Comparison between carvedilol and captopril in rats with partial ablation-induced chronic renal failure

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1 The effect of the novel β -adrenoceptor antagonist and vasodilator, carvedilol (SK&F 105517, $\sim 70 \text{ mg kg}^{-1}$ daily in the food), and captopril ($\sim 38 \text{ mg kg}^{-1}$ daily in the drinking fluid) on the progression of chronic renal failure in rats was studied.

2 Six weeks following partial renal ablation, the urinary protein excretion of the carvedilol- ($60 \pm 21 \text{ mg day}^{-1}$) and captopril-treated ($35 \pm 9 \text{ mg day}^{-1}$) animals was less than 50% that of control rats ($133 \pm 27 \text{ mg d}^{-1}$).

3 Serum creatinine (Scr) and urea nitrogen (SUN) concentrations of the carvedilol-(Scr, $0.63 \pm 0.09 \text{ mg dl}^{-1}$; SUN, $11.3 \pm 1.2 \text{ mg dl}^{-1}$) and captopril-treated (Scr, $0.82 \pm 0.05 \text{ mg dl}^{-1}$; SUN, $14.1 \pm 1.5 \text{ mg dl}^{-1}$) animals were also significantly ($P < 0.05$) lower than that observed in control animals (Scr, $1.4 \pm 0.3 \text{ mg dl}^{-1}$; SUN, $19.2 \pm 3.9 \text{ mg dl}^{-1}$), indicating that glomerular filtration rate was improved by both drugs. Plasma renin activity was significantly ($P < 0.05$) higher in captopril-treated rats ($24.7 \pm 4.6 \text{ ng angiotensin I ml}^{-1} \text{ h}^{-1}$) than in either carvedilol-treated ($7.9 \pm 1.4 \text{ ng angiotensin I ml}^{-1} \text{ h}^{-1}$) or control animals ($7.4 \pm 1.0 \text{ ng angiotensin I ml}^{-1} \text{ h}^{-1}$).

4 Histological examination of the kidneys demonstrated a significantly reduced glomerular hypertrophy and glomerulosclerosis in those animals receiving carvedilol or captopril compared to controls.

5 Serum carvedilol concentration measured every 6 h for 24 h was variable and ranged on average from $57 \pm 13 \text{ ng ml}^{-1}$ at 16 h 00 min to $121 \pm 31 \text{ ng ml}^{-1}$ at 03 h 00 min. These data indicate that the rats probably had 24 h systemic exposure to carvedilol.

6 The present study indicates that carvedilol is effective in attenuating the progression of chronic renal failure in rats.

Keywords: Chronic renal failure; carvedilol; α -adrenoceptor antagonist; β -adrenoceptor antagonist; vasodilator; angiotensin converting enzyme inhibitor; captopril

Introduction

Partial renal ablation in rats leads to progressive renal failure and is characterized by proteinuria, hypertension and glomerulosclerosis (Shimamura & Morrison, 1975). Control of hypertension both in experimental models of renal failure and patients with chronic renal disease can attenuate the progressive decline in renal function (Klahr, 1991). Reduction in blood pressure alone, however, may not be the sole reason why antihypertensive drugs are beneficial since some classes of antihypertensives have advantages over others. For example, angiotensin converting enzyme (ACE) inhibition appears to have a greater benefit than α_1 -adrenoceptor antagonists in human subjects with chronic renal disease (Rosenberg & Hostetter, 1991). It is possible that better control of glomerular hypertension and/or inhibition of the proliferative effects of angiotensin II by ACE inhibitors may be important factors in the possible advantage of this class of drugs over other antihypertensive agents. Carvedilol (SK&F 105517) is a novel multiple action drug that has recently been introduced to the market for the treatment of mild to moderate hypertension (see Ruffolo *et al.*, 1991 for review). Carvedilol is both a competitive β -adrenoceptor antagonist and an arterial vasodilator. At higher concentrations, carvedilol is also a calcium channel antagonist (Ruffolo *et al.*, 1991) and has antiproliferative effects on both vascular smooth muscle (Sung *et al.*, 1993) and mesangial (Albrightson *et al.*, 1992) cells. In the present study, therefore, we have

compared the effects of carvedilol and the angiotensin converting enzyme inhibitor, captopril, on the hypertension, proteinuria and glomerulosclerosis associated with partial renal ablation in rats.

