THE EFFECT OF A SINGLE ORAL DOSE OF PRAZOSIN ON VENOUS REFLEX RESPONSE, BLOOD PRESSURE AND PULSE RATE IN NORMAL VOLUNTEERS

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- 1 A single 500 μ g oral dose of prazosin was associated with significant suppression of sympathetically mediated venoconstriction, as measured by the venous reflex response in six healthy volunteers.
- 2 The impaired venous reflex response consistently preceded orthostatic hypotension and tachycardia, which were associated with faintness and other unpleasant symptoms.
- 3 The plasma prazosin concentration, which was measured by a sensitive, specific h.p.l.c. assay, varied appreciably both between and within individual subjects.
- 4 There was no precise relationship between the plasma prazosin concentration and the symptomatic haemodynamic effects observed.
- 5 It was concluded that reduced venous return to the heart, due to significant suppression of sympathetically mediated venoconstriction by small initial oral dosage of prazosin, contributes to the pathophysiology of the orthostatic hypotension and faintness, described as the 'first-dose phenomenon'.

Introduction

The pharmacologically relevant neural control of peripheral blood vessels is provided by their adrenergic innervation from the sympathetic nervous system (Nies, 1978; Philipp, Distler & Cordes, 1978). Sympathetic adrenergic nerves stimulate both the resistance and capacitance vessels (Shepherd & Vanhoutte, 1978). Changes in systemic venous capacity, by altering venous return to the heart, are capable of disturbing cardiac output sufficiently to produce significant changes in arterial blood pressure (Müller-Rucholtz *et al.*, 1979). Peripheral venoconstriction, measured by the venous reflex response (VRR), has been demonstrated during vasovagal syncope (Epstein, Stampfer & Beiser, 1968). Orthostatic hypotension produced by guanethidine has also been related to sympathetically mediated changes in venous tone, measured by the VRR, when the dietary sodium of hypertensive patients was restricted (Walter *et al.*, 1975).

Current clinical and experimental evidence is consistent with the hypotensive effect of prazosin being mediated via reduced peripheral vascular tone due to selective α -adrenoceptor blockade (Cohen, Wiley & Slater, 1979; Commarato *et al.*, 1978; Davey, 1980; Jauernig, Moulds & Shaw, 1978; Oates, 1979;

Pedersen, Mikkelsen & Andersson, 1979; Stokes & Oates, 1978). The antihypertensive effect of drugs which interfere with sympathetic function is not always predictable. The lack of predictability is exemplified for prazosin by the so-called 'first-dose phenomenon', which is characterized by transient faintness, rarely syncope and palpitation associated with orthostatic hypotension (Bendall, Baloch & Wilson, 1975; Graham *et al.*, 1976; Rosendorff, 1976; Simpson, Bolli & Wood, 1977; Stokes *et al.*, 1977; Turner, Watson & Brocklehurst, 1977). This acute adverse syndrome has been reported to occur in 2% to 100% of hypertensive patients within the first few hours after initiating or increasing treatment with prazosin (Stokes & Oates, 1978).

Previous investigation of the effect of prazosin on forearm blood flow, in both normal subjects and patients with cardiac dysfunction (Awan *et al.*, 1977) demonstrated a decline in forearm venous tone concomitant with a marked decrease in forearm vascular resistance. Effects of prazosin on venous tone were measured in the latter study, using a method which may have reflected changes in arteriolar resistance and which would probably be less dependent than the VRR on additional sympathetic activation by the

stress of posture. The aim of the present study was to measure the effect of prazosin on sympathetically mediated venoconstriction, using the VRR, and to relate this effect to postural changes in blood pressure and pulse rate as well as plasma prazosin concentration after a commonly used initial oral dose of 500 μg in healthy volunteers.

Methods

Subjects

Six healthy volunteers (5 males and 1 female), aged 25 to 39 years, were studied after obtaining their informed, written consent. The only dietary restriction was a 12 h fast prior to the study by three subjects (2, 3, and 6), two subjects (1 and 4) ingesting a light breakfast and one (5) a cup of black coffee approximately 2 h before commencement. Two subjects (3 and 5) ate lunch 3 h post-dose during their extended studies.

Study protocol

Studies were conducted in a quiet, darkened, air-conditioned room, the ambient temperature of which was maintained at 21°C. Supine blood pressure and pulse rate were measured at 5 min intervals until stable values were obtained. After remaining supine for 15 min, the VRR was measured, at least twice, with a minimum of 10 min recovery time between observations. Blood pressure and pulse rate were also measured after the subject had been standing for 2 min. Prazosin (500 μg) was then ingested as half a commercially available tablet of Minipress® together with 150 ml of cold water.

