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# STUDIES ON THE CLINICAL PHARMACOLOGY OF PRAZOSIN. I: CARDIOVASCULAR, CATECHOLAMINE AND ENDOCRINE CHANGES FOLLOWING A SINGLE DOSE

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**1** Cardiovascular, catecholamine and neuroendocrine changes were studied following administration of prazosin to ten normal subjects. In response to a fall in standing blood pressure from $87 \pm 5$ (s.d.) mmHg to $49 \pm 20$ ($P < 0.01$) heart rate (measured by continuous ECG monitoring) rose from $81 \pm 11$ to $118 \pm 20$ ($P < 0.01$). Five of the ten subjects sustained their tachycardia on standing and developed at most mild symptoms. In the other five, tachycardia suddenly gave way to bradycardia and they became syncopal.

**2** In the supine position, when blood pressure was not significantly different from control, plasma noradrenaline concentration (nmol/l) was $2 \pm 0.5$ compared with a control value of $1.2 \pm 0.3$ ($P < 0.01$). In response to standing hypotension plasma noradrenaline was $4.2 \pm 2.7$ compared with a standing control value of $1.9 \pm 0.4$ ($P < 0.02$).

**3** Four hours after taking prazosin five of the subjects stood for 30 min and blood was drawn for plasma renin activity (PRA). Blood pressure at this time was 15 mmHg below control ($P < 0.02$). PRA (ng $ml^{-1}h^{-1}$) was $6.4 \pm 2.3$ compared with time matched placebo control of $1.4 \pm 0.8$ ($P < 0.01$).

**4** At the same time as the PRA sampling, plasma cortisol was $15.6 \pm 2.6$ $\mu$g/100 ml during hypotension and $8.2 \pm 3.9$ following placebo ($P < 0.01$). Growth hormone was $1.4 \pm 0.3$ ng/ml during hypotension and $1.0 \pm 0.2$ following placebo ($P < 0.01$). Prolactin did not rise significantly during hypotension induced by prazosin.

**5** Isoprenaline infusion produced the same change in heart rate during the time of maximum prazosin action as when given alone.

**6** It is concluded that these observations are not in keeping with earlier reports that prazosin lowers blood pressure without producing a reflex increase in heart rate or renin release. Nor are these findings in keeping with current theories of the mechanism of action of prazosin which variously suggest that noradrenaline concentration should not increase, or that the heart is incapable of responding to an adrenergic stimulus in the presence of prazosin.

## Introduction

Since the earliest observations on its hypotensive effect, prazosin has been considered to act by a mechanism novel among drugs used in the treatment of high blood pressure. In 1968 Scriabine, Constantine, Hess & McShane suggested that prazosin might exert an unconventional type of α-adrenoceptor blockade. This hypothesis resulted from the discovery that the drug exerted an effect considered characteristic of α-adrenoceptor blockade (reversal of the adrenaline pressor effect) yet lowered blood pressure without producing a reflex increase in heart rate (Scriabine *et al.*,1968). Several reports have confirmed the absence of reflex tachycardia when prazosin produces hypotension in experimental animals (Constantine, McShane, Scriabine & Hess, 1973; Komarek & Cartheuser, 1977; Massingham & Hayden, 1975) hypertensive patients (Bolli, Wood & Simpson, 1976; Lund-Johansen, 1974; Turner, Watson & Brocklehurst, 1977; Hua, Myers & Kincaid-Smith, 1978) and normal subjects (Wood, Bolli & Simpson, 1976). Concurrently with these observations on heart rate, other reports have suggested that prazosin-induced hypotension in dogs (Massingham & Hayden, 1975) and in patients with high blood pressure (Bolli *et al.*, 1976; Hayes,

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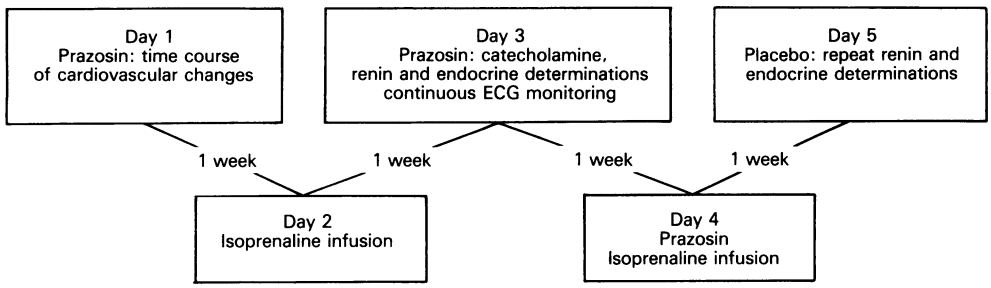


