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A STUDY OF THE EFFECTS OF ATENOLOL AND PROPRANOLOL ON RENAL FUNCTION IN PATIENTS WITH ESSENTIAL HYPERTENSION

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1 The effects of propranolol and atenolol given in random order in a cross-over study to fifteen patients with essential hypertension have been studied.

2 Both drugs were effective in lowering blood pressure and side effects were not markedly different.

3 There was no change in exchangeable sodium or potassium or in total body potassium during treatment with either drug.

4 Ambulant plasma renin activity was reduced by both drugs but the fall in blood pressure was not related to initial plasma renin.

5 Despite equal mean reduction in blood pressure with the two drugs, creatinine clearance fell significantly only during treatment with propranolol.

6 These observations suggest that intra-renal β_2-adrenoceptors may be of importance in the regulation of renal function.

Introduction

The role of β-adrenergic receptor blocking drugs in the treatment of hypertension is well established (Simpson, 1974). It has been shown that the non-cardioselective β_1- and β_2-adrenergic receptor blocking drug, propranolol, causes a reduction in renal blood flow and glomerular filtration rate when administered intravenously (Nayler, McInnes, Swann, Carson & Lowe, 1967; Shirmeister, Decot, Hallauer & Willmann, 1966). A similar reduction in glomerular filtration rate follows the intravenous injection of pindolol (Heierli, Thoelen & Radielovic, 1977). Propranolol has also been shown to reduce renal blood flow and glomerular filtration rate during oral administration in man (Ibsen & Sederberg-Olsen, 1972; Falch, Odegaard & Norman, 1978). Ibsen & Sederberg-Olsen (1972) attributed the reduction in renal function to haemodynamic factors outside the kidney, particularly a reduction in cardiac output, rather than to an effect on renal adrenergic receptors, but Falch *et al.* (1978) interpreted their findings as indicating an interruption of intrarenal auto-regulation of blood flow by propranolol.

The availability of cardioselective β_1-adrenergic receptor blocking drugs permits the separation of the effects of reduced cardiac output and renal β_2-adrenergic receptor blockade on renal function. In this study we have compared the effects of propranolol and the cardioselective β_1-adrenoceptor blocker, atenolol, given in doses bringing about similar reductions in blood pressure, on renal function. We have also measured the effects of the two drugs on exchangeable sodium and potassium and on total body potassium since it has been suggested that changes in sodium balance may

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contribute to the antihypertensive effect of β-adrenoceptor blockers (Brecht, Werner & Schoeppe, 1976).

There is some dispute over the effect of atenolol on plasma renin levels although it is generally accepted that renin secretion is suppressed by propranolol (Gross, 1977). Since this has important implications in relation to the mechanism for the control of renin as well as to the way in which β-adrenoceptor blocking drugs reduce blood pressure, we have studied the effect of both drugs on plasma renin activity.

Methods

Patients

Seventeen patients in whom the diagnosis of essential hypertension had been established following measurements of plasma electrolytes and urea, intravenous urogram, urine culture, estimation of urinary excretion of hydroxymethoxymandelic acid, chest radiograph and electrocardiograph and in whom diastolic pressure following withdrawal of antihypertensive therapy was between 90 and 120 mm Hg were studied. Patients with impaired renal function or with a history of bronchial asthma, heart failure or myocardial infarction were excluded. All patients gave informed consent.

Trial design and protocol

All antihypertensive and diuretic drugs were withdrawn for 3 weeks. After this period creatinine clearance, plasma renin activity at 09.00 h following 2 h recumbency and at 12.00 h following 3 h of ambulation and plasma electrolytes were measured. In addition total body potassium (TBK) was measured using a whole body counter, exchangeable potassium (K_E) by isotope dilution using 30 μCi of K^{42} and a 24 h equilibration period, and exchangeable sodium (Ma_E) using 15 μCi of Na^{24} and a 24 h equilibration period. Blood pressure was measured in triplicate, using the Hawksley random zero sphygmomanometer, the diastolic end point was taken at muffling of sounds (phase four). Measurement of heart rate and blood pressure were taken after 5 min of recumbency, after standing for 2 min and after exercise which consisted of walking up 30 steps (6.1 m). Body weight was recorded at this and each subsequent visit, oedema was sought and the chest examined. Spontaneous complaints were recorded and specific enquiry was made for indigestion, drowsiness, shortness of breath, coldness of the extremities and claudication.