The VRR, with the subject supine, blood pressure and pulse rate, both supine and after standing for 2 min, were then measured at 20 min intervals. Subjects were also asked to comment about symptomatic effects.

Technical procedures

Arterial blood pressure was measured indirectly by sphygmomanometry. Mean arterial pressure (MAP) was estimated by the addition of a third of the pulse pressure to the diastolic pressure, which was determined at the fifth phase of Korotkoff sounds. The pulse rate (PR) expressed as beats/min was determined by doubling the number of beats counted by palpation of the radial pulse for 30 s.

The venous reflex response (VRR) was measured by a modification of the occluded limb technique (Browse & Hardwick, 1969; Samueloff, Bevegard & Shepherd, 1966; Walter *et al.*, 1975). The intra-luminal pressure of a superficial vein on the dorsum

of the hand was measured through a 21-gauge butterfly needle, which was flushed intermittently with heparinized saline. Alteration of intravenous pressure was transmitted via a Bentley Crantec Model 800 transducer to provide a pressure trace on a Beckman dynograph R411 recorder, with the needle point as reference. Chart paper speed was 0.25 mm/s. While the hand rested at chest level, in the same horizontal plane as the pressure transducer, an 8 cm wide wrist cuff was rapidly inflated to 260 mmHg to arrest circulation to the hand. Free pressure transmission was confirmed by producing a rapid, wide-amplitude deflection when the skin over the vein immediately proximal to location of the needle point was lightly tapped. After stabilization of the venous pressure trace, the subject was requested to inhale maximally and to exhale completely within 10 s. The rise in intravenous pressure, immediately following completion of the respiratory manoeuvre, was measured in mm Hg and is referred to as the VRR (Figure 1). The wrist cuff was deflated for at least 10 min between observations to allow the hand to recover from being excluded from the circulation and to ensure recovery of sympathetic function.

Figure 1 Effect of 500 μg of oral prazosin on the venous reflex response (VRR) of a normal volunteer (3). Inset numbers refer to the height of the VRR in mmHg. The pre-dose VRR (31 to 33 mmHg) diminished progressively during the initial 4.5 h post-dose to a minimum value of 7 mmHg. By 5.5 h the response appeared to be recovering although at 7.5 h post-dose the response was still two-thirds suppressed.

Table 1 Time course of the venous reflex response (VRR) (mmHg) after 500 µg prazosin in six normal subjects.

Subject	0	20	40	60	Post-dose interval (min)					
					80	100	120	140	160	180
1	24	9	11	6	4	9	8			
2	50	41	38	34	38	32	36	38	29	35
3	33	21	23	23	21	19	16	14	16	11
4	15	10	12	14	13	7	6	5		
5	25	17	9	13	6	8	7	12	5	9
6	21	18	25	29	4	9	16	20	24	23
Mean ± s.e. mean	28±5	19±5	20±5	20±4	14±5*	14±4*	14±4*			

Table 1 (continued)

Subject	200	220	240	260	Post-dose interval (min)					
					300	330	340	390	410	440
1										
2										
3	11	11		7		17			15	13
4										
5	8				3					
6										

*Two-way analysis of variance indicated significant ($P < 0.05$) reduction of the VRR at 80, 100 and 120 min compared to values at 0 to 60 min.

Venous blood samples (10 ml) were collected into lithium-heparinized polypropylene tubes, centrifuged and the separated plasma stored in polystyrene tubes at -20°C . Blood samples were drawn pre-dose and at 20 min intervals for at least 2 h after the dose. The plasma prazosin concentration was assayed by a high-performance liquid chromatographic method with a detection limit of 40 pmol/l and relevant intra- and inter-assay coefficients of variation of 3% (Reece, 1980).

Statistical analysis

A two-way analysis of variance of haemodynamic data, obtained during the initial 120 min post-dose, was performed between subjects with respect to time. Comparison of the pre- v post-prazosin data within subjects was made by Student's paired *t*-test.

Results

Time course of prazosin-induced changes in venous reflex response (VRR) mean arterial pressure (MAP) and pulse rate (PR).

