Comparison of the effects of penbutolol and propranolol on glomerular filtration rate in hypertensive patients with impaired renal function

J. VAN DER MEULEN, E. REIJN, G. A. K. HEIDENDAL, P. L. OE & A. J. M. DONKER
Academic Hospital Free University, Amsterdam, The Netherlands

- 1 Penbutolol and propranolol were administered orally in a dosage of 40 mg once daily and 80 mg twice daily, respectively to 12 patients with hypertension and impaired renal function.
- 2 Both drugs caused a significant decrease in mean arterial pressure and heart rate.
- 3 Serum creatinine concentration increased significantly by 10% during therapy with propranolol without concomitant decrease in creatinine clearance. No such effect was seen with penbutolol. GFR measured with [125 I]-iothalamate showed no significant changes with both drugs.

Keywords hypertension impaired renal function propranolol penbutolol glomerular filtration rate

Introduction

Several investigators have reported that long-term administration of β -adrenoceptor blockers causes a reduction in glomerular filtration rate (GFR) as a consequence of diminished renal blood flow. This unwanted side effect has been most frequently described after the use of propranolol. It was found in hypertensive patients with normal GFR (Ibsen & Sederberg-Olsen, 1973) and in hypertensive patients with impaired GFR (Warren *et al.*, 1974; Swainson & Winney, 1976). However, in later studies no significant decrease in GFR was found (Bauer, 1983) or no decrease was found when propranolol was given after another β -adrenoceptor blocker (Danesh *et al.*, 1984).

Penbutolol, a non-cardioselective β -adrenoceptor blocker with moderate intrinsic sympathomimetic activity was found to increase GFR when administered to normal subjects. However, no data are available on the effect of this drug when given to hypertensive patients with impaired renal function. If this increase

could be reproduced in such patients, the possible impact is obvious. Therefore, a comparative study on the effect of oral penbutolol and propranolol on GFR was started. Both drugs were given for 4 weeks in a double-blind cross-over design to hypertensive patients with chronic renal insufficiency.

Methods

Study design

The study was carried out as a double-blind cross-over study. It covered 14 weeks in total. At the start there was a 2 week period in which the used β -adrenoceptor blocker was withdrawn cautiously (tapering-off period), followed by a 2 week placebo period (stabilizing period). Then the patients were treated for 4 weeks with either penbutolol or propranolol, according to the randomization chart (period 1). This period was

Correspondence: Dr J. van der Meulen, Academic Hospital of The Free University, Department of Haemodialysis, de Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

followed by a 2 week placebo period (period 2). Then the patients cross over to the other drug for a second period of 4 weeks (period 3). The doses given during the 4 week treatment were penbutolol 40 mg once daily or propranolol 80 mg twice daily, which are equivalent antihypertensive doses. A double dummy technique was used to keep the study double-blind. The capsules had to be taken before breakfast and evening meal during the whole study.

Patients

The study started with 13 patients with hypertension and an impaired renal function. They were already taking antihypertensive medication to control their blood pressure. Informed consent was obtained from all patients. One patient, allocated to start with propranolol, had to be excluded after 2 weeks in period 1 because of the occurrence of a myocardial infarction. The clinical data of the remaining 12 patients are shown in Table 1. Hypertension was defined as a diastolic pressure between 95–110 mm Hg at the end of the stabilizing period. Disappearance of the sounds (Korotkoff phase V) was held at the diastolic value. Blood pressure was measured after 60 min resting in the supine position and during 2 min standing. Mean arterial pressure (MAP) was calculated as the sum of the diastolic blood pressure and one third of the pulse pressure. Blood pressure and heart rate were recorded by the same observer 3 h after breakfast.

Impaired renal function was defined as a creatinine clearance between 10 and 80 ml min⁻² 1.73 m⁻¹ of body-surface area, measured at the end of the stabilizing period.

All other anti-hypertensive medication, except the β -adrenoceptor blocker, was continued. No alterations in dosage were allowed. Any other concomitant medication or change in diet was discouraged during the course of the study. All adverse experiences, observed by the investigator or reported by the patient, were recorded at each visit.

Biochemical studies

The concentration of electrolytes and creatinine in serum and urine were measured by standard laboratory procedures.

Plasma renin activity (PRA) was determined according to the method described by Gunnells *et al.* (1967) and serum aldosterone according to Ito *et al.* (1972). PRA and serum aldosterone were measured at the end of placebo and active treatment periods.

