Effect of orally administered prostaglandin E₁ on gastric secretion and gastrointestinal motility in man

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Prostaglandins are fatty acids which have been found in a wide variety of tissues (Bergström, 1967; Pickles, 1967), including human gastric mucosa (Bennett, Murray, and Wyllie, 1968). One member of this group, prostaglandin E₁, has recently been shown to inhibit the secretion of gastric juice in rats (Shaw, 1968; Ramwell and Shaw, 1968) and dogs (Robert, 1968; Robert, Nezamis, and Phillips, 1967). The investigation reported here was undertaken in an attempt to extend these observations to man.

METHODS

COLLECTION OF GASTRIC JUICE Three healthy male subjects aged 30, 31, and 38 years and weighing 70, 60, and 80 kg respectively, were fasted overnight for 10 hours. A $\frac{1}{4}$ in. plastic stomach tube was passed via the nose into the stomach at approximately 8.30 am. The subject then lay horizontally on his left side throughout the remainder of the experiment. Blood pressure in the right brachial artery and pulse rate were recorded at five to 15 minute-intervals.

Fasting gastric juice was removed as completely as possible and further samples were withdrawn 15 and 30 minutes later.

Two-fifths of the total dose of prostaglandin E₁ (or solvent control) diluted in 25 ml water was then drunk by the subject. Fifteen minutes later, residual fluid in the stomach was aspirated and one-fifth of the total prostaglandin dose dissolved in 5 ml water was administered through the tube. Pentagastrin, 6 μ g/kg, was then injected subcutaneously. The stomach was emptied as completely as possible at 15, 30, 45, 60, and 75 minutes after the injection. Two further doses, each amounting to one-fifth of the total dose, of prostaglandin E₁ dissolved in 5 ml water were administered via the tube after the 15- and 30-minute samples were withdrawn. Each dose was washed in with 5 ml water. In the control experiments the same procedure was followed using the solvent control.

PROSTAGLANDIN E₁ SOLUTION AND SOLVENT CONTROL A stock solution (1 mg/ml) of prostaglandin E₁, kindly supplied by Professor D. A. van Dorp of the Unilever

Research Laboratories, Vlaardingen, was prepared by dissolving 9.5 mg in 1 ml ethanol and making up the volume to 9.5 ml with water. A solvent control was prepared by diluting 1 ml ethanol to 9.5 ml with water.

ESTIMATION OF TOTAL ACIDITY The volume of each sample was measured. The total acidity of each was measured by titration with $N/20$ sodium hydroxide solution using phenolphthalein as indicator.

EXPERIMENTS TO CHECK THE PURITY, TOXICITY, AND BIOLOGICAL ACTIVITY OF PROSTAGLANDIN E₁ Since the prostaglandin E₁ used in this investigation had been subjected to extensive purification procedures before despatch, elaborate tests of identification or purity were considered unnecessary. An aliquot of the material was chromatographed on a plate of silica gel in Gréen and Samuelsson's AI solvent system (Gréen and Samuelsson, 1964). It behaved like a single substance with an R_f value equal to that of a sample of authentic prostaglandin E₁.

A second aliquot of the prostaglandin E₁ was tested for biological activity and toxic effects in mice. Intravenous injection of 5 and 10 mg/kg to three mice produced signs (sedation, ptosis, and moist faeces) which have been described previously with lower doses of prostaglandin E₁ (Holmes and Horton, 1968). There were no deaths. The higher dose in mice was 250 times greater than the largest dose (40 μ g/kg) administered (orally) to man in this investigation.

Using the Ghosh and Schild (1958) technique, it was confirmed that this particular batch of prostaglandin E₁ perfused through the stomach of a rat in a concentration of 6 μ g/ml caused up to 45% inhibition of gastric acid secretion induced by continuous intravenous infusion of pentagastrin 9 μ g/kg/hour.

Finally, the prostaglandin E₁ was given to one subject to detect unexpected toxic effects. The subject, who had fasted overnight, was given prostaglandin E₁ (10 μ g/kg) as a single dose (total 0.8 mg) dissolved in 25 ml water. The only side effect was the passing of loose faeces two hours after the prostaglandin administration. Thereafter defaecation was normal and no change in frequency was observed. The arterial blood pressure and heart rate were unaffected.