Table 1 and Figure 1 demonstrate the changes in the VRR with time following an oral dose of 500 µg of prazosin. Significant suppression of the VRR was observed in all subjects 80 to 120 min after the dose

(Table 4) and was still evident at 7.5 h in one subject (3, Figures 1 and 2). Symptomatic reduction of standing MAP occurred maximally at 40 to 180 min post-dose (Table 2) and followed 52 to 67% suppression of VRR in five subjects and 32% suppression in the other (2). The symptomatic reduction in MAP after 2 min standing contrasted with the consistent supine MAP throughout (Table 2). Table 3 demonstrates the

Figure 2 Haemodynamic effects of 500 µg of oral prazosin in a normal volunteer (3). The progressive reduction in sympathetically mediated venous tone was associated with pronounced orthostatic tachycardia, which preceded the orthostatic hypotension and faintness.

Table 2 Time course of mean arterial pressure (mmHg) after 500 µg prazosin in six normal subjects

Subject	Posture	Post-dose interval (min)									
		0	20	40	60	80	100	120	140	160	180
1	Supine	80	69	71	73	73	73	73			
	Standing	59	62	21*	75	74	76	81			
2	Supine	83	83	87	83	88	79	75	77	80	83
	Standing	80	81	84	35*	62*	69*	61*	23*	22*	0*
3	Supine	83	79	83	79	78	76	78	81	78	77
	Standing	82	81	90	92	81	81	87	78*	64*	76
4	Supine	65	56	69	59	70	71	86	86		
	Standing	69	69	69	74	86	74*	74*	67*		
5	Supine	114	117	108	99	128	129	121	108	99	103
	Standing	107	105	100	108	99	93*	89*	77*	86	93
6	Supine	103	103	103	104	103	100	100	96	96	
	Standing	103	111	101	101	101	88*	93*	93	90	
	Mean supine ± s.e. mean†	89±7	85±9	87±7	83±7	90±9	88±9	86±8			
	Mean standing ± s.e. mean†	83±8	85±8	78±12	81±11	84±6	80±4	80±5			

Table 2 (continued)

Subject	Posture	Post-dose interval (min)									
		200	220	240	260	300	330	340	390	410	440
1	Supine										
	Standing										
2	Supine	88									
	Standing	53*									
3	Supine		80		77			77	81	75	75
	Standing		77		85			87	87	93	88
4	Supine										
	Standing										
5	Supine	93				97	94				
	Standing	96				86	84*				
6	Supine										
	Standing										

*Symptomatic faintness after standing for 2 min.
†No significant differences between supine and standing MAP within or between post-dose interval values by two-way analysis of variance.

Table 3 Time course of pulse rate (beats/min) after 500 µg prazosin in six normal subjects

Subject	Posture	Post-dose interval (min)									
		0	20	40	60	80	100	120	140	160	180
1	Supine	68	64	63	62	64	58	64			
	Standing	88	82	88	84	84	72	88			
2	Supine	66	60	66	70	66	68	64	70	66	64
	Standing	86	90	92	112	108	126	120	120	124	116
3	Supine	64	60	60	68	64	66	64	68	68	66
	Standing	74	68	76	80	86	104	98	98	90	90
4	Supine	84	80	86	78	72	78	76	72		
	Standing	96	98	98	98	100	112	106	106		
5	Supine	76	72	74	76	76	74	80		70	70
	Standing	98	82	100	114	114	114	126	128	114	116
6	Supine	84	96	80	96	108	116	108	104	100	
	Standing	104	104	104	132	132	132	130	136	120	
	Mean supine $\pm$ s.e. mean	74 $\pm$ 4	72 $\pm$ 6	72 $\pm$ 4	75 $\pm$ 5	75 $\pm$ 7	77 $\pm$ 8	76 $\pm$ 7			
	Mean standing $\pm$ s.e. mean	91 $\pm$ 4	87 $\pm$ 5	93 $\pm$ 4	103 $\pm$ 8*	104 $\pm$ 7*	110 $\pm$ 9*	111 $\pm$ 7*			

Table 3 (continued)

Subject	Posture	Post-dose interval (min)									
		200	220	240	260	300	330	340	390	410	440
1	Supine										
	Standing										
2	Supine	70									
	Standing	124									
3	Supine		68		77			74	80	82	74
	Standing		90		96			96	104	96	88
4	Supine										
	Standing										
5	Supine	76				90	84				
	Standing	110				114	108				
6	Supine										
	Standing										

*Two-way analysis of variance indicated significantly ($P < 0.05$) higher standing pulse rates at 60, 80, 100 and 120 min compared to 0, 20 and 40 min post-dose.

predominantly orthostatic tachycardia which was maximal prior to or at the time of symptomatic orthostatic hypotension (Table 2 and Figure 2).

