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CIRCULATORY AND α-ADRENOCEPTOR BLOCKING EFFECTS OF PHENTOLAMINE

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1 Intravenously administered phentolamine provoked immediate decreases in diastolic blood pressure but increases in heart rate and cardiac output.

2 These immediate circulatory effects had largely disappeared twenty minutes after administration and at this time phentolamine did not inhibit increases in blood pressure which were provoked during hand immersion in ice-cold water.

3 Log dose-response curves of noradrenaline induced increases in systolic and diastolic pressure 20 min after intravenous phentolamine were shifted to the right in a parallel manner compared with the curves before phentolamine administration.

4 It was concluded that the immediate and short acting effects induced by phentolamine are due to a non-specific vasodilator effect but in addition phentolamine causes a longer acting α-adrenoceptor blockade at vascular adrenoceptor sites. However, by producing both pre-and post-synaptic α-adrenoceptor blockade this may explain why this drug exerts only a weak antihypertensive effect.

Introduction

Phentolamine was introduced into therapeutics as an antihypertensive agent (Moyer & Caplowitz, 1953) but was quickly found to be impractical in use because of limited antihypertensive effect and unacceptable side effects. More recently its use has been revived as an antihypertensive agent in combination with β-adrenoceptor blocking drugs (Majid, Meeran, Benaim, Sharma & Taylor, 1974). Its use in this context has been advocated because of its effects upon the circulation which in combination with β-adrenoceptor blockade provided obvious beneficial circulatory effects (Majid *et al.*, 1974).

In hypertensive patients phentolamine administered intravenously produced satisfactory lowering of blood pressure and chronic oral administration in combination with a β-adrenoceptor blocking agent maintained satisfactory control of blood pressure in the group. (Majid *et al.*, 1974). However, using the same daily dose of oral phentolamine as used by Majid *et al.*, (1974), two other groups of investigators failed to show any enhanced reduction in blood pressure from the phentolamine over that already achieved with a β-adrenoceptor blocking drug alone (Johnson, Labrooy & Munro-Faure, 1976; Winchester Ward McKillop & Kennedy 1976). It is possible therefore that in man the α-adrenoceptor blocking effects of phentolamine may be short-lived and/or relatively weak. It has been shown that phentolamine does not inhibit the sympathetically mediated component of Valsalva's manoeuvre (Taylor, Sutherland, MacKenzie, Staunton & Donald, 1965 a), nor the forearm vasoconstriction induced by supine leg exercise (Taylor, Sutherland *et al.*, 1965 a). We have investigated the α-adrenoceptor blocking property of phentolamine in two studies; in one using a physiological approach with a cold pressor test which depends upon reflexly mediated vasoconstriction and in the other by inducing a pressor response exogenously by infusing noradrenaline intravenously. Some of these data have been presented in preliminary form elsewhere (Maconochie, Richards & Woodings 1977).

Methods

Study 1

Seven normal male subjects took part whose ages ranged from 20–40 years and weights from 61–87 kg. In each subject blood pressure was measured in the left arm using an Elag-Koln automatic sphygmomanometer and heart rate taken from a Narco biosystems biotachometer. In addition cardiac impedance was recorded on an IMF Impedance Cardiograph which necessitated placing electrodes on

the chest and neck in order to obtain traces of thoracic impedance. An electrocardiogram and phonogram were also obtained.

Each subject lay in the supine position throughout and at 5 min intervals during a 15 min period, blood pressure and heart rate were recorded. Five minutes before drug administration, a recording of cardiac impedance was made. Under double-blind conditions on a randomised basis, each subject then received either intravenous phentolamine 0.1 mg/kg or sterile water as placebo. On each occasion the drug was injected over a period of 1 min. Blood pressure and heart rate were recorded at minute intervals over the subsequent 10 min period and cardiac impedance at 1, 3 and 8 min after completion of the injection.

Nine minutes after drug administration each subject then placed his hand into warm water at 30°C for 1 min during which blood pressure and heart rate were recorded at 30 and 60 s of this period. This procedure was used only to familiarize the subjects with the technique and was repeated formally, 14 min after drug administration. Measurement of cardiac impedance was also obtained before and at 30 and 60 s during water immersion.