Methods

Male Sprague-Dawley rats with initial body weights between 250 and 300 g were used. All rats were fed a powdered rodent chow (23.5% protein by weight; Ziegler Brothers, Inc., open formula, NIH-07). One week before and 1, 2, 4, and 6 weeks after partial renal ablation, rats were housed individually in metabolic cages for 48 h and urine collected for the second 24 h period. Food and fluid intakes and urine volume were measured over the second 24 h period and urinary protein excretion determined by the sulphosalicylic method (Davidsohn & Henry, 1969). Twenty-four hours before renal ablation, 14 rats were given powdered rodent chow containing 600 p.p.m. carvedilol (SK&F 105517) and 14 rats were given captopril in their drinking water (250 mg l^{-1}). A further 14 rats served as controls. Following baseline measurements (week 0) animals underwent 5/6 renal ablation. Under sodium pentobarbitone anaesthesia a midline incision was made, the right kidney was removed; and approximately 2/3 of the left kidney was infarcted by ligating 2 or 3 branches of the left renal artery. A small number of animals did not survive beyond the first week following surgery (control group, 2; carvedilol group, 3; captopril group, 1) and the data for these animals were not included in

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the study. All available data from animals who died subsequently (i.e., after week 1) were included. Ten control, 10 carvedilol-treated and 13 captopril-treated rats completed the study.

During the final week of study, blood samples from the tail vein of the carvedilol-treated rats were taken every 6 h for 24 h (09 h 00 min, 15 h 00 min, 21 h 00 min, 03 h 00 min) to determine serum carvedilol concentrations. Serum carvedilol concentration was determined by high performance liquid chromatographic methods as described in detail previously (Reiff, 1987). The lower limit of detection was 3 ng ml⁻¹ based on 0.1 ml of serum. The average between day coefficient of variation for this assay was 3.9%.

At the conclusion of the experiment, the animals were anaesthetized with Inactin (100 mg kg⁻¹, i.p.; Andrew Lockwood Associates, Sturdevant, WI, U.S.A.) and the femoral artery catheterized with Tygon tubing in order to measure mean arterial blood pressure and heart rate with a Satham transducer and Gilson recorder. This was performed during the morning (i.e., within approximately 6–12 h after feeding). A blood sample was taken for measurement of serum creatinine, serum urea nitrogen concentrations (Synchro AS8 clinical analyzer), plasma renin activity, and the kidneys removed for histological examination.

Plasma samples for the assay of renin activity were treated with EDTA and stored at -30°C. Plasma renin activity was determined with an angiotensin I (AI) radioimmunoassay kit (New England Nuclear, Boston, MA, U.S.A.): 0.5 ml plasma was used and angiotensin I generated for 2 h in pH 6 maleate buffer. Data are expressed as ng AI ml⁻¹ h⁻¹.

Kidneys were fixed in 10% buffered formalin. Transverse kidney slices were embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin-eosin. Kidneys were examined by light microscopy using coded slides and scored by a pathologist. A total of 75 to 100 glomeruli from each rat were scored from 0 to 4 based on the severity of glomerulosclerosis as follows (Nahas *et al.*, 1991); grade 0, normal glomerulus; grade 1, presence of mesangial expansion/thickening of the basement membrane; grade 2, mild/moderate segmental hyalinosis/sclerosis involving less than 50% of the glomerular tuft; grade 3, diffuse glomerular hyalinosis/sclerosis involving more than 50% of the tuft; grade 4, diffuse glomerulosclerosis with total tuft obliteration and collapse. Mean glomerular score was calculated for each rat. Glomerular scarring was also quantified by the assessment of the percentage of glomeruli displaying significant sclerosis (grade ≥ 2). A computer-assisted morphometric unit (Magiscan Image Analysis System, Vickers Plc., Dukesway, England) was used to measure the mean glomerular cross-sectional areas for 50 glomerular profiles contained in one kidney section in each rat. The mean volume (V_G) of glomeruli was then calculated from the mean glomerular area (A_G) as:

$$V_G = \beta/K \times A_G^{3/2}$$

where $\beta = 1.38$ is the size-distribution coefficient and $K = 1.1$ is the shape coefficient for glomeruli idealized as a sphere (Weibel, 1979; Hirose *et al.*, 1982).

The tubulointerstitium was examined for tubular dilatation, intratubular hyaline casts, tubular atrophy and regeneration, and interstitial infiltration with mononuclear cells and interstitial fibrosis. Tubulointerstitial change was graded on a scale of from 0 to 4 as follows: grade 0, a normal kidney; grade 1, minimal abnormalities affecting <10% of the renal parenchyma; grade 2, mild (10–25%); grade 3, moderate (25–50%); and grade 4, severe (> 50% of the kidney manifested tubulointerstitial abnormalities) (Trachtman *et al.*, 1992).