Plasma concentrations of penbutolol and propranolol were determined as described by Jallow *et al.* (1979) and by Bernard *et al.* (1982), respectively. Plasma samples were extracted by a modification technique as described by Lefebvre *et al.* (1981). The lower limit of sensitivity for this assay was 3 ng l⁻¹ for both compounds. The variation coefficient from day to day was 5.9%. Drug concentrations were measured at the end of the active treatment periods.

Table 1 Clinical data of the 12 patients with impaired renal function

Patient	Age (years)	Sex	BP supine ¹ (mm Hg)	Creatinine clearance ¹ (ml min ⁻¹)	Renal ² disease	Preceding ³ treatment
1	55	male	190/100	28	unknown	B
2	56	male	130/95	30	sclerosis	B
3	64	male	160/100	19	sclerosis	A
4	64	male	195/110	37	sclerosis	C
5	52	female	160/110	12	sclerosis	A
6	55	male	140/95	45	sclerosis	A
7	56	male	170/110	49	unknown	A
8	48	female	150/95	14	m.p.g.n.	B
9	55	male	150/95	20	polycystic	B
10	38	male	160/115	69	polycystic	C
11	57	male	165/110	54	m.p.g.n.	B
12	66	male	160/100	19	sclerosis	A

1. measured at the end of stabilizing period

2. sclerosis = arteriolar nephrosclerosis, m.p.g.n. = membrano-proliferative glomerulonephritis, polycystic = adult polycystic kidney disease

3. A = diuretic plus β -adrenoceptor blocker, B = diuretic plus β -adrenoceptor blocker plus vasodilator, C = diuretic plus β -adrenoceptor blocker plus angiotensin I converting enzyme inhibitor.

Renal studies

Serum creatinine, creatinine clearance and [^{125}I]-iothalamate clearance were used as parameters of GFR. [^{131}I]-hippuran clearance was performed to measure the effective renal plasma flow (ERPF). Renal studies followed each placebo and treatment period. [^{125}I]-iothalamate clearance (C-IOT) and [^{131}I]-hippuran clearance (C-IOH) were measured by simultaneous infusion of [^{125}I]-iothalamate and [^{131}I]-hippuran as described by Donker *et al.* (1977). The measurements were done 4 h after breakfast.

In brief, the measurement of the C-IOH is based on the constant infusion technique. The clearance rate is calculated from the formula IV/P where I = counts per minute (counts min^{-1}) of 1 ml sustaining solution, V = infusion volume (ml min^{-1}) and P = counts min^{-1} of 1 ml plasma. The variation coefficient of C-IOH from day to day is 5.0% (Donker *et al.*, 1977).

The measurement of the C-IOT uses the formula UV/P where U = counts min^{-1} of 1 ml urine, V = urine volume (ml min^{-1}) and P = counts min^{-1} of 1 ml plasma. Two timed urine collections were made at 120 min intervals. Plasma was obtained at the start, in between and at the end of the urine collections. For errors due to incomplete urine collection and dead-space the C-IOT was corrected by the equation $\text{C-IOH (IV/P)/C-IOH (UV/P)}$. The variation coefficient from day to day of the corrected C-IOT is 2.2% (Donker *et al.*, 1977).

Filtration fraction (FF) was calculated as the ratio GFR/ERPF . Creatinine clearances were calculated from 24 h urine. All clearances were adjusted to 1.73^2 body surface.

Statistics

Wilcoxon's signed rank test for paired observations was used in statistical analysis. An observed difference was considered statistically significant when the P value was less than 0.01. All results are expressed as mean $\pm$ s.e. mean. The Chi square test was used in the analysis of the occurrence of adverse reactions after drug and placebo.

Results

The mean values of all parameters were compared with the corresponding values at the end of the previous placebo period. Data on blood pressure and heart rate are listed in Table 2.

Five patients started with propranolol and seven patients with penbutolol after the stabilizing period. Both penbutolol and propranolol induced a significant ($P < 0.01$) reduction in MAP and heart rate in supine and upright position. No difference in magnitude of decrease in upright MAP was observed between penbutolol and propranolol. The fall in MAP in supine position was 18 mm Hg after propranolol and 8 mm Hg after penbutolol. However, this difference was not statistically significant.

