Eur J Clin Pharmacol (1992) 43: 85–88

European Journal of Clinical Pharmacology

Pharmacokinetic and blood pressure effects of carvedilol in patients with chronic renal failure

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Received: July 12, 1991/ Accepted in revised form: January 6, 1992

Summary. The pharmacokinetic and acute systemic haemodynamic effects of a single oral dose of 50 mg carvedilol has been studied in 24 hypertensive patients with chronic renal failure. The patients were stratified into 3 groups according to the creatinine clearance: I 51–90 ml · min^{-1}; II 26–50 ml · min^{-1}; III 4–25 ml · min^{-1}.

The area under plasma level time curve AUC, the elimination half-life $t^1/_2$, the maximum plasma concentration C_{max}, the time to peak concentration t_{max} were not significantly different between groups, whereas the amount of unchanged drug or metabolite excreted in urine A_e and the renal clearance CL_R of carvedilol and its metabolites M2, M4, M5 were significantly decreased in Group III. Blood pressure and heart rate decreased in all 3 groups of patients after acute administration of 50 mg carvedilol. Mild adverse effects were reported in 6 patients. Despite a decrease in the renal clearance of carvedilol and of its metabolites with decreasing kidney function, its main pharmacokinetic parameters remained unchanged. The present results suggest that the dose of carvedilol need not be reduced in hypertensive patients with chronic renal failure.

Key words: Hypertension, Carvedilol; chronic renal failure, pharmacokinetics, adverse effects

Carvedilol is a non-selective β-adrenoceptor blocking drug with vasodilating activity primarily due to α_1-adrenoceptor blocking properties, and to a minor extent to calcium channel blocking activity (little or no contribution to the antihypertensive effect) at a high concentration [1]. The total clearance of carvedilol is 590 ml · min^{-1}, its renal clearance is 4 ml · min^{-1}, and the distribution volume is 132 l [6, 7]. The absolute bioavailability of carvedilol has been estimated to be 24 %, indicating some degree of first pass extraction, and the protein binding is 95 % [6, 7].

Carvedilol has been shown to be effective in the treatment of patients with essential and renal hypertension, and angina pectoris [2–5]. Extensive pharmacokinetic studies of carvedilol have been done in healthy volunteers, in hypertensive patients and in patients with liver cirrhosis, but its pharmacokinetics in hypertensive patients with chronic renal failure has only been reported in a preliminary paper [6–12]. In addition, little information is available in the literature about the pharmacokinetics of the metabolites of carvedilol in hypertensive patients with chronic renal failure [12]. Pharmacological activity is attributed only to carvedilol metabolites M2, M4 and M5 (Sponer, unpublished). The chemical structures of carvedilol and its metabolites are displayed in Fig. 1.

The pharmacokinetics and effects of acute oral administration of 50 mg carvedilol in hypertensive patients with chronic renal failure of differing severity have now been investigated.

Patients and methods

Twenty-five hypertensive in-patients with chronic renal failure were enrolled in an open multicentre trial to study the pharmacokinetics and blood pressure effects of acute oral administration of a 50 mg capsule of carvedilol, after an overnight fast.

Carvedilol capsules were supplied by Boehringer Mannheim and were taken with 100 ml water, but with no concomitant medication. Patients were allowed food and drink after 3 h. One patient was withdrawn from the study due to non-compliance. The study protocol was approved by the local Ethics Committee. All patients gave their informed consent to the study. A diastolic blood pressure $\geq$ 95 mm Hg and $\leq$ 115 mm Hg (measured 3-times on at least 2 occasions, in the sitting position, after a 10 min rest) was taken as the inclusion criterion.

The patients were stratified into 3 groups according to their creatinine clearance: Group I 51–90 ml/min; Group II 26–50 ml/min; Group III 4–25 ml/min. Plasma and urine levels of carvedilol and metabolites M2, M4, M5 were measured for 72 h after dosing by HPLC with fluorometric detection [13]. Systolic (SBP) and diastolic blood pressure (DBP, Korotkoff Phase V sounds) were measured with a sphygmomanometer for 72 h after dosing. Patients were asked to remain supine during the first 6 h after the administration of 50 mg carvedilol, so only supine SBP and DBP are available for that period. After the first 6 h following intake of carvedilol standing blood pressure (data not shown) was measured, too. Supine blood pressure was measured after resting supine for at least 15 min.