RESULTS

EFFECTS OF PENTAGASTRIN ON SUBJECTS DOSED WITH THE SOLVENT CONTROL The gastric secretory response to pentagastrin (6 $\mu\text{g/kg}$) was detectable after 15 minutes but had passed its maximum by 45 minutes. The response lasted 60 to 75 minutes. Pentagastrin caused flushing of the face, an effect which began two minutes after the injection and subsided completely within 15 minutes. This effect was reported by the subjects and was usually apparent to the observer. In one experiment vasodilatation of the skin was widespread over the body and an unpleasant sensation of severe heat accompanied by sweating was experienced.

EFFECT OF PROSTAGLANDIN E_1 ON GASTRIC SECRETION IN MAN In four experiments prostaglandin E_1 was given orally in doses of 10, 20, 25, and 40 $\mu\text{g/kg}$ to three subjects. In none of these experiments was there any detectable reduction in volume or acid content of the gastric juice secreted in response to pentagastrin compared with the controls (Table I). There may even have been an increase in secretion following prostaglandin administration. The pentagastrin-induced flushing was also of similar intensity and duration in subjects who had received prostaglandin to that observed in the control experiments. There was no change in pulse rate or arterial blood pressure.

EFFECT OF PROSTAGLANDIN E_1 ON THE PRESENCE OF BILE IN GASTRIC SAMPLES In three subjects treated with prostaglandin E_1 in doses of 20, 25, and 40 $\mu\text{g/kg}$, there were large amounts of bile in the samples, particularly those collected 30 and 45 minutes after pentagastrin. In two subjects bile was

detected in the gastric juice sample collected 15 minutes after the administration of prostaglandin, that is, before the pentagastrin had been injected. In none of the subjects was any bile observed in the gastric juice secreted in response to pentagastrin, when prostaglandin had not been administered.

EFFECTS OF PROSTAGLANDIN E_1 ON INTESTINAL MOTILITY In the five experiments in which prostaglandin E_1 was administered, the passing of loose faeces was observed between two and four hours after administration. At the 40 $\mu\text{g/kg}$ level the faeces were completely liquid, but defaecation was subsequently normal. From one hour after the prostaglandin administration until defaecation occurred sensations of increased intestinal motility were felt. There were sometimes mild colicky pains. In the control experiments the faeces were unchanged and defaecation did not occur with any regular time relationship to the administration of the test solution. Between experiments faeces were of normal consistency in all subjects and there was no change in normal frequency of defaecation.

PROSTAGLANDIN CONTENT OF THE GASTRIC JUICE In four experiments in which prostaglandin E_1 was administered to the subjects, part of the dose was removed from the stomach at each aspiration. The total amount of prostaglandin E_1 recovered in this way is shown in Table I.

The prostaglandin content of fasting gastric juice (nine experiments) and juice secreted in response to pentagastrin (four experiments) was estimated.

No prostaglandin (1.5 ng E_1 equivalent/ml) could be detected except in one fasting sample when activity equivalent to a concentration of 7 ng

TABLE I

EFFECT OF PROSTAGLANDIN E_1 ON PENTAGASTRIN-INDUCED GASTRIC SECRETION AND ON INTESTINAL MOTILITY¹

Experiment No.	Subject	Dose ($\mu\text{gE}_1/\text{Kg}$)		Vol (ml)	Acid (m-equiv)	Bile	Increase in Intestinal Motility
		Administered	Recovered				
Control experiments (pentagastrin only)							
1	EH	—	—	184	8.8	0	nil
2	EH	—	—	175	14.5	0	nil
3	HM	—	—	140	11.4	0	nil
4	PW	—	—	148	14.9	0	nil
5 ^a	HM	—	—	N.T.	N.T.	0	nil
Prostaglandin administration							
1	EH	10	3	170	10.0	0	+
2	EH	40	11	241	15.4	+++	+++
3	HM	20	7	314	24.8	+++	+
4	PW	25	13	241	18.0	++	++
5 ^a	EH	10	0	N.T.	N.T.	N.T.	++

¹The volume (ml) and acidity (m-equiv) refer to the total samples collected during the first hour after pentagastrin injection. N.T. = not tested. Presence of bile in the aspirated samples is indicated by ++ or +++. 0 indicates absence or only trace amounts of bile.

^aPreliminary experiment to study the side effects of pentagastrin alone.

^bPreliminary experiment to study the side effects of prostaglandin E_1 alone (no pentagastrin).

prostaglandin E_1 /ml was found. This was not positively identified as a prostaglandin.

