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STUDIES ON THE CLINICAL PHARMACOLOGY OF PRAZOSIN. II: THE INFLUENCE OF INDOMETHACIN AND OF PROPRANOLOL ON THE ACTION AND DISPOSITION OF PRAZOSIN

P. RUBIN,* G. JACKSON** & T. BLASCHKE

Divisions of Clinical Pharmacology and Cardiology,
Stanford University Medical Center, Palo Alto, California, USA

1 The possibility of pharmacodynamic and pharmacokinetic interactions of prazosin with indomethacin and with propranolol have been studied in healthy subjects.

2 In four out of nine individuals indomethacin considerably attenuated prazosin-induced hypotension, but noradrenaline concentrations were unchanged from the day when blood pressure fell greatly. The effect of prazosin in the other five subjects was not influenced by indomethacin.

3 Indomethacin prevented the rise in plasma renin activity seen following administration of prazosin alone.

4 Propranolol did not prevent the syncope associated with the first dose of prazosin.

5 Propranolol affected neither the absorption nor elimination of prazosin.

6 It is concluded that in certain subjects indomethacin can largely prevent the hypotensive effect of prazosin, possibly by increasing adrenergic receptor sensitivity. The theoretical possibility that propranolol could influence prazosin disposition or syncope was not substantiated.

Introduction

Treatment of hypertension often involves the use of drug combinations to enhance the therapeutic effects while minimizing toxicity of individual agents (Nies, 1978). Moreover, treated hypertensive patients may receive drugs for other conditions, and these drugs may alter the response to antihypertensive agents. Prazosin, a recently released hypotensive drug, is commonly administered together with a β-adrenoceptor blocking agent such as propranolol because of the reported enhanced therapeutic benefit of such a combination (Brogden, Heel, Speight & Avery, 1977). A previous study carried out by us (Rubin & Blaschke, 1980) suggested that the combination of propranolol and prazosin might be appropriate since, in addition to its intrinsic hypotensive activity, it would decrease the reflex tachycardia produced by prazosin alone. Furthermore, we showed that prazosin-induced syncope was associated with tachycardia followed by bradycardia, and we wished to determine whether this sequence, and therefore the syncopal episode, could be prevented by this combination.

Another interaction with hypotensive drugs which is of probable clinical significance involves the prostaglandin-synthetase inhibitor indomethacin. This agent has been reported to attenuate the antihypertensive action of propranolol (Durao, Prata & Goncalves, 1977; Abbott, Daniel, Watkins & Dollery, 1978) and of hydralazine. (Slack, Warner & Keiser, 1978). The mechanism of this effect is unclear.

The present study was designed to investigate the pharmacodynamic and possible pharmacokinetic interactions of prazosin with both propranolol and indomethacin in a group of healthy volunteers. The neuroendocrine and haemodynamic responses to prazosin alone had been well characterized in these subjects, and the disposition of oral prazosin had been studied with a sensitive analytical method.

Methods

Baseline prazosin study

The study design is shown in Figure 1. Ten normal young men aged 20–30 were studied. Subjects were

* Present address and address for correspondence: Department of Materia Medica, Stobhill General Hospital, Glasgow G21 3UW

** Present address: Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS.

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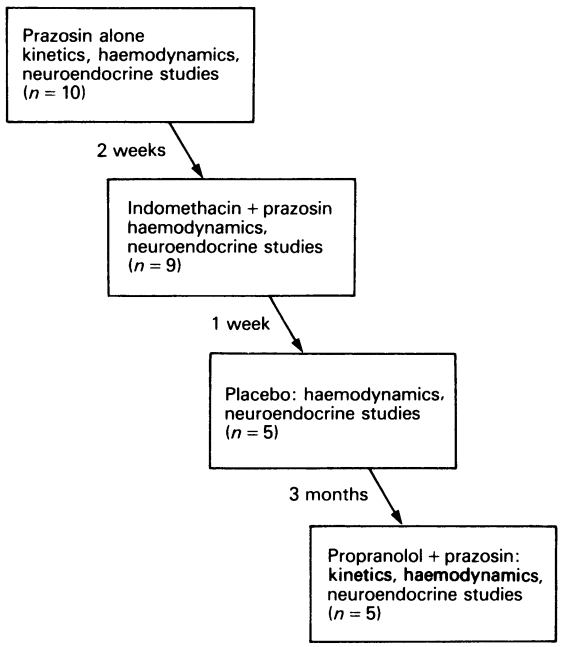

