The effect of celiprolol on glomerular filtration rate and renal blood flow in patients with chronic renal impairment and healthy volunteers

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A double-blind, placebo controlled study investigated the effects of celiprolol, 200 mg daily for 7 days, on glomerular filtration rate (GFR) and estimated renal blood flow (ERBF) in eight healthy volunteers and eight patients with chronic renal insufficiency. In healthy volunteers the mean difference in GFR was 4.8 ml min⁻¹ (95% CI -8.2 to 17.7 ml min⁻¹) and the mean difference in ERBF was 49.8 ml min⁻¹ (95% CI -47.5 to 147 ml min⁻¹) after celiprolol. In patients with chronic renal insufficiency the mean difference in GFR was -2.1 ml min⁻¹ (95% CI -5.7 to 1.2 ml min⁻¹) and the mean difference in ERBF was 0.6 ml min⁻¹ (95% CI -64.6 to 65.8 ml min⁻¹). The study had sufficient power to detect a 15% change in GFR for normals and 10% for patients, and for ERBF, changes of 14% and 23% were detectable. Celiprolol at a dose of 200 mg daily for 7 days can be used in patients with chronic renal insufficiency without adversely affecting GFR or ERBF.

Keywords celiprolol renal blood flow glomerular filtration rate
volunteers patients

Introduction

Celiprolol is a cardio-selective β -adrenoceptor blocking agent which is used for the treatment of angina pectoris and hypertension. In animal studies, celiprolol has been shown to have vasodilatory, anti-arrhythmic and bronchodilator effects (Riddell *et al.*, 1987). Pre-clinical data suggest that celiprolol may have advantages over other β -adrenoceptor blockers in patients with reduced renal function. The haemodynamic effects of celiprolol, metoprolol, acebutolol, atenolol and propranolol were evaluated in anaesthetised dogs. Celiprolol produced comparable decreases in both systolic arterial pressure and heart rate, but produced a small increase in femoral arterial flow, whereas the other β -adrenoceptor blockers decreased femoral flow (Pittner, 1983a). Preliminary studies in rats indicated that celiprolol does not reduce glomerular filtration rate (GFR) or estimated renal blood flow (ERBF) as measured by inulin and *p*-amino hippurate clearances (Pittner, 1983b).

Patients with renal disease frequently have associated hypertension. β -adrenoceptor blockers are widely used for treating hypertension but they may reduce ERBF and GFR (Wilkinson, 1982). The effects of β -adrenoceptor blockers on renal haemodynamics are of little clinical significance in hypertensive patients with

normal renal function but in patients with impaired renal function the observed reductions in ERBF and GFR, with non-selective β -adrenoceptor blockers can be clinically significant.

A double-blind, placebo controlled, cross-over study was therefore undertaken to assess the effects of celiprolol 200 mg tablets daily for 7 days on ERBF and GFR in healthy volunteers and in patients with stable chronic renal failure.

Methods

Two groups of subjects were studied. The first group consisted of eight non-smoking (four female, four male) volunteers aged 25 ± 9.63 (mean $\pm$ s.d.) (range 18–45) years and weighing 69 ± 9.64 (mean $\pm$ s.d.) (range 54–85.5) kg who were healthy as determined by medical history, physical examination and standard biochemical and haematological parameters. The second group consisted of non-smoking hypertensive patients with stable chronic renal failure defined as a GFR between 7–90 ml min⁻¹ with less than a 10% change over the previous 3 months. Eight patients (five male,

three female) aged 49 ± 14.8 (mean $\pm$ s.d.) (range 20–66) years and weighing 74 ± 13.2 (mean $\pm$ s.d.) (range 62–96) kg with a mean GFR of 39.4 ml min^{-1} (range 7.9 – 86.6 ml min^{-1}) were entered into the study. Patients and healthy volunteers were excluded if they were known to have sensitivity or contraindications to β -adrenoceptor blockers, or had abnormal screening tests, or systolic and diastolic pressures exceeding 200 mm Hg and 120 mm Hg, respectively, when off therapy for 2 weeks. A randomised, double-blind, cross-over design was used with at least 7 days washout between each phase. The study details were fully explained to each subject who then gave written consent approved by the Canterbury Area Health Board's Ethics Committee.

