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Intraindividual Comparison of Moxonidine and Prazosin in Hypertensive Patients

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Summary. Thirty hypertensive outpatients were treated with moxonidine for 4 weeks in an intraindividual comparison study. After a wash-out period of at least 2 weeks the same patients were given prazosin for 4 weeks. The initial daily doses were 0.2 mg moxonidine and 1 mg prazosin. The antihypertensive dose was titrated individually until the diastolic blood pressure (BP) fell below 95 mm Hg.

Within 3 days of dose titration, a mean dose of 0.37 mg moxonidine produced a significant decrease in BP from a mean of 184/100 to 155/90 mm Hg, while in prazosin treated patients 5 to 8 days were necessary to reduce the BP from 180/100 to 149/89 mm Hg; the mean prazosin dose was 2.8 mg. In addition to the lower dose of moxonidine compared to prazosin, it was found that in 67% of patients moxonidine was given once daily whilst prazosin was administered three-time daily in 73%.

Within the first week of moxonidine treatment 14/30 patients experienced dryness of the mouth, but it was so mild that the patients did not want to discontinue the trial. In contrast, 3/30 patients discontinued therapy with prazosin because of side effects. The most frequent adverse effects of prazosin were orthostatic dysregulation in 6 patients, pain in the chest in 5, giddiness and tachycardia in 4 and nervousness in 3 patients; no patient had these complaints whilst on moxonidine.

In intraindividual comparisons with moxonidine, efficacy, tolerance and the well-being of the patients were significantly better than when on prazosin.

Key words: moxonidine, prazosin, hypertension; intraindividual comparison, side-effects

Moxonidine (BE 5895-base), 4-chloro-5-(2-imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine, is a new centrally acting α_2-adrenoceptor agonist [1]. In contrast to other central acting antihypertensive drugs, moxonidine is the only α_2-full agonist with high potency and α_2-selectivity. The full intrinsic activity of moxonidine was found on human platelet α_2-adrenoceptors by Bergerhausen [2]. Its antihypertensive efficacy in patients with primary essential and secondary hypertension has previously been demonstrated [3, 4].

Crossover studies with moxonidine in comparison to clonidine have already been published [5, 6], but there do not appear to be any comparing its efficacy with that of other existing therapies. The aim of the present study was to compare moxonidine with an agent that reduces blood pressure by a different pharmacological mechanism. Prazosin lowers arterial blood pressure by selective antagonism of peripheral postsynaptic α_1-adrenergic receptors [7]. It has been shown, as has moxonidine, to be effective as a single agent in the treatment of hypertension [8-12].

An intraindividual comparison of moxonidine and prazosin monotherapy has been carried out in 30 patients with all degrees of hypertension who also suffered from different accompanying diseases.

Patients and Methods

Patient Selection

Thirty hypertensive outpatients (mean age 64 years, range 36-89 years, 13 patients older than 70 years) were treated by 3 investigators. The baseline data of the patients are shown in Table 1 a. Seventeen of the 30 patients had had some previous antihypertensive therapy which was gradually reduced and interrupted for at least 2 weeks prior to the study without any risk; 5 had been on treatment with combinations of reserpine and diuretics, 1 with reserpine, a diuretic and a vasodilator, 4 with combinations of a β-block-

Table 1 a. Details of the patients

Males [%]	50
Age [years] mean	64
range	36-89
Weight [kg]	75 ± 11
Creatinine [mg/dl]	1.0 ± 0.28
Classification of hypertension	
by etiology: Secondary hypertension	5-10 (16.7-33.4%)
by stage: WHO I-II	12 (40%)
WHO II	16 (53.3%)
WHO III	2 (6.7%)
by ocular fundal changes: THIEL 0	11 (36.7%)
THIEL 1	14 (46.7%)
THIEL 2-3	5 (16.6%)
Duration of hypertension [years]	
< 2	6 (20%)
⩾ 2 and < 10	19 (63.4%)
⩾ 10	5 (16.6%)
Number of patients with additional diseases	24 (80%)
1	5 (16.7%)
> 1	19 (63.3%)