Figure 1 Schematic outline of study methodology

admitted to the Stanford General Clinical Research Center (GCRC) during the evening, slept on the unit and were allowed no caffeine-containing foods or alcohol. Following a light breakfast at 06.45 h a heparin lock was established in a forearm vein and the subjects lay quietly for 30 min. Blood was then drawn for analysis of catecholamines, the subjects stood for 5 min and the catecholamine blood sampling was repeated. Continuous ambulatory ECG monitoring apparatus was attached and three control values for supine and standing blood pressure and heart rate were determined. A five mg capsule of prazosin was given and subsequently lying and standing blood pressure and heart rate were determined for 8 h. Catecholamine blood sampling following 30 min supine and 5 min standing was performed during the phase of maximum hypotension. In addition to the catecholamine analyses, five of the subjects (chosen at random) had blood drawn for prolactin analysis before prazosin administration. These same suvjects subsequently had blood drawn for analysis of prolactin and plasma renin activity (PRA) following 30 min standing during the phase of prazosin induced hypotension. Blood for prazosin analysis was drawn on 15 occasions during the study.

Indomethacin–prazosin study

This was performed 2 weeks after the baseline study. The overall experimental design was identical to that described above, with the exception that one subject was unable to participate.

Subjects received indomethacin 50 mg twice a day for 3 days and 50 mg on the morning of the study. Weights were determined on both the baseline study day and the indomethacin-prazosin day.

Placebo study

One week after the indomethacin study, the five subjects who had the most extensive data collection (PRA, etc) underwent the same procedures as on the baseline day but received placebo in a single-blinded fashion.

Propranolol–prazosin study

Three months after the initial study, five subjects returned in order to assess the influence of propranolol on the disposition and effect of prazosin. These five individuals had all developed reproducible syncope during our earlier studies on prazosin (Rubin & Blaschke, 1980). On this occasion they received propranolol 80 mg twice a day for 7 days and 80 mg on the morning of the study. The remaining experimental design was identical to that of the baseline day. Three of these five subjects had been involved in the extensive data collection, including placebo, in the earlier part of the study.

Analytical methodology

Prazosin concentrations in whole blood were determined by high pressure liquid chromatography using fluorescence detection as we have described elsewhere (Yee, Rubin & Meffin, 1979).

Blood for catecholamine analysis was drawn into chilled plastic syringes containing solid reduced glutathione in sufficient amount to produce a final concentration of 5 mmol/l. This blood was rapidly transferred to a chilled heparin tube and centrifuged for 5 min at 3000 *g* in a refrigerated centrifuge at 4°C. The plasma was immediately frozen on dry ice and subsequently stored at −76°C until analysed by simultaneous single isotope radioenzymatic assay (Peuler & Johnson, 1977).

Blood for plasma renin or prolactin analysis was drawn into chilled plastic syringes, immediately transferred to chilled EDTA tubes and centrifuged at 3000 *g* for 5 min at 4°C. Plasma was immediately frozen on dry ice and stored at −20°C until analysed by radioimmunoassay.

All blood sampling was performed at appropriately time-matched occasions on the various study days.

Continuous ambulatory ECG data were subject to computer analysis (Harrison, Fitzgerald & Winkle, 1976).

Pharmacokinetic calculations

The slope of the disappearance phase (K) was estimated by fitting the terminal log-linear phase of the blood prazosin concentration-time curve to a monoexponential decay function using the non-linear least-squares regression program MLAB (Knott & Reece, 1972). Based on equal assay coefficients of variation at high and low concentrations, data were weighted by the inverse of the squared concentration when fitted to the monoexponential function. The area under the blood prazosin concentration *v* time curve (AUC) during the sampling interval was calculated by the trapezoidal rule. The area beyond the last data point, extrapolated to infinity, was calculated by dividing the concentration at the last data point by the value for K, obtained from the computer fit of the data. The total area-under-the-curve ($AUC_{0-\infty}$) is the sum of these two areas.

Data are expressed as mean ± s.d. Results were compared by paired *t*-test. Blood pressure is expressed as the mean (diastolic + 1/3 pulse pressure).

The study was approved by the Stanford Committee on the Involvement of Human Subjects in Research and all subjects gave written informed consent.