Data were expressed as mean ± s.e.mean and were compared statistically by analysis of variance for repeated measures and subsequently a Scheffe *F* test.

Carvedilol (SK&F 105517) was synthesized by Boehringer Mannheim, and captopril was purchased from Sigma.

Results

Partial renal ablation resulted in a progressive proteinuria in control rats with urinary protein excretion increasing from a baseline of approximately 9 mg day⁻¹ to 133 mg day⁻¹ at week 6 (Figure 1). Treatment with either carvedilol or captopril resulted in a significant blunting of proteinuria throughout the period of study such that by week 6, urinary protein excretion in the carvedilol- and captopril-treated groups was less than 50% of the control value (Figure 1).

Control animals grew at a slightly slower rate than animals receiving either carvedilol or captopril, but by week 6 there was little difference in body weight between that 3 groups. The slower growth of control animals during the first few weeks of the study may have been due to a smaller food intake in the control rats compared to the carvedilol- and captopril-treated rats during the first week following surgery. The food intake in the captopril- and carvedilol-treated animals tended to be higher than control animals during week 1. Fluid intake was variable throughout the study, increasing slightly over time in the control group. Measurement of food and fluid intakes permitted calculation of the carvedilol and captopril doses, respectively (Table 1). Thus, average doses of carvedilol and captopril over the time course of the experiment averaged approximately 70 and 38 mg kg⁻¹ day⁻¹ respectively. During the last week of study, the carvedilol dose (55 mg kg⁻¹ day⁻¹) was associated with mean serum carvedilol concentrations ranging between

Figure 1 Effect of vehicle (solid columns), carvedilol (600 p.p.m. in the food; hatched columns) or captopril (250 mg l⁻¹ in the drinking water; stippled columns) on the urinary protein excretion (UPROTV) of rats with partial renal ablation ($n = 10$ –13 rats/group). Data are mean ± s.e.mean. * $P < 0.05$ vs week 0; † $P < 0.05$ vs control.

Table 1 Calculated doses of carvedilol and captopril based on food (carvedilol concentration 600 p.p.m.) and fluid (captopril concentration 250 mg l⁻¹) intakes respectively

	Time (weeks)			
	1	2	4	6
Carvedilol (mg kg ⁻¹ day ⁻¹)	109 ± 31	62 ± 11	55 ± 8	55 ± 13
Captopril (mg kg ⁻¹ day ⁻¹)	43 ± 15	43 ± 3	39 ± 3	28 ± 15

Data are mean ± s.e.mean

$57 \pm 13 \text{ ng ml}^{-1}$ and $121 \pm 31 \text{ ng ml}^{-1}$ over a 24 h period. Although the serum concentrations of carvedilol were highly variable at each sampling time, all rats studied had measurable concentrations over the sampling period. This suggests that the rats had 24 h systemic exposure to carvedilol.

Renal function as assessed by serum creatinine and serum urinary nitrogen concentrations and measured during the final week of study was significantly improved in both carvedilol- and captopril-treated animals. Thus, the serum creatinine and serum urea nitrogen concentrations in carvedilol-treated animals were approximately half those observed in the control animals (Figure 2). Serum creatinine

Figure 2 Effect of vehicle (solid columns), carvedilol (hatched columns) or captopril (stippled columns) on the serum creatinine concentration (SCR; a), serum urea nitrogen concentration (SUN; b) and plasma renin activity (PRA; c) of rats 6 weeks following partial renal ablation ($n = 10-13$ rats/group). Data are mean $\pm$ s.e.mean. * $P < 0.05$ vs control.

and urea nitrogen concentrations in captopril-treated animals were similar to those observed in the carvedilol-treated animals (Figure 2). Plasma renin activity in carvedilol-treated animals was not significantly different from that observed in control animals, however, plasma renin activity was approximately 3 times higher in rats receiving captopril (Figure 2).

Mean arterial blood pressure was significantly lower in both the carvedilol- and captopril-treated animals when compared to control animals, as determined by direct measurement from an arterial catheter in inactin-anaesthetized rats. Heart rate in the captopril-treated animals was similar to that observed in control animals. Rats receiving carvedilol had a lower heart rate than those animals receiving captopril (Figure 3). However, the difference in heart rate between carvedilol-treated and control animals did not reach statistical significance. The small effect of carvedilol on heart rate was presumably due to its β -adrenoceptor blocking activity.

