ACUTE EFFECTS OF COMBINED VASODILATION AND β -ADRENOCEPTOR BLOCKADE WITH PRIZIDILOL ON RENAL FUNCTION

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- 1 The effects of a single oral dose of 600 mg of prizidilol on renal function were studied 5 to 6 h after dosing in six normal subjects and eight patients with essential hypertension.
- 2 Mean arterial blood pressure was reduced to 92% of the control value in normal subjects and to 75% in hypertensive patients. Heart rate increased slightly.
- 3 In normal subjects, effective renal plasma flow was increased to 107% of control values while glomerular filtration rate (83%), filtration fraction (79%), sodium (84%) and potassium (50%) clearances were significantly decreased.
- 4 In hypertensive subjects, effective renal plasma flow was increased to 120% of control values, while glomerular filtration rate (67%), filtration fraction (57%), sodium (27%) and potassium (72%) clearances were significantly decreased.
- 5 Plasma noradrenaline increased significantly in normal subjects (150%) and in patients (173%). Plasma renin activity, aldosterone and epinephrine levels did not change consistently.
- 6 The results indicate that the acute effects of prizidilol on blood pressure and renal function are more marked in hypertensive than in normotensive subjects. Prizidilol increases renal plasma flow like hydralazine and depresses glomerular filtration rate and fractional sodium excretion like endralazine. In addition to the fall in arterial pressure, efferent vasodilation and/or a specific effect on the glomerular ultrafiltration coefficient K_f may account for the striking decrease in filtration fraction.

Introduction

Most antihypertensive drugs, when given in single doses, produce changes in renal function. The effects most frequently observed are a slight decrease in renal plasma flow and a more marked fall in the glomerular filtration rate, sodium clearance, and urine volume (Freis *et al.*, 1953; Notter *et al.*, 1956; Novack *et al.*, 1961; Vorburger *et al.*, 1968; Reubi, 1978). However, vasodilating drugs such as hydralazine and the pyrogenic substances increase the renal plasma flow (Golding & Chasis, 1944; Imhof *et al.*, 1956; Reubi, 1978).

Prizidilol is a new compound which possesses both arteriolar vasodilating and β -adrenergic receptor blocking properties and may effectively lower blood pressure by decreasing total peripheral resistance in normal or hypertensive animals and man (Bianchetti *et al.*, 1982; Fariello *et al.* 1981; Larsson *et al.*, 1981; Karlberg *et al.*, 1981; Taylor *et al.*, 1979). Its chemical structure is that of a hydrazino-pyridazine derivative which contains a side chain common to many β -adrenoceptor blockers (Figure 1). The vasodilating

(±)-3-[2-(3-t-butylamino-2-hydroxypropoxy)phenyl]-6-hydrazinopyridazine

Figure 1 Chemical structure of prizidilol.

moiety, 3-phenyl-6-hydrazino-pyridazine, has been shown more than 20 years ago to possess good anti-hypertensive properties (Druey & Tripod, 1967). The attached side chain is the same as in the β -adrenoceptor blocking agents timolol and terbutaline. It was therefore interesting to assess the renal effects produced by a single dose of prizidilol and to compare them with the changes, observed in this and other laboratories, following hydralazine, some hydrazinopyridazine derivatives and various β -

adrenoceptor blocking agents. Prizidilol was administered in a single oral dose to six normal subjects and eight patients with essential hypertension. The data show that the drug possesses definite antihypertensive and renal vasodilating properties.

Methods

Eight patients with benign essential hypertension and six healthy volunteers formed the study group. Male/female ratio in the hypertensive group was 3/5 and in the normal subjects 5/1. The age was 53 ± 14 years (mean $\pm$ s.d.) in the hypertensive and 27 ± 6 years in the normal subjects. None of the hypertensive subjects had major cardiovascular complications such as cerebrovascular attack, clinical or electrocardiographic evidence of ischaemic heart disease, cardiac or renal failure, hypertensive retinopathy Keith-Wagener grade III or IV, peripheral ischaemic macroangiopathy, or other systemic or organ diseases. Secondary forms of hypertension were excluded by the usual tests.