**Figure 1** Schematic outline of study design

Graham, O'Connell, Speers & Humphrey, 1976; Koshy, Mickley, Bourgoigne & Blaufox, 1977) is not accompanied by an increased release of renin. The concept of an atypical α-adrenoceptor blockade to explain these observations has been further developed by studies on rabbit pulmonary artery strips which suggest that prazosin has a marked affinity for post-synaptic alpha receptors (Cambridge, Davey & Massingham, 1977; Cambridge, Davey & Massingham, 1978). Selectivity of this type would leave presynaptic α-adrenoceptors free to participate in the negative feedback control of noradrenaline release (Langer, 1977). However, the finding that the post-synaptic α-adrenocaptor selectivity of prazosin appears to be species dependent (Cavero, Lefevre & Roach, 1977) suggests that caution should be used in extrapolating these data to man to explain the mechanism of action of prazosin.

Alternative hypotheses have been proposed to explain the action of prazosin. One is the inhibition of phosphodiesterase which results in accumulation of cyclic AMP in smooth muscle of arterioles to produce relaxation while cyclic GMP concentration increases in cardiac tissue to prevent the occurrence of reflex tachycardia (Hess, 1975). A major objection to this theory is that the prazosin concentrations required to inhibit phosphodiesterase far exceed those achieved therapeutically (Hess, 1975; Scott, Krider, Newquist, Chasin & Gresnilade, 1978). A similar objection applies to another suggestion that prazosin acts in part by inhibiting dopamine-β-hydroxylase, thereby decreasing noradrenaline release (Frigon, Samples & Stone, 1978).

A further unexplained response to prazosin is the occurrence of sudden collapse associated with the first dose of the drug but rarely recurring thereafter. This 'first dose phenomenon' as it has been called is said to occur with an overall frequency of 1% using a voluntary reporting system (Committee on the Safety of Medicines, 1975) but one study quoted an incidence of 16% (Rosendorff, 1976).

The study reported here was designed to investigate several issues related to the mechanism of action of prazosin in man. In order to test the hypothesis that the absence of reflex tachycardia could be explained by selective postsynaptic α-adrenoceptor blockade with unimpaired presynaptic negative feedback control of catecholamine release, plasma noradrenaline was measured both before and during hypotension produced by prazosin. The suggestion that accumulation of cardiac cyclic GMP could explain the lack the heart rate response was tested by studying cardiac response to isoprenaline before prazosin and when the drug was acting maximally. In addition, the cardiovascular and neuroendocrine changes accompanying the first dose of prazosin were investigated to assess their relevance to the 'first dose phenomenon' and to provide additional information about the site(s) of action of this agent.

This study has been presented in part at the national meeting of the American Federation for Clinical Research, Washington, D.C., May 1979.

## Methods

Ten male subjects 20 to 30 years of age participated in this study. All had a normal physical examination and had normal haematological, biochemical and electrocardiographic indices. None was taking any prescription or non-prescription drugs. The study protocol was approved by the Stanford Committee on the Use of Human Subjects in Research and all subjects gave informed written consent. Investigations were all performed on the General Clinical Research Center. Subjects were admitted for five 24 h periods each separated by 1 week; the study design is shown in Figure 1. Subjects were admitted during the evening and slept on the unit. No alcohol was permitted for the 24 h preceding admission and caffeine-containing food or drink were not permitted during admission. On each study day a light breakfast was provided at 06.45 h and a regular lunch was taken at noon. An indwelling venous cannula was established in each subject at 07.00 h and a physician was present throughout each day.

Day 1: The major aim on this day was to collect baseline data concerning the time course of blood

pressure and heart rate changes following prazosin administration. A 5 mg capsule of prazosin was given at 08.30 h and blood pressure and heart rate were measured at 15 min intervals in both lying and standing positions. This dose was chosen because it had previously been reported to cause substantial hypotension without reflex tachycardia in normal young men (Wood *et al.*, 1976).

Day 2: No prazosin was given but at the time of day corresponding to maximum prazosin-induced hypotension for each subject, as determined on Day 1, isoprenaline was infused using a constant rate infusion pump. The subjects remained supine throughout the procedure. The rate of infusion was increased until the subject felt a definite change in heart beat and was then kept constant until the new increased heart rate (recorded by continuous ECG monitoring) became stable. The dose of isoprenaline used varied between 1 and 2 $\mu$g/min in individual subjects.

