normal people there is only a low level of sympathetic activity. By analogy, the insignificant fall in resting heart rate suggests there must be only a small level of sympathetic activity in the hyperthyroid patient who is not in cardiac failure. Furthermore, the resting tachycardia in this disease must be due to the thyroid hormone itself.

The propranolol-induced fall in heart rate in patients with hyperthyroidism with cardiac failure was significant, indicating that increased sympathetic activity was present. A similar observation has been made in other forms of cardiac disease.[26]

In a dose of 2 mg, which approximates much more to the usual therapeutic dose, propranolol reduced cardiac contractility by only a modest amount in patients with uncomplicated hyperthyroidism. This suggests that in this condition catecholamines are responsible for a relatively small proportion of the enhanced cardiac function, the major portion being due to thyroid hormone. It therefore seems that the only rational indication for beta-blocking drugs in this setting would be to provide symptomatic benefit.

The situation in patients with thyrotoxic cardiac failure is different. The same dose produced a much greater relative fall in cardiac output and rise in venous pressure—that is, cardiac "contractility." This hitherto unreported observation shows that function in the failing thyrotoxic heart is maintained by the sympathetic system just as in cardiac failure from any other cause, since autonomic overactivity is a normal compensatory mechanism. Thus there seems to be no rational basis for giving beta-blockers in this condition; indeed, they are contraindicated.

These observations were made using intravenous propranolol, so they apply only to this mode of administration. The orally administered drug may have different haemodynamic effects in thyrotoxic heart failure.

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Mrs F Stock kindly typed the manuscript.

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Influence of dosage and dietary sodium on the first-dose effects of prazosin

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Summary

The effects of the first dose of prazosin were assessed in hypertensive patients on different sodium intakes. Patients received 250, 100, or 30 mmol sodium per 24 hours for a week before taking 2 mg or 0·5 mg prazosin. The acute effects of prazosin on blood pressure and pulse rate were milder with a high sodium intake. On the 100-mmol intake symptomatic postural hypotension occurred in five out of seven patients given 2 mg prazosin and in two out of four given a 0·5-mg dose, whereas those taking 2 mg or 0·5 mg and a 250-mmol sodium intake experienced no postural symptoms. These findings indicate that particular care should be taken in starting prazosin treatment in sodium-depleted patients.

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Introduction

Transient postural hypotension is a potential hazard for patients starting treatment with prazosin.[1 2] We have attempted to ameliorate this problem by manipulating dietary sodium intake.

Patients and methods

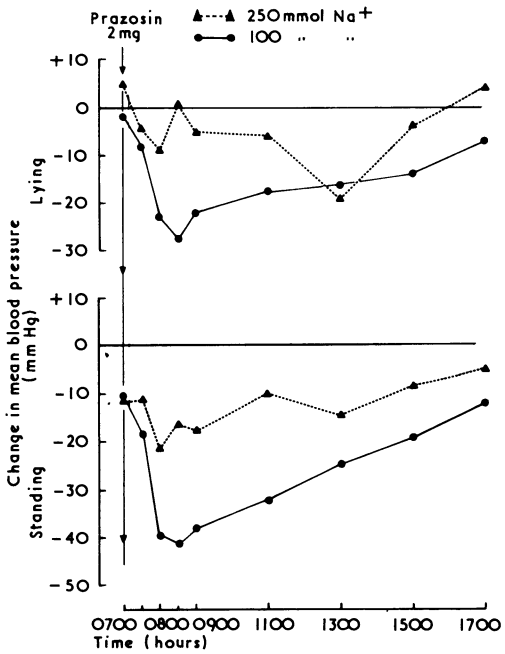
Eighteen studies were performed on 11 patients, most of whom (see table) had untreated essential hypertension. For a week before each study they received a diet containing 250 (n=11), 100 (n=6), or 30 (n=1) mmol (mEq) of sodium per day. On the first day of the

Details of patients and treatments

Case No	Age and sex	Body weight (kg)	Serum creatinine concentration (μmol/l)	Average baseline blood pressure (mm Hg)	Dose(s) of prazosin (mg)	Sodium content (mmol/24 h) and sequence of diets
1	38 M	61	282*	144/106‡	2	100§ and 250
2	40 M	88	88	138/90	2	250 and 100§
3	43 M	63	79	136/88	2	250 and 100§
4	50 F	93	344†	165/109	2	250 and 100§
5	63 M	72	70	168/87	2	250, 100, and 30§
6	27 M	73	79	143/98	2	100§ only
7	62 M	95	141	205/121	2	100 only
8	22 F	55	53	148/101	0·5	100§ and 250
9	50 F	58	70	179/105	0·5	100§ only
10	39 F	46	70	158/103	0·5	100 only
11	62 M	75	88	187/101	0·5	100 only