Histological examination of kidneys demonstrated lesions consisting of segmental to global glomerulosclerosis, with tubular regeneration, tubular dilatation with proteinaceous casts, and a lymphocytic interstitial infiltrate. The severity of glomerulosclerosis was considerably reduced in carvedilol- and captopril-treated rats (score 1.15 ± 0.14 and 0.93 ± 0.14 , respectively) compared to control rats (score 1.95 ± 0.30). Furthermore, a smaller percentage of glomeruli were sclerotic in carvedilol- and captopril-treated rats ($23\% \pm 8\%$ and $18\% \pm 7\%$, respectively) than in control rats ($55\% \pm 10\%$; Figure 4). Tubulointerstitial changes were characterized by tubular dilatation with hyaline casts, tubular atrophy and regeneration, and interstitial infiltration with mononuclear

Figure 3 Effect of vehicle (solid columns), carvedilol (hatched columns) or captopril (stippled columns) on mean arterial pressure (MAP; a) and heart rate (HR; b) of rats 6 weeks following partial renal ablation ($n = 10-13$ rats/group). Data are mean $\pm$ s.e.mean. * $P < 0.05$ vs control; # $P < 0.05$ vs captopril.

cells and interstitial fibrosis. The severity to tubulointerstitial changes was less in carvedilol- and captopril-treated rats (score 1.20 ± 0.36 and 0.77 ± 0.20 , respectively) than in control rats (score 2.6 ± 0.45). Morphometric studies showed that glomerular volume was decreased 33–35% in carvedilol-

or captopril-treated rats, compared to control rats. Glomerular volume averaged $1.62 \pm 0.13 \times 10^6 \mu\text{m}^3$ in carvedilol-treated rats and $1.55 \pm 0.10 \times 10^6 \mu\text{m}^3$ in captopril-treated rats; these values were significantly less ($P < 0.05$, *t* test) than mean glomerular volume of $2.4 \pm 0.28 \times 10^6 \mu\text{m}^3$ in control rats.

Discussion

In the present study we have demonstrated that carvedilol attenuated the hypertension, proteinuria and glomerulosclerosis associated with 5/6 renal ablation in rats. Furthermore, 6 weeks following partial renal ablation, rats receiving carvedilol had a significantly better renal function than control rats as demonstrated by lower concentrations of serum creatinine and urea nitrogen. These data are consistent with the 'renal sparing' activity of antihypertensive doses of carvedilol in spontaneously hypertensive rats (Gellai *et al.*, 1990) and the antiproteinuric effects observed in carvedilol-treated spontaneously hypertensive rats that had undergone 3/5 nephrectomy and had a high salt diet (Nakamoto *et al.*, 1988).

The protective effects of carvedilol in partially nephrectomized rats appear to be greater than those reported for propranolol (Radin *et al.*, 1987) and are noteworthy since pure β -adrenoceptor antagonists may exacerbate renal dysfunction in hypertensive patients (Ibsen & Sederberg-Olsen, 1973; Warren, 1976; Weber & Drayer, 1980). Thus, improved renal function and reduced proteinuria observed in the present study suggests that multiple actions of carvedilol are responsible for the reno-protective effects of this drug. Carvedilol did not appear to provide any protection by inhibition of renin production since the plasma renin activity of carvedilol-treated and control animals was similar. The increased plasma renin activity observed in the captopril-treated animals was expected and was presumably due to removal of the negative feedback effects of angiotensin II on renin secretion.

The beneficial effects of carvedilol were comparable to those observed with the ACE inhibitor, captopril, which has been reported to delay the progression of renal failure in rats (Hall *et al.*, 1985). Furthermore, ACE inhibitors have been shown to provide a greater benefit than α -adrenoceptor antagonists in human patients with chronic renal disease (Rosenberg & Hostetter, 1991), suggesting that additional effects of carvedilol beyond β -adrenoceptor and α_1 -adrenoceptor blockade contribute to the protective effects observed in the present study.