	Moxonidine	Prazosin
Systolic BP [mm Hg][a]		
supine	184 ± 19	180 ± 21
standing	180 ± 21	172 ± 17
Diastolic BP [mm Hg][a]		
supine	100 ± 8	100 ± 8
standing	99 ± 10	97 ± 7
Pulse rate [beats/min][a]		
supine	78 ± 11	78 ± 12
standing	83 ± 15	83 ± 14

[a]Mean pretreatment values are average of 3 measurements in 30 patients on 3 different days before moxonidine and prazosin treatments, respectively; $\bar{x} \pm SD$

er, a thiazide diuretic and a vasodilator, 2 with a β-blocker and thiazide diuretic, 3 with amiloride or triamterene in combination with a thiazide diuretic, and 1 patient each with spironolactone + furosemide and single-agent β-blocker, respectively. Based on electrocardiogram, appearance of the ocular fundus and extent of organ damage, the hypertension was graded as WHO I, II and III. Fourteen patients had ocular fundus changes of Grade I, 5 of Grade II or III, and 11 had no changes at all. 80% of the patients were reported to have one or more additional diseases, as detailed in Table 1 b.

Design of the Study

When systolic blood pressure was above 160 mm Hg and/or diastolic blood pressure above 95 mm Hg after 2 weeks without antihypertensive medication, i.e. during both wash-out periods, subjects were put on moxonidine or prazosin therapy for 4 weeks. During the last week of both wash-out periods patients were

Table 1 b.

Concomitant diseases	24 (80%)
Most frequent diagnoses	
Heart failure	16
Arteriosclerosis	14
Coronary disease	9
Diabetes mellitus	7
Cerebral sclerosis	7
Deviation of vertebral column	6
Hyperlipaemia	5
Hepatic disease	4
Bronchopathy	3
Varicosis	3
Renal disease	2
Parkinson's syndrome	2
Calf cramps	2
Hyperuricaemia	1
Concomitant medication	17 (56.7%)
Most frequent drugs	
Cardiac glycosides	15
Nitrates	7
Blood flow stimulating drugs	6
Antidiabetics	4
Lipid-lower	3
Hepatotherapeutics	3
Anti-asthmatics	3
Antiphlogistics	2

Table 2. Supine blood pressure (BP, mm Hg) and heart rate (HR, beats/min) before, during and after discontinuation of moxonidine and prazosin therapy, respectively; mean ± SD; $n = 30$

		Moxonidine	Prazosin	
Before therapy	BP	184/100 19 8	180/100 21 8	
	HR	78 ± 11	78 ± 12	
4th week of therapy	BP	149[a]/89[a] 16 6	150[a]/87[a] 14 8	($n = 27$)
	HR	74 ± 10	77 ± 11	
1st day after withdrawal	BP ($n = 29$)	168/ 93 23 6	166/ 94 12 6	($n = 26$)
	HR	77 ± 12	78 ± 12	
2nd day after withdrawal	BP	172/ 97 20 6	170/ 94 13 5	($n = 26$)
	HR	77 ± 12	78 ± 12	
3rd day after withdrawal	BP	175/ 95 21 6	171/ 97 14 5	($n = 27$)
	HR	80 ± 10	79 ± 11	

