Gastrointestinal actions of carbacyclin, a stable mimic of prostacyclin

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Prostacyclin (PGI_2), besides being a potent vasodilator and inhibitor of platelet aggregation (Moncada et al 1976) is also active as an inhibitor of rat gastric erosions and gastric acid secretion in the rat (Whittle et al 1978a) and dog (Gerkins et al 1978; Kauffman et al 1979). Since prostacyclin is unstable at physiological temperatures and pH, the actions of stable analogues are of interest. Previously, we have shown that a 5,6-dihydroprostacyclin, 6β-PGI_1 was some 15 times less potent than prostacyclin as an antisecretory agent in the rat (Whittle et al 1978b) and dog (Kauffman et al 1979). We now describe the gastrointestinal actions of a new potent stable analogue (6a)-carba prostaglandin I_2 (carbacyclin) which has proved to be an excellent mimic of the haemodynamic and platelet actions of prostacyclin (Whittle et al 1980; Aiken & Shebuski 1980).

The inhibition of pentagastrin-stimulated acid secretion into the perfused gastric lumen of the urethane-anaesthetized rat and concurrent cardiovascular changes were determined as described before (Main & Whittle 1975). During steady submaximal rates of acid output (1·5–2·5 μmol min^{-1}) induced by pentagastrin (0·5 μg kg^{-1} min^{-1}, i.v.), prostacyclin or the analogue carbacyclin, which was synthesized as described previously (Johnson et al 1979†), were dissolved freshly in isotonic sodium bicarbonate solution (1·25% w/v pH 8·6; 0 °C) and infused intravenously. Both compounds caused a dose-related significant ($P < 0·01$ for each) inhibition of acid output (Fig. 1) which reached steady levels within 30 min of each infusion, with carbacyclin being 2·4 times less active than prostacyclin. The ID50 values (dose causing 50% inhibition) were 0·6 μg kg^{-1} min^{-1} for carbacyclin and 0·25 μg kg^{-1} min^{-1} for prostacyclin. Infusion of either compound caused a dose-related fall in BP (Fig. 1) with concurrent increase in heart rate. In doses causing an equivalent degree of acid inhibition, carbacyclin produced less cardiovascular actions (Fig. 1), although this selectivity of action was not as marked as a previously described series of 16-phenoxy-prostacyclin analogues (Whittle & Boughton-Smith 1979).

The ability of carbacyclin to protect the gastric mucosa from damage was also assessed. Indomethacin (20 mg kg^{-1}, s.c.) was dissolved in $NaHCO_3$ solution (5% w/v) and injected immediately following administration of carbacyclin (stored in ethanol, 10 mg ml^{-1} at — 40 °C; and diluted in isotonic sodium bicarbonate solution before use). The number and severity of the gastric mucosal erosions after 3 h was assessed as described before (Whittle & Boughton-Smith 1979). Carbacyclin caused a dose-dependent inhibition of indomethacin-induced gastric erosions (Table 1) with an ID50 of 290 μg kg^{-1}, s.c. compared with 500 μg kg^{-1}, s.c. for prostacyclin and 400 μg kg^{-1}, s.c. for prostaglandin E_2 (PGE_2).

Prostacyclin analogues have previously been shown to prevent the intestinal lesions induced by indomethacin (Whittle & Boughton-Smith 1979), as shown originally with PGE_2 and its analogues (Robert 1974, 1976). In the present investigation, prostacyclin or carbacyclin (0·5–1 mg kg^{-1}, s.c.) was administered as a single injection immediately before indomethacin (10 mg kg^{-1}, s.c.) in fed rats and the incidence and severity of the intestinal damage after 48 h was assessed as before (Robert 1976; Whittle & Boughton-Smith 1979). These lesions, which occurred in the ileal and jejunal regions, were characterized by the presence of nodules, adhesions and perforations. As shown in Table 2, a single bolus dose of prostacyclin or carbacyclin reduced the intestinal damage induced by indo-

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Table 1. Inhibition of indomethacin-induced gastric erosions. Indomethacin (20 mg kg^{-1}, s.c.) was injected immediately before the subcutaneous administration of the prostanoids, and the erosion index assessed after 3 h. Results, expressed as % inhibition of the control erosion index, are shown as mean ± s.e. mean of (n) values.

	dose (μg kg^{-1})	% inhibition	(n)
Carbacyclin	125	24 ± 14	15
	500	68 ± 12	17
Prostacyclin	250	25 ± 8	18
	500	50 ± 10	10
PGE_2	125	41 ± 17	18
	500	54 ± 11	31

Table 2. Inhibition of the intestinal lesion formation 48 h following administration of indomethacin (10 mg kg^{-1}, s.c.) by a single subcutaneous injection of prostacyclin, carbacyclin or PGE_2. Results are mean ± s.e. mean of (n) values, where statistical significance is represented by *$P < 0·05$, ** $P < 0·01$, *** $P < 0·001$.

