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DIMINISHING HYPOTENSIVE EFFECT OF INCREASING DOSES OF PINDOLOL IN DOCA/SALINE HYPERTENSIVE RATS

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In DOCA-saline hypertensive rats, pindolol (4, 20 or 50 mg/kg orally) produced a hypotensive effect which was inversely related to dose. Following adrenal demedullation, a hypotensive response to the highest dose of pindolol was unmasked and the magnitude of the responses to lower doses was increased. The results suggest that adrenal catecholamines moderate the hypotensive effects of high doses of pindolol.

Introduction The non-selective β-adrenoceptor blocking drug, pindolol, has been shown to lower the blood pressure of deoxycorticosterone acetate (DOCA)-saline hypertensive (DS) rats after oral administration of small doses (Buckingham, Hamilton & Robson, 1977). The effect was dose-related and appeared to be mediated by a metabolite(s) acting by stimulation of vascular β_2-adrenoceptors. However with higher doses of pindolol we have encountered an inverse relationship between drug dose and blood pressure response. This paper describes, and provides evidence to explain, this phenomenon.

Methods DS-rats were prepared by the method previously described (Buckingham *et al.*, 1977). In some rats unilateral adrenalectomy and contralateral adrenal demedullation were performed at this operation (adrenal demedullated DS-rats). Four to six weeks after DOCA implantation, blood pressure and heart rate were measured directly in conscious animals (Buckingham, 1976) before, and at intervals after pindolol, 4, 20 or 50 mg/kg orally. Pindolol (Sandoz) was suspended in water. Data were analysed by Student's t test (2-tailed); P values < 0.05 were considered significant.

Results In DS-rats pindolol, 4 or 20 mg/kg, significantly reduced mean blood pressure (Figure 1a) and increased heart rate (40–70 beats/min) for 4 h, but a higher dose, 50 mg/kg, failed to alter these parameters. At 1 and 2 h after dosing the hypotensive response evoked by pindolol, 4 mg/kg, was significantly greater than that produced by 20 mg/kg.

In adrenal demedullated DS-rats pindolol, 4, 20 or 50 mg/kg significantly reduced mean blood pressure throughout 4 h (Figure 1b). The hypotensive response to pindolol, 4 mg/kg, was significantly greater than that to 20 (1 h) or 50 mg/kg (1 and 2 hours). Furthermore, the hypotensive response to pindolol, 20 mg/kg, significantly exceeded that to 50 mg/kg at 1 hour. Pindolol, 50 mg/kg, significantly reduced heart rate at 1 h (45 beats/min), but lower doses were without significant effects.

Discussion Pindolol, 10–50 µg/kg orally, produces a dose-dependent hypotensive response in DS-rats (Buckingham *et al.*, 1977). However, the present study, demonstrates that with higher oral doses (4, 20 and 50 mg/kg) of pindolol there is an inverse relationship between dose and blood pressure response, with no effect apparent following the highest dose. There is evidence that the effects of some β-adrenoceptor blocking agents on rat blood pressure may include a pressor component which is dependent on the integrity of the adrenal medulla (Brunner & Hedwall, 1970; Grewal & Kaul, 1970). Consistent with these observations we found a considerable blood pressure reduction in adrenal demedullated DS-rats following 50 mg/kg pindolol, which, by 3 h, was essentially equivalent in magnitude to the effects produced by 4 and 20 mg/kg of the drug. Whilst adrenal demedullation abolished (3–4 h) the negative correlation between dose and response described, the absence of a positively correlated dose-response plot following adrenal surgery suggests that the doses used were supramaximal on blood pressure.

Two possibilities may account for the persisting inverted dose-response relationship during the onset of the hypotensive response (1-2 h) in adrenal demedullated DS-rats. Firstly the higher doses of pindolol may be releasing residual adrenal catecholamines, due to incomplete adrenal demedullation, during this early phase of the response. Secondly, metabolism may be an important factor. Pindolol is extensively metabolized in rats (Kiechel, Niklaus, Schreier & Wagner, 1975) and has a short plasma half life after

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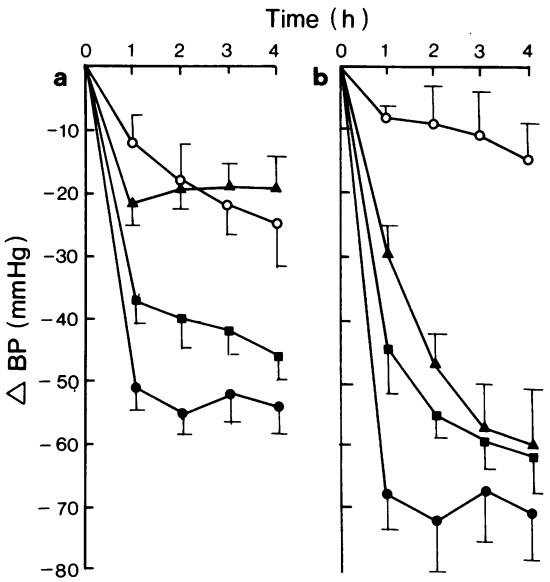

Figure 1 Time course (h) of change in mean blood pressure (△BP mmHg) of conscious intact (a) and adrenal demedullated (b) deoxycorticosterone acetate/saline-treated rats (DS-rats), after oral administration of pindolol 4 mg/kg (●), 20 mg/kg (■), and 50 mg/kg (▲) or control vehicle (○). Vertical lines indicate s.e. mean. Groups of 8 to 11 rats were used. The resting mean arterial blood pressures of control groups were respectively 172 ± 3 mmHg and 180 ± 7 mmHg for DS-rats and adrenal demedullated DS-rats. These values were not significantly different from each other, or from values for their respective treatment groups.

oral administration (Pacha, 1969). Our earlier studies (Buckingham *et al.*, 1977) suggested that the hypotensive response to pindolol in the DS-rat is mediated through a metabolite(s) formed predominantly in the liver. Over-loading of the hepatic extraction process, by administration of a sufficiently large oral dose, would reduce the fraction of drug removed on its first passage through the liver, as occurs with propranolol in the rat (Shand, Rangno, & Evans, 1972). Since the hypotensive effect in the DS-rat is apparently due to stimulation of vascular β_2-receptors (Buckingham *et al.*, 1977) an increase in the fraction of circulating parent drug, with its inherent β-adrenoceptor blocking properties, might be expected to attenuate the response. Subsequent metabolism of the parent drug would account for the diminution of differences in effect of the three pindolol doses at 3 and 4 hours.

The differences in heart rate responses produced by pindolol in adrenal demedullated DS-rats (no change following 4 or 20 mg/kg; bradycardia following 50 mg/kg) or DS-rats (tachycardia following 4 or 20 mg/kg; no change following 50 mg/kg) suggest that circulating adrenal catecholamines are important also in determining the cardiac response to high doses of this drug.

On the basis of differences in metabolism alone there would be little justification for drawing parallels between observations in the rat and in man. Nevertheless, it is interesting to note that at high doses of pindolol a pressor response has been reported in some patients (e.g., Waal-Manning & Simpson, 1975). Although this effect of pindolol has been tentatively attributed to a predominating sympathomimetic property, the phenomenon has not been studied in detail. In view of the results obtained in our studies, the involvement of adrenal catecholamines should perhaps be considered in this paradoxical effect of pindolol in man.

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