Results

Indomethacin and prazosin: blood pressure and heart rate.

For the group as a whole, indomethacin did not influence the fall in blood pressure caused by prazosin. However, when the time course of blood pressure changes was studied for each subject, four individuals demonstrated an attenuation of hypotension on the day when indomethacin was given, the maximum fall in standing blood pressure being an average of 20 mmHg less on this day. In addition, three of these four had become syncopal following prazosin alone but developed no postural symptoms with the indomethacin/prazosin combination. The time course of blood pressure response in these four subjects on the 2 days is shown in Figure 2. Time matched prazosin concentrations were similar on the 2 days. On the day when prazosin was given alone weight was 79.6 ± 6.3 kg compared with 80.1 ± 6.9 kg on the indomethacin day ($P = 0.3$).

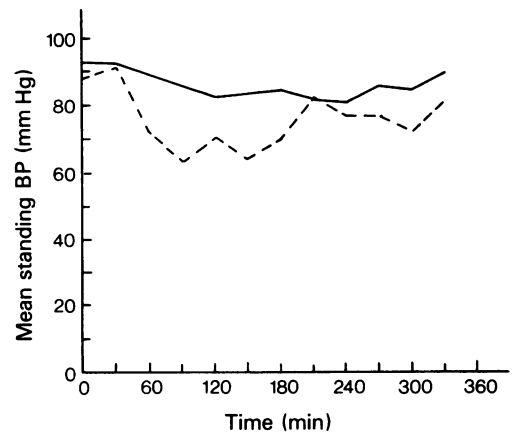

Figure 2 Mean standing blood pressure in four subjects whose hypotensive response to prazosin was attenuated by indomethacin. Prazosin 5 mg was administered at time = 0 on each study day. Before one of these days indomethacin 50 mg twice daily was administered for 3 days, including the morning of prazosin administration. ---- prazosin, —— prazosin + indomethacin

Indomethacin and prazosin: neuroendocrine function

Indomethacin completely prevented the rise in plasma renin activity seen in response to hypotension

Table 1 Blood pressure, renin and catecholemine data (prazosin-indomethacin interaction)

	Prazosin alone	*Prazosin + indomethacin*	*Placebo*
PRA (ng ml^{-1} h^{-1}) (30 min standing)	6.4 ± 2.3	1.1 ± 0.5*	1.4 ± 0.8*
Mean blood pressure (mmHg)	75 ± 9	74 ± 13	91 ± 2*
Noradrenaline (standing)	4.2 ± 0.9	4 ± 0.3	
(supine)	2 ± 0.1	2.6 ± 0.4	
Adrenaline (standing)	0.8 ± 0.1	0.7 ± 0.3	
(supine)	0.4 ± 0.1	0.3 ± 0.03	
Mean blood pressure (mmHg) (standing)	62 ± 7	70 ± 9	

Mean blood pressure recorded at time of blood sampling
All data expressed as mean ± s.d.
*$P < 0.01$ compared with prazosin alone
The same five subjects were used throughout the PRA studies. Ten subjects had catecholamine sampling following prazosin alone and nine of these ten had catecholamine sampling on the indomethacin day (see text).

caused by prazosin alone (Table 1). Blood pressure was similar between the two groups at the time of blood samping for renin analysis. Indomethacin did not influence the catecholamine response to prazosin hypotension. This was true both for the group as a whole (Table 1) and for the four subjects whose fall in blood pressure was attenuated by indomethacin. In this latter group, the standing blood pressure at the time of catecholamine blood sampling was 63 ± 27 mmHg on the day when prazosin was given alalone and 87 ± 6 mmHg when indomethacin was also used ($P = 0.05$). The corresponding noradrenaline concentrations were 3 ± 1.4 nmol/l and 3.6 ± 0.5 nmol/l respectively ($P > 0.1$) and adrenaline concentrations were 0.97 ± 0.6 nmol/l and 0.69 ± 0.6 nmol/l ($P > 0.1$).