Twenty minutes after drug administration the subject's hand was immersed in cold water at 0°C for a period of 1 min and all measurements repeated. Either at the beginning or at the end of the whole procedure 1 ml of blood was obtained for the determination of haematocrit for use in the calculation of cardiac impedance.

Study 2

Five normal male subjects aged 30–41 years weighing 59–74 kg took part. Each subject rested supine for at least 15 min during which an antecubital vein was cannulated with a butterfly needle which was maintained patent by slow infusion with heparinized saline. Chest electrodes were attached and an electrocardiogram was obtained throughout. Blood pressure was measured with a London School of Hygiene and Tropical Medicine sphygmomanometer (Rose, Holland and Crowley 1964).

When the subject's blood pressure and heart rate were stable, noradrenaline was infused intravenously commencing at a rate of 4 μg/min for 4 min followed by 8 μg/min for 4 min and 16 μg/min for a further 4 min in order to plot a log-dose response curve of increases in blood pressure. During this procedure blood pressure was measured at 1 min intervals. After an interval of 15 min during which time blood pressure and heart rate returned to normal, phentolamine 0.1 mg/kg was injected intravenously over a period of 1 min. Over the next 10 min, blood pressure and heart rate were recorded at 1 min intervals. Twenty minutes after phentolamine administration noradrenaline was again infused. On this occasion the infusion rate was 8, 16 and 32 μg/min, each for 4 min, since the objective was to increase the blood pressure to the same extent as observed before phentolamine.

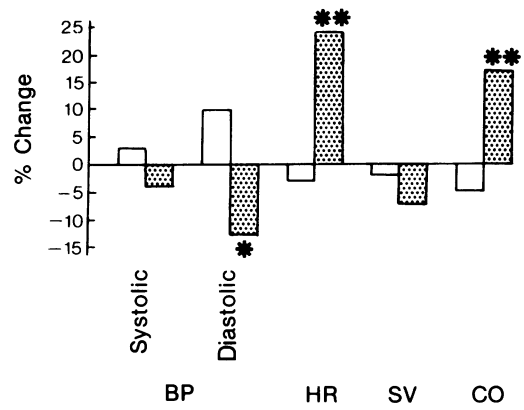

Figure 1 Circulatory changes after i.v. phentolamine (■, 0.1 mg/kg) and placebo (□). * $P<0.05$; ** $P<0.001$. HR heart rate; SV stroke volume; CO cardiac output.

Analysis of data

Data in study 1 were subjected to analysis of variance and quoted P values refer to differences between the values after phentolamine compared with placebo. Because of the type of measurement obtained with impedance cardiography, the effects of phentolamine and placebo were assessed as relative differences from pre-treatment control values in each case. Log-dose response curves of increases in blood pressure induced by noradrenaline were constructed using the method of least squares and tested for non-parallelism.

Results

Immediate circulatory effects (Study 1)

One minute after phentolamine administration average mean (±s.e.mean) diastolic blood pressure was significantly reduced by 20 (3.3) mmHg compared with the equivalent placebo value ($P<0.05$). At the same time a significant increase occurred in mean heart rate of 14 (1.7) beats/min ($P<0.001$) (Table 1). Mean cardiac output increased by 17% compared with pre-treatment and this differed significantly from the change during placebo administration ($P<0.001$). Stroke volume was reduced by a mean of 8% but this did not differ significantly from the change after placebo (Figure 1). These immediate circulatory changes returned to normal twenty minutes after administration except for mean heart rate which remained somewhat elevated.

Table 1 Cardiovascular changes in seven subjects after i.v. phentolamine 0.1 mg/kg and placebo and after hand immersion

