THE EFFECT OF CHRONIC OXPRENOLOL THERAPY ON BLOOD PROLACTIN, GROWTH HORMONE, RENIN AND ALDOSTERONE LEVELS

Long term treatment with β -adrenoceptor blockers will interfere with physiological regulatory mechanisms. For example, there is evidence that they reduce noradrenaline biosynthesis (Raine & Chubb, 1977) and noradrenaline release (Lewis, 1974). They also increase central dopamine levels (Morinan & Leonard, 1977), but their effect on prolactin, whose secretion from the pituitary is decreased by dopamine (del Pozo & Flückiger, 1973) has not previously been evaluated. Prolactin is known to increase the arterial response to noradrenaline (Horrobin, Manku & Burstyn, 1973) and also the renal retention of salt and water (Horrobin, Lloyd, Lipton, Burstyn, Durkin & Muiruri, 1971). Chronic β -adrenoceptor blocker therapy could therefore lower blood pressure by this mechanism. Indeed, the dopaminergic agonist bromocriptine has been shown to lower serum prolactin and blood pressure (Lewis, Henderson & Fisher, 1976; Stumpe, Kolloch, Higuchi & Kruck, 1977).

Acute and chronic administration of some β -adrenoceptor blockers also reduces plasma renin. They could therefore lower blood pressure through the renin-angiotensin—aldosterone mechanism. nevertheless, the hypotensive effect of β -adrenoceptor blockers is not dependent on their renin lowering property (Stokes, Weber & Thornell, 1974).

We here report the effect on serum prolactin and renin and aldosterone levels of chronic oxprenolol therapy given to patients with essential hypertension.

We also measured growth hormone as an example of another hormone whose secretion is influenced by central dopaminergic activity.

Fourteen patients (13 male, age range 41–64 years) with previously untreated essential hypertension were studied before and after at least 2 months (mean 4.7 ± 0.4 months) on oxprenolol (120–480 mg/day, mean 289 ± 32 mg, in divided doses) as sole drug therapy. Patients were seen at two weekly intervals. Measurements were made on the two consecutive pretreatment occasions and on two consecutive treatment occasions at the end of the study period. Venous blood was taken at the end of the clinic visit with the patient sitting for at least 10 min and at the same time of day (10.00–12.00 h). For the renin, prolactin and growth hormone assays blood was collected in tubes containing E.D.T.A., and for the aldosterone assay in plain tubes. Plasma and serum were separated within 1 h and stored at -4°C for the hormone assays. Plasma prolactin, growth hormone and renin activity and serum aldosterone levels were estimated by radioimmunoassay, details of which are published elsewhere (Waite, 1973; Oparil, Koerner & Haber, 1974; Wilson & James, 1975; Groom, 1977; Wilton, Davies & Jones-Williams, 1977). All the study samples for each hormone were assayed at the same time to eliminate errors due to inter-assay variability. Serum electrolytes and urea and 24 h urinary electrolytes were also measured. The means of the two pretreatment and of the two treatment

Table 1 Effect of oxprenolol treatment on blood pressure, heart rate, plasma and urine electrolytes and plasma hormone levels

	BP_L (mm Hg)	BP_S (mm Hg)	HR_L (beats min^{-1})	HR_S (beats min^{-1})	Weight (kg)
Pretreatment	$172/97 \pm 8/2$	$169/105 \pm 8/2$	77 ± 1	79 ± 1	78 ± 2
Treatment	$154/89 \pm 7/2^*$	$150/96 \pm 7/2^*$	$67 \pm 2^*$	$69 \pm 1^*$	79 ± 2
	Na_{pl} (mM/l)	K_{pl} (mM/l)	U_{pl} (mM/l)	Na_u (mM/24 h)	K_u (mM/24 h)
Pretreatment	138 ± 0.7	3.8 ± 0.1	4.8 ± 0.4	176 ± 14	56 ± 5
Treatment	139 ± 0.6	3.9 ± 0.1	4.8 ± 0.4	161 ± 14	56 ± 4
	Prolactin (mU/100ml)	Growth hormone (mU/ml)	Renin (ngA1 $\text{ml}^{-1} \text{h}^{-1}$)	Aldosterone (pmol/l)	
Pretreatment	18.1 ± 2.1	2.36 ± 0.48	0.42 ± 0.07	224 ± 20	
Treatment	19.1 ± 1.5	2.29 ± 0.44	$0.11 \pm 0.03^*$	225 ± 22	

Blood pressure lying and standing (BP_L and BP_S), heart rate lying and standing (HR_L and HR_S), plasma sodium (Na_{pl}), potassium (K_{pl}) and urea (U_{pl}), 24 h urinary excretion of sodium (Na_u) and potassium (K_u). * $P < 0.005$ compared with pretreatment level.

measurements were used for all these determinations in order to minimize scatter. No difference was apparent between the first and second samples of either the pretreatment or the treatment pairs for any of these assays. Blood pressure was measured by the same observer throughout the study, using a standard sphygmomanometer (diastolic phase 5), lying and standing (2 min). Heart rate and blood pressure readings are presented as the stable pretreatment and treatment levels. Data are given as mean $\pm$ s.e. mean. Results are compared by paired *t*-test.

