Reticulocytosis may cause a false positive direct AHG test result.¹⁸ This occurs when the AHG reagent contains anti-transferrin which binds to the transferrin found normally on the surface of reticulocytes. Since our positive direct AHG test result was obtained with several reagents, used in different laboratories, this did not appear to be a valid explanation in our case. Furthermore, reticulocyte fractions gave weaker results with AHG than did the spherocyte-rich fractions.

Both Pirofsky² and Brodeur¹⁹ have suggested that red cell antigenicity might be altered by mechanical damage, resulting in an autoimmune reaction to modified cells. In our case, mechanical fragmentation was not seen so that this explanation is again improbable.

Drug-induced haemolysis would not seem likely in our case because small doses of drugs were used, and antibody testing was not dependent on the presence of drugs in the test system. One irrefutable proof of an autoimmune pathogenesis would be if the haemolysis continued longer than the lifespan of all the transfused blood cells. On this criterion, many previously recorded cases cannot be explained on an autoimmune basis, and delayed haemolytic transfusion reaction is a more likely explanation. In our case haematological recovery was conspicuous 28 days after transfusion, and complete within 43 days, except for the persistence of low titre antibody. Only two previous short reports have suggested isoimmunity as a cause for this syndrome,^{20 21} and mechanical red cell fragmentation was present in one of these. Our case clearly shows that isoantibody formation alone can produce marked haemolysis after cardiac surgery and emphasises the careful transfusion management which is required in these cases.

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Use of prazosin in management of hypertension in patients with chronic renal failure and in renal transplant recipients

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Summary

Prazosin was used in combination with other antihypertensive drugs in the successful management of hypertension in seven patients with chronic renal failure and six renal transplant recipients, also with chronic renal failure. The addition of small doses of prazosin (mean 3 mg/day) to the antihypertensive regimen produced significant falls in systolic and diastolic blood pressures in both the lying and standing positions. The standing blood pressures were significantly lower than the lying blood pressures during prazosin treatment. Neither the mean blood urea concentrations nor the mean plasma creatinine concentrations changed significantly during prazosin administration. Chromium-51 edetic acid clearances did not change significantly during prazosin treatment in the seven patients in whom it was measured.

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Severe symptomatic postural hypotension occurred in one patient a week after starting prazosin 3 mg/day. This hypotensive episode was associated with a transient and reversible deterioration in renal function. Another patient developed a rash while on prazosin but it was probably related to propranolol rather than prazosin. Prazosin is thus an effective antihypertensive drug in patients with chronic renal failure, and it may be used with a variety of other drugs. It should be used cautiously, however, since patients with chronic renal failure may respond to small doses, and significant postural falls in blood pressure may result. There was no evidence that the use of prazosin resulted in progressive deterioration in the residual renal function of the patients with chronic renal failure.

Introduction

Prazosin is a relatively new antihypertensive drug, which has been used in patients with normal renal function.¹ We report here its use in combination with other antihypertensive drugs in the management of hypertension in patients with chronic renal failure. Preliminary observations suggested that patients with chronic renal failure might respond to relatively small doses of the drug and that use of the drug, at least in combination with others, was associated with significant postural falls in blood pressure and a slight fall in the ⁵¹Cr-edetic acid clearance.²

Methods

Twelve patients with chronic renal failure, five of whom were renal transplant recipients, were studied. One patient was studied twice. All patients gave their informed consent to the use of prazosin. Details of the patients are shown in table I.

TABLE I—Age, sex, diagnosis, and initial renal function of patients studied

Case no	Age and sex	Diagnosis	⁵¹ Cr-edetic acid clearance (ml/min)
1	53 M	Nephrosclerosis	34
2	55 M	Chronic glomerulonephritis	309*
3	56 F	Nephrosclerosis	57
4	65 M	Chronic obstructive nephropathy	65.0†
5	64 M	Renal artery stenosis, nephrosclerosis	186*
6	67 M	Polyarteritis nodosa	239*
7	73 M	Renal artery stenosis, nephrosclerosis	38
8	28 M	Renal transplant recipient	54
9	28 M	Renal transplant recipient	47
10	36 F	Renal transplant recipient	28
11	53 M	Renal transplant recipient	40
12	23 M	Renal transplant recipient	33
12	23 M	Renal transplant recipient	23

*Plasma creatinine $\mu\text{mol/l}$ ($1 \mu\text{mol/l} \approx 0.0113 \text{ mg/100 ml}$).