Day 3: Between 07.00 h and 08.00 h five subjects had blood drawn through a heparin lock for analysis of plasma renin activity (PRA) following 30 min in the supine position and 30 min standing. These blood samples were drawn into chilled syringes, immediately transferred to chilled EDTA tubes and centrifuged at 3000 *g* for 5 min at a temperature of 4°C. The plasma was stored in screw-top vials at −20°C until analyzed by radioimmunoassay (Hsueh, Carlson, Leutscher & Grislis, 1978). During the same time period all ten subjects had blood drawn for catecholamine analysis following 30 min supine and 5 min standing. This blood was drawn into chilled syringes containing solid reduced glutathione in sufficient amount to produce a final concentration of 5 mmol/l. The blood was rapidly transferred to chilled heparinized tubes, centrifuged at 3000 *g* for 5 min at 4°C and the plasma transferred to screw-top glass vials, immediately frozen on dry ice and subsequently stored at −76°C. Noradrenline and adrenaline were analyzed by simultaneous radioenzymatic assay (Peuler & Johnson, 1977).

Continuous ambulatory cardiac monitors were attached at 08.00 h. Because of the substantial equipment demands only five of the ten subjects could be monitored by this technique and in the remainder the heart rate was recorded manually. Blood pressures were recorded by the same research nurse using the same mercury manometer in each subject. Three lying and standing (for 5 min) readings were obtained between 08.00 h and 08.30 h and at that time a 5 mg capsule of prazosin was given. Thereafter lying and standing blood pressures were performed every 30 min for 9 h. In the standing position blood pressures were measured repeatedly and the values given represent either those at 5 min or the reading immediately preceding the point when the subject was unable to remain standing.

At the time corresponding to that at which maximum hypotension occurred on Day 1, blood for catecholamine analysis was drawn through the heparin lock with the subject in the supine position and after 5 min standing. As described in the results section, certain of the latter samples were taken immediately after the subject became syncopal.

When the subjects were able to stand without severe symptoms of postural hypotension (3 to 4 h following drug administration) blood was drawn for PRA measurements after 30 min in the supine position and for PRA, cortisol, prolactin and growth hormone following 30 min standing. Blood samples for hormone analysis were centrifuged and stored as described above for PRA, and cortisol, prolactin and growth hormone concentrations were measured by radioimmunoassay.

During the day fifteen blood samples were taken for whole blood prazosin analysis using high pressure liquid chromatography and fluorescence detection as we have described elsewhere (Yee, Rubin & Meffin, 1979). This method has a lower limit of sensitivity of 520 pmol/l (200 pg/ml) with a typical coefficient of variation of 4.9% in the range 520 pmol/l to 130 nmol/l (50 ng/ml).

The ambulatory monitoring tapes were subjected to computer analysis (Harrison, Fitzgerald & Winkle, 1976).

Day 4: Prazosin, 5 mg, was given at 08.30 h and the subjects remained supine throughout the study period. At the time corresponding to that of the previous infusion, isoprenaline from the same lot was infused at exactly the rate which was used on Day 2. Continuous ECG monitoring was employed in all subjects.

Day 5: Blood pressure and heart rate measurements were made at the same times as on Day 3. Five subjects received placebo at 08.30 h and had blood sampling for PRA cortisol, prolactin and growth hormone at times matched exactly to those of day 3. The remaining five received prazosin 5 mg in order to demonstrate that there had been no loss of responsiveness during the study period. These five subjects had the same extent and duration of cardiovascular changes as seen on days 1 and 3.

### *Statistical analysis*

All values are expressed as mean ± s.d. Data following prazosin administration were compared with control values by means of a paired *t*-test. Blood pressures are expressed as mean values (diastolic + 1/3 pulse pressure).

