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Comparison of the effects of prizidilol and propranolol on renal haemodynamics at rest and during exercise

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1 Effective renal plasma flow and glomerular filtration rate were measured in 22 mild-to-moderate, uncomplicated, essential hypertensive patients during placebo and after 3 months of randomly assigned treatment either with prizidilol (n = 10) or propranolol (n = 12). Measurements were performed at rest and during cycloergometer exercise.
2 For a comparable effect on blood pressure effective renal plasma flow was significantly increased at rest by prizidilol (+9%) and decreased by propranolol (−13.6%); these patterns were maintained during exercise. Glomerular filtration rate was immodified after the treatment with both drugs.
3 It is concluded that prizidilol is an effective hypotensive agent with no deleterious effects on renal haemodynamics.

Keywords prizidilol propranolol renal haemodynamics

Introduction

The changes induced on systemic and regional haemodynamics play a fundamental role in the appearance of clinical effects and side effects of antihypertensive agents (see Frishman, 1981). Therefore, in order to rationalize the treatment, the haemodynamic characterization of the individual drugs represent a prerequisite to their clinical use.

Prizidilol (SK&F 92657) is a new effective antihypertensive agent which shows both β-adrenoceptor blocking and vasodilating activities (Taylor *et al.*, 1980; Collier & Pitcher, 1980; Pitcher *et al.*, 1982). The drug, in the long term, induces a favourable haemodynamic pattern in that it lowers blood pressure levels without modifying heart rate and cardiac output both at rest and during exercise (Lund-Johansen & Omvik, 1982). On the other hand, the acute administration of the drug has been reported to increase renal perfusion, but to depress glomerular filtration rate (Boehringer *et al.*, 1983).

Our aim was to assess the long term effects of prizidilol on renal haemodynamics at rest and during exercise and to compare them with those obtained in a parallel group of patients treated with propranolol, selected as reference treatment, in a randomized study. This work was presented in part at a symposium on 'Renal blood flow, sodium and hypertension' held in Dunedin, New Zealand in February 1983.

Methods

Twenty-four outpatients (age range 25 to 54 years) affected by mild-to-moderate previously untreated, uncomplicated, essential hypertension were enrolled for the study. After 2 to 4 weeks of placebo treatment (1 tablet twice daily) the patients underwent the renal studies (see below), and then were randomly assigned, single blind, to treatment either with propranolol (40 mg twice daily) or prizidilol (200 mg twice daily).

The drugs were titrated in the initial 6 weeks of treatment, and thereafter their dosage was kept unchanged until the completion of the study, which totalled 12 weeks of active treatment.

Titration was effected until normalization of BP (<95 mm Hg diastolic BP (Korotkoff phase

5) after 5-min lying) unless important side effects appeared or the ceiling dose of 480 mg/day of propranolol and 800 mg/day of prizidilol was reached.

Patients were requested to keep as constant as possible for the duration of the study both their dietary habits (with particular respect to sodium intake) and their physical activity. Renal haemodynamics assessment was performed again at the end of the study, 6–8 h after last drug intake.

Renal studies

The patients were prepared for measurements and allowed to rest in the sitting position for 1 h.

Methods for measurement of renal haemodynamic parameters were previously described in detail (Malini *et al.*, 1983). In brief, effective renal plasma flow (ERPF) was determined by means of bi-compartmental analysis of the plasma disappearance curve after a single injection of ^{131}I-labelled ortho-iodo-hippurate (Pritchard *et al.*, 1965); glomerular filtration rate (GFR) was determined after a single injection of ^{125}I-labelled iothalamate (Cohen *et al.*, 1969). No correction of the calculated GFR was made for the effects of iothalamate protein binding.

The measurements were carried out both at rest (sitting) and during a 45 min long steady state cycloergometer exercise (Meditronic 40, Keiper Dynavit, Kaiserlautern, W. Germany). The methods were previously validated both at rest and during exercise *vs*, the *p*-aminohippurate and inulin constant infusion techniques. Variability of the single injection methods *vs.* constant infusion for two repeated measures in the same volunteer (n = 7) was found to be less than 6.6%.

The exercise work load had been tailored in a previous dummy run according to patient's sex, age and physical fitness with a view to achieve at least a 70% increase of rate pressure product-systolic BP × heart rate-(RPP) over basal values at the fifth minute of exercise. This corresponded to a range of 50 to 100 W in absolute terms. The preset level of exercise could be maintained stable by the patients for the entire period of the test by the aid of an electronic visual feedback on the speed of pedalling.