†Endogenous creatinine clearance ml/min.

All patients were on a variety of other antihypertensive drugs, including one or more of the following: propranolol, clonidine, chlorothiazide, frusemide, and methyldopa. These drugs were continued through the control and prazosin treatment periods. The renal transplant recipients were also on routine immunosuppression with azathioprine and prednisone. The blood pressure was recorded with a random zero sphygmomanometer (Hawksley, England) in the lying and standing positions. The means of at least two measurements of blood pressure, blood urea, and plasma creatinine concentrations during the month before starting prazosin were used as the control observations in the seven patients with chronic renal failure who were not transplanted. In the case of the five transplanted patients control observations taking the mean of at least two measurements of blood pressure, blood urea, and plasma creatinine were made over two to three days since most of these patients presented as hypertensive emergencies; indeed, in three patients parenteral treatment with clonidine and hydrallazine was initially necessary to keep the diastolic blood pressure below 120 mm Hg.

After the control observations prazosin was added to the antihypertensive regimens of these patients, initially in a dose of 1 mg three times a day. One patient developed severe symptomatic postural hypotension after one week on this dose, so that subsequent patients were started on a dose of 1 mg twice a day. The dose was increased at intervals of two to four weeks, depending on the response of the blood

pressure. The mean dose of prazosin was 3 mg/day (range 2-6 mg), and the mean period of prazosin treatment was 10 weeks (range 4-18 weeks). Patients were seen during prazosin treatment every one to four weeks, when lying and standing blood pressures were recorded with a random zero sphygmomanometer, and blood was taken for estimation of blood urea, plasma creatinine, liver function, and blood sugar. In seven of the patients ⁵¹Cr-edetic acid clearances were measured before and during prazosin treatment. The mean blood pressure and blood urea and plasma creatinine concentrations during prazosin treatment were based on an average of four separate observations (range 2-13).

Results

Table II shows the mean systolic and diastolic blood pressures in each patient before and during prazosin treatment and drug dosages for each patient.

The standing systolic blood pressure fell significantly during prazosin administration when compared with the control ($T=1$; critical value of T for $N=13$ is 10 at level of significance of 0.01 for a two-tailed test using Wilcoxon's matched-pairs signed-ranks test). Lying systolic and lying and standing diastolic blood pressures fell significantly during prazosin administration when compared with the control period ($T=0$; critical value of T for $N=13$ is 10 at level of significance of 0.01 for a two-tailed test using Wilcoxon's matched-pairs signed-ranks test).

There was no significant difference between the lying and standing systolic blood pressures during the control period ($T=17.5$; critical value of T for $N=12$ is 14 at level of significance of 0.05 for a two-tailed test using Wilcoxon's matched-pairs signed-ranks test). There was no significant difference between the lying and standing diastolic blood pressures during the control period ($T=20$; critical value of T for $N=9$ is 6 at level of significance of 0.05 for a two-tailed test using Wilcoxon's matched-pairs signed-ranks test). There was, however, a significant fall in the standing systolic blood pressure when compared with the lying systolic blood pressure during the period of prazosin administration ($T=0$; critical value of T for $N=13$ is 10 at level of significance of 0.01 for a two-tailed test using Wilcoxon's matched-pairs signed-ranks test). There was also a significant fall in the standing diastolic blood pressure when compared with the lying diastolic blood pressure during the period of prazosin administration ($T=1.5$; critical value of T for $N=12$ is 7 at level of significance of 0.01 for a two-tailed test using Wilcoxon's matched-pairs signed-ranks test).

The average blood pressure for all patients before prazosin treatment was 194/120 mm Hg lying, and 187/119 mm Hg standing. The average blood pressure for all patients during prazosin treatment was 167/103 mm Hg lying and 149/96 mm Hg standing.

