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STUDIES ON THE CARDIOVASCULAR EFFECTS OF PINDOLOL IN DOCA/SALINE HYPERTENSIVE RATS

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1 A hypotensive response to orally administered pindolol in conscious normotensive and deoxycorticosterone acetate (DOCA)/saline hypertensive rats (DS-rats) is described. In DS-rats, pindolol (10–50 μg/kg) produced a dose-dependent fall in blood pressure and elevation of resting heart rate.

2 The hypotensive response and tachycardia produced by oral pindolol (50 μg/kg) in DS-rats were prevented by propranolol (5 mg/kg), suggesting that pindolol's effects are mediated by β-adrenoceptor stimulation.

3 After mecamylamine (10 mg/kg), oral pindolol (50 μg/kg) produced a further fall in blood pressure in DS-rats, suggesting that its hypotensive effects are probably mediated in the peripheral vasculature.

4 Pretreatment with oral pindolol (10 or 50 μg/kg) resulted in a reduction of neuronally-induced tachycardia in pithed DS-rats; neuronally-evoked pressor effects were also antagonized by pindolol (50 μg/kg, orally).

5 Whereas pindolol, 50 μg/kg orally or intraperitoneally, produced a marked and progressive hypotensive response of rapid onset (20 min) in DS-rats the same dose intravenously produced a smaller response of delayed onset (80 minutes).

6 In anaesthetized DS-rats, an equivalent degree of cardiac β-adrenoceptor blockade was produced by pretreatment with pindolol, 50 μg/kg orally (2 h previously) or intravenously (1 h previously).

7 After administration of pindolol, 2 mg/kg intravenously, to conscious DS-rats, the tachycardia produced by intravenous isoprenaline, 3 μg/kg, was almost abolished for the first 60 min of the study, whereas a hypotensive response to pindolol was delayed in onset (100 minutes).

8 The hypotensive response and tachycardia produced by oral pindolol, 50 μg/kg, in DS-rats were prevented by inhibition of metabolic enzyme activity by pretreatment with Proadifen (SKF 525-A), 80 mg/kg.

9 The results suggest that pindolol's effects on blood pressure and heart rate in the conscious DS-rat are mediated by a metabolite(s) acting by stimulation of peripheral β-adrenoceptors.

Introduction

Pindolol is a potent, non-selective β-adrenoceptor blocking drug (Giudicelli, Schmitt & Boissier, 1969). possessing intrinsic sympathomimetic activity (Barrett & Carter, 1970). Like many other β-adrenoceptor blocking drugs (see review by Simpson, 1974), pindolol is an effective anti-hypertensive drug in man (e.g. Feltham, Watson, Peel, Dunlop & Turner, 1972; Thorpe, 1972; Van Coller, 1973; Morgan, Sabto, Anavekar, Louis & Doyle, 1974; Stokes, Weber & Thornell, 1974) although a pressor response has been reported in some patients (Collins & King, 1972; Morgan, Louis, Dawborn & Doyle, 1972; Waal-Manning & Simpson, 1975).

In laboratory studies prolonged oral or subcutaneous administration of pindolol has been shown to reduce the blood pressure of spontaneously hypertensive and normotensive rats (Garvey & Ram, 1975), although the course of development of renal or deoxycorticosterone acetate (DOCA)/saline (DS) hypertension is apparently not influenced by prolonged oral dosage (Takeda, Sakurai & Imai, 1975). In the rabbit, a small acute reduction in blood pressure has been reported following the intravenous administration of pindolol (Weber, Thornell & Stokes, 1974).

In the experiments described here we have studied the cardiovascular effects of pindolol in normotensive and DS-rats using single oral doses that are appreciably lower than those hitherto used in rats (Garvey & Ram, 1975; Takeda *et al.*, 1975). Furthermore, in the knowledge that pindolol is extensively metabolized in rats (Kiechel, Niklaus, Schreier & Wagner, 1975), we have investigated the

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possibility that the acute cardiovascular responses observed following pindolol administration are dependent upon metabolic activation of the parent drug.

Methods

Male Sprague-Dawley rats were used for these studies.

Induction of experimental hypertension

Rats, 120–150 g, were made hypertensive by unilateral nephrectomy, subcutaneous implantation of 2 compressed tablets each containing 25 mg deoxycorticosterone acetate (DOCA) and replacement of drinking water by 0.9% w/v NaCl solution (saline) until experimental use 4–6 weeks later.

Implantation of catheters for the direct measurement of arterial blood pressure and the intravenous administration of drugs

Polythene catheters were implanted, under ether anaesthesia, in the abdominal aorta for direct blood pressure measurement, and also in the abdominal vena cava of some animals to facilitate intravenous drug administration. The operative procedure has been previously described (Buckingham, 1976). The rats were allowed 1 to 2 days to recover before use. Normotensive rats used for these experiments weighed 290–360 grams.

Direct measurement of arterial blood pressure and heart rate in conscious rats

Groups of 7–13 rats were used for each treatment. Blood pressure was recorded in conscious unrestrained animals with a Statham P23 Db pressure transducer (1 mmHG$\approx$133 Pa) connected to a Grass (Model 7) Polygraph. Heart rate was recorded either from a Grass tachograph, triggered by the arterial pulse pressure wave, or was counted from the record after increasing the chart speed.