## Results

### *Heart rate and blood pressure*

Unless otherwise stated the values reported here refer to observations on Day 3. Following the

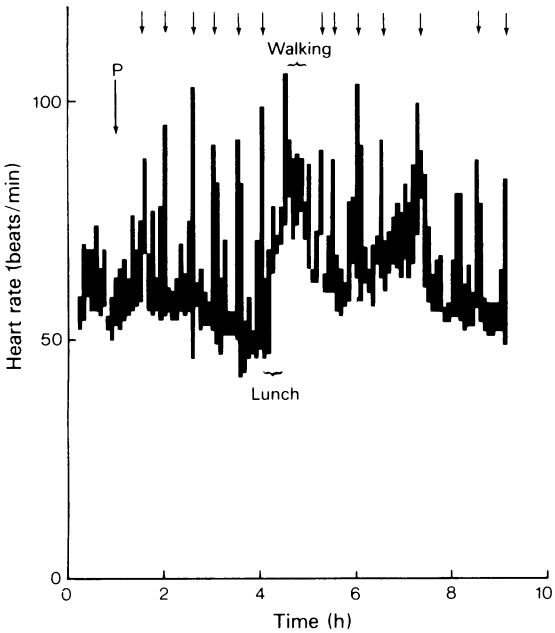


**Figure 2** Computer display of heart rate as measured by continuous ECG monitoring in a typical subject. After three lying and standing control readings 5 mg prazosin (P) was administered. Subsequently each arrow represents a standing reading.

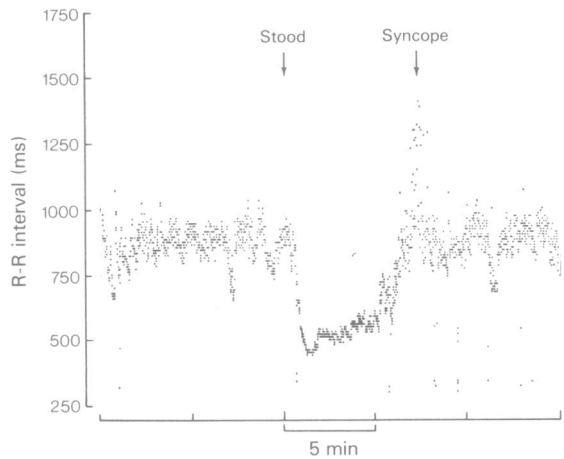


**Figure 3** Heart rate in a subject who developed syncope. The continuous ECG data is expressed as R-R interval, a decreased R-R interval representing an increased heart rate. Immediately before syncope heart rate falls rapidly from 120 to 40 beats/min. This was a typical finding in subjects who developed syncope.

administration of prazosin all subjects experienced an increase in standing heart rate. The changes were substantial and at its maximum heart rate was $118 \pm 20$ beats/min compared with a pre-drug control value of $81 \pm 11$ ($P < 0.01$). The increase in standing heart rate was present at 30 min after drug administration, when prazosin concentrations were very low ($9.2 \pm 13.7$ nmol/l; 3.5 ng/ml) and persisted for the duration of the nine hour observation period (Figure 2). Blood pressure in the standing position fell markedly. The lowest mean blood pressure, occurring between 90 and 180 min, was $49 \pm 20$ mmHg compared with the pre-drug control pressure of $87 \pm 5$ mmHg ($P < 0.01$). Maximum postural hypotension occurred in all subjects within 1 min of standing.

Supine blood pressure fell to a smaller extent from $87 \pm 5$ mmHg to $76 \pm 5$ mmHg ($P < 0.01$) and the rise in heart rate in this position did not achieve statistical significance ($68 \pm 11$ control compared with $74 \pm 10$ at the time of maximum change; $P = 0.13$).

*Syncope, heart rate and blood pressure*

Five of the ten subjects became syncopal on standing. Three subjects noticed only light-headedness on standing while the remaining two experienced no symptoms.

In those subjects who developed syncope its onset was immediately preceded by a sudden and precipitous fall in heart rate, a marked tachycardia giving way to a striking bradycardia (Figure 3). In contrast, the five subjects who experienced only light-headedness or who remained asymptomatic maintained their tachycardia, often in the face of substantial hypotension. These findings are summarized in Table 1. Both the bradycardia and the symptoms rapidly reversed when the subjects who became syncopal returned to the supine posture.

The development of syncope was not clearly related to the extent of blood pressure decrease (Table 1). Thus, one subject developed syncope with a 16 mmHg fall in mean blood pressure while another experienced only light-headedness even though his mean blood pressure had dropped by 67 mmHg. Only the failure to sustain a reflex tachycardia was consistently associated with the onset of syncope.