Blood pressure (BP) (mercury sphygmomanometer) and heart rate (HR) (monitor one lead trace) were measured every 5 min during both resting and exercise periods. Data reported below for these two parameters represent the mean value of all readings in the two activity periods.

Renal vascular resistances (RVRs) were calculated as:
Mean BP/renal blood flow (RBF) where RBF = ERPF/(1-haematocrit), and mean BP = diastolic BP + 1/3 pulse pressure.

Informed consent was obtained from all patients. Student's *t*-test for paired or unpaired data, analysis of variance and multivariate analysis were used in statistical calculations, as appropriate. All results are expressed as mean ± s.e. mean.

Results

All the 12 patients in the propranolol treatment group and 10 patients out of 12 in the prizidilol treatment group completed the study. The two drop outs in the latter group were due to non-medical reasons. Reported data do not include these two patients.

Placebo period

Mean age was 39.9 ± 1.76 years in the propran-

Table 1 Haemodynamic parameters at rest in the two treatment groups during placebo and active treatment.

	Prizidilol		*Propranolol*	
	Placebo	*Treatment*	*Placebo*	*Treatment*
SBP (mm Hg)	164 ± 4.1	144 ± 4.5*	159 ± 5.3	142 ± 4.3*
DBP (mm Hg)	106 ± 1.8	90 ± 1.6*	105 ± 1.4	93 ± 2.5*
MBP (mm Hg)	126 ± 2.1	108 ± 2.5*	123 ± 2.4	109 ± 3.4*
HR (beats/min)	72 ± 2.8	73 ± 1.4	76 ± 3.0	58 ± 2.8*
RPP (mm Hg/min)	11885 ± 487	10594 ± 411	12293 ± 706	8292 ± 387*
ERPF (ml min^{-1} 1.73m^{-2})	531 ± 35	579 ± 33*	595 ± 35	514 ± 35*
GFR (ml min^{-1} 1.73 m^{-2})	102 ± 5.2	105 ± 3.4	109 ± 3.9	101 ± 6.4
RVRs (dyn s cm^{-5})	10825 ± 696	8565 ± 526*	9930 ± 774	10344 ± 846

SBP systolic blood pressure, DBP diastolic blood pressure, MBP mean blood pressure; other abbreviations see text.
* at least $P < 0.05$ *vs* placebo.

olol and 43.1 ± 2.81 years in the prizidilol treatment group. Known duration of hypertension was 70 ± 11.7 and 76 ± 4.0 months, respectively. The two groups were homogeneous both for baseline values and their modification on exercise (Tables 1 and 2).

Active treatment period

Normalization of BP was obtained in nine patients treated with propranolol (median dosage 160 mg; range 80 to 240 mg/day) and in nine patients treated with prizidilol (median dosage 600 mg; range 400 to 800 mg/day).

Interruption of dosage titration was necessary in three patients during propranolol treatment due to symptomatic bradycardia (two patients), and vivid dreams in the remaining one.

Except when specifically indicated, the changes mentioned hereafter are statistically significant. Significance levels are reported in Tables 1 and 2.

Rest Data are reported in Table 1. Propranolol and prizidilol induced similar reductions of systolic BP, diastolic BP and mean BP; HR was not modified by prizidilol, while it was markedly reduced by propranolol (−26.6%); consequently the RPP was definitely lower after the latter (−32.5%) than after prizidilol (−10.8%).

Propranolol reduced ERPF (−13.6%), while prizidilol increased it (+9.0%). Neither drug modified GFR significantly.

After propranolol, as noted above, mean BP decreased percentagewise to the same extent as ERPF and therefore calculated RVRs—obtained from the ratio of the two parameters—did not show any significant variation (+4.0%). On the contrary, the increase of EPRF after prizidilol brought about a significant decrease of RVRs (−20.8%).

The changes in renal haemodynamics elicited by the two drugs were unrelated to the basal values, reduction of BP levels, daily dosage of the drugs and induced degree of β-adrenergic receptor blockade.

Exercise Results are reported in Table 2.

Systolic BP, diastolic BP and mean BP were reduced to the same extent after propranolol and after prizidilol treatment. HR was reduced more markedly by propranolol than by prizidilol (−22.4% *vs* 10.9%, $p < 0.001$).

ERPF was significantly increased by prizidilol (+12.8%) and reduced by propranolol (−20.3%) treatment while GFR was unchanged after both drugs. Calculated RVRs were non-significantly increased after propranolol (+8.1%), but significantly reduced after prizidilol (−23.7%) treatment, for the same considerations expressed in the previous paragraph.