Informed consent was obtained from all patients and normal volunteers. Antihypertensive and other drugs were withdrawn at least three weeks before the study.

The subjects were allowed to have a light breakfast before the test (bread, cereals or yoghurt and 0.5 l of lime-blossom tea). Following their admission to the Renal Clearance Laboratory at 07.30 h, arterial blood pressure (BP) was measured in the upright position; thereafter the subjects took the supine position. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by the conventional constant infusion clearance technique, using ^{51}Cr -EDTA and PAH, respectively (Goldring & Chasis, 1944; Reubi, 1963; Vorbürger *et al.*, 1969). Urine sampling was obtained by catheter. A plastic cannula was inserted into an antecubital vein, and an intravenous priming dose of $25 \mu\text{Ci}$ ^{51}Cr -EDTA and 6 ml of a 20% solution of Na-PAH in 200 ml 0.9% NaCl delivered at a rate of 3 ml/min.

For blood sampling, a second plastic cannula was inserted in a vein on the contralateral arm. Following a 1 h equilibration period in the supine position, the bladder was emptied; this was followed by two control clearance determinations with 40 to 60 min urine collection periods and blood samplings. A dose of 600 mg of prizidilol was then administered orally (at about 09.30 h). Since preliminary observations had indicated that the fall in BP was maximal after 4–6 h, the determination of the three experimental clearance periods was delayed until 5.5 h after dosing. In the meantime (at 12.00 h) every subject received a light lunch (sandwich and water). The subjects maintained the supine position throughout the procedure.

Urine and blood samples were used for determinations of ^{51}Cr -EDTA, PAH, sodium, potassium; clearances of these substances were calculated according to standard formula. Plasma catecholamines, renin and aldosterone levels were also measured at 08.30 h and 14.30 h. BP and heart rate were measured at intervals of 1 h. BP was measured with a mercury sphygmomanometer and cuff. Each recorded value represented the mean of three consecutive measurements. Mean BP was calculated as the sum of diastolic BP and one third of pulse pressure. Plasma and urinary sodium and potassium concentrations were determined by flame photometry, plasma renin activity and aldosterone levels were measured by radioimmunoassay (Sealey *et al.*, 1972; Vetter *et al.*, 1973), noradrenaline and adrenaline concentrations in plasma by radioenzymatic methods (Da Prada & Zürcher, 1976).

For statistical comparisons two-tailed paired *t*-test and linear regression analysis were performed.

Results

Blood pressure and heart rate

Maximal changes in BP were observed in normal and hypertensive subjects 4 to 6 h after ingestion of prizidilol. The values of the three measurements recorded during the period after prizidilol did not differ consistently among each other.

In normal subjects systolic BP was decreased slightly from an average of 129 ± 6 mm Hg during the two control clearance periods to 123 ± 8 mm Hg during the three clearance periods after prizidilol dosing; diastolic BP was decreased from 79 ± 7 to 70 ± 13 mm Hg and mean BP from 96 ± 4 to 88 ± 10 mm Hg (Figure 2). These changes did not reach statistical significance. Heart rate was comparable before (72 ± 6 beats/min) and 4 to 6 h after prizidilol (75 ± 13 beats/min).

In hypertensive patients systolic BP was decreased from 175 ± 12 to 131 ± 26 mm Hg, diastolic BP from 114 ± 14 to 85 ± 15 mm Hg, and mean BP from 134 ± 12 to 100 ± 18 mm Hg ($P < 0.001$) (Figure 2). Heart rate increased slightly ($P < 0.05$) from 74 ± 13 to 81 ± 9 beats/min (Figure 2).