Following this assessment after 3 weeks without treatment the patients continued without treatment and were seen at weekly intervals for a further 3 weeks to establish the baseline blood pressure. They were then randomly allocated to either atenolol 25 mg three times daily or propranolol 40 mg three times daily. Since we were interested primarily in objective measurements of blood pressure, renin, sodium and renal function and the patients' subjective reactions to the drugs were of only secondary interest in this work, the study was open to both patient and physician. The drug dosage was then doubled at weekly outpatient visits to a maximum of propranolol 160 mg three times daily or atenolol 100 mg three times daily if diastolic blood pressure was above 80 mm Hg unless heart rate was less then 50 beats/min or the patient complained of troublesome nausea. The maximum dose given was then continued for 2 months at the end of which the investigations outlined above were repeated. All treatment was then withdrawn for 6 weeks before introducing the other drug and then repeating the procedure.

Methods

Plasma and urinary sodium and potassium were measured using the flame photometer. Urea and creatinine were measured using the Autoanalyser. Plasma renin activity was measured by the radioimmunoassay of generated angiotensin I using the method of Haber, Koerner, Page, Kliman & Purnode (1969), the normal range for our laboratory is 18 ± 12 (s.d.) pmol l^{-1} (23 ± 15 ng $l^{-1}min^{-1}$) at 09.00 h after 2 h of recumbency and 31 ± 19 (s.d.) pmol $l^{-1}min^{-1}$ (40 ± 24 ng $l^{-1}min^{-1}$) at 12.00 h after 3 h of ambulation, for patients on free diet.

Results

Blood pressure

The blood pressure reduction achieved was significant with both propranolol and atenolol and the degree of reduction was similar (Tables 1 and 2, and Figure 1), as would be expected when final dosage was based on blood pressure response. There were no significant differences in recumbent, ambulant or post-exercise blood pressures, either systolic or diastolic, between periods on treatment with propranolol and with atenolol.

Drug dosage

The mean dose of propranolol to achieve these reductions in blood pressure was 289.4 ± 153 (s.d.) mg/day and of atenolol 220.6 ± 100.9 (s.d.) mg/day.

Table 1 Clinical details of patients

Patient	Age (years)	Sex	Recumbent blood pressure (mmHg) Pre-treatment S D	During propranolol S D	During atenolol S D	Plasma renin activity pre-treatment (pmol l^{-1} min^{-1}) Recumbent	Ambulant	Body weight (kg) Pre-treatment	Post-propranolol	Post-atenolol
TB	51	M	182/121	150/101	130/86	11.3	33.9	68.1	66.8	67.2
DB	46	F	150/90	131/86	126/89	13.1	24.7	74.0	74.45	76.45
GC	45	M	185/113	181/118	183/113	42.5	45.5	82.5	84.5	82.2
EE	51	F	169/106	141/83	151/92	8.5	12.7	62	60.3	62
JH	40	F	156/101	118/77	121/80	17.4	23.0	60	63.4	63.5
JH	27	M	150/114	122/87	132/94	3.1	23.5	80.7	81	80.5
RH	42	F	164/102	—	154/90	7.9	13.8	69.7	—	69.8
AJ	31	F	164/106	134/90	131/83	15.3	30.5	51.8	50.8	53.45
WK	49	M	152/99	133/85	150/97	11.6	30.7	77.6	77.3	78.6
EM	57	M	161/102	149/96	165/92	27.4	62.2	66.3	67.6	66.3
RMcN	49	F	181/111	167/103	133/93	8.1	7.9	60	58.3	62.9
EMcN	53	F	174/93	—	147/82	8.3	17.2	66	—	66
JS	26	M	142/97	122/78	126/87	4.3	13.9	63	63.9	64.35
RS	53	M	171/97	150/76	129/72	29.3	47.9	68.7	71.2	70.6
MS	55	F	185/95	156/93	168/93	11.6	15.4	69.4	70.6	70.9
JS	46	F	181/112	144/106	147/74	6.5	13.7	87.5	85.9	88.8
HT	48	F	210/109	160/116	189/99	8.3	18.3	51.5	51.5	51

S Systolic
D Diastolic

Table 2 Changes in mean blood pressure, heart rate, renal function, renin, sodium and potassium with propranolol and atenolol