Propranolol and prazosin: blood pressure, heart rate syncope

The baseline blood pressures after 80 mg twice daily of propranolol, prior to prazosin administration, were decreased compared to baseline values on the day when prazosin alone was given (Table 2). Propranolol did not influence the fall in standing blood pressure produced by prazosin, but markedly attenuated the heart rate response to this hypotension (Figure 3). Although the reflex tachycardia in response to a postural fall in blood pressure was blunted by propranolol, it did not prevent the development of syncope. All five subjects participating in this phase of the study again developed syncope and in each case it was preceded by a sudden fall in heart rate. Recovery of consciousness was rapid following assumption of the supine position and did not appear to be affected by propranolol.

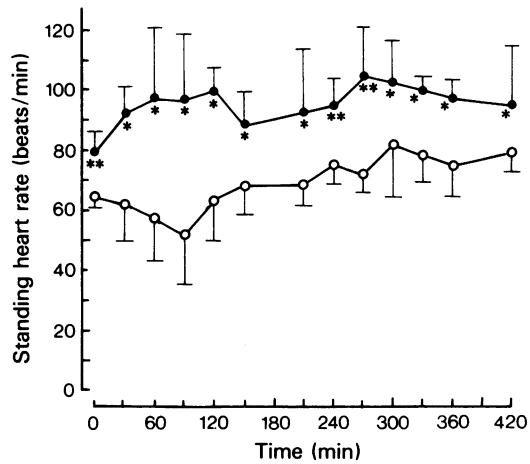

Figure 3 Standing heart rate response to prazosin 5 mg either alone (●) or after 7 days of propranolol 80 mg twice daily (○). Results are expressed as mean ± s.d. $*P < 0.05$; $**P < 0.01$. The same five subjects were involved on each study day.

Prazosin disposition following propranolol

Although propranolol clearly attenuated the cardiac response to prazosin, it did not influence the blood concentration *v* time profile after oral administration of this drug. The AUC $oral_{0-\infty}$ produced by 5 mg prazosin was 16.5 ± 4.3 μmol l^{-1}min following prazosin alone and 14.9 ± 5.6 μmol l^{-1}min during propranolol treatment ($P > 0.1$). K, the slope of the disappearance phase, was 0.0049 ± 0.0003 following prazosin alone and 0.0045 ± 0.0005 during propranolol co-administration ($P > 0.1$).

Table 2 Blood pressure and catecholamine data (prazosin-propranolol interaction)

	A *Prazosin alone (pre-drug)*	*B* *Propranolol alone (pre-drug)*	*C* *Prazosin + propranolol*	*D* *Prazosin alone*
Noradrenaline (nmol/l) (supine)	1.2 ± 0.3	1.8 ± 0.8†	3.4 ± 0.7	2.1 ± 0.5††
(standing)	1.8 ± 0.2‡	3.3 ± 0.3†	4.6 ± 1.5	4.9 ± 3.7
Adrenaline (nmol/l) (supine)	0.2 ± 0.08	0.1 ± 0.04*	0.4 ± 0.1	0.53 ± 0.3
(standing)	0.3 ± 0.2	0.3 ± 0.2	0.9 ± 0.8	0.9 ± 0.3
Mean blood pressure (mmHg) (supine)	87 ± 5‡	78 ± 5†	70 ± 5	88 ± 4**
(standing)	90 ± 7‡‡	82 ± 7*	56 ± 24	46 ± 28

Blood pressure expressed as mean (diastolic + 1/3 pulse pressure), recorded at time of blood sampling.
All data expressed as mean ± s.d.
‡$P < 0.01$, ‡‡$P < 0.05$, Column A compared with Column B
*$P < 0.01$, †$P < 0.05$, Column B compared with Column C
**$P < 0.01$, ††$P < 0.05$, Column D compared with Column C
The same five subjects were studied throughout.

Table 3 Blood pressure and prolactin data (prazosin-propranolol interaction)

	Control (08.00h)	*Propranolol (08.00h)*	*Placebo (12.00h)*	*Prazosin (12.00h)*	*Prazosin + propranolol (12.00h)*
Prolactin (ng/ml)	9.9 ± 0.9	12.5 ± 4.6	3.5 ± 0.25	4.8 ± 1.2	9.2 ± 3*
Mean blood pressure (mmHg)	90 ± 5	83 ± 7†	91 ± 2	75 ± 9††	69 ± 9

Mean blood pressure recorded at time of blood sampling.
All data expressed as mean ± s.d.
†$P < 0.05$ compared with control
††$P < 0.05$ compared with placebo
*$P < 0.05$ compared with prazosin alone
Five subjects (see methods for subject details)

Propranolol and prazosin: neuroendocrine function

Propranolol administration for 1 week resulted in a highly significant increase in standing noradrenaline concentration from 1.8 ± 0.2 nmol/l to 3.3 ± 0.3 nmol/l ($P < 0.01$). Noradrenaline concentrations in the supine position and adrenaline concentrations in both positions were unchanged by propranolol. Table 2 shows the influence of the prazosin/propranolol combinations on catecholamine concentrations during maximum hypotension compared with the effect of prazosin alone and propranolol alone.

