Colonic and small intestinal response to intravenous prostaglandin $F_{2\alpha}$ and E_2 in man

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SUMMARY The effects of intravenous infusions of prostaglandins (PGs) $F_{2\alpha}$ (0.4 or 0.8 $\mu\text{g kg}^{-1} \text{min}^{-1}$) or E_2 (0.08 or 0.1 $\mu\text{g kg}^{-1} \text{min}^{-1}$) on net colonic movement of water and electrolytes and on ileal flow were measured in eight healthy males by simultaneous ileal and colonic perfusion. Ileal flow was increased by $\text{PGF}_{2\alpha}$ (six subjects) from a mean of 1.69 ml min^{-1} to 4.63 ml min^{-1} ($P < 0.01$); it also increased in the two subjects given PGE_2 . Colonic absorptive function was not significantly diminished by either prostaglandin. These results suggest that diarrhoea due to prostaglandins originates in the small intestine.

Prostaglandins (PGs) are known to cause diarrhoea when administered orally or intravenously. We have previously shown that intravenous $\text{PGF}_{2\alpha}$ stimulates net secretion of water and electrolytes by the human jejunum and ileum (Cummings, Newman, Misiewicz, Milton-Thompson, and Billings, 1973). Prostaglandin E_1 perfused intraluminally causes the human jejunum to secrete (Matuchansky and Bernier, 1973) whilst in dogs infusion of PGA_1 , E_1 , or $F_{2\alpha}$ into the superior mesenteric artery has a similar effect (Pierce, Carpenter, Elliot, and Greenough, 1971). Net secretion of fluid into the intestinal lumen occurs in acute undifferentiated diarrhoea (Banwell, Pierce, Mitra, Brigham *et al.*, 1971) and cholera (Banwell, Gorbach, Pierce, Mitra, and Mondal, 1971) and it may be mediated indirectly through PGs and cyclic AMP (Bennett, 1971). The colon is an important site of fluid absorption but the response of the large bowel to PGs has not been investigated. We have measured the effect of intravenous infusions of $\text{PGF}_{2\alpha}$ and PGE_2 on fasting ileal flow rates and on net colonic absorption of water and electrolytes in man using simultaneous ileal and colonic perfusion.

Methods

Studies were attempted in 13 healthy male volunteers (age 20-43). The procedure was fully explained to them and approval was obtained from the ethical committees of the Central Middlesex Hospital and

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the Royal Navy in accordance with MRC recommendations. The subjects were intubated with the six-lumen tube illustrated in fig 1 on the morning preceding the study. After intubation metoclopramide 10 mg was given by mouth and a liquid diet allowed throughout the day. The balloon (fig 1) was inflated with 15 ml of air when it reached the duodenum and remained inflated until it reached the colon as shown on fluoroscopy. Delay in the passage of the tube most commonly occurred in the terminal ileum and was not shortened by oral metoclopramide (10 mg). The tube was deemed to be in the correct position when the distal perfusion port was in the caecum. During the experiment the position of the tube was monitored by reference to the pressures recorded with the open-ended tip. At the end of the study the position of the tube was again confirmed by fluoroscopy.

When the tube had reached the correct position the colon was washed out with a solution of colonic perfusate warmed to 37°C. The washout was continued until the rectal effluent was free of faecal debris and colouring. This took two to four hours and required 3 to 5 litres of fluid. A 24 Fr soft rubber catheter was then inserted into the rectum. The subject lay supine throughout the study.

The ileum was perfused at 0.87 ml min^{-1} ($\pm$ SD 0.03) using a Schuco Scientific Ltd pump with an isotonic solution containing Na^+ 135 m-equiv l^{-1} , K^+ 5 m-equiv l^{-1} , Cl^- 110 m-equiv l^{-1} , HCO_3^- 30 m-equiv l^{-1} , and the non-absorbable marker poly-

ethylene glycol 4000 (PEG) 10 g l⁻¹. Ileal contents were aspirated continuously with a Watson-Marlow pump through two sampling ports 20 and 30 cm distal to the ileal perfusion port. The colon was perfused at 9.8 ml min⁻¹ (± SD 0.6) with a solution of identical electrolyte composition containing phenol red 8.0 mg 100 ml⁻¹ as the marker instead of PEG. Ileal and rectal samples were collected in 20-minute periods throughout the study which lasted six hours.

Fig 1 Simultaneous ileal and colonic perfusion system. External diameter of the six-lumen tube was 5.5 mm, tube terminates in mercury bag and air balloon.