		Pre-treatment		*Propranolol*		*Atenolol*		*Statistical significance of difference between means*		
		Mean	*s.e. mean*	*Mean*	*s.e. mean*	*Mean*	*s.e. mean*	*Propranolol v pre-treatment*	*Atenolol v pre-treatment*	*Propranolol v atenolol*
Recumbent blood pressure (mnHg)	Systolic	165.71	5.66	143.87	4.6	146.00	4.97	$P<0.001$	$P<0.01$	NS
	Diastolic	103.88	2.08	93.00	3.47	89.18	2.35	$P<0.001$	$P<0.001$	NS
Ambulant blood pressure (mmHg)	Systolic	155.88	3.52	132.93	5.92	133.94	5.21	$P<0.001$	$P<0.001$	NS
	Diastolic	105.71	2.26	91.20	4.35	87.47	3.68	$P<0.001$	$P<0.001$	NS
Post-exercise blood pressure (mmHg)	Systolic	166.06	5.52	148.87	6.87	140.35	5.53	$P<0.05$	$P<0.01$	NS
	Diastolic	106.69	2.2	92.87	3.37	91.71	2.92	$P<0.001$	$P<0.01$	NS
Heart rate (beats/min)	Recumbent	73.29	2.01	61.13	1.88	55.88	1.34	$P<0.001$	$P<0.001$	$P<0.05$
	Ambulant	81.00	2.32	69.87	2.76	65.88	2.46	$P<0.01$	$P<0.001$	NS
	Post-exercise	109.06	2.88	80	4.83	73.65	3.16	$P<0.001$	$P<0.001$	NS
Plasma creatinine (μmol/l)		75.59	3.01	82.47	3.24	78.71	3.09	NS	NS	NS
Creatinine clearance (l/24 h)		161.63	9.36	131.89	8.52	152.13	13.95	$P<0.01$	NS	$P<0.0125$
Exchangeable sodium (mmol)		2,530.4	77.96	2,588.58	93.63	2,490.97	58.50	NS	NS	NS
Total body potassium (mmol/kg)		42.29	1.31	43.49	1.49	42.46	1.30	NS	NS	NS
Exchangeable potassium (mmol/kg)		39.26	1.70	36.81	1.42	36.85	1.14	NS	NS	NS
Plasma renin activity (pmol l^{-1} min^{-1})	Recumbent	13.79	2.50	15.69	3.74	12.34	2.04	NS	NS	NS
	Ambulant	25.58	3.58	20.85	4.51	14.55	2.36	$P<0.05$	$P<0.01$	NS
Body weight (kg)		68.16	3.17	68.5	3.3	69.09	3.15	NS	NS	NS

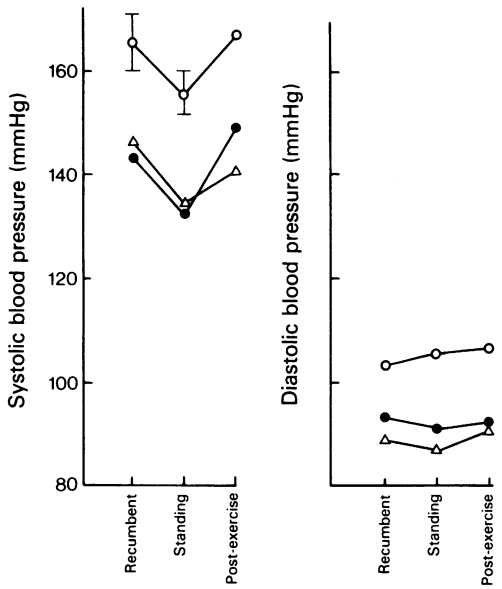

Figure 1 The effects of treatment with propranolol (●) and atenolol (△) on recumbent, standing and post-exercise blood pressure in fifteen patients with essential hypertension. Both drugs significantly reduced blood pressure, the differences between the drugs did not reach significance (Table 2). ○ pretreatment values.

Heart rate

Both propranolol and atenolol reduced the heart rate significantly during recumbency, ambulation and following exercise (Table 2, Figure 2). Recumbent heart rate during atenolol treatment was significantly lower than that during propranolol treatment, $P<0.05$.