Seven patients reported an increased tiredness on completion of the exercise after treatment with propranolol. Prizidilol affected the subjective exercise tolerance in one case.

Discussion

At the dosages used, the two drugs were found to be equally effective in controlling BP both at rest and during exercise and induced decreases in BP in agreement with the previous extensive findings on propranolol and with the reports published to date on long-term prizidilol (Leonetti *et al.*, 1980; Larsson *et al.*, 1981; Lund-Johansen & Omvik, 1982; Luscher *et al.*, 1982).

Thus, for a comparable control of BP prizidolol and propranolol induced diverging effects on renal haemodynamics. Both at rest and during exercise prizidilol significantly increased

Table 2 Haemodynamic parameters during exercise in the two treatment groups during placebo and active treatment.

	Prizidilol		*Propranolol*	
	Placebo	*Treatment*	*Placebo*	*Treatment*
SBP (mm Hg)	179 ± 4.6	154 ± 4.1*	180 ± 6.5	150 ± 4.8*
DBP (mm Hg)	100 ± 1.8	86 ± 2.2*	103 ± 2.6	89 ± 2.9*
MBP (mm Hg)	127 ± 2.4	108 ± 2.1*	128 ± 3.5	109 ± 3.4*
HR (beats/min)	119 ± 5.6	106 ± 3.7	129 ± 6.2	100 ± 4.0*
RPP (mm Hg/min)	21489 ± 1279	16378 ± 820*	23429 ± 1509	15069 ± 807*
ERPF (ml min^{-1} 1.73m^{-2})	406 ± 28	458 ± 32*	468 ± 33	373 ± 31*
GFR (ml min^{-1} 1.73 m^{-2})	88 ± 4.9	91 ± 3.5	99 ± 4.9	93 ± 6.6
RVRs (dyn s cm^{-5})	14191 ± 756	10828 ± 718*	13318 ± 1110	14407 ± 1254

SBP systolic blood pressure, DBP diastolic blood pressure, MBP mean blood pressure; other abbreviations see text.
* at least $P < 0.05$ *vs* placebo.

renal perfusion while propranolol, as previously described, depressed it (see Wilkinson, 1982).

In this study we did not measure cardiac output and therefore no inference on the relation between central and peripheral haemodynamics can be made. It is doubtful, however, whether the changes in central haemodynamics elicited by β-adrenoceptor blocking drugs represent the major determinant of their effects on renal perfusion (Wilkinson, 1982).

The prizidilol induced increase in renal perfusion, which takes place without change in cardiac output and fluid volumes (Lund-Johansen & Omvik, 1982), can probably be attributed to a selective renal vasodilation which is maintained beyond the acute administration of the drug (Boehringer *et al.*, 1983).

The increased renal perfusion that we observed persisting notwithstanding non-selective beta-blockade indicates that the direct vasodilating property of prizidilol is quantitatively and/or qualitatively different from that of hydralazine, which alone (Vanderkolt *et al.*, 1954) or in combination with propranolol (Falch *et al.*, 1978) does not modify ERPF in the long term. Otherwise, it should be assumed that the β-adrenoceptor-blocking moiety of the drug possesses a still undefined property which interferes with the renal autoregulation similarly to other β-adrenergic receptor blockers (Textor *et al.*, 1982) or α/β-adrenergic receptor blockers (Malini *et al.*, 1982). Further studies are warranted to clarify this aspect.

Contrary to previous observations after acute administration of prizidilol (Boehringer *et al.* 1983) we could not observe a decrease of GFR: this further underlines that changes in renal haemodynamics observed in the short term may not necessarily be extended to long term treatment.

It has been hypothesized that it would be more rational to treat hypertensive patients with agents that reduce calculated RVRs and increase renal perfusion (Britton, 1981), but in clinical terms it is not established if a different effect on renal haemodynamics may bear different therapeutic and prognostic implications both in patients with normal or reduced renal function (Wilkinson, 1982).

The effects of the two drugs on renal haemodynamics during exercise could prove to be of clinical value. Standing and exercising, by lowering renal perfusion, reduce the clearance of renally excreted drugs (Roberts & Denton, 1980; Mason *et al.*, 1980). This phenomenon could be more important in patients known to have lower baseline renal perfusion (elderly, severe hypertensives, patients with renal insufficiency), who may further be disadvantaged from the reduction of renal flow caused by drugs like propranolol. These patients could take benefit from the increase induced by drugs like prizidilol. Awareness of this possibility, which needs further evaluation, may prevent unexpected adverse reactions from drug/drug haemodynamic interactions.

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