Failure of intraluminal and intra-arterial prostaglandin $F_{2\alpha}$ to modify drug absorption from the rat small intestine in situ

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Prostaglandins (PG) have many effects in the body, including effects on the gastrointestinal tract, which is seen e.g. when using $PGF_{2\alpha}$ in obstetrics to induce abortion, when diarrhoea frequently supervenes (Bennet 1973). Various PGs are known to be 'enteropooling', leading to accumulation of fluid into the small intestine (Robert 1975). The 'enteropooling' effect of PGs results from a reduced absorption and an increased secretion of fluid into the small intestine as shown e.g. with PGE_1 and $PGF_{2\alpha}$ in the rat (Beubler & Juan 1977), with PGE_1, PGA_1 and $PGF_{2\alpha}$ in the dog (Pierce et al 1971), and PGE_1 (Matuchansky & Bernier 1973) and $PGF_{2\alpha}$ (Cummings et al 1973) in man.

PGE_1, E_2 and $F_{2\alpha}$, whether intraluminally or intra-arterially, are also able to inhibit glucose absorption from the rat jejunum (Coupar & McColl 1972, 1975). Therefore the present study was undertaken in order to see if $PGF_{2\alpha}$ might modify drug absorption from the rat small intestine in situ. An acidic (sulphafurazole = sulfisoxazole), a neutral (isoniazid) and a basic drug (quinidine) were used as representatives of different drugs.

Material and methods. 63 female Sprague-Dawley and 20 female Wistar rats, 200–250 g, and kept on a standard laboratory pellet diet were used. After an overnight fast the rats were anaesthetized with urethane (1·0–1·5 g kg^{-1} i.m.), and the small intestine cannulated at the proximal end of duodenum and the distal end of ileum, respectively. The cannulas were connected to glass syringes and the small intestine rinsed with warm (37 °C) perfusion solution, pH 6·0 (Doluisio et al 1969; Venho 1976). Thereafter, depending on the weight of the rat, 10–15 ml of the same perfusion solution containing the drug was introduced into the intestinal lumen. The solution was expelled at 10 min intervals alternately to either syringe, a sample was obtained, and the solution returned to the intestinal lumen. The duration of the experiment was 40 min at the end of which the remaining solution was taken as a sample, its volume measured and it was then stored at −20 °C for assay. At 40 min whole blood was taken by heart puncture and the whole small intestine taken as a sample and stored at −20 °C.

The rectal temperature of the rats was monitored during the experiments.

The perfusion solution contained either sulphafurazole 500, isoniazid 100 or quinidine sulphate 100 μg ml^{-1} together with phenol red 10 μg ml^{-1} used as an unabsorbable marker.

Spectrophotometric methods were used to assay sulphafurazole (Varley 1954), isoniazid (Tiitinen et al 1973) and phenol red (Miller & Schedl 1972). Quinidine was assayed fluorimetrically (Cramer & Isaksson 1963).

$PGF_{2\alpha}$ was administered intraluminally in the perfusion solution at 100 or 500 μg ml^{-1} together with the drug. In six isoniazid experiments the perfusion solution contained acetylsalicylic acid (ASA), an inhibitor of PG synthesis, 1 mg ml^{-1}, and no $PGF_{2\alpha}$. In another series of experiments in Wistar rats the left carotid artery was cannulated and $PGF_{2\alpha}$ infused into the aortic arch at a rate of 50 μg min^{-1}. The infusion was started 20 min before the actual absorption experiment and it continued throughout the experiment. The controls were infused with 0·9% NaCl.

Student's *t*-test and regression analysis were employed as statistical methods.

Results. The pH of the intestinal perfusion fluid increased slightly (to 6·1–6·4) during the experiment and there were no differences between control and PG-experiments.

There were no differences in the rectal temperature of the control, PG- or ASA-treated rats. The rats given $PGF_{2\alpha}$, particularly intra-arterially, had an increased tendency to expel the thermometer probably due to a PG-effect.

The absorption half-lives measured from the disappearance of drugs from the intestinal perfusion fluid are shown in Tables 1 and 2.

