Effects of a 72-hour prostacyclin infusion on the hormone levels in patients with obliterative arterial disease


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Abstract. Effects of a 72-h prostacyclin (PGI$_2$) infusion (5 ng/kg/min) on hormone levels were studied in 11 patients (5 males, 6 females) suffering from obliterative arterial disease of the lower extremities. ACTH, cortisol, TSH, prolactin (Prl), GH, LH, FSH, T$_3$, T$_4$, calcitonin, parathyroid hormone (PTH), insulin, plasma renin activity (PRA), aldosterone and testosterone levels were measured at –15, 0, 30, 120, 240 min and 24, 48, 72 and 96 h after the infusion. During the first 240 min Prl and GH levels showed an increase that was thought to be either an effect of release of hormones or a consequence of stress. At the same time the thyroid hormones, T$_3$, T$_4$ and calcitonin decreased, presumably owing to an alteration in the blood flow to the thyroid gland. All these hormone levels returned to normal at 24 h in spite of the infusion continuing. PRA increased only during the second half of the infusion. No changes were found in the levels of ACTH, cortisol, TSH, LH, FSH, PTH, insulin, aldosterone and testosterone during the infusion. Five diabetics showed the same hormonal changes as the non-diabetics and their blood sugar levels remained unafected during and after the procedure.

Prostacyclin (PGI$_2$) is a prostanoid having potent vasodilatating and antiaggregating effects. Its use as a therapeutic agent has a great scope in diseases affecting the cardiovascular system — obliterative arterial diseases (Szczechlik et al. 1979; Hossmann et al. 1981), ischaemic stroke (Gryglewski et al. 1983), pulmonary hypertension (Watkins et al. 1980; Higgenbottom et al. 1984), Raynaud’s phenomenon (Dowd et al. 1982), and extracorporeal circulation (Coppe et al. 1981; Ditter et al. 1983).

Since a widespread use of PGI$_2$ either in the form of continuous iv infusion or oral tablets is expected, the endocrinological effects of the drug must be explored too. PGI$_2$ increases the TSH and Prl levels in vitro (Wright & Hedge 1981), but shows no effects on the isolated adrenal gland cells (Layhock 1979). An increase in the Prl and a decrease in the LH levels has been observed in rats (Kimball et al. 1979). In healthy humans PGI$_2$ increases the plasma renin activity (Fitzgerald et al. 1979; Scherthaler et al. 1981; Chaignon et al. 1982; Patrono et al. 1982; Ylikorkala et al. 1982). As to other hormones, the data are few and controversial. PGI$_2$ increases the levels of serum Prl (Scherthaler et al. 1981; Ylikorkala et al. 1982), GH (Ylikorkala et al. 1982), LH (Scherthaler et al. 1981), cortisol (Ylikorkala et al. 1982), norepinephrine (Chaignon et al. 1982), and glucagon (Ylikorkala et al. 1982). An elevated level of Prl and cortisol has been attributed to the stress situation caused by the infusion (Allolio et al. 1980). No change has been found in the serum concentration of LH (Allolio et al. 1980; Ylikorkala et al. 1982), FSH (Allolio et al. 1980; Scherthaler et al. 1981; Ylikorkala et al. 1982), GH (Scherthaler et al. 1981), T$_3$ and T$_4$ (Scherthaler et al. 1981; Ylikorkala et al. 1982), cortisol (Scherthaler et al. 1981), insulin (Date et al. 1981; Scherthaler et al. 1981; Patrono et al. 1981; Ylikorkala et al. 1982), aldosterone (Fitzgerald et al. 1979; Ylikorkala et al. 1982), norepinephrine (Fitzgerald et al. 1979), testosterone, progesterone and oestadiol (Ylikorkala et al. 1982). These data were obtained during short-term PGI$_2$ infusions (30 min – 4 h). We have treated patients with obliterative arterial diseases
with long-term (72 h) PGI2 infusion and at the same studied the changes in various hormones during the infusion.

Material and Methods

Eleven patients (5 males, 6 females), aged between 50 and 60 years, with obliterative arterial disease of the lower extremities were treated with PGI2 (Epiprostanol) infusion of 5 ng/kg/min (Chinoin Pharmaceutical and Chemical Works Ltd., Budapest). Five patients were diabetics. Two of them were on insulin treatment, 3 received glibenclamide. A written consent was obtained from each patient.

PGI2 was dissolved in glycine buffer, 0.1 M pH 10.5, and an infusion pump with a 20 ml syringe was used to avoid the volume-load and to reach and maintain a continuous dose of 5 ng/kg/min during the 72 h. The infusions started at 8.00 a.m.

The blood samples were collected via an indwelling catheter 15 min before starting the infusion, at 0 min and further at 30, 120, 240 min, at 24, 47, 72 h and 1 day after discontinuing the infusion — at 96 h. All the blood samples were collected and handled appropriately for each assay.

