Br. J. clin. Pharmac. (1980), **9**, 27–31

PLASMA NORADRENALINE CONCENTRATION IN ESSENTIAL HYPERTENSION DURING LONG-TERM β-ADRENOCEPTOR BLOCKADE WITH OXPRENOLOL

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1 Chronic β-adrenoceptor blockade with oxprenolol causes elevation of plasma noradrenaline levels, as compared with placebo, despite a significant fall in blood pressure and pulse rate.

2 The plasma noradrenaline concentration is not influenced by the frequency of administration or the formulation of the drug.

3 Plasma noradrenaline levels are not correlated with the plasma concentration of the drug.

4 The changes in plasma noradrenaline concentrations support a peripheral rather than central mechanism of action of β-adrenoceptor blockers in man.

Introduction

During the last decade, there has been a considerable increase in the use of β-adrenoceptor blocking drugs in the treatment of hypertension. Dichloroisoprenaline was the first catecholamine analogue to exhibit competitive blockade of the agonist action of the catecholamines at the β-receptor (Powell & Slater, 1958), and oxprenolol was amongst the early antagonists to gain official approval (Regårdh, 1975).

Despite the number of β-adrenoceptor blockers available for clinical use, there is still lack of agreement as to their mechanism of action; the theories of the mode of action have been reviewed by Fitzgerald (1975). If a central effect of β-adrenoceptor antagonists, with a reduction in efferent sympathetic activity were the main mechanism of action in effecting a fall in blood pressure, it would be expected that there should be a fall in plasma noradrenaline levels. This has been described for clonidine, which appears to act in the central nervous system (Wing, Reid, Hamilton, Sever, Davies, Dollery, 1977). β-adrenoceptor blockers do cause central nervous effects (Prichard & Gillam, 1969; Lewis & Haeusler, 1975). We have made an indirect assessment of the central contribution to the actions of β-adrenoceptor blockers in man by observing the effects on plasma noradrenaline, an index of sympathetic activity (Lake, Ziegler & Kopin, 1976).

The study was designed to examine the effect of chronic oxprenolol therapy on plasma noradrenaline levels in patients with mild essential hypertension. The effect of a different formulation and frequency of administration of the drug on plasma noradrenaline concentration was also examined.

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Methods

The duration of the study was 24 weeks, and six mild essential hypertensive patients, aged 37–62 years, attended at two weekly intervals. Written consent for the study was obtained. Before starting the trial, each patient's blood pressure was controlled with twice daily oxprenolol (in a dose of 160, 240 or 480 mg daily) with or without a thiazide diuretic. The study was double-blind, and no other drugs were taken throughout its duration. Four periods, each of 6 weeks, allowed every patient to take the following regimes:

(1) twice daily conventional oxprenolol
(2) once daily conventional oxprenolol
(3) once daily sustained release oxprenolol
(4) placebo

The drugs were taken on a twice daily basis, and matching dummy tablets were used when all the active therapy was being taken once daily. The regimes were allocated randomly to the patients, in a Latin square pattern, to exclude order effects. The total amount of drug taken during the three periods of active therapy was kept constant.

Full clinical examination was performed at the beginning and end of the study, and an ECG was recorded at six weekly intervals. The patients were seen fortnightly for measurement of pulse rate and blood pressure, and for recording of side effects. On the last day of each treatment period, the patients attended the clinical laboratory for an 8 h study, which involved hourly pulse and blood pressure measurements, together with measurement of plasma noradrenaline and oxprenolol level at zero time, and 2, 4 and 8 h following the ingestion of the morning tablets.

0306–5251/80/010027–05 $01.00

Blood pressure readings were made in duplicate using the automatic ultrasound sphygmomanometer (Arteriosonde 1217, Roche) with the patients having been supine for 10 min. The average values of the readings were recorded. The pulse rate was counted for 1 min prior to the blood pressure measurements. Blood was withdrawn by venipuncture from the antecubital vein for plasma noradrenaline and oxprenolol determinations. Blood pressure and pulse rate measurements were also made after 2 min in the standing position.

Plasma noradrenaline concentration was estimated by a sensitive and specific radioenzymatic assay technique (Henry, Starman, Johnson & Williams, 1975), and plasma oxprenolol levels by a gas-liquid chromatographic method (Jack & Riess, 1974).

The data from the pulse and blood pressure readings, the plasma oxprenolol and the plasma noradrenaline concentrations were analysed by three way analysis of variance.

Results

Blood pressure and pulse rate

For the 8 h studies, the zero reading represented the 12 h time point following the previous evening dose in the twice daily conventional formulation regime, or that of the 24 h time point following the previous morning dose in the once daily regime (when the evening tablet was a placebo).

Supine and standing blood pressure readings were significantly lower during the active treatment than during placebo (Table 1), the mean falls being 8.5/5.7 and 16.9/9.5 mm Hg for the supine and standing readings respectively. The reduction in the supine and standing pulse rates (9 and 17 beats/min) was also statistically significant. No significant difference ($P > 0.05$) was seen when the blood pressure measurements and the pulse rates during the three active periods were compared.