*Isoprenaline-induced tachycardia*

The supine heart rate immediately before the isoprenaline infusion was begun on Day 2 was $65 \pm 10$ and was $71 \pm 12$ ($P = 0.2$) immediately before isoprenaline on Day 4. During the isoprenaline infusion on the control day (Day 2, when no prazosin was given) a heart rate of $103 \pm 14$ was obtained. On Day 4 at the time of maximum prazosin effect on blood pressure (between 90 and 180 min after drug ingestion, depending on the individual) the identical

**Table 1** Symptoms and heart rate associated with blood pressure changes

| *Subject* | *Maximum fall in mean B.P. (mmHg)* | *Heart rate at maximum hypotension (beats/min)* | *Heart rate sustained* | *Symptoms* |
|---|---|---|---|---|
| 1 | 16 | 120 | No | Syncope |
| 2 | 15 | 120 | Yes | None |
| 3 | 38 | 112 | Yes | Light headed |
| 4 | 33 | 120 | No | Syncope |
| 5 | 12 | 80 | Yes | None |
| 6 | 29 | 110 | Yes | Light headed |
| 7 | 42 | 110 | No | Syncope |
| 8 | 60 | 150 | No | Syncope |
| 9 | 67 | 144 | Yes | Light headed |
| 10 | 66 | 150 | No | Syncope |

rate of isoprenaline infusion as was used on the control day produced the same heart rate: $103 \pm 21$ ($P=0.9$). The percentage increase in heart rate caused by isoprenaline on the control day was 58% compared with 45% on the prazosin day ($P=0.3$).

Subjects who developed syncope demonstrated the same pattern of isoprenaline response as those who experienced mild or no symptoms.

*Renin and blood pressure*

The fall in standing blood pressure produced by prazosin was accompanied by a substantial elevation of plasma renin activity after 30 min standing in all five subjects in whom PRA was measured. During the prazosin-induced hypotension the PRA was $6.4 \pm 2.3$ $ng\,ml^{-1}\,h^{-1}$ compared with $1.5 \pm 0.4$ $ng\,ml^{-1}\,h^{-1}$ before prazosin administration ($P<0.01$) and $1.4 \pm 0.8$ $ng\,ml^{-1}\,h^{-1}$ on the time-matched placebo day ($P<0.01$). Table 2 presents these data together with corresponding blood pressures and heart rates.

In the supine position the rise in plasma renin activity associated with prazosin did not achieve statistical significance ($P=0.2$).

The five subjects in whom renin was measured included three who had developed syncope earlier in the morning and two who experienced only light-headedness. In the presence of hypotension the three subjects who had developed syncope demonstrated a rise in standing plasma renin activity compared with pre-drug control of 98%, 180% and 650%. The two subjects who had not become syncopal earlier showed a rise of 300% and 500%. At the time of renin blood sampling, blood prazosin concentration averaged 42 nmol/l (16 ng/ml).

*Catecholamines and blood pressure*

Plasma concentrations of noradrenaline were increased by prazosin in both supine and standing positions. In the supine position, plasma noradrenaline increased from $1.2 \pm 0.3$ nmol/l to $2.0 \pm 0.5$ nmol/l ($P<0.01$). At the time of sampling there was no significant change in blood pressure (Table 3). Standing noradrenaline was $1.9 \pm 0.4$ nmol/l before prazosin and $4.2 \pm 2.7$ nmol/l during hypotension ($P<0.02$). The range of standing noradrenaline concentrations during prazosin

**Table 2** Renin response to prazosin induced hypotension, five subjects

| | *PRA* ($ng\,ml^{-1}\,h^{-1}$) | *Mean BP (mmHg)* | *Mean heart rate (beats/min)* |
|---|---|---|---|
| Standing (before prazosin) | $1.5 \pm 0.3$* | $91 \pm 4$* | $80 \pm 7$† |
| Standing (prazosin) | $6.4 \pm 2.3$ | $75 \pm 9$ | $97 \pm 15$ |
| Standing (placebo) | $1.4 \pm 0.8$* | $91 \pm 2$† | $81 \pm 15$* |
| Supine (before prazosin) | $0.9 \pm 0.3$ | $91 \pm 3$† | $68 \pm 7$ |
| Supine (prazosin) | $1.6 \pm 1.1$ | $84 \pm 7$ | $71 \pm 6$ |

Blood was drawn following 30 min in each position.
* $P<0.01$; † $P<0.05$ compared with prazosin data (paired $t$-test).