A slow intravenous infusion of 0.15 M saline was given throughout the study. Prostaglandin F_{2α} (0.4 or 0.8 µg kg⁻¹ min⁻¹) or PGE₂ (0.08 or 0.1 µg kg⁻¹ min⁻¹) was infused by motor-driven syringe pump (Scientific Instruments Ltd) at a constant rate through the intravenous line during the last three hours of the study. Comparisons between the control and PG periods were made on the basis of data obtained during the final hour of each part of the study. Electrolytes and phenol red were measured by standard techniques on a Technicon AutoAnalyzer and PEG estimated by a modification of the method of Hyden (1956); tryptic activity in the ileal contents

was measured by the method of Wiggins (1967). Ileal flow rates were calculated from standard formulae, assuming that the perfusate was not absorbed in the study segment (Phillips and Giller, 1973). Measurements of colonic absorption of water and electrolytes were corrected for contamination by ileal contents.

For the purposes of statistical analysis by Student's t test, the results of electrolyte and water movements in the colon during PGF_{2α} infusion have been averaged for the final hour in the control and PG periods.

Results

Thirteen studies were attempted but five had to be abandoned because the tube failed to reach the required position. This was due to the balloon leaking in two of these studies. Ileal flow data are therefore presented for eight studies (six with PGF_{2α} and two with PGE₂). Because of excessive reflux of colonic contents into the ileum during PG infusion, calculation of colonic absorption data was possible in only five of these studies (four with PGF_{2α} and one with PGE₂).

ILEAL FLOW

Table I shows the ileal flow rates in each of the eight subjects during the control period and during PG

Study No.	Prostaglandin (PG)	Dose of PG (µg/kg/min)	Ileal Flow (ml/min)	
			Control	PG
1	F _{2α}	0.4	0.22	4.13
2	F _{2α}	0.4	2.50	5.64
3	F _{2α}	0.4	1.78	3.53
4	F _{2α}	0.8	1.88	7.72
5	F _{2α}	0.8	1.49	3.53
6	F _{2α}	0.8	2.28	3.27
Mean			1.69	4.63
± SEM			0.33	0.71
t = 4.1079			P < 0.01	
7	E ₂	0.08	1.29	1.42
8	E ₂	0.1	0.55	1.35

Table I Ileal flow rates during the final hour of the control and PG infusion periods

infusion. Ileal flow increased during administration of PG in all the subjects. The characteristic response is shown in fig 2 (PGF_{2α}, study 4). A marked increase in ileal flow occurred shortly after the start of PG infusion and continued to the end of the study. Mean ileal flow in the six subjects given PGF_{2α} increased significantly from 1.69 ml min⁻¹ to 4.63 ml min⁻¹ (P < 0.01). Ileal flow also increased in both the subjects given PGE₂ (table I).

Fig 2 Ileal flow rate for each 20-minute collection period in study 4 before and during the infusion of prostaglandin $F_{2\alpha}$.

WATER AND ELECTROLYTE TRANSPORT IN THE COLON

In all five subjects net water absorption occurred throughout the control period (mean 2.35 ml min^{-1} , SEM $\pm 0.47 \text{ ml}$, table II).

During the infusion of PGs there was a slight fall in the rate of water absorption in four of the five studies, but the change was not significant in the four studies with $\text{PGF}_{2\alpha}$ ($P < 0.2$). Water absorption fell from 2.18 to 2.05 ml min^{-1} in the study with PGE_2 . In all the subjects the colon continued to absorb water during the PG infusion (mean 1.84 ml min^{-1} , SEM $\pm 0.67 \text{ ml}$), after allowance had been made for the increased flow of ileal contents into the large bowel.

Net absorption of sodium and of chloride was also observed during the control period in all the subjects. It did not change significantly in the studies with $\text{PGF}_{2\alpha}$ ($P < 0.2$) and showed only a slight fall in the PGE_2 experiment. Bicarbonate was secreted

into the colonic perfusate throughout all the studies. Bicarbonate secretion increased from 69.5 ± 24.3 (SEM) $\mu\text{-equiv min}^{-1}$ during the control period to 102.5 ± 39.4 (SEM) $\mu\text{-equiv min}^{-1}$ during the $\text{PGF}_{2\alpha}$ infusion, but the difference was not significant. In the PGE_2 study bicarbonate secretion rose from 27 to $34 \mu\text{-equiv min}^{-1}$. Alterations of potassium movements were small and variable: they did not change significantly with PG infusion (table II).

TRYPTIC ACTIVITY OF ILEAL CONTENTS

In order to assess the possible contribution of pancreatic secretion to the increase in ileal flow during PG infusion, tryptic activity of the ileal contents was measured in studies 3, 4, and 5 (table III). Trypsin concentration in the ileal fluid fell during $\text{PGF}_{2\alpha}$ infusion in all three studies.