Drug administrations in conscious rats

(a) The effects of single doses of pindolol, 10, 25 or 50 μg/kg orally were studied in normotensive and DS-rats. Mean arterial blood pressure and heart rate were recorded immediately before dosing and then at hourly intervals for 4 hours.

(b) The effects of pindolol, 50 μg/kg orally, and propranolol, 5 mg/kg intraperitoneally both alone and in combination were studied in DS-rats. Blood pressure and heart rate were monitored as in (a).

(c) The effects of pindolol, 50 μ/kg orally, and mecamylamine, 10 mg/kg intraperitoneally, both alone and in combination were studied in DS-rats. Blood pressure and heart rate were monitored as in (a).

(d) The effects of pindolol, 50 μg/kg orally, intraperitoneally or intravenously, were studied in DS-rats. Blood pressure and heart rate were recorded immediately before dosing and then at 20 min intervals for 2 hours.

(e) The effect of pindolol, 2 mg/kg intravenously was studied in DS-rats. Blood pressure was monitored as in (d). In a separate experiment the change in heart rate produced by isoprenaline, 3 μg/kg intravenously was determined immediately before dosing with pindolol, 2 mg/kg intravenously, and then at 20 min intervals for 2 hours.

(f) The effect of pindolol, 50 μg/kg orally, was studied in DS-rats following treatment with Proadifen (SKF 525-A), 80 mg/kg intraperitoneally, 4 h previously. Blood pressure and heart rate were recorded immediately before dosing with pindolol and then at 20 min intervals for 2 hours.

In all experiments the changes in cardiovascular parameters were related to the values obtained immediately before dosing (zero time).

Stimulation of sympathetic outflow in pithed rats

DS-rats received pindolol, 10 or 50 μg/kg orally, or vehicle 2 h before the start of frequency-response determinations. Animals were prepared in pairs for stimulation of the entire sympathetic outflow by the method of Gillespie & Muir (1967). The 3 treatments were randomized throughout the group of 30 rats. Each animal received intravenous atropine, 1 mg/kg, tubocurarine, 2 mg/kg, and heparin, 100 units/kg, after pithing, Preparations were electrically stimulated for periods of 20 s every 8 min by monophasic, square-wave pulses of 0.5 ms duration at supramaximal voltage over the frequency range 0.25–8 hertz. Changes in diastolic blood pressure were recorded from the left carotid artery with a Statham P23 Db pressure transducer connected to a Grass Polygraph; heart rate was recorded with a Grass tachograph.

Assessment of β-adrenoceptor blocking activity in anaesthetized rats

DS-rats received pindolol, 50 μg/kg orally or intravenously, or appropriate vehicle treatment. At 45 min after intravenous treatment or 105 min after oral dosing, the animals were anaesthetized with pentobarbitone sodium, 75 mg/kg intraperitoneally and prepared for recording blood pressure and heart rate. Fifteen minutes later changes in heart rate were recorded in response to isoprenaline, 0.3, 1, 3 and 10 μg/kg intravenously. Dose-response curves to isoprenaline were completed within 30 min in each animal.

Drugs

The following drugs were used: isoprenaline sulphate (Burroughs Wellcome); pindolol (Sandoz); Proadifen (β-diethyl-aminoethyl-diphenylpropylacetate hydrochloride) (Smith, Kline and French); atropine sulphate (BDH); heparin (Roche); mecamylamine hydrochloride (Merck, Sharp and Dohme); propranolol hydrochloride (ICI) and (+)-tubocurarine chloride BP (BDH).

Doses of atropine sulphate, pindolol and isoprenaline sulphate are expressed as base equivalents. Doses of propranolol hydrochloride, mecamylamine hydrochloride and (+)-tubocurarine chloride are expressed as the salts.

Pindolol was suspended in water for oral administration, and dissolved in acidified saline (pH 5) for intravenous injection. Other drugs were dissolved in saline.

Statistical analysis

Data were analysed by Student's t test; P values < 0.05 were considered significant.

Results

Effect of oral pindolol on the blood pressure and heart rate of conscious normotensive rats

Pindolol, 10 or 25 μg/kg did not significantly alter blood pressure, whilst 50 μg/kg produced a significant hypotension (11–16 mmHg) for 4 hours. Pindolol, 10 μg/kg, did not alter heart rate in normotensive rats, but 25 μg/kg produced a significant tachycardia (29–33 beats/min) at 1, 2 and 4 h after dosing, and 50 μg/kg evoked a more marked response (47–54 beats/min) for 4 hours.

Effect of oral pindolol on the blood pressure and heart rate of conscious DS-rats

In DS-rats pindolol, 0.5 or 2.5 μg/kg, did not significantly affect blood pressure or heart rate. A significant and dose-dependent hypotension was produced by pindolol at doses of 10 μg/kg (1–3 h), 25 μg/kg (1–4 h), and 50 μg/kg (1–4 h) (Figure 1a). In the same studies pindolol, 10 μg/kg, did not significantly alter heart rate whilst 25 or 50 μg/kg significantly increased heart rate for 3 h after dosing (Figure 1b).

Effect of propranolol on the blood pressure and heart rate response evoked by oral pindolol in conscious DS-rats

Simultaneously administered propranolol, 5 mg/kg intraperitoneally, abolished the fall in blood pressure produced by pindolol, 50 μg/kg, between 1 and 4 h (Figure 2a) and also prevented the significant tachycardia produced by pindolol 1 h after administration (Figure 2b). Compared with control DS-rats, propranolol significantly reduced heart rate between 1 and 4 h and significantly raised blood pressure 1 h after dosing (Figure 2).