Subjects received celiprolol 200 mg daily for 7 days in the active phase. In the placebo phase subjects received matching placebo tablets daily for 7 days. Celiprolol and matching placebo tablets were supplied by Rhone-Poulenc Rorer. On day 7 of each phase, after an overnight fast, and after a 48 h abstinence from coffee, tea and alcohol, ERBF and GFR were measured 3 h after the administration of the celiprolol or placebo. ERBF and GFR were measured using a 1 ml injection containing 50 mCi [^{125}I]-hippuran and 540 mCi [$^{99\text{m}}\text{Tc}$]-diethylenetriamine pentaacetic acid (DTPA). Venous blood samples (5 ml) were taken via an indwelling catheter at 7, 10, 12, 15, 20, 25, 30, 45 and 60 min and 2, 3, 4, 5 and 6 h to determine [^{125}I]-hippuran activity and at 2, 3, 4, 5 and 6 h to determine [$^{99\text{m}}\text{Tc}$]-DTPA activity. In the patients with renal impairment additional blood samples were taken at 8, 12 and 24 h. Supine blood pressure and heart rate were measured prior to tablet administration and prior to injection of isotope and at 1, 2, 3, 4, 5, 6, 8 and 24 h immediately before blood sampling. Diastolic blood pressure was recorded at phase 5 and the average of two readings recorded.

A standard lunch was provided 6 h after tablet administration and subjects remained in a supine position for the first 6 h of blood sampling.

The areas under the [^{125}I]-hippuran and [$^{99\text{m}}\text{Tc}$]-DTPA plasma concentration-time curves were calculated using the linear trapezoidal rule with extrapolation to infinity by dividing the last measured concentration by the elimination rate constant. Renal clearance (ml min^{-1}) of [^{125}I]-hippuran (effective renal plasma flow) (ERPF) and [$^{99\text{m}}\text{Tc}$]-DTPA (GFR) were calculated from the equation

$$\frac{\text{ERPF}}{\text{or GFR}} = \frac{\text{dose}}{\text{AUC}}$$

Estimated renal blood flow (ERBF) was calculated from

$$\text{ERBF} = \frac{\text{ERPF}}{1 - \text{HCT}}$$

Analysis of variance (order $\times$ subjects $\times$ drug $\times$ hour) was used to compare the effects of celiprolol and placebo on GFR, renal blood flow, heart rate and systolic and diastolic pressure (BDMP Software, Program 2V) (Dixon, 1985). The 95% confidence limits were calculated from the standard error. Power calculations were derived from Hills & Armitage (1979) using the standard errors derived from the data.

Results

Healthy volunteers

After 7 days of placebo treatment the mean GFR was 108 ml min^{-1} and after celiprolol treatment it was 113 ml min^{-1} (mean difference = 4.8 ml min^{-1} , 95% confidence limits -8.2 to 17.7 ml min^{-1}). Mean ERBF was 804 ml min^{-1} after 7 days of placebo and 854 ml min^{-1} after celiprolol (difference = 49.8 ml min^{-1} , 95% confidence limits -47.5 to $147.0 \text{ ml min}^{-1}$). Individual data are shown in Figure 1. The differences between post-treatment means were not statistically different. Celiprolol had no significant effect on heart rate, or systolic or diastolic blood pressure. There were no significant interactions with drug effect and no significant treatment order effect ($P < 0.1$).

Patients with renal insufficiency

The mean GFR after placebo treatment was 39 ml min^{-1} and 37 ml min^{-1} after celiprolol (mean difference = -2.1 ml min^{-1} , 95% confidence limits -5.7 to 1.2 ml min^{-1}). The mean ERBF after placebo was 328 ml min^{-1} and 329 ml min^{-1} after celiprolol treatment (mean difference = 0.6 ml min^{-1} , 95% confidence limits -64.6 to 65.8 ml min^{-1}). Individual data are shown in Figure 2. The differences between the post-treatment means were not statistically significant. There were no significant interactions with drug effect and no significant

Figure 1 The effect of celiprolol on estimated renal blood flow (ERBF) and glomerular filtration rate (GFR) in individual healthy volunteers. ●---● individual result, ▲—▲ mean data.