Study No.	Tryptic Activity (iu/ml)	
	Control	$\text{PGF}_{2\alpha}$
3	2.2	1.2
4	3.5	2.7
5	3.4	1.9

Table III Mean tryptic activity in ileal fluid during the final hour of control and PG infusion periods

No unwanted effects were reported by any of the subjects, all of whom tolerated the procedure well.

Discussion

Disturbance of the equilibrium between the absorptive and secretory functions of the gut may result in diarrhoea. Increased secretion by the small intestine is a well established cause of diarrhoea in cholera and acute undifferentiated diarrhoea. Since the large bowel can secrete in response to stimuli such as intraluminal bile acids or fatty acids (Mekhjian,

Study No.	Prostaglandin		Water (ml/min)		Sodium ($\mu\text{-equiv/min}$)		Chloride ($\mu\text{-equiv/min}$)		Potassium ($\mu\text{-equiv/min}$)		Bicarbonate ($\mu\text{-equiv/min}$)	
	Infusion Period	Dose ($\mu\text{g/kg/min}$)	Control	PG	Control	PG	Control	PG	Control	PG	Control	PG
1	$F_{2\alpha}$	0.4	3.30	2.74	547	421	563	470	8—	10—	22—	93—
3	$F_{2\alpha}$	0.4	3.38	3.70	395	476	445	486	9	3	30—	17—
5	$F_{2\alpha}$	0.8	0.82	0.55	145	128	179	149	2—	5—	102—	92—
6	$F_{2\alpha}$	0.8	2.06	0.14	250	1	348	88	8	34—	121—	208—
		Mean	2.39	1.79	334	257	384	298	1.75	11.5—	69.5—	102.5
		$\pm$ SEM	0.60	0.87	87.5	114	81	105	4.1	8.0	24.3	39.4
		t		1.2811		1.095		1.33		1.3772		1.282
		P		<0.2		<0.3		<0.2		<0.2		<0.2
7	E_2	0.08	2.18	2.05	152	122	193	163	4—	3—	27—	34—
		Mean	2.35	1.84								
All studies		$\pm$ SEM	0.47	0.67								

Table II Net movement of water and electrolytes in the colon during the final hour of the control and PG infusion periods¹

¹Net secretion denoted by —.

Phillips, and Hofmann, 1971; Ammon and Phillips, 1972), it is important to determine the contribution of the colon to diarrhoeal states in which small intestinal secretion has been demonstrated.

Prostaglandins cause secretion into the small intestine which is comparable with that found in acute diarrhoea and therefore provide a suitable model for the study of colonic function in diarrhoeal states. Simultaneous perfusion of the small and large intestine has allowed us to assess the response of both areas of the gut to prostaglandins.

TECHNIQUE

Intubation of the colon can be long and tedious, taking up to five days in some cases (Levitan, Fordtran, Burrows, and Ingelfinger, 1962; Devroede and Phillips, 1969a). In this study the use of an inflatable balloon which stimulates propulsive activity of the gut has enabled us to shorten the time required to reach the colon to 24 hours, but colonic intubation remains a technically exacting procedure. Satisfactory data on colonic transport of water and electrolytes cannot be obtained unless the flow of ileal contents into the colon is measured simultaneously. In order to measure flow in the terminal ileum, accurate positioning of the ileal perfusion system close to the ileo-caecal sphincter is essential. In our experience the length of the small intestine is too variable for the distance of the balloon from the incisor teeth to be a useful guide to the correct positioning of the tube. In this series the distance ranged from 190 to 325 cm when the tube was correctly placed. Fluoroscopy after insufflation of air through the tube is only sometimes helpful in determining its position, but records of the intraluminal pressures through the various lumens of the tubes can localize the region with certainty (Misiewicz, Waller, Fox, Goldsmith, and Hunt, 1968). Since the position of the tube is liable to alter during the perfusion (Mekhjian *et al.*, 1971), this was monitored by means of a continuous pressure record corrected by inflation or deflation of the balloon as necessary.

ILEAL FLOW

The mean fasting ileal flow in our subjects was 1.69 ml min^{-1} , somewhat higher than other reported values which vary from 0.3 to 1.23 ml min^{-1} (Soergel, 1971a; Phillips and Giller, 1973; Rask-Madsen, 1973). The reasons for these differences are not clear. Fasting ileal flow rates can vary considerably with time (fig 2) and between subjects, so that the timing and duration of the measurements and the choice of volunteers will affect the results. Small variations in technique, such as the infusion rate and length of ileum perfused, may also contribute to these differences.