	Time (min)	*−5*	*1*	*3*	*8*	*Warm immersion 15*	*30s*	*60s*	*Cold immersion 20*	*30s*	*60s*
Heart rate (beats/min)	Phentolamine	73	82**	87*	80*	78	80	76	79	86	84
	Placebo	71	68	68	69	70	72	69	69	77	76
	s.e.mean	1.4	1.4	1.7	1.6	1.1	1.3	1.3	1.1	2.6	1.9
Blood pressure (mmHg)	Phentolamine	126/68	121/59*	124/60*	125/69	124/69	128/71	126/74	127/70	134/81	142/94
	Placebo	120/70	123/79	124/76	122/75	121/76	122/79	123/76	123/79	129/95	140/103
	s.e.mean	2.1/2.4	2.7/3.3	2.3/2.9	2.5/2.9	2.8/3.3	2.6/2.2	2.6/2.2	2.7/3.0	2.2/3.4	2.7/3.0
Stroke volume (ml)	Phentolamine	104	95	102	105	105	103	100	105	92	90
	Placebo	121	118	112	117	115	116	115	110	103	106
	s.e.mean	3.3	4.3	3.5	4.1	4.5	4.1	4.2	4.7	6.7	6.3
Cardiac output (l/min)	Phentolamine	6.6	7.7	7.5	7.2	7.1	6.9	6.6	7.3	7.2	6.9
	Placebo	7.4	7.0	6.9	7.1	6.9	7.2	7.1	6.8	7.4	7.1
	s.e.mean	2.8	4.4	3.5	2.9	2.8	2.6	2.9	2.3	2.6	2.3

* $P < 0.05$ difference from placebo
** $P < 0.001$ difference from placebo
s.e.mean—analysis of variance

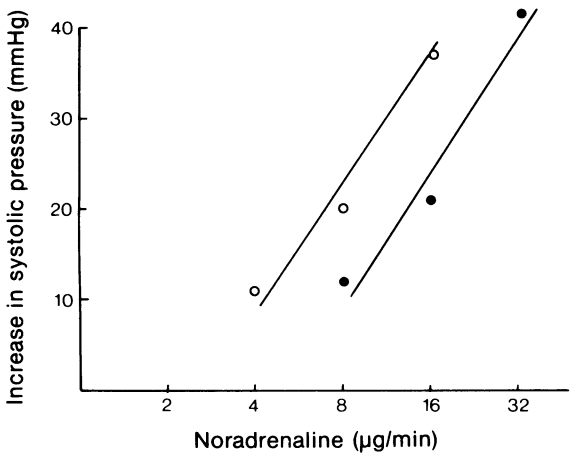

Figure 2 Noradrenaline-induced increases in systolic pressure before (O) and after (●) phentolamine (0.1 mg/kg).

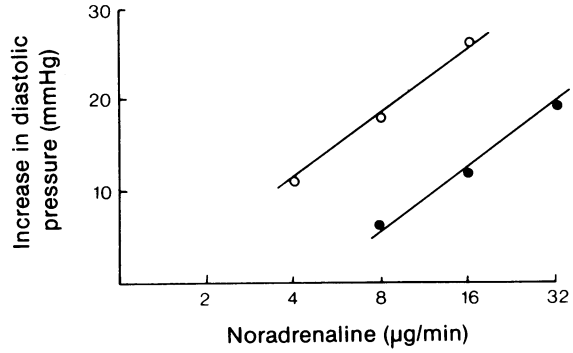

Figure 3 Noradrenaline-induced increases in diastolic pressure before (O) and after (●) phentolamine (0.1 mg/kg).

Effects of cold immersion

Cold immersion for 1 min provoked increases in average (±s.e. mean) systolic blood pressure of 15 (2.7) mmHg after phentolamine and 17 (2.7) mmHg after placebo. Diastolic blood pressure increased by averages of 24 (3.0) mmHg and 24 (3.0) mmHg respectively (Table 1). These changes after phentolamine did not differ significantly from those after placebo. The average (±s.e. mean) diastolic pressure on completion of the cold immersion procedure was 94 ± 3.0 mmHg after phentolamine whereas after placebo it was 103 ± 3.0 mmHg. However, these values were not significantly different. There were small increases in mean heart rate during the cold immersion of 5 (1.8) and 7 (1.9) beats/min during phentolamine and placebo treatment respectively (Table 1). There was no change of any note in mean stroke volume or cardiac output during cold immersion irrespective of prior treatment with phentolamine or placebo.

Effects of increasing doses of noradrenaline

In the second study, after intravenous phentolamine average diastolic blood pressure was reduced by 8 (2.4) mmHg at maximum compared with the pre-phentolamine value but mean heart rate increased by 21 (1.7) beats/min.