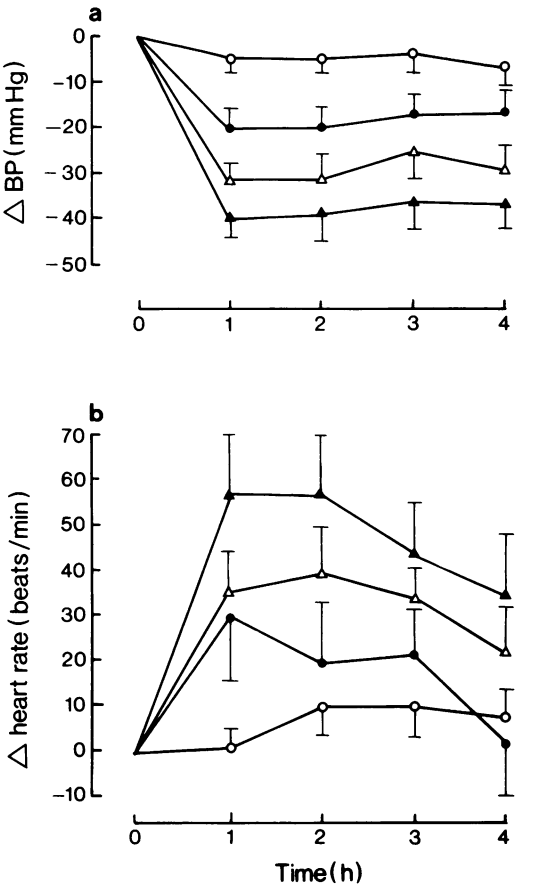

Figure 1 Time course (h) of change in (a) mean arterial blood pressure (ΔBP mmHg) and (b) heart rate (beats/min) of conscious DS-rats, after pindolol, 10 μg/kg (●, $n=12$), 25 μg/kg (Δ, $n=13$), 50 μg/kg (▲, $n=13$) orally or control vehicle (○, $n=13$). Vertical bars show s.e. mean; n is the number of animals per group. The resting mean blood pressure and heart rate of each group were, respectively, for pindolol 10 μg/kg 160 ± 4 mmHg and 375 ± 10 beats/min; for 25 μg/kg 175 ± 6 mmHg and 372 ± 7 beats/min; for 50 μg/kg 173 ± 4 mmHg and 379 ± 6 beats/min; and for the control group, 166 ± 5 mmHg and 368 ± 6 beats/minute.

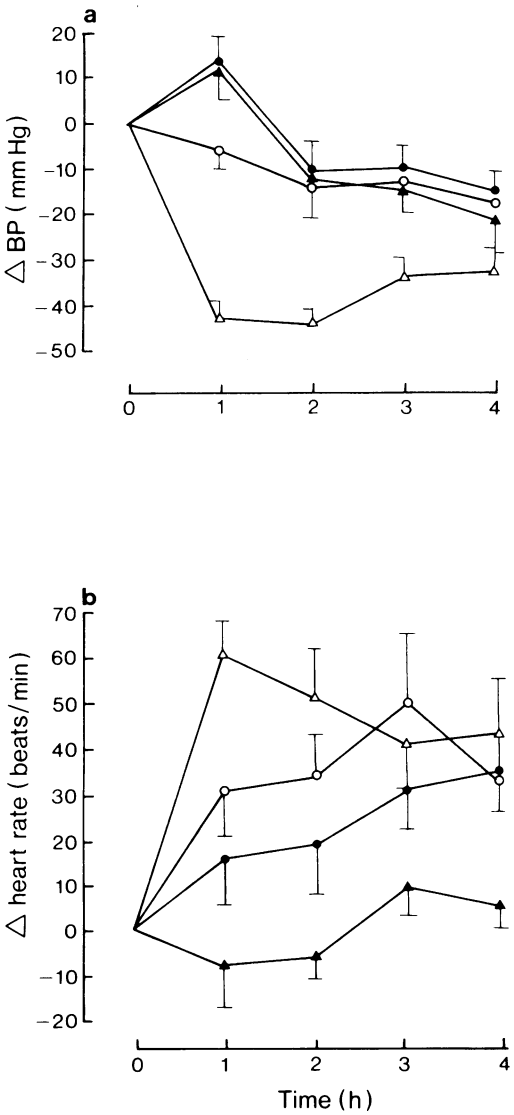

Figure 2 Time course (h) of change in (a) mean arterial blood pressure (ΔBP mmHg) and (b) heart rate (beats/min) of conscious DS-rats after pindolol, 50 μg/kg orally (△, $n=9$), propranolol, 5 mg/kg intraperitoneally (▲, $n=8$), propranolol, 5 mg/kg intraperitoneally + pindolol, 50 μg/kg orally (●, $n=9$) or control vehicle (○, $n=7$). Vertical bars show s.e. mean; n is the number of animals per group. The resting mean blood pressure and heart rate of each group were respectively, for 50 μg/kg pindolol, 162 ± 1 mmHg and 354 ± 9 beats/min; for 5 mg/kg propranolol, 160 ± 5 mmHg and 355 ± 4 beats/min; for the drug combination group, 160 ± 3 mmHg and 342 ± 8 beats/min: and for the control group, 165 ± 3 mmHg and 347 ± 9 beats/minute.