**Table 3** Catecholamine response to hypotension produced by prazosin, ten subjects.

| | *NA* (*nmol/l*) | *A* (*nmol/l*) | *BP* (*mmHg*) | *Heart rate* (*beats/min*) |
|---|---|---|---|---|
| Supine (control) | 1.16±0.31 | 0.19±0.06 | 86±4.7 | 68±11 |
| Supine (prazosin) | 2.0±0.53† | 0.40±0.3 | 85±4.4 | 71±10 |
| Standing (control) | 1.93±0.39 | 0.35±0.14 | 89±4.4 | 80±11 |
| Standing (prazosin) | 4.24±2.70‡ | 0.81±0.48‡ | 62±22‡ | 104±20‡ |

NA: Noradrenaline; A: Adrenaline.

Samples were drawn following 30 min in the supine and 5 min in the standing position.

† $P<0.01$, ‡ $P<0.02$ compared with control (paired *t*-test).

induced hypotension was considerable: 2.3 to 11.1 nmol/l.

Supine adrenaline rose from 0.2±0.1 nmol/l to 0.4±0.3 nmol/l ($P=0.054$). In the standing position adrenaline increased from 0.3±0.1 nmol/l to 0.8±0.5 nmol/l ($P<0.02$). These data are presented together with corresponding blood pressures and heart rates in Table 3.

In five of the ten subjects, blood for standing catecholamines analysis was drawn immediately following a syncopal reaction. The noradrenaline concentrations tended to be slightly lower in the syncopal group (3.8±1.6 compared with 4.6±3.7 while adrenaline tended to be higher in this group (1.0±0.6 compared with 0.6±0.3) but in neither case did the difference achieve statistical significance: $P = 0.7$ for noradrenaline and $P = 0.3$ for adrenaline.

*Cortisol, prolactin and growth hormone*

In response to the hypotension produced by prazosin, plasma cortisol was significantly elevated compared to a time-matched placebo period (Table 4). There was no significant difference in adrenal cortical response between three subjects who had earlier developed syncope (cortisol 109% above placebo value) and those who had not (cortisol 121% above placebo value).

Prolactin and growth hormone both showed modest increases, that for growth hormone being significant at the 0.01 level while that for prolactin was not statistically significant.

*Blood prazosin concentration and pharmacologic effect*

A detailed pharmacokinetic analysis of the whole blood prazosin concentration has been presented elsewhere (Jaillon, Rubin, Yee, Ball, Kates, Harrison & Blaschke, 1979). Linear correlations were sought between peak prazosin concentration, half-life, or area-under-the-curve and percent fall in BP or duration of hypotension. No significant correlations were found.

In six of the ten subjects the prazosin concentration was falling by the time the maximum fall in blood pressure was attained, in three it was still rising and in one subject the time of maximum prazosin concentration and maximum hypotension coincided.

## Discussion

The absence of a reflex increase in heart rate in response to hypotension induced by prazosin has been reported in several separate studies and has formed the basis both of mechanistic theories (Constantine *et al.*, 1973; Hess, 1975; Frigon *et al.*, 1978) and clinical recommendations about this agent (Pitts, 1975). In contrast to these earlier studies, our findings demonstrate that the fall in standing blood

**Table 4** Endocrine response to hypotension produced by prazosin, five subjects.

| | *Cortisol* (*μg/100ml*) | *Prolactin* (*ng/ml*) | *Growth hormone* (*ng/ml*) | *BP* (*mmHg*) |
|---|---|---|---|---|
| Placebo | 8.2±3.9 | 3.5±0.25 | 0.98±0.2 | 91±2.1 |
| Prazosin | 15.6±2.6† | 4.8±1.2 | 1.36±0.35† | 75±9‡ |

Time matched samples following prazosin or placebo.

† $P<0.01$, ‡ $P<0.05$ compared with placebo (paired *t*-test).

pressure produced by prazosin is accompanied by a substantial tachycardia, even when the blood prazosin concentration is very low, and this tachycardia persists for the duration of the hypotension (Figure 2). A consideration of the types of methodology used in previous studies could explain in large part the apparent absence of tachycardia earlier reported. Thus, the fact that a beta-blocker was given to at least half (Bolli *et al.*, 1976; Turner *et al.*, 1977) and in one case all (Hua *et al.*, 1978) of the study patients, the inclusion of heart rate data from subjects whose blood pressure did not fall significantly (Lund-Johansen, 1974; Turner *et al.*, 1977) and failure to measure heart rate in the standing position (Lund-Johansen, 1974) might all have contributed to the finding that there was no significant change in mean heart rate.