To summarize, after prizidilol mean BP was reduced to 92% of the control value in normotensive and to 75% in the hypertensive subjects (Table 1).

Renal function

In normal subjects ERPF tended to be increased after prizidilol from 655 ± 151 to 710 ± 220 ml min⁻¹ 1.73 m^{-2} (NS). GFR was decreased from 124 ± 18 to 102 ± 12 ml min⁻¹ 1.73 m^{-2} ($P < 0.001$) and the filtration fraction from 0.193 ± 0.025 to 0.152 ± 0.033 ($P <$

Figure 2 Acute effects of prazosin on mean blood pressure and heart rate measured during renal clearance studies in six normal subjects (○) and eight patients with benign essential hypertension (●). Mean values and one standard deviation are shown. *P* values denote statistically significant differences as compared to measurements performed before administration of prazosin. **P* < 0.05, ***P* < 0.001.

0.001) (Figure 3). The sodium clearance was decreased from 1.39 ± 0.74 to 0.89 ± 0.42 ml min⁻¹ 1.73 m⁻² (*P* < 0.05), the potassium clearance from 27.5 ± 12.8 to 11.6 ± 5.3 ml min⁻¹ 1.73 m⁻² (*P* < 0.001), and urine volume from 3.62 ± 0.85 to 0.98 ± 0.55 ml min⁻¹ 1.73 m⁻² (Figure 4). Expressed in percent of control values, ERPF was increased to 107%; while GFR was decreased to 83%, filtration fraction to 79%, sodium clearance to 84%, potassium clearance to 50% and urine volume to 28% (Table 1).

In hypertensive patients, ERPF was increased from 422 ± 79 to 504 ± 181 ml min⁻¹ 1.73 m⁻² (*P* < 0.001). GFR was reduced from 100 ± 16 to 69 ± 33 ml min⁻¹ 1.73 m⁻² (*P* < 0.001) and the filtration fraction from 0.238 ± 0.032 to 0.136 ± 0.065 (*P* < 0.001) (Figure 3). The sodium clearance was decreased from 2.01 ± 1.17 to 0.54 ± 0.66 ml min⁻¹ 1.73 m⁻² (*P* < 0.001), the potassium clearance from 18.1 ± 5.5 to 12.7 ± 4.3 ml min⁻¹ 1.73 m⁻² (*P* < 0.001) and urine volume from 5.34 ± 2.72 to 0.84 ± 0.69 ml min⁻¹ 1.73 m⁻² (*P* < 0.001) (Figure 4). Expressed in percent of control values, ERPF was increased to 120%, GFR was decreased to 67%, filtration fraction to 57%, sodium clearance to 27%, potassium clearance to 72%, and urine volume to 23%.

Endocrine findings

Five hours after prazosin, plasma noradrenaline concentration was significantly (*P* < 0.01) increased in both normal ($150 \pm 31\%$) and hypertensive ($173 \pm 89\%$) subjects (Table 1). Plasma renin activity and adrenaline levels were not consistently changed, despite a tendency for increased values in some patients. Plasma aldosterone levels were largely unchanged.

Correlations (Table 2)

Changes in ERPF after administration of prazosin did not correlate significantly with those in mean BP. GFR correlated with ERPF in all subjects, with mean BP in the hypertensive subjects and with the product (mean BP × ERPF) in all subjects. Three-variable regression analysis was also performed, with GFR as dependent and both mean BP and ERPF as independent values (Table 3). In the hypertensive patients, the natural logarithm of both sodium clearance and urine volume correlated with GFR or mean BP. Similarly the fractional excretion rate of sodium ($\ln C_{Na}/GFR$) correlated significantly with mean BP and the product (mean BP × ERPF). The fractional potassium clearance ($\ln C_k/GFR$) correlated in all subjects inversely with ERPF and the product (mean BP × ERPF).