Some characteristics of the patients are given in Table 1. The causes of renal failure were chronic glomerulonephritis (n = 5),

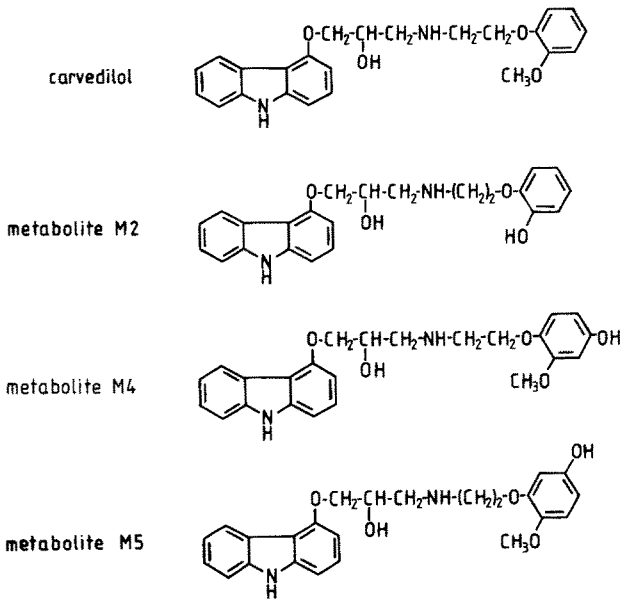

Fig. 1. Chemical structure of carvedilol and the carvedilol metabolites M2, M4, and M5

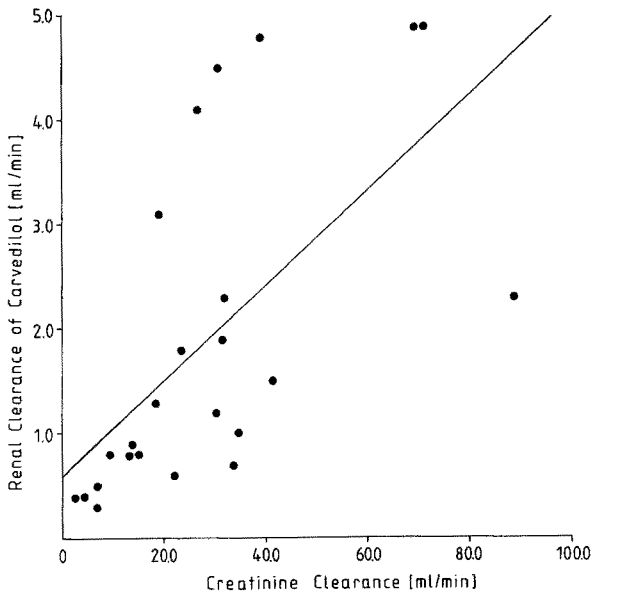

Fig. 2. Renal clearance of carvedilol and creatinine clearance of individual patients (n = 24). The correlation between both variables is characterized by a regression line y = 0.046 × + 0.602, r = 0.628, $p < 0.001$, n = 24

chronic pyelonephritis (n = 5), diabetes mellitus (n = 4), hypertensive nephropathy (n = 2), polycystic kidney disease (n = 2), renal agenesis (n = 1), membranoproliferative glomerulonephritis (n = 1), obstructive nephropathy (n = 1), and unknown (n = 3). The patients had been hypertensive for 9.2 (7.5) (1–28) y. Concomitant medication was nifedipine (n = 17), nitrendipine (n = 3), metoprolol (n = 8), betaxolol (n = 2), propranolol (n = 1), captopril (n = 1), enalapril (n = 1), urapidil (n = 1), prazosin (n = 1), minoxidil (n = 1), clonidine (n = 4), dihydralazine (n = 1), furosemide (n = 11), piretanide (n = 1), prednisolone (n = 1), melphalan (n = 1), phenytoin (n = 1), acetylsalicylic acid (n = 1), levothyroxine (n = 1), digitoxin (n = 2), allopurinol (n = 4), pentoxifylline (n = 1), ranitidine (n = 1), pirenzipine (n = 1), methyldopa (n = 1), bromazepam (n = 1), oxazepam (n = 1), vitamin D_3 derivatives (n = 2). No patient had clinical or laboratory signs of hepatic failure.

Non-compartimental kinetic analysis was done. Calculated pharmacokinetic parameters were maximum plasma concentration C_{max}, time to peak concentration t_{max}, terminal elimination half-life $t^1/_2$, area under the plasma level-time curve extrapolated to infinity AUC, area under the plasma level-time curve from time 0 to end of experiment AUC, amount of unchanged drug or metabolite excreted in urine in the time interval A_e, and renal clearance CL_R. Before and 72 h after drug intake an ECG was recorded and safety laboratory tests (WBC, RBC, serum creatinine, uric acid, potassium, sodium, glucose, total proteins, SGOT, SGPT, alkaline phosphatase, prothrombin time, bilirubin, cholesterol, triglycerides) were done by routine laboratory methods.