[a]$p < 0.001$, compared to pretreatment values

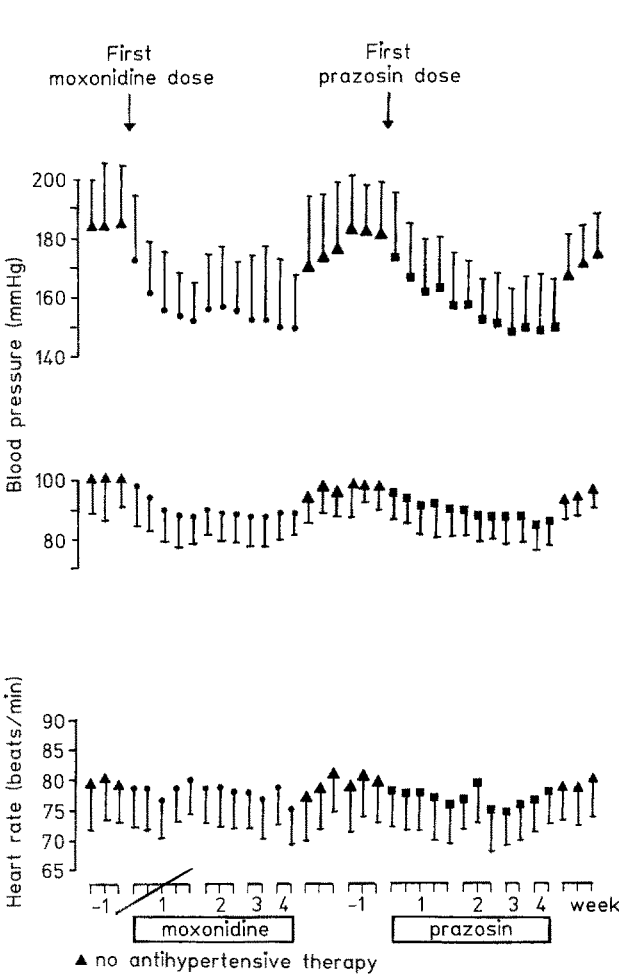

Fig. 1. Supine systolic and diastolic blood pressure and pulse rate before treatment, during and after cessation of moxonidine therapy, and before, during and after cessation of prazosin therapy

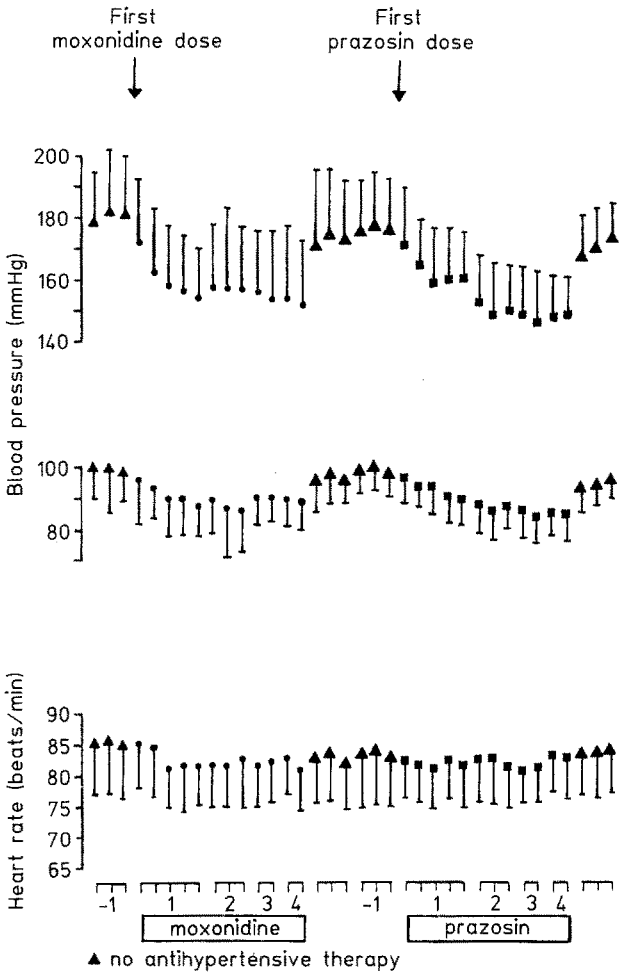

Fig. 2. Standing systolic and diastolic blood pressure and pulse rate before treatment, during and after cessation of moxonidine therapy, and before, during and after cessation of prazosin therapy

seen every Monday, Wednesday and Friday to establish the presence of stable hypertension. Then the treatment periods were begun.