*Patient had chronic glomerulonephritis.
†Patient had polycystic kidneys.
‡Patient was receiving long-term propranolol 240 mg/day.
§On this sodium intake the patient showed symptoms of postural hypotension.
Conversion: SI to traditional units—Creatinine: 1 μmol/l ≈ 0·0113 mg/100 ml. Sodium: 1 mmol/24 h = 1 mEq/24 h.

study urinary sodium excretion averaged (±SE), respectively, 216±15, 96±7, or 28 mmol/24 hours. A placebo tablet was given at 0700 on the first day, and prazosin, 2 mg or 0·5 mg, was given at 0700 on the second day. Blood pressure and heart rate were monitored before and after exercise, as described.[1] The effects of prazosin treatment were expressed as the mean differences (± 1SE) between the observations on the day when placebo was given and those at the same time on the day of active treatment. Statistical analysis was by Student's paired *t* test.



Responses in mean blood pressure (diastolic pressure plus one-third of pulse pressure) of five hypertensive patients to two test doses of prazosin (2 mg) given a week apart during different dietary intakes of sodium. Effects shown are differences between results with placebo and active tablets.

Results

The figure shows the effects of administering prazosin 2 mg to five patients (cases 1-5) who had sodium intakes of 100 mmol/day and 250 mmol/day. At the lower sodium intake prazosin produced significant falls in both lying ($P<0·01$) and standing ($P<0·005$) mean blood pressure, which were greatest one to two hours after treatment. At the higher sodium intake the response was smaller, and the fall in blood pressure was significant only when the patients were standing ($P<0·01$). The differences between the values at the two levels of intake were significant at 0830 for lying pressures ($P<0·005$) and at 0900 for standing pressures ($P<0·05$). The prazosin-induced increase in standing pulse rate (observations between 0730 and 0900) averaged 23±6 beats/min on 100 mmol sodium and 9±5 beats/min on 250 mmol sodium; these effects were significantly different ($P<0·05$).

None of the patients on a sodium intake of 250 mmol/day experienced any orthostatic symptoms after prazosin was started, even after exercise. The maximum postexercise change in standing mean blood pressure was −38±9 mm Hg at 1100. Of those on a 100-mmol sodium intake, however, three felt faint after prazosin and could not exercise, and one became faint after exercise. The remaining patient (case 5), who was asymptomatic during both the 100-mmol and the 250-mmol studies, became hypotensive and faint after exercise during a third study with a sodium intake of 30 mmol/day.

The mean effects of a 0·5-mg dose of prazosin in four patients (cases 8-11) were compared with those of a 2-mg dose in another group of five patients (cases 2, 3, 5, 6, and 7; patients with renal disease were excluded). The dietary sodium intake in each case was 100 mmol/day. One hour after the 0·5-mg dose the mean blood pressure was significantly decreased—lying (−19±5 mm Hg), standing (−26±5 mm Hg), and after exercise (−41±8 mm Hg). After the 2-mg dose the corresponding falls in the lying and standing positions were −21±5 and −41±7 mm Hg; fainting precluded postexercise recordings in three of this group.

Two patients experienced mild postexercise symptoms on the 0·5-mg dose. One of these patients was retested on a 250-mmol sodium intake and had less orthostatic change in blood pressure and no symptoms.

Comment

As observed by Rosendorff,[2] the first-dose effects of prazosin were milder in the patients given 0·5 mg than in those given 2 mg. An increased dietary sodium intake was, however, quite as effective in preventing severe first-dose hypotensive responses as a reduction in dose. Thus the group given a 2-mg test dose at two different levels of dietary sodium experienced no postural symptoms before or after exercise on the high-sodium intake, but four patients felt faint when they were tested on a 100-mmol sodium intake. Another patient felt faint after a 2-mg dose while taking 30 mmol sodium per day. These differences cannot be explained by accommodation to the first-dose response, for the high-sodium intake preceded the low intake in most of the group.

Particular care should be taken when starting prazosin treatment, even with 0·5 mg, in sodium-depleted patients.

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