The combination of propranolol and prazosin potentiated the release of prolactin, while prazosin or propranolol alone did not influence prolactin release (Table 3).

Discussion

Prazosin–indomethacin interaction

Various pieces of evidence suggest that indomethacin can reverse the hypotensive effect of both β-adrenoceptor blockers (Durao *et al.*, 1977; Abbott *et al.*, 1978) and vasodilators (Slack, *et al.*, 1978). One interpretation of this effect has been that the synthesis of prostaglandins is essential to the hypotension produced by these agents (Durao *et al.*, 1977; Slack *et al.*, 1978). An alternative viewpoint is that salt and water retention induced by indomethacin is responsible for this effect (Abbott *et al.*, 1978). The data presented here indicate that indomethacin does not exert a homogenous effect on the action of prazosin. Four subjects had their fall in blood pressure considerably attenuated while the other five experienced the same hypotension as when prazosin was given alone. Weight did not change significantly either for the group as a whole or for the subjects whose fall in pressure was attenuated. This latter group weighed 80.9 ± 2.2 kg on the prazosin-alone day and 81.1 ± 2.7 following indomethacin. This suggests that the observed action of indomethacin following 3 days treatment in those subjects whose hypotension was attenuated did not result from fluid retention.

In these four subjects whose fall in blood pressure was reduced by indomethacin, plasma concentrations of noradrenaline and adrenaline achieved the same elevated levels as on the day when prazosin was given alone and when the blood pressure was significantly lower. We have previously demonstrated that treatment with indomethacin alone does not influence plasma catecholamine concentrations in man (Rubin & Blaschke, 1979), while another group has presented evidence that inhibition of prostaglandin production leads to increased adrenergic receptor sensitivity in man (Bartter, Gill, Frolich, Bowden, Hollifield, Radfar, Keiser, Oates, Seyberth & Taylor, 1976). The equivalence in noradrenaline concentrations in these four subjects between the prazosin alone and indomethacin/prazosin days, coupled with the marked difference in blood pressures, suggests that adrenergic receptor sensitivity could very well be increased on the day when prazosin was given together with indomethacin. If an alteration in receptor sensitivity is responsible for these observations then the fact that only four of the nine subjects had their prazosin-induced hypotension affected by indomethacin suggests that there is considerable individual variation in the interaction between indomethacin, prostaglandin synthesis and adrenergic receptors. The clinical implications of this observation are potentially very important since hypertensive patients well controlled on prazosin are at risk of losing that control if indomethacin (and probably other prostaglandin synthetase inhibitors) are coadministered.

Indomethacin has previously been reported to suppress plasma renin activity (Frolich, Hollifield, Dormois, Frolich, Seyberth, Michelakis & Oates, 1976; Bowden, Gill, Radfar, Taylor & Keiser, 1978). In the five subjects in whom PRA was measured, the blood pressure was very similar at the time of blood

sampling on the prazosin alone and indomethacin/prazosin days (Table 1). However, the marked elevation in PRA seen in response to hypotension produced by prazosin alone was completely prevented by indomethacin. There is some evidence that the suppression of PRA by indomethacin is directly related to the extent of prostaglandin-synthetase inhibition (Frolich *et al.*, 1976). If the low PRA seen in response to prazosin-hypotension during indomethacin treatment does indeed result from suppression of prostaglandin production then it would appear that prostaglandins are intimately involved in the renin response to hypotension.