The levels of Prl, GH, LH, FSH and aldosterone were measured by radioimmunoassay methods using commercial kits of Serono. TSH, PTH and calcitonin were determined by Byk-Mallinckrodt's kits. ACTH and PRA were measured by CIS kits. Insulin was measured with an Amersham-kit, whereas thyroxine and triiodothyronine were determined using the kits of the Isotope Institute, Budapest. The plasma cortisol and testosterone concentrations were measured by using the competitive protein binding method (Murphy et al. 1963; Vermeulen &

![Graph](https://via.placeholder.com/150)

**Fig. 1.**

Prl and GH responses (mean ± SEM) to a long-term (72 h) PGI2 infusion (5 ng/kg/min), in patients with obliterative arterial disease (No. = 11).
Verdonck 1970). The LH and FSH levels were estimated separately in females and males taking into consideration the higher values in postmenopausal women.

The 'sign' test was used by a R-22 computer with a BMDP 3 S statistical soft-ware (Dixon 1981) for determining the significance of the differences between various hormone levels. The 'sign' test is a version of the paired t-test where normalisation of the variables is not required. The mean values of the samples taken at −15 and 0 min served as baseline levels for the reading (see Figs. 1–3).

Results

Thyroxine, triiodothyronine and calcitonin responses (mean ± SEM) to a long-term (72 h) PGI₂ infusion (5 ng/kg/min), in patients with obliterative arterial disease (No. = 11).

The concentrations of Prl showed a significant increase at 120 and 240 min and decreased slowly to normal, despite the unaltered circumstances of the infusion (Fig. 1). The GH level increased at 30 and 120 min and returned to normal faster (Fig. 1).

No significant changes were found in the ACTH, TSH, LH and FSH levels and the cortisol levels did not increase. T₃ and T₄ levels decreased significantly at 120 min, whereas at 24 h a moderate rebound was observed (Fig. 2). The calcitonin levels
decreased significantly at 30 min and a significant rebound was seen at 48 and 72 h (Fig. 2).

The PRA increased significantly only at 72 h (Fig. 3), but an enhancing tendency could be detected from the second day and onwards.

The insulin, PTH, aldosterone and testosterone levels did not change during the infusion.

The 5 diabetic patients showed the same changes as the non-diabetics and no difference in the reaction was found between the two groups.

The blood pressure decreased by 20–30 mmHg during the procedure, whereas the pulse rate did not change. Flush, nausea and itching were noticed during the infusion, but no serious adverse reactions were seen that could have forced us to discontinue the infusion.

Discussion

So far, no data are available as to the effect of long-term PGI₂ infusion on hormonal levels. We found that some 'stress hormones' changed at 30–120 min after the start of PGI₂ infusion, but they returned to normal after 1 day. A rebound phenomenon could also be observed in spite of the fact that the infusion was continuous. This is presumably due to the direct effect of PGI₂ on the release of various hormones. Another possibility is that the stress of the treatment itself causes an increase in the GH and Prl levels. This is supported by the fact that the increase was seen only initially and not during the long-term infusion. The stress concept agree with the finding by other investigators (Allolio et al. 1980; Ylikorkala et al. 1982). What points against this is that the other 'stress hormones', for instance cortisol and ACTH, remained unchanged.

In the reported short-term experiments the dose of PGI₂ was between 8 and 20 ng/kg/min. We used 5 ng/kg/min, which is sufficient for clinical purposes (Szczeklik et al. 1979; Blaskó et al. 1980; Hossmann et al. 1981). Another difference between the short-term experiments and our long-term one is the fact that our patients were elderly and sick, and not young, healthy subjects. Therefore, control experiments with glycine buffer alone were thought to be unethical.

The fact that the PRA increased on the second day only — and not immediately — could be attributed to the arterial disease from which these patients suffered. Patrono et al. (1982) suggested a direct renin stimulation by PGI₂ with no secondary effects on haemodynamic changes. Similarly, a direct effect of PGI₂ on TSH and Prl in vitro was suggested by Wright & Hedge (1981).
The decrease in the thyroid hormone levels including calcitonin could raise the question whether it could be the consequence of a decreased thyroid perfusion. Similarly, the increases in PRL and GH could be a consequence of the alterations in circulation and dopamine levels in the hypothalamus. However, the latter suggestion is not supported by experiments performed in rats (Brus et al. 1981). Indeed, the systolic blood pressure decreased by 20–30 mmHg in our patients in accordance with reported data (O'Grady et al. 1980; Szczeklik et al. 1979).

No difference was found regarding the effects of PGI2 in diabetics and non-diabetics as compared with those before the infusion, the blood sugar levels in diabetic patients treated with either insulin or glibenclamide stayed within the same range during as well after the 72-h PGI2 infusion. After short-term infusion of PGI2 a moderate increase in the blood sugar level has been noted in healthy volunteers (Ylikorkala et al. 1982; Date et al. 1981), but there was no effect of PGI2 on the postprandial glucose levels (Date et al. 1981). We did not measure the glucagon level, which was reported to rise during PGI2 by Ylikorkala et al. (1982). The insulin levels remained unchanged in our long-term experiment as well as in the short-term ones (Date et al. 1981; Scherthaler et al. 1981; Patrono et al. 1981; Ylikorkala et al. 1982).

Concluding our results we can state that no serious hormonal adverse reactions are likely to occur during long-term PGI2 infusion.

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