Discussion

The findings of the present study indicate that the combined vasodilator-β-adrenoceptor blocking agent prazosin, given in a single dose of 600 mg, increases the renal plasma flow and decreases BP, GFR, filtration fraction, sodium and potassium clearances in patients with essential hypertension. The same trend is observed in normotensive subjects but, except for the potassium clearance, the changes are much less pronounced.

This profile of renal function changes differs from most previously observed single dose effects of compounds with vasodilator properties. Acute studies with captopril produced either an increase or no change in ERPF and inconstant changes in GFR (Hollenberg *et al.*, 1981; Mimran *et al.*, 1979; Röckel *et al.*, 1980). Minoxidil or carprazidil (methyl-(3,6-dihydro-1(2H)-pyridyl)-2-oxo-2H-1,2,4-oxodiazolo-2,3-a-pyrimidine-7-carbamate, Ro 12-4713, a new vasodilator) do not significantly modify ERPF, GFR or sodium excretion (Gilmore *et al.*, 1970; Grimm *et al.*, 1981). Pyrogens and hydralazine induce an increase in ERPF; but GFR is largely unchanged while sodium clearance and urine volume tend to be increased slightly (Reubi, 1978). Endralazine does not increase ERPF in acute experiments and

Table 1 Mean $\pm$ s.d. blood pressure, heart rate, renal function and endocrine findings 5 to 6 h after a single oral dose of prazosin

	(% of control values)		
	Subjects		
	Normal	Hypertensive	All
<i>Blood pressure and renal function</i>			
Number of subjects	6	8	14
Number of measurements*	3	3	3
Mean blood pressure	92 $\pm$ 11	75 $\pm$ 13**	82 $\pm$ 15‡
Heart rate	105 $\pm$ 16	112 $\pm$ 20‡	109 $\pm$ 18†
Effective renal plasma flow	107 $\pm$ 35	120 $\pm$ 35**	114 $\pm$ 30**
Glomerular filtration rate	83 $\pm$ 7**	67 $\pm$ 30**	74 $\pm$ 25**
Product (mean blood pressure $\times$ effective renal plasma flow)	88 $\pm$ 22	87 $\pm$ 30	87 $\pm$ 27
Filtration fraction	79 $\pm$ 14**	57 $\pm$ 26**	67 $\pm$ 24**
Sodium clearance	84 $\pm$ 59‡	27 $\pm$ 28**	51 $\pm$ 52**
Potassium clearance	50 $\pm$ 26**	72 $\pm$ 19**	61 $\pm$ 23**
Urine volume	28 $\pm$ 15**	23 $\pm$ 32**	25 $\pm$ 26**
<i>Endocrine findings</i>			
Number of measurements*	1	1	1
Plasma renin activity	177 $\pm$ 128	142 $\pm$ 109	157 $\pm$ 114
Plasma aldosterone	112 $\pm$ 58	116 $\pm$ 106	114 $\pm$ 86
Plasma noradrenaline	150 $\pm$ 31†	173 $\pm$ 89†	163 $\pm$ 69**
Plasma adrenaline	240 $\pm$ 203	424 $\pm$ 497	345 $\pm$ 397

*Number of measurements performed in each subject during the three clearance periods 5 to 6 h after prazosin** = $P < 0.001$ vs control value † = $P < 0.01$ vs control value ‡ = $P < 0.05$ vs control value

decreases BP, GFR and urine volume (Wegmüller & Reubi, 1982). If comparison is restricted to the two chemically related compounds, prazosin increases ERPF like hydralazine but decreases GFR and electrolyte clearances like endralazine (Table 3).