The C-IOT was reduced with 1 ml min^{-1} after penbutolol and with 2 ml min^{-1} after propranolol with a concomitant decrease in C-IOH of 3 ml min^{-1} and 5 ml min^{-1} , respectively (Table 3). These reductions were not statistically significant. There was also no significant difference between the two drugs. In the five patients who started with propranolol, C-IOT decreased with 2 ml min^{-1} and C-IOH decreased with 5 ml min^{-1} . C-IOT and C-IOH returned to pre-propranolol values after the placebo period.

The mean creatinine clearance after the placebo period preceding penbutolol was $34 \pm 6 \text{ ml min}^{-1}$, and did not change. Before propranolol the mean creatinine clearance was $34 \pm 6 \text{ ml min}^{-1}$ and thereafter $37 \pm 8 \text{ ml min}^{-1}$ (Table 3). The difference was not statistically significant. However, propranolol caused a significant increase of the serum creatinine levels. The mean $\pm$ s.e. mean serum creatinine level before propranolol was $250 \pm 33 \mu\text{mol l}^{-1}$ and after propranolol $271 \pm 37 \mu\text{mol l}^{-1}$. For penbutolol these levels were $255 \pm 33 \mu\text{mol l}^{-1}$ and $269 \pm 36 \mu\text{mol l}^{-1}$, respectively (Table 3).

Both penbutolol and propranolol caused significant ($P < 0.01$) reductions in PRA from 4.00 ± 0.50 to 1.66 ± 0.16 and from 4.01 ± 0.56 to $1.72 \pm 0.22 \text{ ng AI ml}^{-1} \text{ h}^{-1}$, respectively (pH 6; 37°C). Serum aldosterone levels showed no significant changes (from 0.41 ± 0.04 (placebo)

Table 2 Mean arterial pressure (MAP) and heart rate response to the administration of penbutolol 40 mg once daily and propranolol 80 mg twice daily

	Placebo	Penbutolol	Placebo	Propranolol
MAP supine (mm Hg)	122 ± 3.6	$114 \pm 4.4^*$	125 ± 4.2	$107 \pm 3.2^*$
MAP upright (mm Hg)	126 ± 4.4	$114 \pm 3.9^*$	125 ± 3.0	$114 \pm 3.2^*$
Heart rate (beats min^{-1})	79 ± 3.3	$63 \pm 1.8^*$	76 ± 1.8	$60 \pm 1.6^*$

All values are the mean $\pm$ s.e. mean (twelve subjects).

* $P < 0.01$

Table 3 Effect of penbutolol and propranolol on renal function

	Placebo	Penbutolol	Placebo	Propranolol
Serum creatinine ($\mu\text{mol l}^{-1}$)	255 $\pm$ 33	269 $\pm$ 36	250 $\pm$ 33	271 $\pm$ 37*
Creatinine clearance (ml min^{-1})	34 $\pm$ 6	34 $\pm$ 6	34 $\pm$ 6	37 $\pm$ 8
[^{125}I]-iothalamate clearance (ml min^{-1})	31 $\pm$ 5	30 $\pm$ 5	31 $\pm$ 5	29 $\pm$ 4
[^{131}I]-hippuran clearance (ml min^{-1})	138 $\pm$ 25	135 $\pm$ 24	135 $\pm$ 24	130 $\pm$ 23
FF	0.22 $\pm$ 0.01	0.20 $\pm$ 0.01	0.23 $\pm$ 0.01	0.23 $\pm$ 0.02

All values are the mean $\pm$ s.e. mean (twelve subjects).

* $P < 0.01$

to $0.38 \pm 0.04 \text{ nmol l}^{-1}$ after the treatment with penbutolol and from 0.31 ± 0.02 (placebo) to $0.46 \pm 0.03 \text{ nmol l}^{-1}$ after propranolol administration).

Patient's compliance was tested by monitoring plasma concentrations of both drugs. In all samples effective serum concentrations of the prescribed drug could be detected.

Adverse reactions are listed in Table 4. Most common were headache, nausea, tinnitus and dizziness. These reactions occurred during the placebo periods as well as during the active treatment periods. Dyspnoea and coldness of extremities were found predominantly during β -adrenoceptor blockade. However, the differences were not statistically significant.

Discussion

The effects of penbutolol and propranolol on GFR in hypertensive patients with impaired renal function were investigated. At the dosages

used, the two drugs were found to lower significantly the MAP and heart rate. No significant differences in the fall of the blood pressure or in adverse reactions were observed between the two drugs.