Plasma renin activity

Plasma renin activity (PRA) during recumbency did not change significantly following treatment with either propranolol or atenolol (Figure 3, Table 2). However, both propranolol and atenolol brought about a significant reduction in ambulant PRA, $P<0.05$ and $P<0.01$ respectively (Figure 3). There was no relationship of the percentage reduction in blood pressure with either recumbent or ambulant pre-treatment PRA, nor with the percentage reduction in PRA with treatment with either drug.

Sodium and potassium

There was no change in exchangeable sodium, exchangeable potassium or total body potassium during treatment with either propranolol or atenolol (Table 2). There was no significant change in body weight during treatment with either drug (Tables 1 and 2).

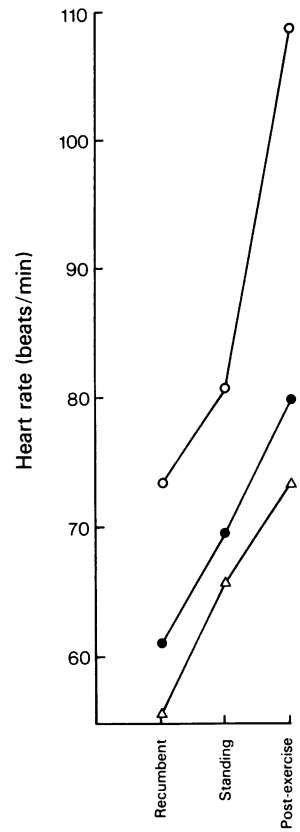

Figure 2 The effects of treatment with propranolol (●) and atenolol (△) on heart rate. Recumbent heart rate was significantly lower during atenolol than propranolol treatment, $P<0.05$. Both drugs resulted in a significant slowing of the heart (Table 2). ○ pretreatment values.

Renal function

Serum creatinine concentration rose from a pre-treatment value of 75.6 ± 3.0 (s.e. mean) μmol/l (0.85 ± 0.03 mg%) to 82.5 ± 3.2 (s.e. mean) μmol/l (0.93 ± 0.04 mg%) during propranolol treatment and to 78.7 ± 3.1 (s.e. mean) μmol/l (0.89 ± 0.03 mg%) during the administration of atenolol. In neither case did this difference reach significance (Figure 4). There was, however, a significant reduction in creatinine clearance during treatment with propranolol from 162 ± 9.4 (s.e mean) 24 h to 132 ± 8.5 (s.e. mean) 24 h, $P<0.01$. During treatment with atenolol there was less reduction in renal function, creatinine clearance 152 ± 13.9 (s.e. mean) and this fall did not reach significance, $P>0.05$. Creatinine clearance during propranolol treatment was significantly lower than that during atenolol administration, $P<0.0125$.

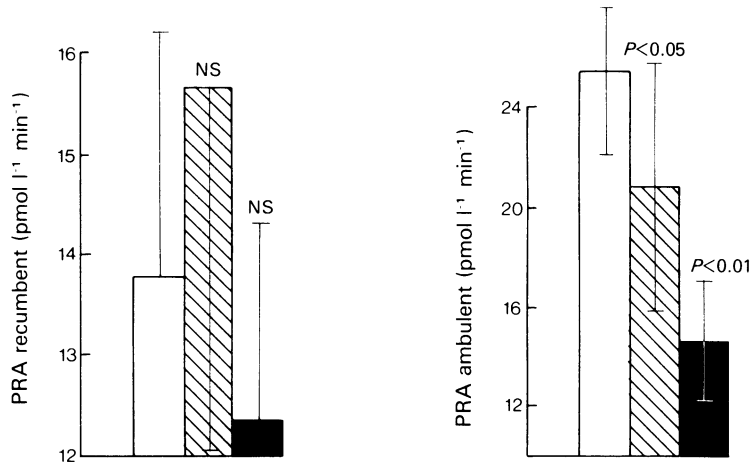

Figure 3 Plasma renin activity (PRA) (mean ± s.d.) before treatment (□) and during the administration of propranolol (▨) and of atenolol (■). Recumbent PRA did not change significantly but ambulant PRA was significantly reduced with both drugs, $P<0.05$, and $P<0.01$ respectively.