During the first treatment period therapy was initiated with 0.2 mg moxonidine daily. If diastolic pressure remained above 95 mm Hg, the treatment dose was raised to 0.4 mg on the following day, thus titrating the dose to produce a diastolic blood pressure <95 mm Hg. After the second wash-out period of at least 2 weeks the same patients were given prazosin for 4 weeks. In the second treatment period patients started with a daily dose of 1 mg prazosin, again increasing until the diastolic blood pressure was <95 mm Hg. Prazosin dose titration was performed according to the dosage instructions on the package circular for Minipress 1 mg.

After acceptance of the study by an ethical committee, it was carried out in general practices by Drs. Faust, Naief, Schwarz.

Procedures

During the first 5 days of both treatment periods, and for 3 days after discontinuation of moxonidine and prazosin therapy, the blood pressure was measured daily in the morning and afternoon. All measurements were taken after 3 min of rest and after standing for 2 min. After individual titration of the dose, the blood pressure was measured twice daily on 7 days over 3 weeks. The pulse rate was taken after blood pressure measurement by palpation of the wrist for 60 s.

Before and on the last day of each treatment period, an electrocardiogram was recorded, and routine blood and urine analyses were performed. Serum and urine sodium, potassium and urine glucose were determined once weekly during each treatment period, and before and after each treatment period. Side-effects were assessed at each visit by a symptom

Table 3. Comparison of moxonidine and prazosin dosage in hypertensive patients

Individually titrated doses [mg]	Number of patients	
	Moxonidine	Prazosin
0.2	12 (40.0%)	
0.3	3 (10.0%)	
0.4	10 (33.3%)	
0.5	2 (6.7%)	
0.6	2 (6.7%)	
1.0	1 (3.3%)	2 (6.7%)
1.5[a]		7 (23.3%)
2.0[a]		4 (13.3%)
3.0		14 (46.7%)
5.0		1 (3.3%)
7.5[a]		2 (6.7%)
Mean dose [mg/day]	0.37	2.8
Change in BP [%]	−21/−11	−17/−13
Frequency of administration		
Once daily	20/30 patients	2/30 patients
t.i.d.	5/30 patients	22/30 patients

[a]Interruption of therapy in 3 prazosin-treated patients

Table 4. Numbers of adverse symptoms reported by all 30 patients at any given time within 4 weeks of moxonidine and prazosin treatment

Side-effects	Moxonidine	Prazosin	McNemar test
Dryness of mouth	16	2	$p=0.002$
Tiredness	6	4	$p=0.705$
Weakness	–	4	
Orthostatic dysregulation	1	13	$p=0.005$
Chest pain	–	5	
Vertigo	–	5	$p=0.103$
Tachycardia	–	5	
Nervousness	1	6	$p=0.157$
Depressive mood	–	2	
Headache	3	3	
Nausea	3	4	
Oedema	–	3	
Others	15	14	
	45 in 25 patients	70 in 24 patients	

Table 5. Intraindividual comparison between moxonidine and prazosin therapy by the sign test of Dixon and Mood

Well-being of the patients, $p=0.001$	
better on moxonidine	$n=15/30$
better on prazosin	$n=1/30$
Tolerance, $p<0.001$	
better on moxonidine	$n=18/30$
better on prazosin	$n=1/30$
Efficacy, $p=0.013$	
better on moxonidine	$n=12/30$
better on prazosin	$n=2/30$

check list of 32 different side-effects, and body weight was measured. Patient compliance was controlled by measuring moxonidine in urine by HPLC.

Statistical Analysis

The effects of both drugs upon all the parameters tested were compared by analysis of variance (repeated measures). Intraindividual comparisons of patient well-being, tolerance and efficacy were evaluated by the sign test of Dixon and Mood. Changes in adverse symptoms were intraindividually compared by the McNemar test.