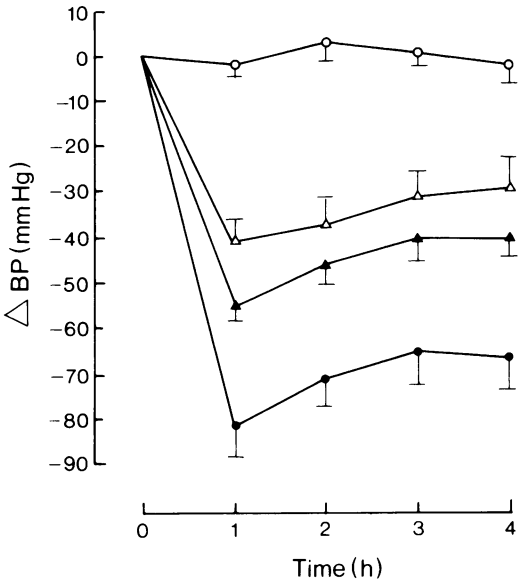

Figure 3 Time course (h) of change in mean arterial blood pressure (ΔBP mmHg) of conscious DS-rats after pindolol, 50 μg/kg orally (△, $n=10$), mecamylamine, 10 mg/kg intraperitoneally (▲, $n=10$), mecamylamine, 10 mg/kg intraperitoneally + pindolol, 50 μg/kg orally (●, $n=9$) or control vehicle (○, $n=9$). Vertical bars show s.e. mean; n is the number of animals per group. The resting mean blood pressure of each group were respectively, for 50 μg/kg pindolol, 145 ± 9 mmHg; for 10 mg/kg mecamylamine, 139 ± 7 mmHg for the drug combination group, 141 ± 9 mmHg; and for the control group, 140 ± 8 mmHg.

Effect of mecamylamine on the blood pressure response evoked by oral pindolol in conscious DS-rats

The hypotensive response which followed simultaneous administration of mecamylamine, 10 mg/kg intraperitoneally, and pindolol, 50 μg/kg, was significantly greater than that produced by either drug alone over the entire 4 h time course (Figure 3).

Effect of oral pindolol pretreatment on neuronally-evoked tachycardia and pressor responses in pithed DS-rats

Heart rate responses. Treatment with pindolol, 10 or 50 μg/kg 2 h previously, significantly reduced the frequency-dependent tachycardia evoked by stimulation of the sympathetic outflow from the spinal cord of pithed DS-rats (Figure 4a).

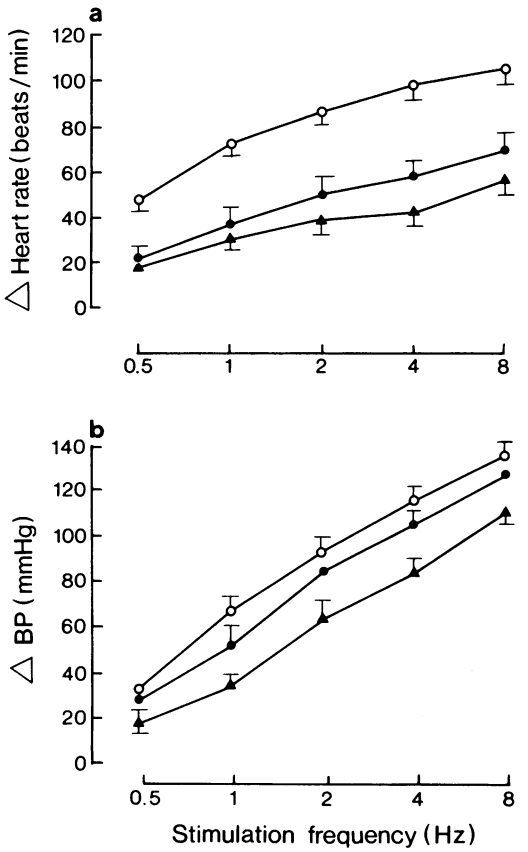

Figure 4 Relationship between frequency of stimulation (Hz) of the spinal cord of pithed DS-rats and (a) increase in heart rate (beats/min) and (b) increase in diastolic blood pressure (ΔBP mmHg) in animals treated 2 h previously with oral pindolol, 10 μg/kg (●), 50 μg/kg (▲), or control vehicle (○). Vertical bars show s.e. mean; 10 animals were used for each group.