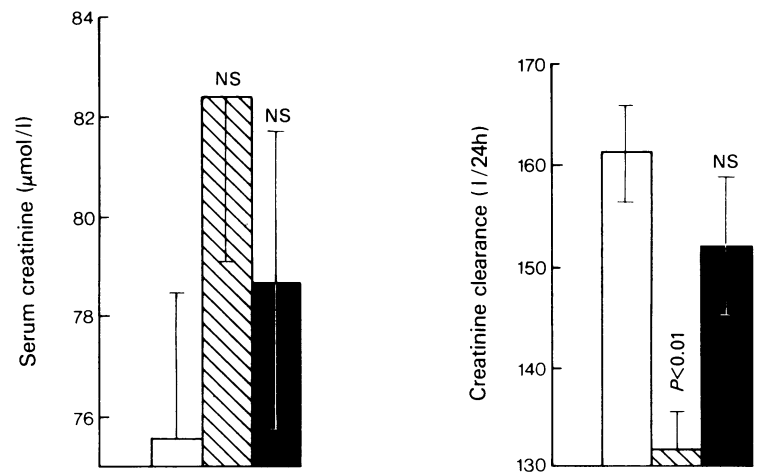

Figure 4 Renal function before and during β-adrenoceptor blocking treatment. Serum creatinine did not change significantly. There was a slight and insignificant fall in creatinine clearance with atenolol and a significant reduction during treatment with propranolol ($P<0.01$). □ pretreatment, ▨ propranolol, ■ atenolol.

Side effects

Two patients had to discontinue propranolol, one because of wheezing and one because she attributed headache to it, all patients completed the atenolol phase of the trial. Six patients complained of tiredness during propranolol treatment and four while taking atenolol. Three patients complained of depression with propranolol and one with atenolol. Nausea developed in two patients taking propranolol and in one patient while taking atenolol. Four patients complained of cold extremities with propranolol and two with atenolol. One patient developed claudication while taking atenolol.

Discussion

This study shows that the cardioselective β_1-adrenergic receptor blocker atenolol is as effective in the control of mild or moderate hypertension as propranolol. The dosages giving similar reductions in blood pressure were 289 ± 153 (s.d.) mg of propranolol and 221 ± 101 (s.d.) mg of atenolol daily.

This similarity in response confirms the observations of Webster, Jeffers, Galloway, Petrie & Barker (1977) and Epstein & Lubbe (1977).

Side effects were probably over-reported since we used a check list (Greenblatt, 1964) and did not incorporate a placebo phase. However, they were similar with the two drugs, apart from bronchospasm which occurred in one patient and only during the propranolol phase of the study.

In this small study we were not able to relate the blood pressure response either to pre-treatment plasma renin levels or to the degree of suppression of renin during treatment, unlike Buhler, Laragh, Baer, Vaughan & Brunner (1973). This may be due to our failure to rigidly control dietary sodium intake before measuring PRA, but this is likely to be an almost universal practical problem (Woods, Pittman, Pulliam, Werk, Waider & Allen, 1976) and an absence of relationship of response to β-adrenoceptor blockers to PRA has been reported by several groups (Leonetti, Mayer, Morganti, Terzoli, Zanchetti, Bianchetti, di Salle, Morselli & Chidsey, 1975; Epstein & Lubbe, 1977). Early studies with atenolol suggested that it only reduced plasma renin concentration slightly (Amery, Billiet, Boel, Fagard, Reybrouck & Willems, 1976). We have confirmed this slight effect on PRA in the recumbent position, but in our patients ambulant PRA was suppressed more strikingly by atenolol than by propranolol, although the difference between the two did not reach significance. A similar effect on recumbent and head-up tilt renin levels to that of atenolol in our patients was observed with the β_1-adrenoceptor blocking drug practolol by Esler & Nestel (1973). It seems, therefore, that renin release is likely to be controlled at least in part by β_1-adrenoceptors.

Following exercise both systolic and diastolic pressures were a little lower during atenolol than propranolol treatment, but the difference did not reach significance. Thus, the theoretical advantage of the cardioselective drug in preventing exercise hypertension by sparing β_2 vasodilator adrenoceptors was not demonstrated. However, blood pressure was measured immediately after exercise rather than during the exercise and peaks of pressure may have been missed (Comerford & Besterman, 1978).