DISCUSSION

The results of this investigation show that prostaglandin E_1 administered orally in man fails to inhibit gastric secretion in doses which have effects on gastrointestinal motility. Shaw and Ramwell reported inhibition of pentagastrin-induced gastric secretion in the rat with prostaglandin E_1 perfused through the stomach at a rate of 0.5 to 1 μ g/min (Shaw, 1968; Ramwell and Shaw, 1968). The conditions of the two investigations were different and a direct comparison cannot be made. In the present study prostaglandin E_1 was present in the stomach continuously for one hour, 15 minutes before and 45 minutes after the pentagastrin injection. In the four experiments reported here, concentrations of prostaglandin E_1 in the empty stomach were at least 13, 22, 24, and 50 μ g/ml at the beginning of each 15-minute period. Our results do not exclude the possibility that human gastric secretion might have been inhibited if a higher dose of prostaglandin E_1 had been used.

Prostaglandin E_1 is released from the rat's stomach when gastric secretion is stimulated (Shaw, 1968; Ramwell and Shaw, 1968). It has been suggested that the action of this released prostaglandin may be to inhibit further actions of the secretagogue by a negative feedback mechanism (Shaw, 1968). We have been unable to obtain convincing evidence in man for the presence of prostaglandin in either fasting juice or in juice secreted in response to pentagastrin. It is possible that any biologically active prostaglandins released could have been destroyed by the gastric juice. This negative finding, coupled with the failure of prostaglandin E_1 to inhibit secretion, does not support a role for this compound in human gastric secretion similar to that postulated for rats. Human gastric mucosa contains prostaglandin E_2 (Bennett *et al*, 1968). It is possible that this compound and not prostaglandin E_1 would be effective in inhibiting gastric secretion in man. However, both prostaglandins are equally active in dogs (Robert, 1968; Robert *et al*, 1967).

The large quantities of bile in the aspirated gastric contents after prostaglandin must have been due to a reflux of duodenal contents; it is possible that prostaglandin E_1 relaxes the pyloric sphincter. Some evidence in support of this comes from the observation that both prostaglandin E_1 and prostaglandin E_2 relax circular muscle of the human stomach *in vitro* (Bennett *et al*, 1968). This side effect may be considered a disadvantage if oral prostaglandin E_1 were to be used therapeutically.

The purgative action of prostaglandin E_1 in man is similar to that observed in mice following intravenous or subcutaneous injection (Holmes and Horton, 1968), and may be due to a direct stimulant action on intestinal smooth muscle as observed *in vitro* (Horton and Main, 1963). Although the effects of prostaglandins on human intestinal smooth muscles have not been reported, prostaglandins E_1 and E_2 do contract longitudinal muscle of the human stomach *in vitro*. Recently, patients with medullary carcinoma of the thyroid have been shown to have raised prostaglandin levels in the blood; all these patients had diarrhoea (Williams, Karim, and Sandler, 1968). Our observations provide some evidence that prostaglandins may indeed be the causal agents. Since prostaglandins have been identified in menstrual fluid (Eglinton, Raphael, Smith, Hall, and Pickles, 1963), they may possibly account for the increased frequency of defaecation observed at the beginning of menstruation (McCance and Pickles, 1960). They also should be borne in mind when considering the mechanism of diarrhoea associated with other disorders.

Numerous side effects have previously been reported in man following administration of prostaglandin E_1 by intravenous infusion (Bergström, Dunér, Euler, Pernow, and Sjövall, 1959; Carlson, 1967; Bygdeman, Kwon, and Wiqvist, 1967). These include cardiovascular effects, headache, and a feeling of oppression in the chest. None of these symptoms nor any obvious cardiovascular change occurred in the present investigation. Conversely, the increase in intestinal motility and diarrhoea observed in our experiments have not been reported by previous groups. This may reflect a difference in route of administration or the dose of prostaglandin, which was considerably higher in the present study.

The facial flushing after pentagastrin injection was a consistent finding which may correspond to the sensation of skin heat reported by others (Logan and Connell, 1966). It is of interest that the flushing was not potentiated after prostaglandin administration, since prostaglandin E_1 is a potent vasodilator and itself caused facial flushing in 10 out of 13 cases on intravenous infusion (Bergström *et al*, 1959; Carlson, 1967; Carlson, Irion, and Orö, 1968).

SUMMARY

The effects of prostaglandin E_1 administered orally in doses of 10 to 40 μ g/kg have been studied in three human subjects. There was no inhibition of pentagastrin-induced gastric secretion. Following the higher doses of prostaglandin, gastric juice contained large amounts of bile. Prostaglandin E_1 also increased intestinal motility resulting in loose faeces.

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