EFFECT OF PINDOLOL AND PROPRANOLOL ON RENAL FUNCTION OF PATIENTS WITH HYPERTENSION

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- 1 Pindolol and propranolol were administered orally in equipotent antihypertensive doses to 14 subjects with mild to moderate hypertension in an open cross-over study.
- 2 Pindolol caused a smaller decrease in plasma renin activity and heart rate than propranolol.
- 3 Glomerular filtration rate and effective renal plasma flow remained unchanged during therapy with either agent.

Introduction

A number of investigations have shown that intravenous administration of the β -adrenoceptor blocking agent propranolol reduces both renal blood flow and glomerular filtration rate (Nies *et al.*, 1971; Shirmeister *et al.*, 1966; Bufano & Piacentini, 1969). Prolonged oral use of this agent has also been shown to reduce both inulin clearance and PAH clearance (Bauer & Brooks, 1979) as well as ^{51}Cr -EDTA clearance (Ibsen & Sederberg-Olsen, 1973). On the other hand, also opposite results have been reported from studies in which renal function, estimated by serum creatinine and urea levels, has remained unaltered. This applies to the use of pindolol (Fyhrqvist *et al.*, 1977), metoprolol (Weber *et al.*, 1980), acebutolol (Alhenc-Gelas *et al.*, 1978) and propranolol (Lydkin *et al.*, 1972). It is not known whether these controversial results are due to variability in methods used or agents tested.

We performed an open cross-over study on the effect on renal function of pindolol and propranolol given to hypertensive patients in equipotent antihypertensive doses.

Methods

The study was carried out as an open cross-over study in 15 subjects with essential hypertension. The design of the study is shown in Figure 1. The study covered 24–32 weeks, preceded by a 4-week drug-free wash-out period for each individual. After the wash-out period the patients were randomized to start with either pindolol or propranolol. Each treatment period was preceded by a 4-week placebo period. The optimal equipotent antihypertensive dose of the agents studied was defined as the dose that reduced diastolic blood pressure by more than 50% of the difference between the diastolic blood pressure at the end of the drug free wash-out period minus 95 mmHg. The dose was adjusted at 2 weekly intervals. The doses given during the final 4-week therapy period were pindolol 10 mg/day (12 patients) and 20 mg/day (2 patients), propranolol 120 mg/day (11 patients) and 240 mg/day (3 patients).

One of the patients, randomized to start with propranolol, had to be excluded after 9 weeks on prop-

Figure 1 Design of the study.

Table 1 Clinical data on patients included in the study

Males 10, Females 4
Age 22–54 years, median 39 years
Hypertension stage:
WHO I 11 patients
WHO II 3 patients
Duration of hypertension:
6 months–8 years, median 2 years 5 months

ranolol because of a paradoxical rise in blood pressure. The clinical data on the remaining 14 patients are shown in Table 1.

Blood pressure was recorded by the same observer using the same instrument throughout the study. The pressure was read at 2 mmHg intervals. Disappearance of the sounds (Korotkoff V) was held as the diastolic value. Values were registered after 5 min in lying and 2 min in standing position. The lower value of two successive measurements in each position was recorded.

Renal function was studied at the end of each placebo and active drug period. The glomerular filtration rate (GFR) was estimated as ^{51}Cr -EDTA clearance (Veall, 1968). The measurement is based on the determination of the activity in two plasma samples taken at 90 and 150 min after an intravenous injection of $14\ \mu\text{Ci}\ ^{51}\text{Cr}$ -EDTA.

Effective renal plasma flow (ERPF) was estimated as ^{131}I -hippuran clearance according to the principle developed by Rösler (1967). The measurement is based on the determination of the activity of two

plasma samples taken at 7 and 17 min after an intravenous injection of $12\ \mu\text{Ci}\ [^{131}\text{I}]\text{-hippuran}$.

Plasma renin activity (PRA) was determined at the end of the placebo and active drug periods by radioimmunoassay of angiotensin I released in incubation according to the method described by Fyhrqvist *et al.* (1976).

The evaluation of statistical probability (*P*) was carried out using Student's *t*-test on paired data.

Results

Blood pressure and heart rate in the supine position at the end of the various periods of the study are shown in Figure 2. The antihypertensive responses and the effect on heart rate were very much the same in the two patient groups, i.e. in those starting with pindolol and in those starting with propranolol.

The mean values of GFR and ERPF at the end of the active drug periods were compared in the statistical analysis with the corresponding values at the end of the preceding placebo periods. No significant differences were observed (Table 2). The same was done with the mean values of blood pressure and heart rate. Both drugs caused comparable and highly significant decreases in systolic and diastolic blood pressure in both supine and upright positions. Heart rate decreased highly significantly in both postures after propranolol but significantly only in the supine posture after pindolol (Table 2).