During the infusion of noradrenaline increasing the dose to 16 μg/min produced average (±s.e.mean) increase in systolic blood pressure of 37 (5.6) mmHg and in diastolic blood pressure of 26 (2.8) mmHg (Table 2). During the same period mean heart rate was reduced from 75 (3.4) to 56 (5.1) beats/min. Twenty minutes after phentolamine the noradrenaline infusion was repeated using higher doses and subsequently log-dose response curves were constructed for increases in systolic pressure (Figure 2) and diastolic pressure (Figure 3) before and after phentolamine administration. In each case the log-dose response curve after phentolamine was shifted to the right in a parallel manner.

Discussion

The immediate circulatory effects of intravenous phentolamine producing marked reductions in diastolic blood pressure but increases in heart rate and cardiac output in normal subjects, were consistent with those previously reported by Taylor, Sutherland, Mackenzie, Staunton & Donald (1965 b). They concluded that the immediate effects of phentolamine upon the cardiovascular system were predominantly due to a direct non-specific vasodilator effect. Indeed, based upon evidence from their extensive studies in man (Taylor, MacKenzie *et al.*, 1965; Sutherland *et al.*, 1965 a, b), it appears that this direct vasodilator effect is much more active than the additional α-adrenoceptor blocking effect for which phentolamine is noted.

Hand immersion in ice-cold water provokes marked increases in systolic and diastolic blood pressure (Hines & Brown 1932). The perception of pain plays an important role in the generation of the pressor response (Wolf & Hardy, 1941) but studies of the haemodynamic events occuring during the pressor response show that the major change induced is an increase in peripheral resistance and there are only minor changes in heart rate and cardiac output (Cuddy, Smulyan, Keighley, Markason & Eich, 1966).

β-adrenoceptor blockade with propranolol in hypertensive patients did not inhibit cold induced pressor responses (Guazzi, Fiorentine, Polese, Olivari & Magrini, 1976). Propranolol was also ineffective in normal subjects but the combined α- and β-adrenoceptor blockade induced by labetalol produced a significant inhibitory effect upon the pressor responses (Maconochie *et al.*, 1977). In that study propranolol and labetalol were used in comparable β-adrenoceptor blocking doses. In addition, that dose of labetalol has been shown to possess significant α-adrenoceptor blocking activity (Richards, Tuckman & Prichard 1976). From this it was concluded that it was the α-adrenoceptor blocking component of labetalol which was responsible for the pressure inhibitory effects observed. However, from observations made in the present study of phentolamine it is clear that although this drug exerted a marked vasodilator effect leading to immediate circulatory changes, it did not exert any inhibitory effect upon the increase in pressure induced by cold.

Nevertheless we have shown that at the same dose level and after the same time-lapse, intravenously administered phentolamine did antagonize the pressor

Table 2 Cardiovascular responses to i.v. noradrenaline before and after phentolamine

		Before		*After phentolamine (0.1 mg/kg i.v.)*	
	Subject	*Blood pressure (mmHg)*	*Heart rate (beats/min)*	*Blood pressure (mmHg)*	*Heart rate (beats/min)*
Control	1	92/62	70	102/64	80
	2	113/72	75	117/78	80
	3	116/63	65	114/57	65
	4	98/58	84	111/67	96
	5	109/77	80	120/78	92
	Mean	106/66	75	113/69	83
	(±s.e.mean)	(4.6) (3.5)	(3.4)	(3.1) (4.1)	(5.4)
Noradrenaline (4 μg/min)	1	106/75	70		
	2	123/83	50		
	3	127/73	60		
	4	112/72	76		
	5	115/80	72		
	Mean	117/77	66		
	(±s.e.mean)	(3.8) (2.1)	(4.7)		
Noradrenaline (8 μg/min)	1	110/81	70	110/75	65
	2	124/85	50	129/82	80
	3	142/87	55	133/68	60
	4	132/85	82	128/76	74
	5	121/80	66	—	—
	Mean	126/84	65	125/75	70
	(±s.e.mean)	(5.4) (1.3)	(5.7)	(5.1) (2.9)	(4.5)
Noradrenaline (16 μg(min)	1	134/96	70	124/81	60
	2	146/95	45	137/84	65
	3	160/99	45	149/78	55
	4	148/88	56	139/79	72
	5	128/84	68	122/82	82
	Mean	143/92	56	134/81	67
	(±s.e.mean)	(5.6) (2.8)	(5.1)	(5.0) (1.1)	(4.8)
Noradrenaline (32 μg/min)	1			138/88	55
	2			150/88	58
	3			177/82	55
	4			157/85	72
	5			148/91	72
	Mean			154/87	62
	(±s.e.mean)			(8.3) (1.9)	(4.0)