Ileal flow rate increased significantly during infusion of prostaglandin $F_{2\alpha}$. This was to be expected from the results of previous similar experiments with intravenously administered $\text{PGF}_{2\alpha}$ (Cummings *et al.*, 1973). It is interesting that the increased ileal flow rate occurred with doses of infused $\text{PGF}_{2\alpha}$ as low as $0.4 \mu\text{g kg}^{-1} \text{ min}^{-1}$. In our previous studies of the jejunum and ileum no change in net fluid movement was detected below $0.65 \mu\text{g kg min}^{-1}$ of infused prostaglandin $F_{2\alpha}$. The slow perfusion technique used in this study would appear to be a more sensitive method of detecting net changes in fluid movement in the small gut than the perfusion of short segments at 10 to 20 ml min^{-1} , as suggested by Soergel (1971b). Infusion of PGE_2 also increased the ileal flow rate. The effects of this PG are particularly interesting as it occurs naturally in the human gut and so may be involved in the mediation of diarrhoea.

The flow rate from the ileum into the colon in both the control period and during PG infusion was sufficiently large to make an appreciable difference to the overall balance of water movement in the colon during perfusion. For this reason the flow rate from the ileum was added to the colon perfusion rate for the calculation. Had this not been done the absorptive capacity of the colon would have been underestimated and colonic secretion wrongly thought to have occurred during PG infusion.

The increase in ileal flow rate may be attributed to increased net secretion by the small intestine, but the contribution that gastric, biliary, and pancreatic secretion make to the overall effect has not been evaluated. Tryptic activity, however, fell in the three subjects in which it was measured during $\text{PGF}_{2\alpha}$ infusion, making it unlikely that pancreatic enzyme secretion was stimulated by the prostaglandin.

Little is known of the effect of PGs on human biliary secretion, whilst gastric secretion is either unaffected or inhibited (see review by Waller, 1973; Newman, Prado, Philippakos, and Misiewicz, 1975). Pancreatic enzyme (Rudick, Gonda, Dreiling, and Janowitz, 1971) and electrolyte secretion (Case and Scratcherd, 1972) may be stimulated by PGs, although this effect varies greatly between species and types of experiment (Waller, 1973).

REFLUX FROM THE COLON

In addition to the calculation of ileal flow rate, continuous aspiration from the ileum enables the reflux of colonic contents to be measured. Reflux occurred to some extent in all but one of the studies. In three it was severe, with colonic marker refluxing at least 20 cm proximal to the ileo-caecal sphincter. Such reflux makes the calculation of the ileal flow rate difficult and invalidates colonic absorption data because an unknown length of ileum is included in

the perfusion. In the remaining studies reflux was rarely detected in the control period but it occurred soon after the start of the PG infusion, only to clear as ileal flow rate increased. This observation suggests that PGs may be affecting the ileo-caecal sphincter. Reflux was not detected in the third hour of PG infusion in any of the five studies used for the calculation of colonic absorption.

COLONIC FUNCTION

The net absorption of water, sodium, and chloride, and secretion of potassium and bicarbonate by the colon during the control period in these studies is similar to that found by other investigators (Devroede and Phillips, 1969b; Levitan *et al.*, 1962; Shields and Miles, 1965). At the doses used in the present study PGs diminished the absorptive function of the colon, but the effect was slight in all but one of the studies. These changes were not significant in the four experiments with PGF_{2α} and were small in the one experiment with prostaglandin E₂. The same doses of PG, however, stimulated marked net secretion of water and electrolytes into the small intestinal lumen. Small intestinal absorptive function has thus been shown to be far more sensitive to exogenous PGs than colonic function. Dilution of the colonic marker in the rectal effluent occurred during PG infusion because of the increased ileal flow into the colon. The overall effect was one of increased secretion by the small intestine and increased flow through the colon. This could give rise to diarrhoea, to which the colon—at the range of doses tested—does not contribute by active secretion of fluid. On the contrary, the colon may reduce the effect of increased small intestinal secretion during acute diarrhoea by continuing to absorb water and electrolytes. Our findings suggest that in this form of diarrhoea the increased intestinal flow rate overwhelms colonic absorptive capacity. By contrast in other models of diarrhoea, such as colonic perfusion with bile salts (Mekhjian *et al.*, 1971) or with fatty acids (Ammon and Phillips, 1972) and also in ulcerative colitis (Harris and Shields, 1970), the colon has been shown to secrete fluid and electrolytes.

The relevance of the present model to clinical conditions needs confirmation by direct demonstration of increased PG synthesis or decreased inactivation by the intestinal mucosa in diarrhoeal states, or of the increased levels of PGs reaching the gut through the bloodstream.

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