The reasons for these differences might be sought in the β -adrenoceptor blocking properties of prazosin. Most β -adrenoceptor blockers have been reported to depress renal function (Heierli *et al.*, 1977; Naylor *et al.*, 1967; Zech *et al.*, 1976). Pindolol induces in hypertensive patients consistent decreases in ERPF (−11%), GFR (−13%), urine volume (−32%), and excretion rates of sodium (−17%) and potassium (−17%) (Heierli *et al.*, 1977); similar results were obtained with acebutolol, atenolol (Zech *et al.*, 1976) or propranolol (Naylor *et al.*, 1967). However, nadolol, whose structural formula is very similar to that of propranolol, actually produces an increase in ERPF and sodium and potassium excretions (Danesh & Brunton, 1981; Hollenberg *et al.*, 1979). Thus, it would seem that the inclusion of a β -adrenoceptor blocking chain into the molecule of prazosin does not necessarily explain its depressive action on GFR and electrolyte clearances.

It has been shown that when the BP of hypertensive patients is acutely lowered by antihypertensive drugs, the behaviour of GFR largely depends on the changes in mean BP and ERPF (Reubi, 1978). This depend-

Figure 3 Acute effects of prazosin on glomerular filtration rate, effective renal plasma flow and filtration fraction in six normal subjects (○) and eight patients with benign essential hypertension (●). ** $P < 0.001$.

Figure 4 Acute effects of prizidilol on renal clearances of sodium and potassium and on urine volume in six normal subjects (○) and eight patients with essential hypertension (●). * $P < 0.05$, ** $P < 0.001$.

ency can be expressed in a three-variable regression equation (Table 3) or by plotting the changes in GFR against the changes in the product (mean BP $\times$ ERPF). However, if several antihypertensive agents are compared, marked individual differences can be demonstrated. For comparable changes in mean BP and ERPF, GFR may be more or less depressed.

Thus, the fall in GFR after prizidilol or endralazine is more marked than after hydralazine (Table 3) and it depends even more on mean BP and less on ERPF after prizidilol than after endralazine. These differences may be explained by assuming that prizidilol exerts the greatest vasodilation of efferent arterioles, thus producing the greatest decrease in the glomerular filtration pressure. Alternatively it is possible that prizidilol decreases the glomerular ultrafiltration coefficient K_f by a direct drug-specific mechanism.

The observed effects on urine volume, sodium and potassium clearances have to be interpreted with caution since the oral water, sodium and potassium intake was not standardized and may have been less in the few hours preceding the experimental periods than prior to the control periods. However, during all urine collection periods the rate of saline administration was the same (3 ml/min). The delivery of sodium exceeded the output during both the control and the experimental periods. In contrast, control diuresis was greater than the rate of water delivery during the sustaining infusion. Experimental diuresis was reduced to the same extent in normotensive and hypertensive patients although natriuresis was much more depressed in hypertensive patients. Thus the data on sodium clearance are more reliable than those on urine volume and potassium clearance.

Urine volume, sodium and potassium clearances depend in part on the GFR. In addition it has been demonstrated that in short-term experiments the fractional sodium and water excretion also depends on the BP (Reubi, 1978). This indicates that the changes in mean BP affect tubular reabsorption. According to current concepts, acute changes in mean BP are probably transmitted to the peritubular capillaries (Andreucci *et al.*, 1976). A decrease in the capillary hydrostatic and interstitial pressures may result in decreased paracellular back-leak into the proximal tubules and/or enhanced reabsorption at

Table 2 Correlations between blood pressure changes and renal function after prizidilol

