RENAL FUNCTION DURING ACUTE AND LONG TERM PINDOLOL TREATMENT IN HYPERTENSIVE PATIENTS WITH NORMAL AND DECREASED GLOMERULAR FILTRATION

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- 1 In an acute study in hypertensive patients with normal and decreased renal function the i.v. administration of pindolol (0.1 mg/kg) caused a decrease in inulin clearance and a concomitant but not significant decrease in PAH clearance with a constant filtration fraction.
- 2 The long-term administration of pindolol (5–20 mg/day) to hypertensive patients with normal renal function was not associated with changes in renal function but in patients with a decreased renal function, pindolol caused an increase in PAH clearance but no change in inulin clearance.

Introduction

It has been reported that propranolol reduces renal plasma flow (RPF) and glomerular filtration rate (GFR) after i.v. or oral administration and sometimes permanently damages renal function (Bauer & Brooks, 1979; Ibsen & Sederberg-Olsen, 1973; Nies *et al.*, 1971).

A β -adrenoceptor blocker not affecting renal function would be of great therapeutic advantage. Pindolol (Visken) with its intrinsic sympathomimetic properties and less effect on renin may belong to this category of antihypertensive drug. Because of the paucity of information concerning the short and long-term effects of pindolol on renal function, the following study was performed.

Methods

Acute administration of pindolol

Acute clearance studies were performed in ten patients with moderate essential hypertension with normal renal function and eight patients with essential hypertension and moderately reduced renal function (mean inulin clearance $66 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$). All patients were studied as out-patients after all medications had been stopped for at least 3 weeks. Inulin and PAH clearances were performed as previously described (Roe *et al.*, 1949; Smith, 1956; Wainer *et al.*, 1980). After three control periods of 20 to 30 min each, the patients received an i.v. bolus dose of 0.1 mg/kg pindolol. After an equilibration period of 30 min three additional 20 min collection periods were obtained. Blood pressure (BP) and heart rate

(HR) were recorded several times during each period and the mean values for each period were calculated. The mean arterial pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic pressure.

Long-term oral administration of pindolol

Ten patients with normal renal function (Group A) and eight with decreased glomerular filtration (Group B) received pindolol on a once a day schedule at doses ranging from 5 to 20 mg/day for a mean of 119 days. Four patients, two from Group A and two from Group B, dropped out because of bronchospasm (two patients), headache in one and uncontrolled hypertension in one. Fourteen completed the study. One patient also took a diuretic throughout the study. Blood pressure and heart rate, lying and standing, were recorded twice a month for the duration of the trial. Values given for the initial blood pressure and pulse rate were the means of at least five measurements performed on three or more separate occasions. Values for the final blood pressure and pulse rate were the mean values obtained on the last three visits before the second short-term clearance study. Plasma renin activity (PRA) was measured with a New England Nuclear kit for radioimmunoassay of angiotensin I in samples collected after 1 h of recumbency before the short-term experiments.

Statistics

All results are expressed as mean $\pm$ s.d. The paired Student's *t*-test was used to analyse the data.

Table 1 Effects of i.v. pindolol (0.1 mg/kg)

Patients	Mean arterial pressure (mmHg)		Heart rate (beats/min)		PAH clearance ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)		Inulin clearance ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)		Filtration fraction	
	A	B	A	B	A	B	A	B	A	B
Normal renal function patients $n = 10$	126.4	121.7	75.5	69.2	481.0	470.0	98.9	94.4	0.20	0.20
(mean $\pm$ s.d.)	± 9.1	± 8.0	± 11.3	± 11.1	± 92.4	± 102.7	± 13.6	± 12.0	± 0.02	± 0.06
<i>P</i>	NS		<0.005		NS		<0.005		NS	
Reduced renal function patients $n = 8$	128.0	125.5	74.3	67.0	363.0	335.0	66.0	60.5	0.19	0.18
(mean $\pm$ s.d.)	± 12.6	± 16.5	± 13.2	± 8.2	± 118.0	± 102.0	± 17.0	± 16.0	± 0.05	0.03
<i>P</i>	NS		<0.01		NS		<0.05		NS	

A – mean values during control period.