Results

Blood Pressure and Pulse Rate

All patients completed the moxonidine treatment period, whereas in 3/30 patients therapy with prazosin was discontinued because of side-effects. The latter were excluded from the evaluation. Baseline data for all 30 patients are shown in Tables 1 a and b.

Blood pressure and pulse rate data before, during and after discontinuation of moxonidine and prazosin therapy are shown in Table 2, and Figs. 1 and 2. In both treatment groups systolic and diastolic pressures fell significantly both in the supine and erect positions. There was no significant difference between mean blood pressure reduction on moxonidine and on prazosin. One of the three patients who stopped prazosin therapy showed no blood pressure reduction whilst on prazosin, but he did suffer orthostatic hypotension and collapse. On 0.5 mg prazosin tid a systolic blood pressure of 180 mm Hg supine and 75 mm Hg erect was measured. In four other patients differences of 25 mm Hg or more were found between the supine and standing systolic pressures.

In both groups there was a gradual increase in blood pressure within 3 days after cessation of moxonidine or prazosin therapy, but no indication of an overshoot (Table 2).

Individual Titration of the Antihypertensive Doses of Moxonidine and Prazosin

The individually titrated doses of moxonidine and prazosin during the 4th week of therapy are listed in Table 3. A mean titrated dose of 0.37 mg/day moxonidine (range 0.2–1.0 mg/day) resulted in a decrease in blood pressure of 21/11%, and 2.8 mg/day prazosin (range 1.0–7.5 mg/day) caused a reduction of 17/13%. No correlation was found between the individual doses of moxonidine and prazosin.

In most of the patients (67%) moxonidine was given once daily, but prazosin was administered thrice daily in 73%.

Titration of the dose of moxonidine was finished within 3 days in 70% of the patients while the titration period in prazosin-treated patients lasted 8 days in 50% and 5 days in 23.3% of the patients.

Adverse Reactions

Side-effects reported by the patients on 12 different days during the 4 weeks of moxonidine and prazosin treatment are listed in Table 4. Mean number of symptoms during this period was 2.8 per patient on moxonidine and 3.1 per patient on prazosin. Reduced by the symptoms reported before treatment, there were 1.0 and 1.2 complaints per patient on moxonidine and prazosin, respectively.

During moxonidine therapy 25 out of 30 patients reported adverse symptoms as did 24 patients on prazosin. A causal relationship between medication and adverse reactions was found in 12 moxonidine-treated and in 14 prazosin-treated patients. Cessation of prazosin therapy was necessary in 3 patients because of orthostatic dysregulation and collapse, chest pain, vertigo and headache. No moxonidine-treated patient interrupted treatment.

The profile of adverse experiences during moxonidine was quite different from that on prazosin. Orthostatic dysregulation, chest pain, vertigo, weakness, tachycardia, nervousness and oedema were found in subjects on prazosin while on moxonidine the only specific untoward effect was mild dry mouth on some days. Patients experienced tiredness on both drugs. No difference between moxonidine and prazosin was found in the symptoms of headache and tiredness. Moxonidine did not show orthostatic dysregulation ($p=0.005$), chest pain, vertigo or oedema.

Tolerance and Efficacy

Intraindividual comparisons of patient well-being, tolerance and efficacy are shown in Table 5. During moxonidine therapy more patients felt significantly better than on prazosin ($p=0.001$) which corresponds very well to the better tolerance of moxonidine ($p<0.001$) reported by the physicians. Very good or good tolerance of moxonidine was found in 93.3% of the patients, but only in 53.5% of those on prazosin. In this intraindividual comparison study, the physician's evaluation of efficacy was better for moxonidine than for prazosin ($p=0.013$); 86.6% of patients showed very good or good efficacy on moxonidine and 70% on prazosin.

Biochemistry, Haematology and ECG

There were no significant or clinically relevant changes in biochemical variables, no haematological abnormalities and no changes in ECG with either therapy.