The 8 h studies showed that the maximal fall in blood pressure with the three forms of therapy occurred at 1 to 2 h, and that the levels then gradually rose towards the predose values. The mean blood pressure values for the 8 h periods during active therapy were similar ($P > 0.05$) but the readings were significantly lower than the predose levels (Table 2).

Plasma oxprenolol levels

The 'zero' time plasma oxprenolol levels reflecting the 12 h or 24 h time points from the previous day, as described above, were low, and were not significantly $P > 0.05$) different. At 2 h after dosing, the once daily conventional regime gave, not unexpectedly as the dose taken was twice as great, a significantly ($P < 0.02$) higher plasma level than the other two regimes, which were not statistically significant from each other. At 4 h following ingestion of the drug, the once daily regimes gave levels which were not statistically different from each other, but which were significantly ($P < 0.02$) greater than that obtained with the twice daily regime. At the 8 h time point, the once daily sustained release regime had a plasma level higher ($P < 0.02$) than the once daily regimes—these not being statistically significantly different from each other. These results are shown in Figure 1.

Plasma noradrenaline concentration

The mean ± s.e. mean plasma noradrenaline level during the placebo 8 h study was 1.65 ± 0.18

Table 1 Mean supine and standing blood pressure and pulse rate (± s.e. mean) during treatment of six mild essential hypertensive patients with placebo, twice daily conventional oxprenolol, once daily conventional oxprenolol, and once daily sustained release oxprenolol

	Treatment period			
	Placebo	*Twice daily conventional oxprenolol*	*Once daily conventional oxprenolol*	*Once daily sustained release oxprenolol*
Supine				
Systolic blood pressure (mm Hg)	138.4 ± 4.6	130.1 ± 4.4†	129.1 ± 3.8†	130.5 ± 4.2‡
Diastolic blood pressure (mm Hg)	86.8 ± 1.7	80.9 ± 1.8*	80.1 ± 2.0*	82.4 ± 1.3*
Pulse rate (beats/min)	71 ± 3	61 ± 2‡	62 ± 2‡	62 ± 2‡
Standing				
Systolic blood pressure (mm Hg)	148.5 ± 5.6	130.5 ± 3.1‡	134.4 ± 3.6‡	129.9 ± 4.2‡
Diastolic blood pressure (mm Hg)	99.6 ± 2.8	89.8 ± 1.7‡	91.0 ± 1.9†	88.8 ± 2.4†
Pulse rate (beats/min)	86 ± 4	69 ± 1‡	69 ± 1‡	68 ± 1‡

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$

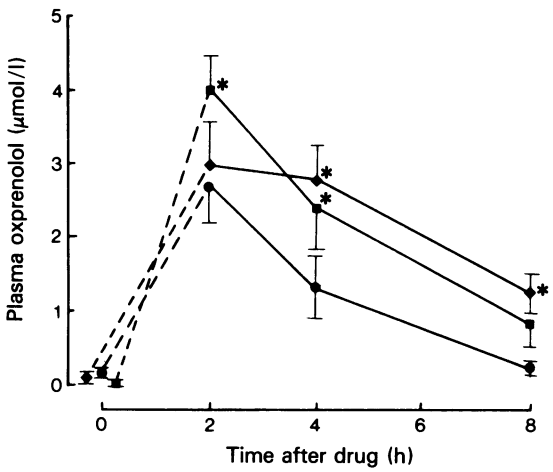

Figure 1 Mean plasma oxprenolol levels (±s.e. mean) in six essential hypertensive patients taking twice daily conventional oxprenolol (●), once daily conventional oxprenolol (■), and once daily sustained release oxprenolol (◆). (*$P<0.02$)

nmol/l; the values during the active treatment periods were:

2.71 ± 0.18 nmol/l for the regime of twice daily dosing;
2.60 ± 0.18 and 2.48 ± 0.24 nmol/l during the periods of once daily dosing with conventional and sustained release formulations respectively.

The treated levels were all significantly higher ($P<0.001$) than during placebo therapy, but no significant differences ($P>0.05$) were seen between the treated levels. These results are shown in Figure 2.

Discussion

Previous studies (Havard & Pearson, 1976; O'Brien & Stephens, 1976) have investigated the role of sustained release oxprenolol in controlling blood pressure. The present study, in which the total daily dose of oxprenolol taken was equal in the three regimes, confirms that there is satisfactory blood pressure control. It also illustrates that the control of pressure is independent of the regime of administration or formulation of the drug. Further, the results indicate clearly that such blood pressure control is not related to the plasma drug concentration as regression analysis of blood pressure and plasma oxprenolol concentration did not give a significant result.