B – mean values after pindolol administration.

Results

Acute clearance study (Table 1)

In the normal renal function group the mean arterial pressure decreased from 126.4 ± 9.1 during the control period to 121.7 ± 8 mmHg after i.v. pindolol. Pulse rate decreased 9.1% from 75.5 ± 11.3 during the control period to 69.2 ± 11.1 beats/min during the experimental periods ($P < 0.005$). As can be seen in Figure 1 the decrease in pulse rate was immediate and was maintained over the entire experimental period. Inulin clearance decreased by 4.6% after intravenous pindolol from 98.9 ± 13.6 to 94.4 ± 12 $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$ during the experimental periods ($P < 0.005$). The decrease in inulin clearance was not immediate and became significant only in the second experimental period (see Figure 1). Inulin clearance in the third experimental period was less than that in the first experimental period ($P < 0.025$). PAH clearance decreased from 481 ± 92.4 to 470 ± 102.7 $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$ but this difference

was not statistically significant. Mean filtration fraction (FF) did not change: 0.20 ± 0.02 before and 0.20 ± 0.05 after pindolol.

In group B with decreased glomerular filtration the mean arterial pressure decreased from a mean of 128.8 ± 12.6 mmHg during control period to a mean of 125.5 ± 16.5 mmHg after i.v. pindolol administration. This change was not statistically significant. The decrease in heart rate from a mean of 74.3 ± 13.2 to 67 ± 8.2 was significant ($P < 0.01$). The i.v. administration of pindolol resulted in a 10% decrease in mean inulin clearance (66 ± 17 $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$ to 60.6 ± 16 $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$ $P < 0.05$). PAH clearance decreased from a mean of 363 ± 118 to a mean of 335 ± 102 $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$, but this difference was not statistically significant. Mean filtration fraction did not change being 0.19 ± 0.05 during control period and 0.18 ± 0.03 after pindolol administration.

Table 2 Effect of long-term oral pindolol (5–20 mg/day)

Patient		Mean arterial pressure (mmHg)		Heart rate (beats/min)		PAH clearance ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)		Inulin clearance ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	
		A	B	A	B	A	B	A	B
Normal renal function patients $n = 8$	Mean	128.8	111.1	76.4	69.5	492.1	495.0	97.4	95.7
	$\pm$ s.d.	± 7.7	± 9.1	± 10.9	± 10.1	± 100.3	± 39.3	± 14.9	± 10.5
	<i>P</i>	<0.001		<0.005		NS		NS	
Reduced renal function patients $n = 6$	Mean	123.1	102.7	78.0	68.0	398.0	511.0	68.0	69.4
	$\pm$ s.d.	± 7.5	± 9.5	± 13.6	± 3.8	± 81.0	± 126.0	± 15.4	± 13.8
	<i>P</i>	<0.001		NS		<0.001		NS	

A – mean values during control period.

B – mean values after pindolol administration.

Figure 1 Acute clearance study. Pindolol 0.1 mg/kg was given as an i.v. bolus at the beginning of the experimental period.

Effects of long-term oral pindolol administration (Table 2)

In the patients with normal GFR the mean arterial pressure decreased by 13.7% from 128.8 ± 7.7 to 111.1 ± 9.1 mmHg ($P < 0.001$) during long-term oral pindolol treatment. Pulse rate fell by 9.25% from 76.4 ± 10.9 to 69.5 ± 10.1 beats/min ($P < 0.005$). Inulin clearance decreased from 97.4 ± 14.9 to 95.7 ± 10.5 ml min⁻¹ 1.73 m⁻²; this difference was not statistically significant. PAH clearance did not change during long-term pindolol administration; it was 492 ± 100.3 before and 495 ± 39.3 ml min⁻¹ 1.73 m⁻² during treatment.