Two-way analysis of variance indicated significant ($P < 0.05$) reduction of the VRR after 80 min and significant ($P < 0.05$) orthostatic tachycardia after 60 min post-dose for all subjects (Tables 1 and 3). The varying temporal occurrence of symptomatic, maximal orthostatic reduction in MAP between subjects accounted for failure of two-way analysis of variance to demonstrate any significant temporal change in MAP for the subjects as a group (Table 2). The latter finding justified comparison of maximal haemodynamic effects with control pre-dose (zero-time) values within each patient by Student's paired *t*-test. The mean post-dose value for VRR (8 mmHg), postural fall in MAP (32 mmHg) and orthostatic increase in mean pulse rate (40 beats/min) were all significantly different, by paired *t*-test within each subject, compared to the corresponding pre-dose mean values (28 mmHg, 5 mmHg and 17 beats/min), respectively (Table 4).

Plasma prazosin levels

The time course of the plasma prazosin concentration varied widely within the first 2 to 3 h, both between individuals (Table 5) and within individuals (personal observations) following the same dose.

Adverse symptomatic effects

Early complaints, which did not tend to coincide with orthostatic effects, included cutaneous flushing and tingling, mental obtundation, drowsiness, yawning, lachrymation, xerostomia and nasal congestion, commencing 15 to 80 min post-dose. Every subject complained of orthostatic faintness, which was usually most pronounced 40 to 180 min post-dose when the standing blood pressure was lowest (Table 2). Faintness was marked in three subjects, who almost lost consciousness after standing for 2 min, and was relieved by sitting, squatting or lying down. Other complaints, which coincided with orthostatic hypo-

tension and tachycardia 40 to 270 min post-dose, included nausea, headache, pallor and clamminess of the skin.

Discussion

Prazosin has been described recently as the first α -adrenergic receptor blocking agent to maintain efficacy when prescribed as monotherapy for reduction of blood pressure in patients with mild to moderate arterial hypertension (Stokes & Oates, 1978). It has also been claimed to be largely devoid of severe adverse effects compared to other peripherally acting hypotensive agents (Stokes & Oates, 1978).

The dramatic haemodynamic effects observed during these studies of healthy subjects were thus rather unexpected, in view of the relatively small dose (500 μ g) administered, but were consistently reproduced on one to two other occasions by doses of prazosin varying between 250 μ g and 2 mg in four of these six subjects (3, 4, 5 and 6) (personal observations). In view of the stability of pre-dose control values for VRR, MAP and PR, which were measured for at least 1 h prior to administration of prazosin, placebo studies were omitted. Other workers also noted similar reproducibility of the VRR for several hours in normal subjects (Samueloff *et al.*, 1966). Moreover, the timing and symptomatic severity of the orthostatic hypotension exhibited by these healthy subjects (Table 2) appeared to be analogous to that since described following similar and larger doses (up to 5 mg) of prazosin, initially administered to both hypertensive patients (Bendall *et al.*, 1975; Graham *et al.*, 1976), and to normal subjects (Dynon *et al.*, 1980; Rubin & Blaschke, 1980). Although previous studies of hypertensive patients suggested lack of significant tachycardia in association with prazosin therapy (Stokes & Oates, 1978), the observation of significant orthostatic tachycardia in these healthy subjects (Tables 3 and 4) is consistent with the significant prazosin-related orthostatic tachycardia recently reported to have occurred in other normal subjects (Dynon *et al.*, 1980; Rubin & Blaschke, 1980).

Table 4 Maximal (mean $\pm$ s.e. mean) effect of a single 500 μ g dose of prazosin in normal volunteers (n = 6).

Observation	Pre-dose	Post-dose	P-value (paired <i>t</i> -test)*
VRR (mmHg)	28 $\pm$ 5	8 $\pm$ 4	< 0.001
Δ MAP† (mmHg)	-5 $\pm$ 4	-32 $\pm$ 8	0.01 < P < 0.02
Δ PR† (beats/min)	17 $\pm$ 2	40 $\pm$ 5	0.001 < P < 0.005

*Comparing stable pre-dose v maximally affected post-dose observations within each subject.

†Difference between standing and supine values.