In none of our cases was irreversible deterioration of renal function as described by others (Warren *et al.*, 1974; Swainson & Winney, 1976) seen. In the latter two reports five patients, of whom three with clinically manifest heart failure, are described. Most likely the irreversible renal damage in the three patients with congestive heart failure must have been the result of insufficient renal perfusion due to the heart failure itself. The other two patients without heart failure showed improvement of renal function after withdrawal of propranolol. However, in these two patients only serum creatinine was used as parameter of GFR. When we should have used only this parameter in our study the same conclusion could have been drawn, i.e. propranolol causes a 10% decrease in GFR. The phenomenon of a significant increase in serum creatinine after

Table 4 Adverse reactions profile of penbutolol and propranolol in 12 hypertensive patients with impaired renal function

Adverse reaction	Placebo	Penbutolol	Placebo	Propranolol
Headache	2	3	2	3
Dizziness	1	2	2	2
Tinnitus	1	3	2	2
Nausea	2	2	2	3
Palpitations	—	—	—	—
Chest pain	1	1	2	1
Dyspnoea on exertion	—	3	2	3
Oedema	1	1	1	1
Coldness of extremities	—	3	1	2
Wheezing	—	—	—	1
Miscellaneous	7	6	8	9

propranolol was also found in a comparative study between enalapril and propranolol (Enalapril in Hypertension Study Group, 1984).

The study claiming no effect of propranolol on renal function in patients with impaired renal function (Thompson & Joeke, 1974) did not use serum creatinine as measure of renal function but creatinine clearance. As shown in our study this parameter of GFR remains constant or even increases after propranolol.

The combination of a significant rise in serum creatinine concentration without a concomitant decrease in creatinine clearance, as observed in our patients, was also found by Bauer (1983) in 14 uncomplicated hypertensive patients. No explanation was provided. However, one may speculate that a rise in serum creatinine concentration augments tubular secretion of creatinine (Shemesh *et al.*, 1985). This being the case, other substances in use for measuring GFR should show a decrease in glomerular filtration rate after propranolol. Two studies measuring GFR with [^{51}Cr]-EDTA showed a significant decrease in renal function after propranolol (Ibsen & Sederberg-Olsen, 1973; Danesh *et al.*, 1984). One study, using inulin, demonstrated a slight, non-significant decrease in GFR after propranolol 320 mg daily, a finding which is similar with ours. Thus, most likely propranolol affects GFR only slight as expressed by a rise in serum creatinine, which is not demonstrable by the creatinine clearance since tubular secretion increases.

To exclude the possibility that any effect of propranolol on GFR could have been masked by combining the data of patients in which the drug was given first with the data of patients who got it as second drug, as was found in a cross-over study comparing propranolol with nadolol (Danesh *et al.*, 1984), the data were analysed for order effect. No such effect was seen: the changes in creatinine clearance or C-IOT were similar, irrespective of the order in which propranolol was given. An explanation that we did not see a significant drop in GFR when propranolol was given first, could be the normal ratio between

GFR and ERPF in our patients. In the study reporting the order effect (Danesh *et al.*, 1984) propranolol was given as first drug to patients with a significantly higher ERPF as compared with the GFR, whereas the patients receiving nadolol first had a normal ratio. One may assume that a high ERPF with a relative low GFR reflects a maximally dilated renal vasculature. Any fall in the blood pressure will result in a drop of GFR because the renal vasculature cannot dilate further to compensate for the diminished pressure.

The reported increment of GFR after penbutolol could not be confirmed in our study either (Meyer *et al.*, 1981). On the contrary, with penbutolol a similar trend as with propranolol was detected: a rise in serum creatinine without concomitant decrease in creatinine clearance and a slight decrease in C-IOT parallel with a slight decrease in renal plasma flow. However, these changes were smaller and all did not reach statistical significance.

To rule out that the quantitative differences between propranolol and penbutolol could have been produced by the smaller fall of MAP in supine position after penbutolol, regression analysis was done between the changes in MAP and serum creatinine in the individual patients. No correlation between these two variables could be demonstrated. However, whether the non-statistically significant rise in serum creatinine after penbutolol indicates that penbutolol has no influence on GFR cannot be substantiated from this study because of the limited number of patients (Freiman *et al.*, 1978).

In conclusion, also in patients with impaired renal function, penbutolol and propranolol can be safely prescribed. Serum creatinine concentration will rise slightly, especially after propranolol. However, the change in GFR is only marginal while the creatinine clearance will show no change due to increased tubular excretion of creatinine.

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