Statistical evaluation was done by means of the Mann-Whitney "U"-test between Groups II and III only, because the very small number of patients in Group I did not permit statistical analysis. Data are given as median and range for pharmacokinetic parameters, and as mean with (SD) for the remaining parameters.

Results

The pharmacokinetic parameters of carvedilol and of the metabolites M2, M4, and M5 are listed in Table 2. AUC, AUC, C_{max}, $t^1/_2$, t_{max} did not differ between the groups, whereas the A_e and CL_R of carvedilol and of the three metabolites were significantly lower in Group III than in Group II ($P < 0.05$; Table 2). The lower renal clearance of carvedilol and its metabolites in Group III was not due to the lower urine flow (urine volume 2296 (919) ml · 24 h^{-1} (Group II) or 2078 (858) ml · 24 h^{-1} (Group III). A significant positive correlation between the renal clearance of carvedilol and its creatinine clearance is displayed in Fig. 2, but no correlation between AUC (n = 22) or AUC(0–72 h) (n = 24) of carvedilol and creatinine clearance could be demonstrated. Both patients with the lowest AUC(0–72 h) values (25 or 126 ng · h · ml^{-1}, respectively), and only those two, were taking vitamin D_3 derivatives as concomitant medication. Blood pressure and heart rate were decreased in all 3 groups of patients after acute administration of 50 mg carvedilol (Table 3).

ECG as well as safety laboratory tests were unchanged before and after 72 h after administration of 50 mg carvedilol; serum creatinine [mg · dl^{-1}]; Group I 1.33 (0.49) vs 1.40 (0.26), Group II 2.40 (0.76) vs 2.30 (0.85), Group III 5.99 (2.88) vs 6.39 (3.57); bilirubin [mg · dl^{-1}]: I 0.7 (0.2) vs 0.7 (0.2), II 0.7 (0.4) vs 0.6 (0.5), III 0.4 (0.2) vs 0.4 (0.2); total protein [g · dl^{-1}] I 6.8 (1.0) vs 6.6 (1.0), II 6.6 (0.9) vs 6.3 (0.9), III 6.6 (0.5) vs 6.6 (1.0); prothrombin time [%] I 101 (2) vs 101 (2), II 100 (26) vs 103 (12), III 93 (12) vs 93 (11); GOT [U · l^{-1}] I 10 (3) vs 9 (3), II 8 (2) vs 6 (2), III 9 (4) vs 9 (4); GPT [U · l^{-1}] I 18 (10) vs 17 (11), II 8 (4) vs 8 (5), III 8 (5) vs 8 (4); gamma-GT [U · l^{-1}] I 34 (34) vs 20 (12), II 29 (31) vs 29 (35), III 27 (20) vs 25 (8).

Adverse effect were reported in 6 patients (headache n = 1; *dizziness* n = 2 accompanied in one patient by

Table 1. Patient characteristics

Patient group	I	II	III
Number	3	9	12
Age (y)	42 (15)	51 (13)	51 (15)
Sex f/m	1/2	4/5	5/7
Body weight [kg]	67 (18)	71 (12)	69 (11)
Height [cm]	172 (12)	169 (11)	169 (9)

Table 2. Pharmacokinetic parameters (median and (range)) after a single oral dose of 50 mg carvedilol in hypertensive patients with chronic renal failure