Table III shows the mean blood urea and plasma creatinine concentrations in the control periods and during prazosin treatment. There was no significant difference between the blood urea concentra-

TABLE II—Blood pressures (mm Hg) before and during prazosin treatment

Case no.	Position	Control		During prazosin		Prazosin (mg/d)	Other drugs
		Systolic	Diastolic	Systolic	Diastolic		
1	Lying	185	110	178	95	2	Propranolol (160 mg tds)
	Standing	195	105	153	92		
2	Lying	190	120	149	97	4	Clonidine (0.15 mg gds), propranolol (240 mg gds), chlorothiazide (500 mg/d)
	Standing	168	120	148	95	3	Clonidine (0.15 mg gds), propranolol (320 mg gds), methyldopa (750 mg gds)
3	Lying	225	137	155	95	3	Propranolol (20 mg gds)
	Standing	210	109	150	95		
4	Lying	200	113	159	110	3	Clonidine (0.2 mg tds), chlorothiazide (500 mg/d)
	Standing	170	120	134	96		
5	Lying	178	118	167	102	3	Propranolol (240 mg gds), clonidine (0.15 mg tds), frusemide (40 mg/d)
	Standing	191	115	162	95	6	Propranolol (80 mg tds), chlorothiazide (500 mg/d)
6	Lying	220	122	177	110	2	Methyldopa (250 mg tds), propranolol (10 tds), azathioprine (150 mg/d), prednisone (15 mg/d)
	Standing	227	132	144	92	2	Propranolol (10 mg bd), azathioprine (100 mg/d), prednisone (10 mg/d)
7	Lying	235	122	223	116	6	Frusemide (40 mg/d), azathioprine (150 mg/d), prednisone (15 mg/d)
	Standing	237	122	206	118	3	Clonidine (0.15 mg tds), chlorothiazide (500 mg/d), azathioprine (150 mg/d), prednisone (8 mg/d)
8	Lying	182	122	161	113	3	Methyldopa (500 mg bd), propranolol (80 mg bd), frusemide (40 mg/d), azathioprine (100 mg/d)
	Standing	166	114	138	97	3	prednisone (10 mg/d)
9	Lying	174	116*	142	89	3	Methyldopa (250 mg bd), propranolol (80 mg tds), frusemide (80 mg tds), azathioprine (100 mg/d), prednisone (10 mg/d)
	Standing	170	116	122	85		
10	Lying	169	122	165	110	3	Clonidine (0.15 mg tds), chlorothiazide (500 mg/d), azathioprine (150 mg/d), prednisone (8 mg/d)
	Standing	159	118	160	108	3	Methyldopa (500 mg bd), propranolol (80 mg bd), frusemide (40 mg/d), azathioprine (100 mg/d)
11	Lying	203	105	196	104	3	prednisone (10 mg/d)
	Standing	199	117	168	100		
12	Lying	167	105*	148	102	3	Methyldopa (250 mg bd), propranolol (80 mg tds), frusemide (80 mg tds), azathioprine (100 mg/d), prednisone (10 mg/d)
	Standing	148	114	128	92		
12	Lying	200	150*	155	108	3	Methyldopa (250 mg bd), propranolol (80 mg tds), frusemide (80 mg tds), azathioprine (100 mg/d), prednisone (10 mg/d)
	Standing	200	150	126	93		

*Admitted as emergencies with severe hypertension requiring parenteral treatment with clonidine and hydrallazine initially to keep diastolic blood pressure less than 120 mm Hg.

tions in the control and prazosin periods ($T=28.5$; critical value of T for $N=12$ is 14 at level of significance of 0.05 for a two-tailed test using Wilcoxon's matched-pairs signed-ranks test). There was no significant difference between the plasma creatinine concentrations in the control and prazosin periods ($T=23.5$; critical value of T for $N=10$ is 8 at level of significance of 0.05 for a two-tailed test using Wilcoxon's matched-pairs signed-ranks test).

TABLE III—Mean blood urea and plasma creatinine concentrations during control and prazosin periods

Case no	Mean blood urea (mmol/l)		Mean plasma creatinine (μ mol/l)	
	Control	During prazosin	Control	During prazosin
1	13.3	13.8	186	186
2	13.8	15.1	309	318
3	5.6	5.6	124	88
4	7.6	6.8	141	115
5	8.6	8.8	186	168
6	15.8	14.6	239	256
7	5.3	6.1	186	168
8	7.8	6.0	124	124
9	6.0	7.8	133	168
10	5.2	8.8	141	168
11	12.5	12.6	168	186
12	9.3	7.5	195	195
12	7.0	9.6	177	203

Conversion: SI to traditional units—Urea: 1 mmol/l $\approx$ 6 mg/100 ml. Creatinine: 1 μ mol/l $\approx$ 0.113 mg/100 ml.