Table 1 Effects of oral pindolol treatment (2 h previously) on the basal heart rate and diastolic blood pressure of pithed DS-rats

Pretreatment	*Basal heart rate (beats/min)*	*Basal diastolic blood pressure (mmHg)*
Control ($n=10$)	341 ± 7	43 ± 3
Pindolol 10 μg/kg ($n=10$)	383 ± 14	41 ± 5
50 μg/kg ($n=10$)	390 ± 9	32 ± 2

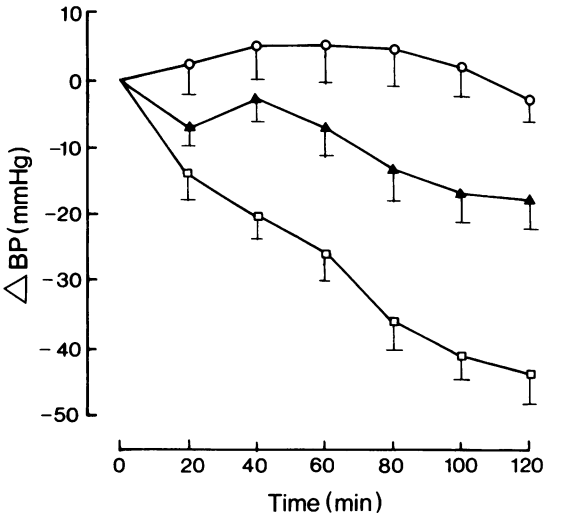

Figure 5 Time course (min) of change in mean arterial blood pressure (ΔBP mmHg) of conscious DS-rats after pindolol, 50 μg/kg intravenously (▲), 50 μg/kg orally (□), or control vehicle (○). Vertical bars show s.e. mean. Groups of 9 rats were used. The resting mean arterial blood pressure and heart rate of each group were for pindolol, 50 μg/kg intravenously, 167 ± 5 mmHg and 375 ± 12 beats/min; for pindolol 50 μg/kg orally, 181 ± 5 mmHg and 379 ± 25 beats/min; and for controls, 168 ± 3 mmHg and 414 ± 15 beats/minute.

Pressor responses. Pretreatment with pindolol, 50 μg/kg, significantly reduced the increase in diastolic blood pressure produced by sympathetic stimulation in pithed DS-rats. Pindolol, 10 μg/kg, produced no significant effect (Figure 4b).

Effect of oral pindolol pretreatment on the basal heart rate and blood pressure of pithed DS-rats

The basal heart rate of pithed DS-rats was significantly elevated and the basal diastolic blood pressure significantly reduced 2 h after treatment with pindolol, 10 or 50 μg/kg (Table 1).

Effect of route of administration on the cardiovascular effects of pindolol in conscious DS-rats

Pindolol, 50 μg/kg orally, produced a significant fall in mean arterial blood pressure (16 mmHg) within 20 min of administration. The magnitude of the response increased with time, a reduction of 40–43 mmHg occurring 80–120 min after dosing (Figure 5). In contrast, pindolol, 50 μg/kg intravenously, was much less effective in lowering blood pressure (Figure 5). The onset of the hypotensive

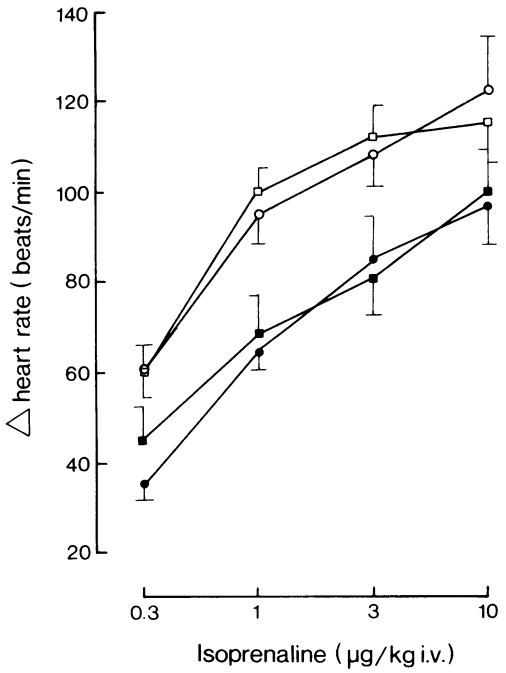

Figure 6 Relationship between dose of isoprenaline (μg/kg i.v.) and increase in heart rate (beats/min) in anaesthetized DS-rats after intravenous control vehicle (○) or intravenous pindolol, 50 μg/kg (●); oral vehicle (□) or oral pindolol, 50 μg/kg (■). Vertical bars show s.e. mean; 7 or 8 animals per group were used for the intravenous study and 10 or 12 animals per group for the oral study.

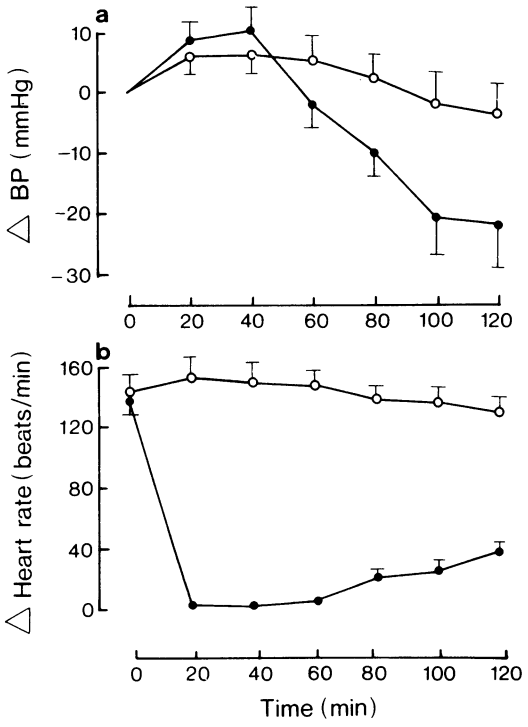

Figure 7 (a) Time course (min) of change in mean arterial blood pressure (ΔBP mmHg) of conscious DS-rats after pindolol, 2 mg/kg intravenously (●), or control vehicle (○). Vertical bars show s.e. mean. Groups of 12 rats were used. The resting mean aterial blood pressure and heart rate of each group were, for pindolol, 2 mg/kg, 178 ± 7 mmHg and 413 ± 13 beats/min, and for controls 180 ± 5 mmHg and 413 ± 11 beats/minute. (b) Time course (min) of increase in resting heart rate produced by isoprenaline, 3 μg/kg intravenously, in controls (○, $n = 11$) and in animals treated with pindolol, 2 mg/kg intravenously (●, $n = 13$). Vertical bars show s.e. mean; n is the number of animals per group.

