogs (Horton and Main, 1965; Ducharme and Weeks, 1967). Since protein binding decreases the activity of PGs (Raz, 1972), it is possible that the evanescent effect of $\text{PGF}_{2\alpha}$ on acid output was due to this form of inactivation. Alternatively, the dose of $\text{PGF}_{2\alpha}$ we have used may have transiently exceeded the capacity of the PG 15-OH dehydrogenase to inactivate the administered prostaglandin. A racemic 20-ethyl $\text{PGF}_{2\alpha}$ analogue (ICI 70,205) had no effect on acid output when infused intravenously (Milton-Thompson and Misiewicz, unpublished data). It would appear, however, that analogues of $\text{PGF}_{2\alpha}$ retaining the capacity to contract the lower oesophageal sphincter and at the same time capable of inhibition of acid secretion would be desirable therapeutic agents for many forms of dyspepsia.

In vitro, both circular and longitudinal gastrointestinal smooth muscle is stimulated by $\text{PGF}_{2\alpha}$, whilst PGE_2 relaxes the circular layer (Bennett, Eley, and Scholes, 1968; Bennett, Murray, and Wyllie, 1968; Bennett and Posner, 1971; Vanasin, Greenough, and Schuster, 1970). Our observation of increase in the frequency of antral contractions with $\text{PGF}_{2\alpha}$ are consistent with these data. The cardiac sphincter is also contracted by $\text{PGF}_{2\alpha}$ (Dilawari *et al*, 1975). The enhanced antral contractility is strikingly different from the effect of $\text{PGF}_{2\alpha}$ on jejunal and ileal segmenting pressures, which are inhibited by similar doses of the same prostaglandin (Cummings, Newman, Misiewicz, Milton-Thompson, and Billings, 1973). Classen, Stürzenhofecker, Koch, and Demling (1973) observed inhibition of antral contractions following intravenous PGE_1 . As our

subjects had only infrequent antral contractions in the basal state, averaging 1 min^{-1} , the demonstration of inhibition may have been an unrealistic goal. Further studies in individuals with more active antral contractions would seem to be indicated.

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