Table IV shows the ^{51}Cr -edetic acid clearance values during the control and prazosin periods in the seven patients in whom it was measured. There was no significant difference between the clearance results in the control period and during prazosin treatment ($T=11$; critical value of T for $N=7$ is 2 at level of significance of 0.05 for a two-tailed test using Wilcoxon's matched-pairs signed-ranks test).

TABLE IV— ^{51}Cr -edetic acid clearance values during control and prazosin periods in seven patients

Case no:	1	7	8*	9*	10	11*	12
Control	34	38	40	47	23	28	24
During prazosin	41	31	27	38	22	24	92

*Suffered possible mild rejection episode before or during prazosin administration.

SIDE EFFECTS

One patient (case 2) developed an unusual erythema nodosum-like eruption after receiving prazosin for about five weeks. This patient was also taking clonidine, chlorothiazide, and propranolol so that it is difficult to be sure of the cause. There was no improvement after the cessation, first of chlorothiazide treatment and then of prazosin, but slow improvement followed the cessation of propranolol treatment. It seems unlikely therefore that prazosin was responsible. A chest x-ray examination showed no hilar lymphadenopathy, and a serum antinuclear factor test gave a negative result.

Another patient (case 9) developed severe symptomatic postural hypotension about a week after being on prazosin 1 mg three times a day together with propranolol 10 mg three times a day. This necessitated a reduction in dose and there was a transient reversible deterioration in renal function, the plasma creatinine rising from 168 to 239 μ mol/l (1.9–2.7 mg/100 ml), and then returning to its previous level over three to four days. This was at the time attributed to, and treated as, a mild rejection episode, but it is more likely to have been due to the severe postural hypotension, the standing systolic blood pressure being between 80–90 mm Hg for about 24 hours.

Standard liver function tests, including estimations of serum bilirubin, plasma alkaline phosphatase, serum transaminase, and

random blood sugar concentrations, were normal in all patients during prazosin administration.

Discussion

Our results showed that prazosin was useful in combination with other antihypertensive drugs in controlling severe hypertension in patients with chronic renal failure. Prazosin must be used with caution in such patients, however, because they may respond to relatively small doses. The manufacturers suggest an initial dose of 2 mg three times a day, increasing gradually to a daily maximum of 20 mg. We found that the mean daily effective dose was 3 mg, with a range of 2–6 mg/day. One patient developed severe postural hypotension while on a dose of 1 mg three times a day, and subsequently all patients with chronic renal failure were started on 1 mg twice a day. Studies in normal subjects (Pfizer's research department, unpublished data) have shown that only 3–4% of a given dose of prazosin is excreted over 24 hours in the urine and that this fraction is largely excreted as a metabolite. It therefore seems unlikely that the increased sensitivity to prazosin in patients with renal failure is due to accumulation of the drug.

The manufacturers have also suggested that prazosin has little tendency to cause orthostatic hypotension. This may be true when it is used alone, but when used in combination with the other antihypertensive drugs in this study a significant postural fall in blood pressure followed the addition of prazosin.

There was no evidence of further deterioration of renal function during treatment with prazosin in the 12 patients with chronic renal failure as judged by the blood urea and plasma creatinine concentrations, with the exception of the patient who developed severe postural hypotension, which was associated with a transient and reversible rise in the plasma creatinine concentration.

It is difficult to evaluate the significance of the ^{51}Cr -edetic acid results, firstly because the numbers studied were small and, secondly, because five of the seven patients were renal transplant recipients, and three of these transplanted patients were considered to have had mild rejection episodes some time before they were treated with prazosin. Consequently, their renal function might not have been in a steady state. Nevertheless, no significant difference between the ^{51}Cr -edetic acid clearances in control periods and during prazosin treatment could be shown in this limited study.

Side effects were few and limited to one patient with pronounced postural hypotension. It is doubtful whether a rash in another patient could be attributed to prazosin. There were no cases of sudden collapse or loss of consciousness occurring within 30 to 90 minutes of the initial dose of prazosin, as has been reported to the Committee on Safety of Medicines.

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