Time 5 Time course of plasma prazosin concentration (nmol/l) after 500 µg oral prazosin

Subject	20	40	50	60	80	100	120	140	160	180	190	200	210	270	300	340	390
1	0	0.9		2.3	3.0	2.4	2.9										
2	0	1.7		4.0	6.5	6.1	7.7	9.3	9.4	12.1							
3	0.4	1.1		2.1	3.6	8.3	8.2	7.0	6.0	5.7			5.6	4.7		3.3	2.6
4	0		0.6		2.0	3.9		4.9									
5	0.9	2.6		4.3	5.6	7.1	6.9	7.1	6.6	5.0		4.6			2.4		
6	0.7		3.9		6.6			6.9			6.6						

Previous studies, utilizing the occluded limb technique (Samueloff *et al.*, 1966), have demonstrated a consistent increase in sympathetically mediated venous tone during vasovagal syncope in normal volunteers (Epstein *et al.*, 1968). In the present studies significant suppression of similarly measured sympathetically stimulated venoconstriction consistently preceded the orthostatic hypotension (Tables 1 and 2; Figures 1 and 2). Hence, suppression of adrenergically mediated, compensatory venoconstriction by prazosin in the present study supports the hypothesis that inability to increase venous return to the heart plays a significant role in the aetiology of the 'first-dose phenomenon' (Jauernig *et al.*, 1978). VRR suppression also preceded the orthostatic tachycardia in all subjects (Tables 1 and 3, Figures 1 and 2), except subject 6 who exhibited an earlier, more marked pulse-rate response. Compared to the other subjects in the present report, subject 6 was the least symptomatically hypotensive when standing. This observation, together with the report of the association of syncope with sudden reduction of increased heart rate in response to orthostatic hypotension in normal young men (Rubin & Blaschke, 1980), suggests that the suppression of reflux tachycardia may be another significant factor in the aetiology of the 'first-dose phenomenon', especially following prazosin administration to hypertensive patients, in whom beta-adrenoceptor blockade has already been induced therapeutically.

The inhibition of the VRR by prazosin in the present studies is consistent with its selective nor-adrenaline antagonism previously reported for human dorsal hand veins, both *in vitro* (Jauernig *et al.*, 1978) and *in vivo* (Collier, Lorge & Robinson, 1978). The major determinants of the calibre of cutaneous veins are ambient temperature, emotion and respiratory reflexes (Browse & Hardwick, 1969; Shepherd & Vanhoutte, 1978). Maintenance of a constant environment, with respect to temperature and a constant, relatively low level of external stimulation, has enabled the use of the VRR, which is also activated by respiratory reflexes (Nies, 1978), as a convenient method for assessment of adrenergic-neuron blockade by guanethidine (Walter *et al.*, 1975). The similar usefulness of the VRR, as a guide to prazosin dosage and compliance, during maintenance therapy for hypertension and cardiac dysfunction, has yet to be evaluated. However, the demonstration of an early, significant effect of prazosin on the VRR of these subjects as a group (Results, and Table 1), in contrast to the varying temporal onset of symptomatic orthostatic hypotension (Table 2), suggests that the VRR following a single small oral dose of prazosin is a convenient predictor of clinically significant orthostatic hypotension. A similar view might also be adopted with respect to orthostatic tachycardia (Table 3) in hyper-

tensive patients whose circulatory reflexes are not attenuated by concomitant therapy, such as β -adrenergic receptor blocking drugs.

There did not appear to be any consistent relationship of the plasma prazosin level to significant suppression of the VRR, orthostatic hypotension or tachycardia (Tables 1, 2, 3 and 5). Although the plasma prazosin concentration may not have reached its peak in two of the subjects (2 and 4), who continued to exhibit symptomatic orthostatic hypotension, the onset of the latter effect appeared to coincide with the peak plasma level in two subjects (5 and 6), whereas it preceded the peak in one subject (1) and followed the peak in another (3) Tables 2 and 5). These findings reflect the reported absence of a precise relationship between peak plasma prazosin concentration and the degree of orthostatic hypotension following oral initial and continued administration of the drug (Bateman *et al.*, 1979; Dynon *et al.*, 1980; Graham *et al.*, 1976; McCarthy *et al.*, 1980; Rubin & Blaschke, 1980). However, the demonstration of a significant relationship between plasma prazosin concentration and hypotensive response

after intravenous administration to normal subjects (Bateman *et al.*, 1979) suggests that the pre-systemic modification of the parent compound confounds the cardiovascular mechanisms determining arterial blood pressure.

It was concluded from the present studies that significant suppression of sympathetically mediated vasoconstriction by a small initial dose of prazosin contributes to the pathophysiology of the orthostatic hypotension and faintness described as the 'first-dose phenomenon'. There was no precise relationship of maximal haemodynamic effect to peak plasma prazosin concentration, the timing and height of which appeared to vary appreciably both between and within normal individual subjects.

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