There were no differences in absorption half-lives of isoniazid during intraluminal $PGF_{2\alpha}$ or ASA compared with controls. The absorption half-life of isoniazid in the presence of $PGF_{2\alpha}$ 100 μg ml^{-1} was shorter than in the presence of 500 μg ml^{-1} ($P < 0.05$) but neither was different from control, however. Sulphafurazole absorption was not modified by intraluminal $PGF_{2\alpha}$ 100 μg ml^{-1}. The absorption half-life of quinidine seemed to be shortened by $PGF_{2\alpha}$ 100 μg ml^{-1} and lengthened by 500 μg ml^{-1} intraluminally, but the changes were not significant (Table 1). Also in Wistar rats the quinidine absorption half-life was longer in the presence of $PGF_{2\alpha}$ 500 μg ml^{-1}, but the change was not significant (Table 2). Neither did intra-arterial infusion of $PGF_{2\alpha}$ affect quinidine absorption in Wistar rats (Table 2).

$PGF_{2\alpha}$ 500 μg ml^{-1} intraluminally or as an intra-arterial infusion significantly decreased fluid absorption during the experiments (Tables 1, 2). 100 μg ml^{-1} of $PGF_{2\alpha}$ did not affect fluid absorption, or even increased it (quinidine, Table 1) ASA had no effect on fluid absorption.

At the end of the experiment $PGF_{2\alpha}$ 100 μg ml^{-1} intraluminally decreased total isoniazid hydrazides, increased total sulphonamides and quinidine in the whole blood (Table 1). $PGF_{2\alpha}$ 500 μg ml^{-1} or ASA 1 mg

Table 1. Absorption of isoniazid, sulphafurazole and quinidine from the Sprague-Dawley rat small intestine in situ and the effect of prostaglandin $F_{2\alpha}$ in the intestinal perfusion fluid on absorption. Drug concentrations in the whole blood and intestinal wall refer to total drug (total isoniazid hydrazides, total sulphonamides). Means ± s.e. Number of experiments in parentheses. ASA = acetylsalicylic acid 1 mg ml^{-1} in the intestinal perfusion fluid, PG 100 and PG 500 = prostaglandin $F_{2\alpha}$ 100 and 500 μg ml^{-1}, respectively, in the perfusion fluid.
* = $P < 0.05$, † = $P < 0.01$ and ‡ = $P < 0.001$, compared with control.

Drugs and treatment		Absorption half-life (min)	Corr. coeff.	Drug concn at 40 min Whole blood (μg ml^{-1})	Intestinal wall (μg g^{-1})	Vol. depletion in 40 min (ml)
			Isoniazid 100 μg ml^{-1}			
Control	(10)	23	0·94	6·3±0·3	1·9±0·7	6·5±0·5
ASA	(6)	24	0·92	7·4±0·7	7·2±0·8‡	5·3±1·6
PG 100	(7)	20	0·93	4·5±0·2‡	4·8±0·3†	6·6±0·4
PG 500	(5)	26	0·93	6·0±0·3	6·7±0·7‡	2·6±0·4‡
			Sulphafurazole 500 μg ml^{-1}			
Control	(9)	36	0·82	67±5	40±3	4·7±0·5
PG 100	(7)	34	0·93	88±3†	39±3	5·6±0·4
			Quinidine 100 μg ml^{-1}			
Control	(8)	66	0·64	0·20±0·02	23·3±0·9	3·6±0·6
PG 100	(8)	48	0·70	0·30±0·03*	29·8±0·7‡	6·3±0·3†
PG 500	(3)	105	0·71	0·20±0·03	21·9±0·9	0·3±0·4†

ml^{-1} intraluminally had no effect on drug concentrations in the whole blood (Tables 1, 2). Intra-arterial $PGF_{2\alpha}$ increased quinidine in the whole blood (Table 2).

Total isoniazid hydrazides in the intestinal wall were increased by ASA, $PGF_{2\alpha}$ 100 and 500 μg ml^{-1} intraluminally (Table 1). Also quinidine was increased by $PGF_{2\alpha}$ 100 μg ml^{-1} intraluminally, but other changes were not significant.

