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Hypotension in response to iloprost, a prostacyclin analogue

Epoprostenol (prostacyclin) has an anti-aggregatory effect on human platelets which it was thought might be of potential benefit for patients with unstable angina pectoris. However, the usefulness of epoprostenol in this latter clinical situation was limited because it caused a reflex increase in heart rate, a rise in myocardial oxygen consumption and a worsening of angina (Bergman *et al.*, 1983a). Furthermore, epoprostenol has been shown to cause episodes of hypotension (Lichstein *et al.*, 1983).

Iloprost is a chemically stable synthetic analogue of epoprostenol which was thought to have a lesser vasodilator action and relatively greater anti-aggregatory effects on platelets (Bergman *et al.*, 1983b; Smith *et al.*, 1984). As a prelude to studying its usefulness in patients with unstable angina pectoris, we have evaluated its pharmacodynamics and tolerability in patients with stable coronary artery disease.

Six male patients with a mean age of 55 years (range 43–63) having routine coronary arteriography for severe angina, were studied after informed written consent had been obtained. The patients were premedicated with diamorphine 5 mg, atropine 0.6 mg and chlorpheniramine 10 mg i.m. prior to the study. After cardiac catheterization and angiography had been performed, a Swan-Ganz thermodilution catheter was introduced into the pulmonary artery via a subclavian vein. Iloprost was administered by intravenous infusion into a forearm vein at an initial dose of 1 ng kg^{-1} min^{-1}. When this dose was not tolerated the infusion was

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Table 1 Haemodynamic effects of iloprost. The values in columns (a) refer to the pre-treatment measurements and those in columns (b) the last values obtained prior to discontinuation of iloprost

Patient	*Pulse (beats min^{-1})*		*BP (mm Hg)*		*Time from start of infusion to dose reduction (h)*	*Cardiac output (l min^{-1})*		*Duration of study (h)*	*Pulmonary artery pressure (mm Hg)*		*PA wedge pressure (mm Hg)*		*Time from premedication to dose reduction or withdrawal (h)*	*Comments*
	(a)	(b)	(a)	(b)		(a)	(b)		(a)	(b)	(a)	(b)		
1	70	68	110/70	105/70	—	5.5	5.7	24	26/9	23/9	4	5	—	No adverse effects
2	76	80	130/90	120/70	2	4.2	5.9	24	20/6	19/6	5	3	5	Hypotension at 2 h. Dose reduced.
3	76	104	130/100	150/110	8	4.9	7.6	24	25/8	27/7	7	8	12	Headache and nausea. Dose reduced.
4	68	70	120/75	125/80	3.5	3.4	4.1	24	29/12	24/11	8	3	7	Nausea. Dose reduced after 3.5 h
5	68	56	125/85	90/60	0.75	3.7	4.5	3.75	24/7	20/8	7	5	7	Hypotension 0.75 h, and 2.5 h after lower dose commenced. Patient withdrawn.
6	72	72	110/80	120/70	0.5	5.1	7.1	1.75	18/4	24/6	2	5	5	Headache. Nausea. Vomiting. Withdrawn after 1 h at lower dose.
Mean ± s.e. mean	72 ± 1.5	75 ± 6.6	121 ± 3.7 83 ± 4.4	118 ± 8.2 77 ± 7.1		4.5 ± 0.3	*5.8 ± 0.6		24 ± 1.6 7.7 ± 1.1	23 ± 1.2 7.8 ± 0.8	5.5 ± 0.9	4.8 ± 0.7		

* $P < 0.02$ by Student's *t*-test for paired data

reduced to 0.5 ng kg^{-1} min^{-1}. The haemodynamic changes and adverse effects which were encountered during the study are summarized in Table 1. Only one of the six patients tolerated the higher dose for the full 24 h study period. Three patients tolerated the lower dose, but two had to be withdrawn from the study.

At the end of the infusion cardiac output was significantly greater ($P < 0.02$) than in the control period. However, there were no statistically significant changes in heart rate, blood pressure, pulmonary artery pressure or pulmonary wedge pressure. Two patients became hypotensive with systolic blood pressures of 60 mm Hg at the higher dose. In one of these patients, the hypotension was accompanied by a sinus bradycardia of 42 beats min^{-1}. Both patients recovered rapidly after discontinuation of the infusion but the second required intravenous atropine to correct the sinus bradycardia. Platelet function, assessed by aggregometry (Born & Cross, 1963), was little affected by infusion of iloprost. Only in patient no. 3 was there a major effect on platelet aggregation (with a rebound increase 1 h after therapy was discontinued), but this was accompanied by a marked increase in heart rate and cardiac output and by headache. However, in the two patients who became hypotensive no significant effects were seen on the aggregability of their platelets.

We conclude that under the circumstances of our study, iloprost had a variable effect on platelet aggregability. When an effect was observed, it was less selective than that seen in previous studies in which iloprost was given for shorter periods of time (Bergman *et al.*, 1983b). Finally, iloprost can cause hypotension and a sudden unheralded sinus bradycardia as reported previously by Pickles & O'Grady (1982) for epoprostenol. Thus, in any future studies of iloprost, blood pressure and heart rate need to be carefully monitored.

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Fenoldopam: effect on aldosterone secretion

We are interested by the recent report of Harvey *et al.* (1985) on the effects of a single oral dose of 100 mg fenoldopam on blood pressure and renal function in healthy subjects. These authors reported that PRA increased significantly 1 h after drug ingestion. Plasma aldosterone (PA) did not show a parallel increase although the plasma concentration at 1 h was significantly higher than after placebo. They explained this by hypothesizing that fenoldopam might have an independent effect inhibiting aldosterone secretion from the adrenal gland by an agonist action at dopamine receptors in the zona glomerulosa.

Evidence is indeed accumulating to suggest the existence of an inhibitory dopaminergic mechanism controlling aldosterone secretion (Aguilera *et al.*, 1984). There is general agreement that the acute administration of metoclopramide increases aldosterone secretion in most species studied (Aguilera *et al.*, 1984). The