Variable	Hypertensive patients		Normal subjects		All subjects	
	r	P	r	P	r	P
ERPF vs mean BP	-0.06	NS	-0.02	NS	-0.26	NS
GFR vs mean BP	0.64	< 0.001	0.25	NS	0.22	NS
GFR vs ERPF	0.41	< 0.05	0.49	< 0.05	0.55	< 0.001
GFR vs product (mean BP $\times$ ERPF)	0.22	NS	0.31	NS	0.31	< 0.05
$\ln C_{Na}$ vs GFR	0.84	< 0.001	0.20	NS	0.79	< 0.001
$\ln C_{Na}$ vs mean BP	0.69	< 0.001	-0.01	NS	0.36	< 0.05
$\ln V$ vs GFR	0.58	< 0.01	0.39	NS	0.56	< 0.001
$\ln V$ vs mean BP	0.74	< 0.001	0.07	NS	0.50	< 0.001
$\ln C_{Na}/GFR$ vs mean BP	0.69	< 0.001	-0.16	NS	0.41	< 0.01
$\ln C_{Na}/GFR$ vs product (mean BP $\times$ ERPF)	0.52	< 0.01	-0.01	NS	0.38	< 0.05
$\ln V/GFR$ vs mean BP	0.56	< 0.01	-0.007	NS	0.42	< 0.01
$\ln C_k/GFR$ vs ERPF	-0.49	< 0.05	-0.50	< 0.05	-0.58	< 0.001
$\ln C_k/GFR$ vs product (mean BP $\times$ ERPF)	-0.59	< 0.01	-0.40	NS	-0.54	< 0.001

Table 3 Comparison of mean blood pressure, renal plasma flow, their product, glomerular filtration rate, and three-variable regression equation after a single dose of either hydralazine, endralazine or prizidilol in patients with essential hypertension (percent of control values). Data on hydralazine from Reubi (1978) and on endralazine from Wegmüller & Reubi (1982).

	Mean BP	ERPF	GFR	Product (mean BP × ERPF)
Hydralazine	88	121	102	107
Endralazine	83	95	67	77
Prizidilol	75	120	67	87

Three-variable regression equation

Hydralazine	GFR = $8.5 + 0.55 \text{ mean BP} + 0.37 \text{ ERPF}$
Endralazine	GFR = $-79.7 + 0.25 \text{ mean BP} + 0.45 \text{ ERPF}$
Prizidilol	GFR = $-87.0 + 1.57 \text{ mean BP} + 0.29 \text{ ERPF}$

more distal sites (Boelpaep, 1972; Earley & Friedler, 1966; Lewy & Windhager, 1968, Stumpe *et al.*, 1970). Accordingly, our data show that the fall in FE_{Na} was more pronounced in hypertensive patients than in normotensive subjects. This can be explained by the greater fall in mean BP in the former group. However, when hydralazine or pyrogens are administered, diuresis and natriuresis are much less decreased than could be accounted for by the fall in GFR and mean BP, and may actually be increased. Since the changes in $\ln V$ and $\ln C_{\text{Na}}$ correlate directly with those in ERPF, it has been assumed that renal hyperaemia may decrease water and sodium reabsorption (Stein *et al.*, 1971a,b; Vander, 1964). It is therefore surprising that after prizidilol, despite a significant increase in ERPF, sodium clearance was more depressed than GFR. The question remains open, whether this specific effect of prizidilol might be related to its β -adrenoceptor blocking properties.

The fall in potassium clearance was of the same order of magnitude as that in GFR in hypertensive subjects, but it was greater in normotensive individuals. The reasons for this difference are not obvious. The changes were unrelated to the plasma aldosterone levels, and correlated inversely with ERPF, in contrast to the conditions prevailing after endralazine (Wegmüller & Reubi, 1982). On the other hand, the decrease in sodium clearance was

greater and that in potassium clearance was smaller in hypertensive patients than in normotensive controls. This suggests that the tubular sodium/potassium exchange mechanism might be involved. However, the inverse correlation between the changes in sodium and potassium clearances for the whole series did not reach the level of statistical significance ($r = -0.286$; the value of $r = -0.304$ would correspond to $P < 0.05$).

To summarize, our data indicate that a single dose of the antihypertensive drug prizidilol produces in hypertensive patients a fall in GFR, sodium and potassium clearances, despite a significant increase in ERPF. The fall in GFR and sodium clearance is greater than it could be anticipated from the changes in BP and ERPF. This may be due either to a marked decrease in filtration pressure related to efferent vasodilation or to a specific effect on the glomerular ultrafiltration coefficient K_f .

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