A further difference in design between the study reported here and others is that we report data following the administration of a single dose of prazosin. While it is possible that this could in part explain the differences in results obtained, we think it unlikely—the methods used in earlier studies impose such serious limitations an data interpretation that it would seem inappropriate on the basis of current knowledge to postulate fundamental changes in prazosin pharmacodynamics between single and multiple dosing of the drug.

Certainly, such an explanation could not be used to reconcile our findings with the observation that, using the same single dose of prazosin (5 mg) in the same number of healthy young people (10) standing heart rate was not elevated even when blood pressure was markedly decreased (Wood *et al.*, 1976). It was for this reason that, having observed the substantial heart rate response on Day 1, we chose to carry out continuous ECG monitoring on Day 3 of the study in order to document clearly both the presence and persistence of the reflex tachycardia. It is possible that these investigators measured heart rate in subjects whose tachycardia had given way to bradycardia, but insufficient data is provided by them to comment further on this point.

A striking relationship revealed by this study is that prazosin syncope is consistently preceded by a rapid and considerable fall in heart rate, while those subjects who sustain their reflex tachycardia develop mild or no symptoms. The sudden fall in heart rate which immediately precedes prazosin syncope is similar to the circumstances associated with a fainting attack. Early in this century Cotton & Lewis (1918) showed that there are two components of a fainting attack: slowing of the heart and a fall in blood pressure. These investigators demonstrated that although atropine prevented the bradycardia it did not abort the faint, suggesting that the fall in heart rate is mediated by the vagal nerves, but is not responsible for the syncope. These findings with atropine were later confirmed by Weissler, Warren, Estes, McIntosh & Leonard (1957) who provided further information on the mechanism of syncope by demonstrating that syncope associated with a 60° head-up tilt was prevented by prior infusion of one litre of 5% albumin in saline. These latter investigators also found that inflating an antigravity suit during a syncopal reaction resulted in a dramatic recovery of consciousness and reversal of the bradycardia. They concluded that poor venous return to the right side of the heart precipitated both the bradycardia and the syncope. Drawing an analogy between syncope induced by posture and that resulting from prazosin, those subjects who experienced a syncopal reaction would be those with the most inadequate venous return.

The prediliction for syncope to accompany only the first dose of prazosin might be explained by this mechanism if the first dose were to stimulate a substantial retention of salt and water. Although it has previously been reported that hypotension produced by prazosin is not associated with an increased release of renin, (Massingham & Hayden, 1975; Bolli *et al.*, 1976; Hayes *et al.*, 1976; Koshy *et al.*, 1977) our results indicate that there are large increases in standing PRA after prazosin administration at prazosin concentrations in the range which is achieved clinically. As in the case of heart rate changes, the discrepancy between renin data presented here and that reported earlier probably finds its origin in methodological differences. Again, the concurrent use of $\beta$-adrenoceptor blockers (Bolli *et al.*, 1976) and the inclusion of data from subjects whose blood pressure was not lowered by prazosin (Koshy *et al.*, 1976) could only have a negative effect on changes in average renin activity. In keeping with our observations on plasma renin activity are reports that weight (Bolli *et al.*, 1976) and plasma volume (Koshy *et al.*, 1977) increase significantly during prazosin treatment. Also in support of a brisk salt and water retention following initial doses of prazosin is the finding that although the first dose might produce a marked fall in blood pressure, if that dose is instituted on a regular three times a day regime then by the fourth day blood pressure is barely different from placebo (Graham, Thornell, Gain, Bagnoli, Oates & Stokes, 1976).

On the basis of our findings we suggest that the 'first dose phenomenon' of prazosin is essentially postural syncope occurring in subjects who are unable to maintain their venous return to the heart in the presence of hypotension. This theory is further supported by the observation that a high sodium diet appears to protect against the development of first dose symptoms (Stokes, Graham, Gain & Davis, 1977).

Experiments in various animal species have

suggested that prazosin exhibits α-adrenoceptor-blocking activity, though the doses used have been very high (Scriabine *et al.*, 1968; Graham, Oates, Stokes & Stokes, 1977). However, concepts about the mechanisms by which prazosin might lower blood pressure have all sought to explain the apparent absence of reflex increases in heart rate or renin release. Thus it has been suggested that the α-adrenoceptor blocking properties of prazosin might demonstrate selectivity for post-synaptic α-adrenoceptors, thereby leaving the presynaptic α-adrenoceptors free to be activated (Cambridge *et al.*, 1977; Cambridge *et al.*, 1978). This in turn would prevent increased noradrenaline release in response to hypotension and would explain the failure to observe a reflex tachycardia or an increase in plasma renin activity. If this theory were correct then prazosin hypotension should not be accompanied by an increase in plasma noradrenaline concentration. Another theory which would predict no increase in plasma noradrenaline during prazosin hypotension concerns the possible inhibition of dopamine-β-hydroxylase by this drug (Frigon *et al.*, 1978).