response was considerably delayed, and a small but significant fall in blood pressure (14–19 mmHg) was observed at 80–120 minutes. The hypotensive response to pindolol, 50 μg/kg intraperitoneally, was similar in time course and magnitude to that produced by this dose orally.

Pindolol, 50 μg/kg orally, produced a significant tachycardia (67 beats/min) at 120 min, whilst 50 μg/kg intravenously significantly raised heart rate at 80 min (50 beats/min) and 100 min (67 beats/minute).

Degree of cardiac β-adrenoceptor blockade produced by pindolol in anaesthetized DS-rats

The degree of cardiac β-adrenoceptor blockade, as estimated by a parallel shift in the isoprenaline (0.3–10 μg/kg intravenously) log dose-response curve, was similar following treatment with pindolol (50 μg/kg) orally (2 h previously) or intravenously (1 h previously) (Figure 6).

Time course of changes in blood pressure, heart rate and degree of cardiac β-adrenoceptor blockade following intravenous pindolol in conscious DS-rats

Following an initial latent period pindolol, 2 mg/kg, produced a significant fall in mean arterial blood pressure (18–19 mmHg) 100–120 min after injection (Figure 7a), without a significant change in heart rate.

In a separate experiment pindolol, 2 mg/kg, produced almost total inhibition of the tachycardia due to isoprenaline, 3 μg/kg intravenously. This antagonism of cardiac β-adrenoceptor stimulation was apparent 20 min after pindolol administration and showed only partial recovery 100 min later (Figure 7b).

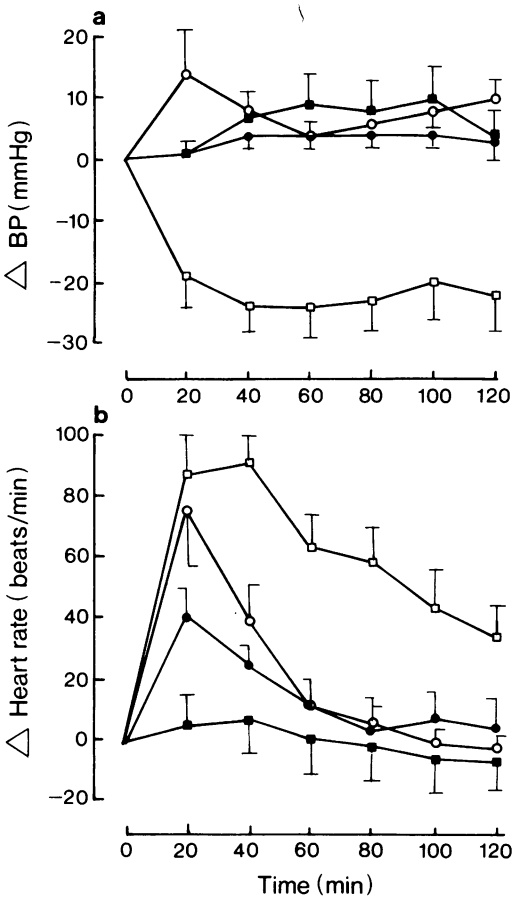

Figure 8 Time course (min) of change in (a) mean arterial blood pressure (ΔBP mmHg) and (b) heart rate (beats/min) of conscious DS-rats. After treatment with Proadifen, 80 mg/kg intraperitoneally, 4 h previously; pindolol, 50 μg/kg orally (■), control vehicle (●). After vehicle pretreatment; pindolol 50 μg/kg orally (□), control vehicle (○). Vertical bars show s.e. mean. Groups of 9 rats were used. The resting mean arterial blood pressure and heart rate of each group were as follows: after Proadifen pretreatment: pindolol, 145 ± 9 mmHg and 351 ± 10 beats/min; controls, 148 ± 10 mmHg and 347 ± 10 beats/min; after vehicle pretreatment: pindolol, 131 ± 6 mmHg and 359 ± 13 beats/min; controls, 134 ± 7 mmHg and 340 ± 6 beats/minute.

Effect of Proadifen (SKF 525-A) pretreatment on the cardiovascular effects of oral pindolol in conscious DS-rats

In vehicle-pretreated DS-rats pindolol, 50 μg/kg, significantly reduced mean arterial blood pressure (28–33 mmHg) over the entire 2 h time course (Figure 8a). In addition, heart rate was significantly elevated (31–53 beats/min) in these animals between 40 min and 2 h after pindolol administration (Figure 8b). After treatment with Proadifen, 80 mg/kg intraperitoneally 4 h previously, the hypotensive response to pindolol was prevented and no tachycardia was observed. Indeed, pindolol produced a significant net reduction in heart rate (36 beats/min) 20 min after administration in Proadifen pretreated rats.