	Dose (mg kg^{-1})	% inhibition	(n)
Prostacyclin	0·5	47 ± 27	10
	1·0	63 ± 20*	10
Carbacyclin	0·5	40 ± 20	12
	1·0	78 ± 8***	12
PGE_2	2·0	83 ± 4**	6

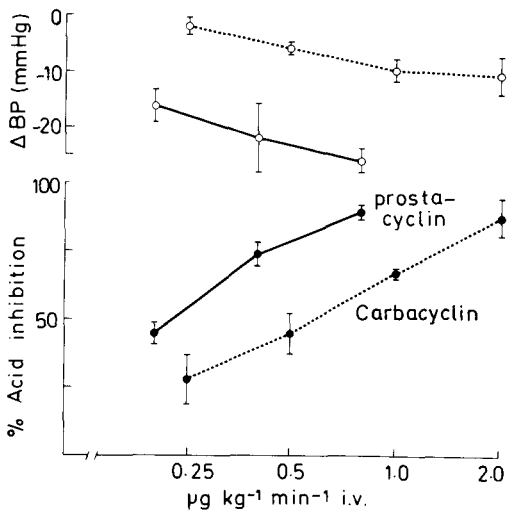

FIG. 1. Inhibition of pentagastrin-stimulated acid secretion and the fall in systemic arterial blood pressure (BP) by intravenous infusion of carbacyclin or prostacyclin in the anaesthetized rat. Results are shown as the mean ± s.e. mean of 5 experiments.

methacin. In the doses used, carbacyclin, like prostacyclin, did not induce diarrhoea in these fed rats, nor in the other experiments where rats had been starved for 18 h before prostacyclin or carbacyclin administration. This contrasts with PGE_2 and its analogues which provoke a high incidence of mucoid diarrhoea in similar studies (Robert 1976; Main & Whittle 1975).

In experiments on the rat isolated stomach strip superfused with Krebs' solution (10 ml min^{-1} at 37 °C) gassed with oxygen (95%) and carbon dioxide (5%), carbacyclin was only a weak spasmogen, being 0·02 times as active as PGE_2 in contracting the tissue when administered by bolus injection (3 experiments). Like prostacyclin, carbacyclin caused a dose-dependent relaxation of superfused isolated vascular tissue. When administered by bolus injection into the superfusion solution, carbacyclin was 0·17 times as active as prostacyclin in relaxing the isolated bovine coronary artery and 0·1 times as active in relaxing the rabbit coeliac artery (3 experiments). As with prostacyclin, carbacyclin had little effect on the tone of rabbit isolated aortic strip. In studies on the guinea-pig spirally-cut trachea, suspended in a 20 ml organ bath containing Kreb's solution at 37 °C gassed with oxygen (95%) and carbon dioxide (5%), incubation with carbacyclin (up to 10^{-6} M) had no effect on tone of the preparation (4 experiments). Higher concentrations of carbacyclin did cause a slight contraction of this tissue although the mechanism or relevance of this small response to such high doses is obscure.

Our previous studies with carbacyclin have suggested its potential clinical usefulness in those situations where prostacyclin has proved of value such as in extracorporeal systems (cardiopulmonary bypass, charcoal haemoperfusion or haemodialysis) and also in peripheral vascular disorders (see Whittle et al 1980 for references). The current study supports the conclusion that carbacyclin has a pharmacological profile close to that of prostacyclin (Whittle et al 1980; Aiken & Shebuski 1980) and is 2·4 times less active than prostacyclin as a gastric antisecretory agent, whilst being chemically stable (at least 30 days in aqueous solution at room temperature). Carbacyclin may thus be useful as a reference standard and pharmacological probe to investigate the gastrointestinal properties and physiological roles of prostacyclin under conditions of pH and temperature (such as in the gastric milieu) where prostacyclin would undergo rapid chemical hydrolysis and hence be inactivated.

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