Three patients had slightly reduced renal function ($\text{GFR} < 100\ \text{ml min}^{-1}\ 1.73\ \text{m}^{-2}$). Their GFR and

Table 2 Effect of pindolol and propranolol on renal function, blood pressure, heart rate and plasma renin activity

	Placebo	Pindolol	P	Placebo	Propranolol	P
^{51}Cr -EDTA clearance ($\text{ml min}^{-1}\ 1.73\ \text{m}^{-2}$)	114 ± 20	115 ± 19	NS	116 ± 21	113 ± 20	NS
^{131}I -hippuran clearance ($\text{ml min}^{-1}\ 1.73\ \text{m}^{-2}$)	667 ± 127	713 ± 199	NS	691 ± 149	698 ± 145	NS
Systolic blood pressure (mmHg)						
upright	154 ± 9	131 ± 13	<0.001	156 ± 14	132 ± 13	<0.001
supine	160 ± 10	138 ± 11	<0.001	162 ± 16	140 ± 11	<0.001
Diastolic blood pressure (mmHg)						
upright	108 ± 8	93 ± 8	<0.001	107 ± 7	95 ± 9	<0.001
supine	104 ± 7	90 ± 8	<0.001	103 ± 7	90 ± 6	<0.001
Heart rate (beats/min)						
upright	73 ± 12	64 ± 5	0.02	73 ± 10	61 ± 4	<0.001
supine	67 ± 12	62 ± 4	NS	69 ± 12	58 ± 6	<0.001
Plasma renin activity ($\text{ng angiotensin ml}^{-1}\ \text{h}^{-1}$)	1.31 ± 0.7	1.07 ± 0.8	0.05	1.33 ± 0.8	0.76 ± 0.5	<0.001

Values are mean ± s.d. (*n* = 14)

Figure 2 Blood pressure and heart rate in the supine position at the end of each study period. Mean $\pm$ s.d.
 □ order of treatment pindolol-propranolol, ▨ order of treatment propranolol-pindolol.

ERPF remained unchanged throughout the study.

The changes in mean PRA are shown in Table 2. The decrease was consistent after propranolol whereas a slight increase was seen in two patients after pindolol. There was no correlation between the changes in GFR or ERPF and PRA.

Discussion

The results of our study indicate that the oral administration of pindolol and propranolol does not alter the clearance of ^{51}Cr -EDTA and ^{131}I -hippuran of hypertensive subjects. This result was obtained by studying in a cross-over design the same subjects with equipotent antihypertensive doses of the two drugs.

Our results with propranolol are opposite to those obtained by Bauer & Brooks (1979) in a study on healthy subjects. They showed that propranolol causes a significant reduction of GFR and ERPF (clearance of inulin and PAH) and that the reduction of GFR was sustained. It is hard to find a conclusive explanation to this diversity of results. The clearance methods that were used in our study are not as exact measures of renal function as are the clearances of

inulin and PAH, and they also tend to overestimate the clearances (Bianchi, 1980). On the other hand a reduction of 27 and 26% of the clearances as was seen in the study of Bauer & Brooks (1979), if present, would have been discernible also by our methods. It should also be noted that the intra-individual clearance values were very stable throughout our study. Although the proportional decreases of blood pressure and heart rate were the same in both studies the subjects were not comparable. We studied hypertensive patients whereas Bauer & Brooks (1979) studied healthy normotensives.

The lack of long-term effect on renal function of oral pindolol therapy shown in this study using clearance methods confirms the earlier results of Fyhrqvist *et al.* (1977) based on serum creatinine determinations. It is important to note that there was no difference in the effect on renal function between pindolol and propranolol in these subjects. Of the two tested non-selective β -adrenoceptor blocking agents only pindolol has intrinsic sympathetic activity. This probably accounted for the very marginal decrease in heart rate and the less pronounced effect on PRA as compared with that of propranolol. This difference, however, seemed to be of no importance for the effect on renal function.

From the practical point of view we consider it important that the renal function parameters also remained unchanged in the few patients with slightly reduced GFR. A comparable result has in fact been demonstrated by Pedersen (1975). He showed that one month's treatment with an antihypertensive dose of alprenolol did not reduce the clearances of [131 I]-

hippuran and 125 iothalamate to any substantial degree in those of his hypertensive patients who had a low GFR. The results imply that these β -adrenoceptor blocking agents can be safely used in hypertensive patients with normal or even slightly reduced renal function.

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