In both the supine and standing positions, plasma noradrenaline concentrations were significantly elevated compared with control values obtained before prazosin administration (Table 3). There is little data available in the literature concerning the behavior of plasma noradrenaline in man during drug-induced hypotension, and such information as does exist concerns agents which act in the central nervous system and tend to suppress sympathetic nerve activity. It is therefore not possible to draw a direct conclusion about whether the rise in plasma noradrenaline is appropriate for the degree of hypotension observed in this study. Nevertheless, noradrenaline concentrations unquestionably rose and this fact coupled with the striking increases in heart rate and plasma renin activity must reshape attitudes towards prazosin's mechanism of action in man. The very occurrence of tachycardia and elevated renin obviate the need to invoke theories of post-synaptic α-receptor selectivity or dopamine-β-hydroxylase inhibition. Increased plasma noradrenaline makes such theories unlikely in addition to unnecessary. Although prazosin appears to exhibit post-synaptic α-receptor selectivity in rabbit aortic strips, it must be seriously questioned whether such selectivity occurs in man.

The increased heart rate also makes it unnecessary to postulate cardiac accumulation of cyclic GMP as a factor in prazosin action. Further strong evidence against this possible effect comes from the isoprenaline data where the chronotropic response to β-adrenoceptor stimulation is shown to be uninfluenced by prazosin.

The significant rise in plasma cortisol, and the similarity in elevations between those subjects who had developed syncope and those who had not, suggest that the hypothalamic-pituitary-adrenal axis responds well to prazosin hypotension, and that inadequacy of this response is not involved in prazosin syncope. In view of the cortisol response, it is interesting that prolactin concentration did not increase, since prolactin release is enhanced in response to stress in general (Noel, Suh, Stone & Frantz, 1972) and hypotension in particular (Gawel, 1977; Nistrio, Trimarchi & Corsolo, 1977). The lack of prolactin response led us to consider whether prazosin might be acting as a dopaminergic agent. We therefore measured growth hormone concentrations in the same samples which were used for the prolactin analysis, since dopaminergic action is a strong stimulus to growth hormone release. Although the concentration of growth hormone was increased to a statistically significant extent, the values remained well within the normal range and were considerably lower than concentrations achieved following the administration of dopaminergic agents such as levodopa. These observations are interesting but their interpretation is unclear at present.

Although the dose of prazosin used in these studies was high, it should be emphasized that the heart rate started to increase at very low prazosin blood concentrations, and that the plasma renin activity measurements were performed at a time when the blood prazosin concentration was well within the ranges reported during clinical use of this drug (Jaillon *et al.*, 1979; Graham *et al.*, 1976).

Blood concentration of prazosin correlated poorly with pharmacologic effect. In part this probably reflects the complex nature of blood pressure control. However, in view of the observations that the maximum fall in blood pressure frequently occurred after the peak blood concentration, it is possibly of relevance that prazosin metabolites have hypotensive activity. Eight-seven percent of an administered dose of prazosin is excreted as two O-demethylated metabolites in dogs (Taylor, Twomey & Schach von Wittenau, 1977). Each of these 0-demethylated compounds has been shown to possess between 22% and 38% of the hypotensive potency of prazosin in dogs (Althuis & Hess, 1977). It is possible, therefore, that metabolites play an important role in the action of prazosin, which might explain certain discrepancies between *in vitro* observations with the parent compound, such as post-synaptic alpha receptor selectivity, and the findings presented here.

In conclusion, we have shown that hypotension caused by prazosin is accompanied by a substantial increase in heart rate, plasma renin activity and plasma noradrenaline concentration. These observations suggest that selective post-synaptic alpha receptor antagonism, though demonstrable in other species, is unlikely to be the mechanism of

prazosin action in man. We have also demonstrated that prazosin syncope is consistently preceeded by a precipitious fall in heart rate and that ability to maintain a reflex tachycardia in the presence of hypotension appears to prevent syncope. We suggest that prazosin syncope is directly analogous to postural syncope and we therefore endorse the suggestions of other authors that prazosin should be used with caution in subjects whose intravascular volume is depleted, or whose venous return is compromised.

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