There is some debate as to the mechanisms involved in the progression of chronic renal failure. Some investigators (e.g. Brenner, 1985) suggest that following 5/6 renal ablation, adaptive processes that lead to increased glomerular capillary pressure, single nephron glomerular filtration rate and single nephron blood flow lead to further nephron damage, thus setting up an inexorable vicious cycle, culminating eventually in end-stage renal failure. Lowering glomerular capillary pressure should reduce glomerular injury and slow the progression of the disease. Angiotensin II is thought to mediate the glomerular hypertension associated with partial nephrectomy. Thus, converting enzyme inhibition may reduce glomerular hypertension and hyperfiltration by preventing the intraglomerular vascular actions of angiotensin II (Anderson *et al.*, 1985; Brenner, 1985). Other investigators have suggested that factors other than glomerular hypertension are important for the progression of chronic renal failure. Thus, glomerular hypertrophy rather than glomerular hypertension has been suggested to be important in the disease process (Yoshida *et al.*, 1988a,b). The protective effect of converting enzyme inhibition might therefore be due to inhibition of angiotensin II-induced mitogenic activity. It is interesting, therefore, that carvedilol, in addition to its antihypertensive activities, also possesses anti-proliferative

Figure 4 Glomerular lesions. (a) Characteristic glomerular lesion from an ablation control rat, exhibiting diffuse glomerular hyalinosis/sclerosis (arrowheads) involving more than 50% of the tuft (grade 3). (b) In comparison, the majority of glomeruli from carvedilol-treated rats had only mesangial expansion and thickening of the basement membrane (grade 1). Glomeruli from captopril-treated rats (c) were similar to carvedilol-treated rats (H&E; calibration bar = 26 μm).

properties. Thus, in mesangial cells, carvedilol (10^{-7} – 10^{-5} M) caused a concentration-dependent inhibition of both EGF and thrombin-induced [3 H]-thymidine incorporation, and carvedilol was more potent than either propranolol or celiprolol (Albrightson *et al.*, 1992). Carvedilol has also been shown to produce a dose-dependent (0.1 – 10 μ M) decrease in basal or stimulated tritiated thymidine incorporation into rat aortic smooth muscle cells in culture (Sung *et al.*, 1993). These antiproliferative actions of carvedilol were not shared by other β -blockers such as propranolol, labetalol or sotalol, while celiprolol augmented thymidine incorporation into vascular smooth muscle cells. The IC_{50} of carvedilol for inhibition of endothelin-1-stimulated vascular smooth muscle cell proliferation was 1 μ M which is not markedly greater than the serum concentration generated in the present study (120 ng ml $^{-1}$ ~ 0.3 μ M). This does not, however, take into account any protein binding, which in the rat is $>95\%$, tissue accumulation or the presence of an active metabolite. It is interesting to note, however, that there is growing evidence that renal endothelin production is increased in rats with partial renal ablation-induced chronic renal failure (Brooks *et al.*, 1991; Benigni *et al.*, 1991).

In this study, the protective effects of carvedilol on glomerulosclerosis and glomerular hypertrophy were comparable to those observed with captopril. Several studies have demonstrated that ACE inhibitors afford protection from glomerulosclerosis in the ablation model in association with a decrease in glomerular volume (Yoshida *et al.*, 1988a,b). Glomerular enlargement is considered to be a crucial factor in the pathogenesis of progressive glomerulosclerosis following renal ablation or initial loss of functioning nephrons from other causes in animals and man (Fries *et al.*, 1989; Fogo & Ichikawa, 1991). However, it is unknown whether this

enlargement is independent from glomerular hypertension (Lafferty & Brenner, 1990).

Carvedilol also possesses other properties including calcium channel blockade (>1 μ M; Ruffolo *et al.*, 1991) and antioxidant activity leading to inhibition of lipid peroxidation ($IC_{50} > 5$ μ M; Yue & Feuerstein, 1992). Any speculation as to the contribution of these actions to the renal protection observed in the present study would be premature. Certainly, data in normotensive animals would indicate that the primary pharmacological effects of carvedilol reside in its β -blocking and vasodilator properties (Ruffolo *et al.*, 1991). Whether it is merely adequate control of hypertension by carvedilol that provides the beneficial effects in chronic renal failure is not clear. Given the complexity of the mechanisms involved in the development of chronic renal failure (see above) this question remains to be answered. Certainly, the data of Anderson *et al.* (1985) indicate that it is control of glomerular rather than systemic hypertension that is of prime importance, and studies on the effects of carvedilol on glomerular haemodynamics might provide some more insight.

In summary, carvedilol, a novel multiple action drug that is currently being used for the treatment of mild to moderate hypertension and is in clinical trials for utility in angina and congestive heart failure, may also demonstrate utility in chronic renal failure. Our observation that carvedilol has similar effectiveness as the converting enzyme, captopril, in reducing the hypertension, proteinuria and glomerulosclerosis associated with 5/6 nephrectomy in rats portends chronic renal disease as a therapeutic target for this drug.

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