SYMPATHETIC REFLEX RESPONSES DURING TREATMENT OF ESSENTIAL HYPERTENSION WITH HYDRALLAZINE AND OXPRENOLOL

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- 1 The short term effects of hydralazine, oxprenolol and oxprenolol plus hydralazine were studied in five patients with essential hypertension.
- 2 The increase in pulse rate caused by hydralazine was prevented by combined treatment with oxprenolol, which also lowered the high plasma noradrenaline levels, associated with the use of hydralazine.
- 3 Plasma renin activity was higher in the supine and standing positions with hydralazine than with oxprenolol alone and with the patients standing this high renin level was prevented by simultaneous treatment with oxprenolol. With the patients supine, combination of oxprenolol with hydralazine resulted in a mean plasma renin activity which was less than half that with hydralazine alone, although this difference was not statistically significant.
- 4 The combination of oxprenolol with hydralazine did not lower the blood pressure further, but reduced the increased sympathetic activity which occurred with hydralazine alone.

Introduction

Hydralazine decreases the peripheral resistance in hypertension by a direct relaxing action on arteriolar smooth muscle (Rowe, Huston, Maxwell, Crosley, Archer & Crumpton, 1955), but its antihypertensive effectiveness is limited in part by a reflex increase in sympathetic discharge that raises heart rate and cardiac output (Freis, Rose, Higgins, Finnerty, Kelley & Partenope, 1953). This can be overcome by simultaneous use of β -adrenoceptor blocking drugs (Zacest, Gilmore & Koch-Weser, 1972). Plasma noradrenaline concentration may reflect sympathetic nervous activity (Sever, Birch, Osikowska & Tunbridge, 1977) and therefore, the changes in plasma noradrenaline produced by hydralazine, oxprenolol and oxprenolol plus hydralazine were measured in five patients with essential hypertension. Plasma renin activity was also determined as this may be altered by hydralazine (Ueda, Kaneko, Ikeda & Shigeru, 1970), β -adrenoceptor blockade (Hollifield, Sheman, Vander Zwagg & Shand, 1976), or sympathetic nervous activity (Davies & Slater, 1976).

Methods

Plasma noradrenaline was determined by a radio-enzymatic method (Henry, Starman, Johnson &

Williams, 1975; Sever *et al.*, 1977). Plasma renin was measured by radioimmunoassay (Boyd, Adamson, Fitz & Peart, 1969). Five patients with essential hypertension were given in random order, each of three drug regimens: hydralazine (50 mg), oxprenolol (80 mg), and hydralazine (50 mg) plus oxprenolol (80 mg). Doses of drugs were given at 08.00 h and 18.00 h for 7 days. On day 7, supine and erect blood pressure, pulse rate, plasma renin and noradrenaline levels were measured at 30 min intervals for 2 to 4 h after the 08.00 h dose of drugs. Thirty minutes were allowed to elapse between each measurement in the supine position, while erect values were estimated after 10 min quiet standing. Plasma renin and noradrenaline show skewed distribution in normals and hypertensives (Sever, Peart, Meade, Davies & Gordon, 1978), but log plasma noradrenaline and plasma renin activity are more nearly normal in distribution and therefore, the common logarithms of each were used in calculating the differences between drug regimens. Results are expressed as means $\pm$ s.d. and the significance of the differences was determined using paired *t*-tests.

Results

All the patients in the study had moderate to severe hypertension when untreated and therefore it was felt unethical to withdraw treatment in order to obtain

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Figure 1 Changes in blood pressure, pulse rate, plasma noradrenaline concentration and plasma renin activity in five patients with essential hypertension after treatment with (a) hydralazine, (b) oxprenolol or (c) oxprenolol plus hydralazine. Values shown are means $\pm$ s.d. in the lying (●) or standing (○) positions. Values for noradrenaline and plasma renin are expressed as the logarithms to the base 10.

control blood pressure readings. However, all the regimens used did result in a significant lowering of blood pressure in all the patients.