Discussion

In acute studies pindolol (10, 25 or 50 μg/kg orally) dose-dependently reduced mean arterial blood pressure and elevated resting heart rate in conscious DS-rats. A fall in blood pressure was also observed in normotensive rats treated with pindolol, 50 μg/kg orally, suggesting that the drug's activity is hypotensive in nature and independent of any aetiological factor(s) specific to hypertensive rats. In DS-rats propranolol prevented the pindolol-induced tachycardia and hypotension, suggesting that these cardiovascular effects are mediated by β-adrenoceptor stimulation. Furthermore, in the presence of ganglion blockade produced by mecamylamine, pindolol induced a further fall in arterial blood pressure, indicating that the drug's hypotensive action is mediated post-ganglionically. These results are consistent with the hypothesis that the effects on blood pressure and heart rate produced by orally administered pindolol in DS-rats are due to partial agonist activity at vascular β_2-adrenoceptors (subserving vasodilatation) and cardiac β_1-adrenoceptors respectively. Partial agonist activity of pindolol at cardiac β-adrenoceptors has also been recognized by Barrett & Carter (1970). Results of studies in the pithed DS-rat are consistent with the observations in conscious animals. Hence a vasodilator effect probably accounts for the observed reductions in basal diastolic pressure and in neuronally-evoked pressor responses in pithed rats pretreated with pindolol, 50 μg/kg orally. Furthermore pindolol (10 or 50 μg/kg orally) increased the basal heart rate of pithed DS-rats and reduced the neuronally-evoked tachycardia, suggesting the presence of both partial agonist activity and measurable cardiac β-adrenoceptor blocking activity. However, the apparent degree of cardiac β-adrenoceptor blockade may have been exaggerated as a result of the raised resting heart rate following pindolol pretreatment.

The magnitude and time course of pindolol's hypotensive effect were dependent upon route of drug administration. When pindolol, 50 μg/kg, was adminstered orally or intraperitoneally to conscious DS-rats, a marked and progressive hypotensive response of rapid onset was produced. In contrast, the

same dose given intravenously resulted in a smaller hypotensive effect with a delayed onset. This difference in the pattern of hypotensive response could not be attributed to a difference in the degree of β-adrenoceptor blockade since in anaesthetized DS-rats, pretreatment with pindolol, 50 μg/kg orally (2 h previously) or intravenously (1 h previously) resulted in a similar degree of cardiac β-adrenoceptor blockade by either route. This independence between the time-course of the hypotensive response and β-adrenoceptor blocking activity was further illustrated following intravenous injection of pindolol, 2 mg/kg, to DS-rats. Once again the hypotensive effect of pindolol was delayed in onset (100 min), whereas the heart rate response to a standard dose of isoprenaline was virtually abolished throughout the first 60 min in a parallel study. These results are consistent with the suggestion that pindolol itself is devoid of hypotensive activity in DS-rats, and that metabolic activation of the drug is required for the expression of its effects on arterial blood pressure and heart rate in this model. The observation that the hypotension and tachycardia normally associated with oral pindolol administration were prevented by pretreatment with Proadifen, an inhibitor of metabolic enzymes, adds further support to this hypothesis. The results suggest, therefore, that whilst pindolol and probably the active metabolite(s) possess β-adrenoceptor blocking properties, the hypotensive activity resides solely in the metabolite(s).

The literature contains a puzzling lack of uniformity with respect to the proposed partial agonist activity of pindolol. Whilst the drug has been shown to possess sympathomimetic activity in rabbit isolated atria (Lubawski & Wale, 1969) and in catecholamine-depleted rat hearts *in vivo* (Barrett & Carter, 1970), no such properties could be shown in canine isolated papillary muscle (Hashimoto, Endoh, Tamura & Taira, 1970) or in intact dogs (Giudicelli *et al.*, 1969), cats (Lubawski & Wale, 1969) or rats (Robak & Gryglewski, 1971). In at least 2 studies in guinea-pig isolated atria (Grodzinska & Gryglewski, 1971) and tracheal chain (Moore & O'Donnell, 1970) the observed sympathomimetic effects of pindolol were attributed to an indirect action involving release of endogenous noradrenaline. In our studies also we have been unable to provide any evidence to suggest that pindolol itself possesses partial agonist activity.

On the basis of metabolic considerations alone there would be no justification in drawing any parallel between these results in DS-rats and observations on pindolol's antihypertensive action in man. For instance in the rat, the biological half-life for the disappearance of pindolol from plasma, following oral or intravenous administration, is reported to be approximately 30 min (Pacha, 1969). Moreover in rats, pindolol is extensively metabolized, the metabolites arising principally from side-chain conjugation with glucuronic acid, hydroxylation or oxidation and conjugation of the indole ring, and oxidative ring scission (Kiechel *et al.*, 1975). In contrast, the biological half-life of pindolol in human plasma, following oral administration, is reported to be approximately 3 h (Pacha, 1969). Furthermore, 40% of an oral dose of pindolol is excreted unchanged in the urine and more than 90% of the metabolites are glucuronides and sulphates (Ohnhaus, Nuesch, Meier & Kalbarer, 1974). Certainly there is no evidence to suggest that pindolol's clinical effectiveness as an antihypertensive drug is in any way attributable to partial agonist activity.