Figure 2 The effect of celiprolol on estimated renal blood flow (ERBF) and glomerular filtration rate (GFR) in individuals with chronic renal insufficiency. ●----● individual result, ▲——▲ mean data.

treatment order effect. Heart rate fell on average by 6.2 beats min⁻¹ on celiprolol (limits -9.6 to -2.9, $P = 0.004$). Blood pressure also fell significantly, average -7, -11.1 (95% confidence limits -18.4, -13.34 and -3.8, -0.7, $P < 0.05$).

The study design was sufficiently sensitive to detect a 14% change in ERBF and a 15% change in GFR in the healthy volunteers with an $\alpha = 0.05$ and $\beta = 0.2$. In the renal failure patients, a 10% change in GFR and a 23% change in ERBF could be detected with an $\alpha = 0.05$ and a $\beta = 0.2$.

Discussion

In this study celiprolol had no effect on ERBF or GFR in healthy volunteers when compared with placebo. Based on the 95% confidence limits, the mean changes due to celiprolol were -8% to 16% for GFR and -6% to 18% for ERBF when the limits are expressed as a percentage of the placebo mean. The small but non-significant fall in blood pressure is an expected effect in the healthy subjects.

In the patients with renal insufficiency celiprolol reduced blood pressure and heart rate, but had no

statistically significant effects on mean GFR or ERBF. No individual had a clinically significant deterioration in the measured parameters. The mean changes due to celiprolol were -14% to 3% GFR and -20 to +20% for ERBF. A fall of 20% or greater in ERBF or GFR can be regarded as clinically significant. Although it has been reported that the use of β -adrenoceptor blockers for the management of hypertension in patients with normal or mild pre-existing renal impairment does not result in any deterioration in renal function, there are clinical reports describing deterioration in renal function in hypertensive patients with severely impaired renal function receiving different β -adrenoceptor blockers. Warren *et al.* (1974) first reported that treatment of hypertension with β -adrenoceptor blockers in patients with moderately severe chronic renal failure may be followed by a rapid deterioration in renal function. It was suggested that this deterioration was due to reduced ERBF secondary to a reduction in cardiac output.

The use of the β -adrenoceptor blockers, propranolol and oxprenolol group (Bufano & Piacentini, 1969; Shirmeister *et al.*, 1966), has been shown to reduce GFR in hypertensive patients, but this is not thought to be of functional significance in patients with normal renal function. Review of the more recent published literature indicates that variable effects on ERBF have been found in hypertensive patients with or without existing impairment of renal function. It is postulated that β -adrenoceptor blockers reduce renal function predominantly by blocking β_2 -receptors in the kidney (Wilkinson, 1982); however, atenolol (Imai *et al.*, 1986) and disoprolol (Gluck & Reubi, 1986) both cardio-selective β -adrenoceptor blockers, have been reported to reduce GFR or ERBF significantly. The non-selective β -adrenoceptor blockers, propranolol (Danesh *et al.*, 1984) and nadolol (O'Callaghan *et al.*, 1983), have been reported to reduce ERBF during short term oral administration as has the vasodilator β -adrenoceptor blocker, prazosin (Andersen *et al.*, 1985). Another study of nadolol showed a significant increase in ERBF (Boehringer *et al.*, 1983). Acebutolol, timolol, penbutolol and bevantolol have been reported as having no significant effect on GFR or ERBF (Solimon *et al.*, 1986; Valvo *et al.*, 1984; Van der Meiracker *et al.*, 1988; Van der Meulen *et al.*, 1986).

Although statistically significant reductions in GFR and ERBF have been found with β -adrenoceptor blockers, the reductions are not generally of clinical significance.

In view of the relatively small and variable changes in ERBF and GFR in the patients with renal insufficiency during short term treatment with celiprolol, it can be concluded that celiprolol (at a dose of 200 mg daily for 7 days) can be used with safety in patients with renal impairment.

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