Prazosin—propranolol interaction

Our interest in studying the effects of propranolol on the haemodynamic and neuroendocrine effects of prazosin and on prazosin syncope stems from our earlier studies on the mechanism of action of prazosin. We found that prazosin-induced syncope was always preceded by a sudden change from tachycardia to bradycardia (Rubin and Blaschke, 1980). We felt that the bradycardia might be a protective action to prevent the heart contracting onto empty ventricles. Thus propranolol was used in order to produce a slower overall heart rate with consequent increase in time for ventricular filling. Although propranolol substantially decreased the tachycardia seen in response to prazosin, it did not prevent syncope. The inference to be drawn from this observation is probably that, in those subjects who are predisposed to prazosin syncope, the cardiac venous return is so low in the period just before syncope that slowing heart rate by itself is insufficient to ensure adequate ventricular filling.

In view of suggestions that propranolol might act in part by an effect in the central nervous system, with a consequent reduction in sympathetic nerve activity (Conway, Greenwood & Middlemiss, 1978), the noradrenaline data are of interest. Although propranolol treatment for 7 days reduced baseline blood pressure in both supine and standing positions, in neither case did noradrenaline concentrations fall. In the standing position they rose significantly from 1.8 to 3.3 nmol/l ($P < 0.01$). Similarly, propranolol did not decrease the rise in noradrenaline seen following postural hypotension produced by prazosin. In the supine position the noradrenaline concentration was actually higher on the propranolol/prazosin day than following administration of prazosin alone (Table 2). This presumably reflects the lower supine blood pressure resulting from the combination of drugs. In so far as plasma noradrenaline can be used as an index of sympathetic activity it appears that 7 days of propranolol therapy do not cause suppression of sympathetic nervous system activity.

Prolactin concentrations were measured because of an interest in possible effects of propranolol and prazosin on central dopaminergic function. Neither the fall in blood pressure produced by prazosin alone, nor that caused by propranolol alone, resulted in a statistically significant alteration in prolactin concentrations. However, administration of the two drugs together resulted in a significant elevation of prolactin concentration (Table 3). Although the concentration did not exceed the normal range, the blood was drawn at a time when prolactin would normally be at its lowest level. While the clinical relevance of this observation is uncertain, it seems possible that the combination of propranolol and prazosin could result in about a two-fold elevation in prolactin concentration. The mechanism of this effect is unclear, though it is possible that prazosin and propranolol combined have sufficient non-specific adrenergic receptor blocking activity to block partially central dopaminergic receptors which are thought to mediate the inhibition of prolactin release (Smythe, 1977).

The extensive hepatic biotransformation of prazosin (Taylor, Twomey & Schach von Wittenau, 1977), the increased concentrations and prolonged half-life observed in congestive heart failure (Jaillon, Rubin, Yee, Ball, Kates, Harrison & Blaschke, 1979) and the ability of propranolol to decrease the clearance of drugs showing blood-flow limited hepatic clearance (Branch, Shand, Wilkinson & Nies, 1973; Branch, Shand & Nies, 1973) led us to investigate whether propranolol might influence the disposition of prazosin. The clinical relevance of studying this potential interaction is the frequency with which these two drugs are administered together. No effect of propranolol on prazosin disposition was observed. A full analysis of prazosin pharmacokinetics was not possible because of the continued unavailability of an intravenous formulation. However, the extent of prazosin absorption as measured by AUC did not differ following propranolol suggesting that the first pass metabolism of prazosin was not altered by propranolol. Similarly, the slope of the prazosin disappearance phase, and therefore half-life, did not change. Propranolol was given in the dose of 80 mg twice a day. While it is possible that higher doses of propranolol might have produced changes in prazosin disposition, it should be noted that sufficient propranolol was administered to cause a significant reduction in blood pressure and to produce a marked attenuation of the tachycardia seen after prazosin alone is given. Thus the haemodynamic effects of propranolol seen in this study probably reflect closely the situation following administration of this drug in clinical practice. The inference to be drawn from these observations would seem to be that, although

we have presented data elsewhere to indicate that prazosin should be used with caution in patients whose hepatic function is impaired (Jaillon *et al.*, 1979), any effects which clinical doses of propranolol have on liver blood flow in man are insufficient to change prazosin disposition.

In conclusion, we have demonstrated that propranolol influences neither the disposition of prazosin nor the onset of syncope following the first dose of this drug. While prazosin alone and propranolol alone failed to elevate prolactin concentrations, the two drugs in combination caused a twofold increase in prolactin concentration. In four out of nine subjects indomethacin attenuated the hypotensive effect of prazosin, possibly by increasing adrenergic receptor sensitivity through inhibition of prostaglandin production.

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