Plasma noradrenaline is accepted as the single most useful index of sympathetic nervous activity (Lake *et al.*, 1976), and its reduction during therapy with the centrally acting antihypertensive drugs is one indication that such drugs influence the central sympathetic pathways. A study by Polak, Reid, Hamilton, Jones & Dollery (1978) in three groups of hypertensive patients treated with a single drug regime consisting of either a thiazide diuretic, propranolol or methyldopa, showed that the mean plasma noradrenaline level for the methyldopa treated group was significantly lower than that for the other groups, which would be consistent with the view that methyldopa has an important central nervous site of action. However, as there were no control data before treatment available in this study, it was difficult to interpret the plasma noradrenaline in the β-adrenoceptor blocker treated group.

Other centres have suggested that there is an elevation of plasma noradrenaline levels during chronic β-adrenoceptor blockade. Philipp, Cordes, Walter, Walter, Beyer & Distler (1976) found that with basal and dynamic exercise, plasma noradrenaline concentration increased when essential hypertensive patients were treated with atenolol; Rahn, Gierlichs, Planz, Planz & Stephany (1976) showed that there was elevation of plasma catecholamines in patients treated with propranolol for 10 days, although others have demonstrated falls in noradrenaline (Brecht, Banthien, Ernst & Schoeppe, 1976).

The present study, in which order and carry over effects have been considered in the design, and in which patients acted as their own controls, also confirm the earlier reports that chronic β-adrenoceptor blockade results in elevated plasma noradrenaline levels. Further, it provides indirect evidence that the peripheral effects of β-adrenoceptor blockers probably predominate over any putative

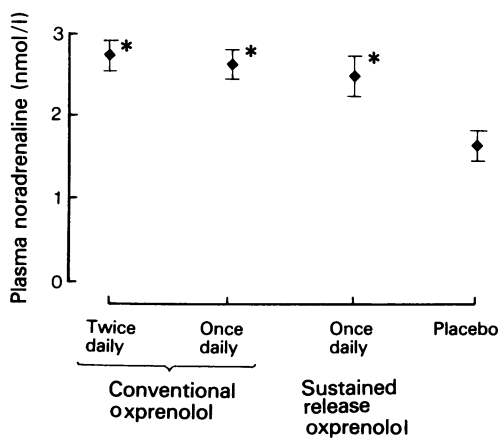

Figure 2 Mean plasma noradrenaline levels (±s.e. mean) in six essential hypertensive patients during 8 h studies on four regimes: placebo, twice daily conventional oxprenolol, once daily conventional oxprenolol and once daily sustained release oxprenolol. (*$P<0.001$)

Table 2 Mean supine and standing blood pressure and pulse rate (± s.e. mean) during 8 h studies of six mild essential hypertensive patients given placebo, twice daily conventional oxprenolol, once daily conventional oxprenolol, and once daily sustained release oxprenolol

	Treatment period			
	Placebo	*Twice daily conventional oxprenolol*	*Once daily conventional oxprenolol*	*Once daily sustained release oxprenolol*
Supine				
Systolic blood pressure (mm Hg)	136.0 ± 2.8	131.6 ± 2.5*	127.6 ± 2.4‡	129.1 ± 2.9‡
Diastolic blood pressure (mm Hg)	85.9 ± 1.0	83.1 ± 0.8†	82.6 ± 0.9‡	80.6 ± 1.0‡
Pulse rate (beats/min)	65 ± 1	59 ± 1‡	61 ± 1‡	59 ± 1‡
Standing				
Systolic blood pressure (mm Hg)	142.5 ± 2.6	132.3 ± 2.1‡	130.7 ± 2.6‡	129.4 ± 2.9‡
Diastolic blood pressure (mm Hg)	96.3 ± 1.6	91.2 ± 0.9‡	91.4 ± 1.1‡	88.0 ± 1.1‡
Pulse rate (beats/min)	77 ± 1	66 ± 1‡	68 ± 2‡	66 ± 1‡

* $P<0.05$; † $P<0.01$; ‡ $P<0.001$

central effects in lowering blood pressure. The mechanism by which peripheral β-adrenoceptor blockade causes elevations in circulating noradrenaline is not clear. It may be a consequence of post-synaptic blockade with attempts to compensate for this, or may represent a balance between pre-synaptic and post-synaptic blockade of β-adrenoceptors.

There is evidence from the results of this study that the plasma noradrenaline level is not directly affected by the plasma oxprenolol level as the latter is influenced by the frequency of administration and the formulation of the drug, while plasma noradrenaline concentration is independent of such factors.

Thus, chronic β-adrenoceptor blockade in six mild essential hypertensive patients causes elevation of plasma noradrenaline, the degree of elevation being unrelated to the drug formulation and the frequency of administration. The findings tend to support a peripheral antihypertensive action of β-adrenoceptor blockers.

The tablets were kindly supplied by CIBA laboratories, who also arranged for measurement of the plasma oxprenolol levels. The packaging and dispensing of the tablets was performed by the Pharmacy department, Hammersmith Hospital. Miss Ava Petrie, Royal Postgraduate Medical School, kindly advised on statistical analysis. The work was supported by the Medical Research Council of Great Britain (DHJ) and the Wellcome Foundation (JLR).

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(*Received March 15, 1979*)