Discussion

Moxonidine and prazosin given as single agents each decreased systolic and diastolic blood pressure. Consistent with the results of others prazosin lowered standing more than supine blood pressure [10, 13]. This effect may cause the high incidence of orthostatic dysregulation during prazosin therapy. The dosages employed did not show any significant difference in the antihypertensive effectiveness of the drugs. It should be emphasized that in every patient in this study an important goal was to titrate the minimal antihypertensive dose necessary to achieve the therapeutic objective. Recent observations on moxonidine have shown comparable dose ranges of 0.2–0.4 mg/day [3, 5, 6] and 0.4–0.6 mg bid [4]. The prazosin dose range of 1–7.5 mg/day found here is consistent with the recommended dosage of 1–15 mg/day [14]. Fauchald et al. [15] found a mean dose of 4.9 mg/day prazosin, Rosenthal et al. [16] 5.16 mg/day, Seideman et al. [10, 17] 3×0.5 mg/day and 3×0.5–2.5 mg/day, respectively. Other authors have reported mean daily doses of prazosin which seem to be high compared to those required here. The discrepancies may result from substantial variation in plasma prazosin concentration between patients, and the day-to-day variations described by Grahnén [18].

Consistent with published clinical findings [3, 4, 6], moxonidine did not lower heart rate after acute or chronic treatment, nor did it cause orthostatic hypotension or postural symptoms, in contrast to prazosin. The profile of side-effects on an α_1-antagonist, like prazosin, is quite different from that of an α_2-agonist, like moxonidine, but remarkably, the incidence of tiredness and headache did not differ between the drugs. The most prominent and well-known adverse effects of prazosin, namely orthostatic dysregulation, chest pain, vertigo, weakness, tachycardia and oedema [19, 20], were observed in patients when on prazosin but not when on moxonidine. The only frequently reported adverse effect of moxonidine was dryness of the mouth, but it seemed so mild that no one discontinued moxonidine therapy, while, 10% of patients discontinued treatment with prazosin because of side-effects and/or an un-

satisfactory hypotensive effect, according to the results of Fauchald et al. [15].

The overall incidence of adverse effects was high and was similar on moxonidine and on prazosin. This may be related to the method of monitoring unwanted effects during therapy. Borghi et al. [21] showed that unwanted effects appear frequently to be overreported when a checklist is used. In the present study the checklist, consisting of 32 symptoms, was very detailed, and patients were systematically questioned 12 times during therapy. It should be emphasized that 43% of the patients were more than 70 years old, and about half of them suffered from heart failure and arteriosclerosis which may promote postural symptoms. Further, numerous concomitant diseases were reported (Table 1). Several adverse effects were of a nonspecific type and were not related to the investigated drugs.

In conclusion, moxonidine and prazosin are potent antihypertensive agents, each with a characteristic profile of adverse effects. In this intraindividual comparison study, moxonidine showed better individual efficacy (Table 5), significantly better tolerance and a shorter and less complicated dose titration period without any "first dose phenomenon". As, in comparison to prazosin, moxonidine is given in a lower dose and only once or sometimes twice daily, and second, in contrast to many thiazides and beta-blockers, it does not appear to cause metabolic derangements, like deleterious changes in lipids, uric acid, glucose or electrolytes, it may become an alternative antihypertensive agent, especially when thiazides and beta-blockers are contraindicated.