Exchangeable sodium (Na_E) has been said to be reduced and total body potassium (TBK) increased during treatment of patients with essential hypertension with a non-cardioselective β-blocker (Brecht *et al.*, 1976) and these authors suggest that changes in sodium balance may contribute to the antihypertensive effect. We have been unable to demonstrate any change in either Na_E or TBK (Table 2) with propranolol or atenolol despite suppression of renin and presumably, therefore, of aldosterone secretion. A surprising finding in the work of Brecht *et al.* (1976) was that Na_E was significantly increased in untreated hypertensives whereas most studies report that it does not differ significantly from normal (Lebel, Schalekamp, Beevers, Brown, Davies, Fraser, Kremer, Lever, Morton, Robertson, Tree & Wilson, 1974; Wilkinson, 1978).

One possible explanation for the reduction in Na_E which they observed during the course of treatment with pindolol was the reduction in body weight which averaged 2.0 kg, some of this may have been due to loss of lean tissue. In our patients there was a slight increase in mean body weight during the course of treatment (Table 1) but this did not reach significance. We would therefore, conclude that changes in sodium status do not contribute to the reduction in blood pressure with β-adrenoceptor blocking drugs. We were also unable to confirm the increase in TBK reported by Brecht *et al.* (1976) during β-adrenoceptor blocker therapy.

A reduction in glomerular filtration rate during long-term treatment with propranolol has been demonstrated by Ibsen & Sederberg-Olsen (1972). They concluded this was due to a reduction in renal blood flow secondary to changes in systemic haemodynamics, rather than to blockade of renal β-adrenergic receptors, on the basis of the findings of Nies, McNeil & Schrier (1971) in dogs. The latter group found a reduction in renal blood flow and inulin clearance following intravenous propranolol, but there were no ipsilateral changes in para-amino hippurate or inulin clearances when propranolol was infused into one renal artery. A similar lack of effect on renal blood flow and glomerular filtration rate of infusion of propranolol into the renal artery in dogs has been reported by Winer, Chokshi & Walkenhorst (1971). Ibsen & Sederberg-Olsen (1972) were not able to explain the reduced renal function by reduction in plasma volume as has been reported by Tarazi, Frohlich & Dustan (1971). In their patients plasma volume was practically unchanged. Our observations confirm the reduction in glomerular filtration rate with propranolol. The absence of a significant reduction in renal function with atenolol despite an equivalent reduction in blood pressure, strongly suggests that blockade of renal β_2-adrenergic receptors may be responsible for at least part of the reduction in creatinine clearance observed with propranolol, even though Anderson, Taher, Cronin, McDonald & Schrier (1975) concluded that in dogs β-adrenoceptors did not mediate renal autoregulation.

There is evidence to suggest that renin is responsible for the reduction in renal blood flow and glomerular filtration rate which accompanies sodium depletion (Hollenberg, Williams, Taub, Ishikawa, Brown & Adams, 1977). Renal blood flow may depend on a balance of the effects of renin secretion tending to reduce flow and stimulation of β_2 vascular adrenoceptors tending to increase flow. From our observations it seems that with non-selective β-

adrenoceptor blockade with propranolol the vasodilating effect of the suppression of renin is not sufficient to compensate for the loss of the vasodilator effect of β_2-adrenoceptor stimulation and the net result is a reduction in renal blood flow. With the cardioselective drug atenolol, renin is suppressed to a similar degree and because vasodilating β_2-adrenoceptors are relatively spared glomerular filtration rate is maintained despite an equivalent reduction in arterial pressure.

Wright, Barber, Kendall & Poole (1979) have recently reported a greater increase in blood urea in diabetics treated with propranolol than in those given the cardioselective drug metoprolol. This observation supports our conclusion that the β_2-adrenoceptors may be of importance in the maintenance of glomerular filtration rate.

Hollenberg, Adams, McKinstry, Williams, Borucki & Sullivan (1979) have demonstrated an increase in renal blood flow in salt depleted patients given the non-cardioselective β-adrenoceptor blocking drug, nadolol. They are not able to fully explain this but suggest that the increase may be due to inhibition of renin release coupled possibly with a direct vasodilating action of the drug.

The reduction in renal function which we have observed is probably not of clinical importance in essential hypertension (Ibsen & Sederberg-Olsen, 1972). It may be however that in patients with renal disease the differences are magnified, the evidence on this is conflicting (Heierli *et al.*, 1977; Warren, Swainson & Wright, 1974; Thompson & Joekes, 1974; Kincaid-Smith & Hua, 1974), and further studies are required.

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