In the group with decreased GFR (Group B) the mean arterial pressure decreased from 123.1 ± 7.5 to 102.7 ± 9.5 mmHg ($P < 0.001$) during chronic oral administration of pindolol. Heart rate fell by 12% from a mean of 78 to a mean of 68 beats/min (NS). Mean inulin clearance did not change. It was 68 ± 15.4 ml min⁻¹ 1.73 m⁻² prior to the treatment

and 69.4 ± 13.8 ml min⁻¹ 1.73 m⁻² during treatment. PAH clearance increased from a mean of 398 ± 81 ml min⁻¹ 1.73 m⁻² to a mean of 511 ± 126 ml min⁻¹ 1.73 m⁻² ($P < 0.001$) after prolonged oral pindolol administration.

Discussion

In individuals with normal and decreased renal function the intravenous administration of pindolol produced a decrease in inulin clearance and a concomitant but not significant decrease in PAH clearance with a constant filtration fraction. This reduction in glomerular filtration rate and renal blood flow is most probably secondary to a decrease in cardiac output or an increase in renal vascular resistance.

Heierli *et al.* (1977) have described similar results after i.v. pindolol administration in patients with normal renal function but showed no change in patients with reduced renal function. The reason for this discrepancy is not clear.

The overall change in RPF was not significant but nevertheless decreased sufficiently to maintain a constant filtration fraction. The only other change was a significant decrease in pulse rate.

The long-term administration of pindolol in normal patients with normal renal function was not associated with changes in renal function, but in patients with decreased GFR the administration of pindolol was associated with an increase in RPF and a constant GFR. These results would suggest that the effects of the chronic administration of pindolol and possibly other β -adrenoceptor blockers are different from those seen after acute administration. Atterhöög *et al.* (1976) studied the changes in cardiac output and peripheral vascular resistance after oral administration of pindolol over a period of 16 months. They found that cardiac output, which was significantly decreased after 2 months, had increased to the pre-treatment level after 16 months. Peripheral vascular resistance, which was not affected after 2 months, had decreased significantly in the long-term study. They concluded that while a decrease in cardiac output is an early mechanism in the lowering of blood pressure, changes in systemic vascular resistance seem to be more important after long-term treatment with pindolol. Thus the increase in RPF, which was found in our patients after prolonged oral treatment, may be explained by a reduction in peripheral and renal vascular resistance.

Long term oral administration of pindolol does not affect the glomerular filtration rate in hypertensive patients with normal or reduced GFR, in spite of significant decreases in blood pressure and heart rate. Thus renal failure is not a contra-indication for the use of pindolol.

References

- ATTERHÖG, J.H., DUNER, H. & PERDNOW, B. (1976). Experience with pindolol, a beta receptor blocker, in the treatment of hypertension. *Am. J. Med.*, **60**, 872–876.
- BAUER, J.H. & BROOKS, ChS. (1979). The long-term effect of propranolol therapy on renal function. *Am. J. Med.*, **66**, 405–410.
- HEIERLI, C., THOELEN, H. & RADICLOVIC, P. (1977). Renal function following a single dose of pindolol in hypertensive patients with varying degrees of impairment of renal function. *Int. J. Pharmac.*, **15**, 65–71.
- IBSEN, H. & SEDERBERG-OLSEN, P. (1973). Changes in glomerular filtration rate during long-term treatment with propranolol in patients with arterial hypertension. *Clin. Sci.*, **44**, 129–134.
- NIES, A.S., McNEIL, B.S. & SHRIER, R.W. (1971). Mechanism of increased sodium reabsorption during propranolol administration. *Circulation*, **44**, 596–604.
- ROE, J.E., EDSTEIN, J.H. & GOLDSTEIN, N.P. (1949). A photometric determination of inulin in plasma and urine. *J. biol. Chem.*, **178**, 839.
- SMITH, H.W. (1956). *Principles of renal physiology*. New York: Oxford University Press.
- WAINER, E., BONER, G. & ROSENFELD, J.B. (1980). Effects of pindolol on renal function. *Clin. Pharmac. Ther.*, **28**, 575–580.