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References

1. Armah B, Stenzel W (1981) BE-5895, a new clonidine-type antihypertensive aminopyrimidine derivative. Naunyn Schmiedeberg's Arch Pharmacol 316 [Suppl]: R42
2. Bergerhausen J (1985) Moxonidine (BE 5895) a full agonist at human platelet α_2-adrenoceptors. Naunyn Schmiedeberg's Arch Pharmacol 329 [Suppl]: R80
3. Plänitz V, Hoffmann K (1983) First clinical data on moxonidine · HCl for treatment of mild to moderate hypertension. Naunyn Schmiedeberg's Arch Pharmacol 324 [Suppl]: R79
4. Frisk-Holmberg M, Plänitz V (1985) Selective alpha-adrenoceptor agonists in arterial essential hypertension. Clinical experience with moxonidine. Filed for publication
5. Plänitz V (1984) Crossover comparison of moxonidine and clonidine in mild moderate hypertension. Eur J Clin Pharmacol 27: 147–152
6. Plänitz V, Stenzel W, Hoffmann K (1985) Double-blind crossover comparison of moxonidine and clonidine-HCl. Herz/Kreislauf 17: 420–25
7. Cambridge D, Davey MJ, Massingham R (1977) The pharmacology of antihypertensive drugs with special reference to vasodilators, α-adrenergic blocking agents and prazosin. Med J Austr 2 [Specl. Suppl]: 2–6
8. Bolli P, Wood AJ, Simpson FO (1976) Effects of prazosin in patients with hypertension. Clin Pharmacol Ther 20: 138–141
9. Stokes GS, Gain JM, Mahony JF, Raftos J, Stewart JH (1977) Long-term use of prazosin in combination or alone for treating hypertension. Med J Austr 2 [Specl. Suppl]: 13–16
10. Seideman P, Grahnén A, Haglund K, Lindström B, von Bahr C (1981) Prazosin dynamics in hypertension: Relationship to plasma concentration. Clin Pharmacol Ther 30: 447–454
11. Guthrie GP, Kotchen TA (1983) Effects of prazosin and clonidine on sympathetic baroreflex function in patients with essential hypertension. J Clin Pharmacol 23: 348–354
12. Hubbell FA, Weber MA, Drayer JIM, Rose DE (1983) Combined central and peripheral sympathetic blockade: Absence of additive antihypertensive effects. Am J Med Sci 285: 18–25
13. Hubbell FA, Weber MA, Drayer JIM, Rose DE (1984) Comparative antihypertensive and endocrinologic effects of clonidine and prazosin in patients with essential hypertension. South Med J 77: 1264–1268
14. Deutsche Liga zur Bekämpfung des hohen Blutdrucks (1984) Empfehlungen zur Hochdruckbehandlung in der Praxis und zur Behandlung hypertensiver Notfälle der Deutschen Liga zur Bekämpfung des hohen Blutdrucks e.V., 6. Auflage, Im Neuenheimer Feld 366, Heidelberg
15. Fauchald P, Helgeland A (1979) Treatment of hypertension with prazosin. An open study in general practice. Acta Med Scand 205 [Suppl 625]: 141–142
16. Rosenthal J, Gabriel H (1984) 24-Stunden-Blutdruckprofile unter Behandlung mit Prazosin. Medwelt 35: 1534–1536
17. Seideman P, Grahnén A, Haglund K, Lindström B, von Bahr C (1982) Prazosin first dose phenomenon during combined treatment with a β-adrenoceptor blocker in hypertensive patients. Br J Clin Pharmacol 13: 865–870
18. Grahnén A, Seideman P, Lindström B, Haglund K, von Bahr C (1981) Prazosin kinetics in hypertension. Clin Pharmacol Ther 30: 439–446
19. Pitkäjärvi T, Kyöstilä S, Kontro J, Mattila MJ (1977) Antihypertensive drug combinations: Prazosin, hydrochlorothiazide and clonidine. Ann Clin Res 9: 296–300
20. Colucci WS (1983) Alpha-Rezeptorenblockade mit Prazosin. Therapiewoche 33: 1894–1913
21. Borghi C, Pallavini G, Comi D, Grillo G, Lombardo M, Mantero O, Minetti L, Selvini A, Suppa G (1984) Comparison of three different methods of monitoring unwanted effect during antihypertensive therapy. Int J Clin Pharmacol Ther Toxicol 22: 324–328

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