References

BARRETT, A.M. & CARTER, J. (1970). Comparative chronotropic activity of β-adrenoceptive antagonists. *Br. J. Pharmac.*, **40**, 373–381.

BUCKINGHAM, R.E. (1976). Indwelling catheters for direct recording of arterial blood pressure and intravenous injection of drugs in the conscious rat. *J. Pharm. Pharmac.*, **28**, 459–461.

COLLINS, I.S. & KING, I.W. (1972). Pindolol (Visken, LB 46) a new treatment for hypertension: report of a multicentric open study. *Curr. Ther. Res.*, **14**, 185–194.

FELTHAM, P.M., WATSON, O.F., PEEL, J.S., DUNLOP, D.J. & TURNER, A.S. (1972). Pindolol in hypertension: A double-blind trail. *N.Z. med. J.*, **76**, 167–171.

GARVEY, H.L. & RAM, N. (1975). Comparative antihypertensive effects and tissue distribution of beta-adrenergic blocking drugs. *J. Pharmac. exp. Ther.*, **194**, 220–233.

GILLESPIE, J.S. & MUIR, T.C. (1967). A method of stimulating the complete sympathetic outflow from the spinal cord to blood vessels in the pithed rat. *Br. J. Pharmac. Chemother.*, **30**, 78–87.

GIUDICELLI, J.F., SCHMITT, H. & BOISSIER, J.R. (1969). Studies on *dl*-4-(2-hydroxy-3-isopropylaminopropoxy)-indole (LB 46), a new potent *beta* adrenergic blocking drug. *J. Pharmac. exp. Ther.*, **168**, 116–126.

GRODZINSKA, L. & GRYGLEWSKI, R. (1971). Action of beta-adrenolytics on the isolated guinea-pig atria. *Arch. int. Pharmacodyn.*, **191**, 133–141.

HASHIMOTO, K., ENDOH, M., TAMURA, K. & TAIRA, N. (1970). Comparison of β-adrenergic blocking activity of DCI, H 56/28, ICI 50, 172, LB 46, methoxamine, MJ 1999 and propranolol in the blood perfused canine papillary muscle preparation. *Experientia*, **26**, 757–759.

KIECHEL, J.R., NICKLAUS, P., SCHREIER, E. & WAGNER, H. (1975). Metabolites of pindolol in different animal species. *Xenobiotica.*, **5**, 741–754.

LUBAWSKI, I. & WALE, J. (1969). Studies with LB 46, a new β-receptor blocking drug. *Eur. J. Pharmac.*, **6**, 345–348.

MOORE, G.E. & O'DONNELL, S.R. (1970). A potent β-adrenoceptor blocking drug: 4-(2-hydroxy-3-isopropylaminopropoxy) indole. *J. Pharm. Pharmac.*, **22**, 180–188.

MORGAN, T.O., LOUIS, W.J., DAWBORN, J.K. & DOYLE, A.E. (1972). The use of pindolol (Visken) in the treatment of hypertension. *Med. J. Aust.*, **2**, 309–312.

MORGAN, T.O., SABTO, J., ANAVEKAR, S.N., LOUIS, W.J. & DOYLE, A.E. (1974). A comparison of β-adrenergic blocking drugs in the treatment of hypertension. *Postgraduate med. J.*, **50**, 253–259.

OHNHAUS, E.E., NÜESCH, E., MEIER, J. & KALBARER, F. (1974). Pharmacokinetics of unlabelled and ^{14}C-labelled pindolol in uraemia. *Eur. J. clin. Pharmac.*, **7**, 25–29.

PACHA, W.L. (1969). A method for the fluorimetric determination of 4-(2-hydroxy-3-isopropylamino-propoxy)-indole (LB 46), a β-blocking agent, in plasma and urine, *Experientia*, **25**, 802–803.

ROBAK, J. & GRYGLEWSKI, R. (1971). Influence of INPEA, pindolol and propranolol on the chronotropic and metabolic responses to β-adrenergic stimulation in intact rats. *Biochem. Pharmac.*, **20**, 2749–2758.

SIMPSON, F.O. (1974). β-adrenergic receptor blocking drugs in hypertension. *Drugs*, **7**, 85–105.

STOKES, G.S., WEBER, M.A. & THORNELL, I.R. (1974). β-blockers and plasma renin activity in hypertension. *Br. med. J.*, **1**, 60–62.

TAKEDA, K., SAKURAI, H. & IMAI, S. (1975). Antihypertensive effects of β-blockers in hypertensive rats. *Jap. J. Pharmac.*, **25**, 82–84.

THORPE, P. (1972). A controlled study of pindolol (Visken) in hypertension. *Med. J. Aust.*, **2**, 306–309.

VAN COLLER, P.E. (1973). Clinical experience with Visken (Pindolol) in essential hypertension: its special comparative action to Aldomet (Methyldopa). *J. Int. Med. Res.*, **1**, 561–566.

WAAL-MANNING, H.J. & SIMPSON, F.O. (1975). Paradoxical effect of pindolol. *Br. med. J.*, **3**, 155–156.

WEBER, M.A., THORNELL, I.R. & STOKES, G.S. (1973). Effects of beta adrenergic blocking agents on plasma renin activity in the conscious rabbit. *J. Pharmac. exp. Ther.*, **188**, 234–240.

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