Table 1 shows that chronic oxprenolol treatment significantly lowered lying and standing systolic and diastolic blood pressures and heart rate without altering body weight, plasma sodium, potassium or urea, or urinary 24 h excretion of sodium or potassium. Chronic oxprenolol treatment significantly reduced plasma renin activity. It did not alter aldosterone or growth hormone levels, nor did it alter plasma prolactin levels as measured in this study. This contrasts with a report of increased plasma prolactin levels in rats 15 min after a single massive dose (50 mg/kg) of $\pm$ -propranolol (Nasrallah, Freed, Rogol & Wyatt, 1977), though we observed no change in plasma prolactin levels measured hourly up to 6 h following a single 40 mg dose of oxprenolol in four patients (unpublished data). The present study thus provides no direct support for the idea that beta blockers may lower blood pressure by lowering prolactin levels. It remains possible that other β -adrenoceptor blockers in appropriate dosage might influence plasma prolactin levels in man. It may also be necessary to study the diurnal rhythm of prolactin (Lacey, Crisp, Groom & Seldrup, 1977) before excluding any such effect.

Plasma renin activity was lowered as previously described (Davies, Payne & Slater, 1975). There was however no associated lowering of aldosterone levels. A similar dissociation has recently been reported between plasma renin and aldosterone levels following acute propranolol therapy (Davies, Slater, Melionis, Jowett & Payne, 1978). The reasons for this dissociation with β -adrenoceptor blockers remain to be explained.

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HEPARIN ADMINISTRATION INCREASES PLASMA WARFARIN BINDING IN MAN

There have been several recent reports that heparin administration can reduce the plasma binding of some drugs and hormones (Storstein & Janssen, 1976; Wood, Shand & Wood, 1979; Kessler, Leech & Spann, 1979; Desmond, Roberts, Wilkinson, Wood & Dunn, 1979; Thomson, Baird & Thomson, 1977). The effect of heparin administration on the plasma binding of warfarin is less clear. It was reported that *in vivo* elevation of non-esterified fatty acids (NEFA) by exercise or adrenaline administration markedly reduced the plasma binding of warfarin in rats (Gugler, Shoeman & Azarnoff, 1974). Since heparin also increases the plasma concentration of NEFA, it might be expected to produce similar changes in warfarin binding. In three human subjects studied by Nilsen, Storstein & Jacobsen (1977) however, intravenous administration of heparin (70 IE/kg) was associated with increased plasma binding of warfarin. The following study was performed to assess the effect of heparin on warfarin binding in a larger number of subjects and to examine the relationship between these changes and total and individual NEFA.

Heparin sodium, 1000 USP units (Upjohn, Kalamazoo, Michigan) was administered to seven healthy young male volunteers 2–3 h after a light breakfast. Blood samples were collected by direct venipuncture (immediately before and 15 min after the heparin injection) into glass tubes containing 10 USP units of heparin per ml of added blood.

These were immediately centrifuged (at 4°C) and the plasma separated. Plasma warfarin binding was assessed after equilibrium dialysis of this fresh plasma against Sorenson's phosphate buffer (containing 0.5% w/v sodium chloride) adjusted to pH 7.4 in Teflon^R dialysis cells at 37°C for 3 h. [¹⁴C]-warfarin (Amersham Corp. Arlington Heights, IL) was added to the buffer to achieve a concentration of 3 µg/ml and quench correction was performed using the external standards ratio method. The free fraction of

warfarin in plasma was calculated as the ratio of absolute disintegration rates in buffer and plasma. Individual NEFA ($C_{16:0}$, $C_{16:1}$, $C_{18:0}$, $C_{18:1}$, $C_{18:2}$) were measured by a modification of the gas chromatographic method of Sampson & Hensley (1975) and 'total' NEFA was calculated as the sum of these five individual NEFA.

The free fraction of warfarin in plasma fell by an average of 37% (range 28–45%) after heparin, that is from 0.0092 ± 0.0007 to 0.0058 ± 0.008 (mean $\pm$ s.d., $P < 0.001$). The changes in individual subjects are illustrated in Figure 1. These changes were accompanied by a rise in total NEFA from $83 \pm$

Figure 1. Free fraction of warfarin in plasma immediately before and 15 min after 1000 USP units of heparin intravenously.