The mean supine blood pressure was no different with hydralazine (Figure 1) (127 ± 14 mmHg), or oxprenolol (138 ± 30 mmHg), but was significantly ($P < 0.05$) lower with the combination of these drugs (120 ± 20), than with oxprenolol alone. Mean standing blood pressure was significantly lower ($P < 0.05$) with hydralazine (122 ± 12 mmHg) than with oxprenolol (136 ± 12); use of oxprenolol with hydralazine did not lower the blood pressure further than with hydralazine alone (120 ± 11 mmHg). Supine and standing heart rates were higher ($P < 0.05$) with hydralazine (91 ± 23 /min and 104 ± 19 /min, respectively), than with oxprenolol (69 ± 8 /min, 75 ± 6 /min), or oxprenolol plus hydralazine (69 ± 5 /min, 79 ± 6 /min).

Supine plasma noradrenaline was significantly higher ($P < 0.05$) with hydralazine (5200 ± 850 pmol/l) than with oxprenolol (2880 ± 1150 pmol/l) alone, or combined with hydralazine (3350 ± 670 pmol/l). The supine noradrenaline level was also higher ($P < 0.01$) with hydralazine plus oxprenolol than with oxprenolol alone. Standing noradrenaline levels were higher with hydralazine

(8500 ± 2800 pmol/l, $P < 0.01$) or oxprenolol plus hydralazine (5200 ± 1600 pmol/l, $P < 0.05$) than with oxprenolol alone (4000 ± 750 pmol/l). There was no significant difference between the noradrenaline levels in the standing position with hydralazine or hydralazine plus oxprenolol. The supine plasma renin with hydralazine (4877 ± 6540 units, 1 unit of renin activity = 1 pmol of angiotensin I produced $l^{-1} h^{-1}$) was significantly ($P < 0.05$) higher than with oxprenolol (849 ± 897 units). There was no significant difference between the plasma renin activity with hydralazine or hydralazine plus oxprenolol (1163 ± 948 units), although the mean plasma renin with hydralazine was about four times that with oxprenolol plus hydralazine. Standing plasma renin activity was higher ($P < 0.05$) with hydralazine (3568 ± 210 units), than with oxprenolol (670 ± 288 units), or oxprenolol plus hydralazine (1359 ± 971 units).

Discussion

The increased sympathetic nervous activity resulting from vasodilatation was reflected by the higher noradrenaline with hydralazine or hydralazine plus oxprenolol than with oxprenolol alone. This observation is at variance with previous studies with intravenous hydralazine, which failed to demonstrate a significant release of catecholamines (Van Zwiiten, 1968).

In all our patients in spite of the increased sympathetic activity, oxprenolol combined with hydralazine prevented the rise in pulse rate and lowered plasma noradrenaline levels. After chronic administration of a β -adrenoceptor blocker, this may be supplemented by decreased noradrenaline synthesis (Raine & Chubb, 1977) which may account for the further decrease in blood pressure observed in one study (Sannerstedt, Stenberg, Vedin, Wilhelmsson & Werkö, 1972) after addition of a β -adrenoceptor blocker to a regimen consisting of hydralazine alone.

Following the administration of hydralazine, the significantly higher plasma renin with the patients supine, probably resulted from vasodilatation (Ueda *et al.*, 1970). In the supine position, combination of oxprenolol with hydralazine resulted in a lower plasma renin, but this was not statistically significant. However, with the patients standing, the higher plasma renin caused by hydralazine therapy, was prevented by combination of oxprenolol with hydralazine. Prevention of renin release in response to hydralazine (Ueda *et al.*, 1970) by oxprenolol or another β -adrenoceptor blocker may be one factor increasing the hypotensive effect of hydralazine in combination with β -adrenoceptor blocking drugs

(Pedersen & Kornerup, 1975). However, there is no evidence from this study to indicate a causal relationship between the suppression by oxprenolol of the increase in plasma renin activity caused by

hydrallazine and any enhancement of the hypotensive effect of hydrallazine.

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