effects of exogenous noradrenaline. Indeed log-dose response curves of increases in systolic and diastolic pressure were shifted to the right after phentolamine in a manner suggestive of competitive antagonism at vascular α-adrenoceptor sites. Thus the failure of phentolamine to inhibit the pressor response to cold was not likely to be due to a short lasting α-adrenoceptor blocking effect. However, the type of α-adrenoceptor blockade produced by phentolamine might explain its failure to inhibit vasoconstrictor responses induced by physiological mechanisms. It has been shown in other circumstances where physiological responses are involved, that the α-adrenoceptor blocking effect of phentolamine does not significantly influence the sympathetically mediated components of the Valsalva manoeuvre (Taylor, Sutherland *et al.*, 1965 b), nor does it inhibit the increase in forearm vascular resistance due to supine leg exercise (Taylor, MacKenzie *et al.*, 1965). It is now known that there are α-adrenoceptors situated at sympathetic nerve terminals i.e. pre-synaptic α-adrenoceptors which take part in a negative feed-back system which particularly under conditions of high sympathetic nerve outflow reduce the output of noradrenaline from those nerve terminals (Langer, Adler, Enero & Stefano, 1971). It is to be expected therefore under conditions of high adrenergic activity which appears to be the case during Valsalva's manoeuvre and cold provocation, the pre-synaptic α-adrenoceptor blockade would tend to limit any post-synaptic blockade affecting the end-organ responses. This type of α-adrenoceptor blockade therefore is likely to be self-limiting in situations where there are high levels of physiological stimulation. It has been established in animal studies that phentolamine blocks pre- and post-synaptic α-adrenoceptors concurrently and that the blockade of pre-synaptic sites is the more active (Doxey, Smith & Walker 1977). If this is true in man then this type of adrenoceptor blockade would be self-limiting to powerful physiological stimuli and may explain why phentolamine failed to block the cold pressor response. However, in the case of labetalol this drug produces blockade of post-synaptic α-adrenoceptors without affecting those at pre-synaptic sites (Blakeley & Summers, 1977) and this may explain why it did inhibit the α-adrenoceptor mediated vasoconstrictor effects induced by cold immersion (Maconochie *et al.*, 1977).

Exogenously infused noradrenaline stimulates post-synaptic vascular α-adrenoceptors to produce pressor responses such as we observed. It is unlikely that pre-synaptic α-adrenoceptor activity would influence these responses under the conditions of the study and thus the effects of phentolamine in this context are probably due to its ability to block post-synaptic α-adrenoceptors. Furthermore, this evidence is consistent with extensive data on phentolamine describing it as an α-adrenoceptor blocking agent.

It is interesting to note that the circulating effects of oxprenolol plus phentolamine which were described by Majid *et al.*, (1974) as being beneficial, occurred when phentolamine was being infused intravenously. Subsequent studies of chronically administered phentolamine have failed to confirm a beneficial anti-hypertensive effect (Johnson *et al.*, 1976; Winchester *et al.*, 1976). In our study in normal subjects we have shown that intravenously administered phentolamine in doses recommended for clinical usage does have a marked blood pressure lowering effect but that its circulatory effects are short-lived. Furthermore, phentolamine does antagonize in a competitive manner the pressor effects of exogenous noradrenaline but does not seem to inhibit pressor responses which are reflexly mediated. Thus it seems that the type of α-adrenoceptor blockade induced by phentolamine would lead to a restricted antihypertensive effect in chronic usage and suggests an explanation why the drug is of limited value as an antihypertensive agent.

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