Discussion. Prostaglandins are fairly rapidly inactivated in the body and e.g. higher concentrations of $PGF_{2\alpha}$ are needed intraluminally than intra-arterially to inhibit glucose absorption (Coupar & McColl 1972, 1975). In the present experiments, in spite of an expected 'entero-pooling' effect, relatively high concentrations of $PGF_{2\alpha}$ (100 μg ml^{-1} intraluminally) did not have any clear effect on net water flux or drug absorption. Only still higher concentrations of $PGF_{2\alpha}$ (500 μg ml^{-1}) seemed to have some slight inhibitory effect on drug absorption. The results of a decreased fluid absorption are consistent with previous reports of $PGF_{2\alpha}$ decreasing fluid absorption and enhancing secretion (Pierce et al 1971; Beubler & Juan 1977), but this decreased solvent drag did not significantly modify drug absorption.

The experiments with intra-arterial infusion of $PGF_{2\alpha}$ were conducted in order to get $PGF_{2\alpha}$ directly to the serosal side of the intestinal wall. Although only a fraction of the 50 μg min^{-1} dose eventually reaches the intestinal wall, it probably exceeds the 2–3 μg min^{-1} dose previously infused into the superior mesenteric artery (Pierce et al 1971; Coupar & McColl 1975). The infusion was started 20 min before the actual absorption experiment, because in man (Cummings et al 1973) and in the rat (Beubler & Juan 1977) about 30 min will pass until the fluid secretion reaches its maximum. In spite of a decreased water flux no change in quinidine absorption was seen, which is in accordance with the insignificant inhibition of glucose absorption reported by Coupar & McColl (1975).

Table 2. Quinidine absorption in Wistar rats and the effect of intraluminal (PG 500 vs control) and intra-arterial ($PG_{i.a.}$ vs $control_{i.a.}$) prostaglandin $F_{2\alpha}$ on absorption. In intra-arterial experiments $PGF_{2\alpha}$ was infused into the aortic arch through a cannula in the left carotic artery at a rate of 50 μg min^{-1}. Controls were given saline. Other details as for Table 1.

Drugs and treatment		Absorption half-life (min)	Corr. coeff.	Drug concns at 40 min Whole blood (μg ml^{-1})	Intestinal wall (μg g^{-1})	Vol. depletion in 40 min (ml)
			Quinidine 100 μg ml^{-1}			
Control	(4)	29	0·90	0·17±0·02	19·4±1·1	4·4±0·7
PG 500	(4)	39	0·89	0·18±0·03	26·4±1·4	2·6±0·6
$Control_{i.a.}$	(5)	36	0·83	0·20±0·03	22·2±2·2	4·5±0·4
$PG_{i.a.}$	(7)	34	0·86	0·41±0·06*	38·7±6·2	2·4±0·5*

When the endogenous PG synthesis is inhibited by indomethacin the effects are opposite to those of intraluminal PGE_1, and the indomethacin effect can be reversed by PGE_1 (Beubler & Juan 1977). In the present experiments ASA was administered together with isoniazid to block the possible endogenous PG synthesis, but it did not change isoniazid absorption or net water flux. So, in these experiments endogenous PGs did not seem to have any significant role in modifying isoniazid absorption.

No far-reaching conclusions must be drawn from the drug concentrations in the intestinal wall or whole blood measured only at the end of the experiment. It is noteworthy, however, that sulphafurazole and quinidine in the whole blood were increased by intraluminal $PGF_{2\alpha}$ 100 μg ml^{-1} and also after intra-arterial infusion, but not after 500 μg ml^{-1} of $PGF_{2\alpha}$ intraluminally. Whether this is due to dose-related changes in e.g. intestinal blood flow, cannot be stated, but all drugs did not behave in the same way, because isoniazid in the whole blood after intraluminal $PGF_{2\alpha}$ 100 μg ml^{-1} was decreased.

In conclusion, the 'enteropooling' effect or decreased net water flux could be demonstrated only after very high doses of $PGF_{2\alpha}$, and the effects on drug absorption were slight and mostly insignificant when the drugs were in solution in the small intestinal lumen. Whether the same applies when the drugs are administered in solid dosage form to humans cannot be stated from the present results.

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