Patient group	I $n = 3$	II $n = 9$	III $n = 12$
carvedilol			
AUC [ng·h·ml^{-1}]	1320 (1220–1900)	1110 (646–2950)[a]	1060 (140–1816)[b]
AUC(0–72 h) [ng·h·ml^{-1}]	1260 (1170–1850)	939 (25–2920)	946 (126–1780)
C_{max} [ng·ml^{-1}]	318 (291–356)	180 (5–579)	174 (23–275)
t_{max} [h]	0.5 (0.5–3.0)	1.0 (0.5–2.0)	1.3 (0.5–4.0)
$t^1/_2$ [h]	21.9 (18.0–27.2)	12.8 (6.0–34.9)[a]	13.4 (4.7–30.3)[b]
A_e(0–48 h) [%]	0.7 (0.5–0.7)	0.2 (0.0–0.8)	0.1 (0.0–0.3)*
CL_R [ml·min^{-1}]	4.9 (2.3–4.9)	1.9 (0.7–4.8)	0.8 (0.3–3.1)*
metabolite M2			
AUC(0–72 h) [ng·h·ml^{-1}]	77 (47–144)	57 (28–157)[a]	62 (17–145)
C_{max} [ng·ml^{-1}]	18 (11–19)	13 (4–20)[a]	11 (4–25)
t_{max} [h]	1.5 (1.0–3.0)	1.5 (1.0–2.0)[a]	1.5 (1.0–4.0)
A_e(0–48 h) [%]	0.07 (0.06–0.08)	0.01 (0.00–0.08)	0.00 (0.00–0.01)*
CL_R [ml·min^{-1}]	7.7 (4.6–10.2)	1.8 (0.2–5.4)[a]	0.1 (0.0–0.7)*
metabolite M4			
AUC(0–72 h) [ng·h·ml^{-1}]	64 (39–82)	62 (24–129)[a]	54 (14–128)
C_{max} [ng·ml^{-1}]	15 (9–21)	12 (8–51)[a]	14 (4–26)
t_{max} [h]	1.0 (0.5–2.5)	1.3 (0.5–2.0)[a]	1.3 (0.5–4.0)
A_e(0–48 h) [%]	0.13 (0.10–0.14)	0.03 (0.00–0.12)	0.01 (0.00–0.03)*[c]
CL_R [ml·min^{-1}]	17.0 (16.9–20.6)	3.5 (1.7–18.8)[a]	1.3 (0.5–3.4)*[c]
metabolite M5			
AUC(0–72 h) [ng·h·ml^{-1}]	53 (47–89)	30 (16–123)[a]	32 (6–70)
C_{max} [ng·ml^{-1}]	14 (13–17)	10 (5–25)[a]	10 (3–18)
t_{max} [h]	1.0 (1.0–2.5)	1.3 (1.0–2.0)[a]	1.3 (0.5–4.0)
A_e(0–48 h) [%]	0.10 (0.08–0.17)	0.02 (0.00–0.17)	0.00 (0.00–0.02)*[b]
CL_R [ml·min^{-1}]	15.6 (14.9–16.1)	6.3 (1.8–15.7)[a]	0.9 (0.2–3.2)*[b]

* $P < 0.05$, [a] $n = 8$, [b] $n = 11$, [c] $n = 10$

nausea; thrombocytopenia, anaemia, leucopenia, small-spotted generalized exanthem $n = 1$; uric acid increase $n = 1$; triglyceride increase $n = 1$), none was classified as serious. Using a causality assessment algorithm for adverse events, dizziness, nausea, headache, and increase of triglycerides were thought to be related to carvedilol intake, whereas the other reported events seemed to be unrelated (e.g. the leukopenia, thrombocytopenia, anaemia in one patient was due to pretreatment with melphalan and prednisolone and the small-spotted generalized exanthema in the same patient was probably due to pretreatment with ranitidine hydrochloride or concomitant treatment with allopurinol).

Discussion

After oral administration of 50 mg carvedilol to hypertensive patients with chronic renal failure, renal clearance CL_R and the percentage renal excretion of carvedilol and metabolites M2, M4, M5 were significantly reduced in the patient group with the most severe impairment of kidney function. However, the main pharmacokinetic parameters AUC, AUC(0–72 h), $t^1/_2$, c_{max}, t_{max} both for carvedilol and metabolites were not different between the patient groups. Because of the present results and the known small amount of carvedilol and metabolites excreted via the kidneys [6, 7], and see [12], a reduction in the dose of carvedilol is not thought to be necessary in hypertensive patients with chronic renal failure.

Hakusui & Fujimaki [12] investigated the pharmacokinetic effect of 5 to 10 or 20 mg carvedilol in 9 patients with varying stages of renal failure; very little information about pharmacokinetic parameters was provided. Plasma levels of carvedilol and desmethylcarvedilol (metabolite M2) did not differ significantly between patients with impaired and normal renal function [12]. In contrast to the present results, Hakusui & Fujimaki [12] did not find a decrease in the amount of unchanged carvedilol excreted in the urine in patients with chronic renal failure. This is probably explained by the fact that they did not analyze subgroups of the patients; in addition, comparison with our results is hampered because it appears that 5 mg carvedilol was used in that part of their study. The possible accumulation of carvedilol or metabolites during long-term administration, although highly improbable, should be investigated in further studies. AUC and terminal half-life assessed here were in the same range as reported in healthy volunteers and hypertensive patients; AUC 717 (270) ng·h·ml^{-1} [8], 1097 (761) or 1136 (810) ng·h·ml^{-1} [9], 1073 (202) or 1595 (324) ng·h·ml^{-1} [10]; terminal half-life $t^1/_2$ 14.6 (4.0) h [8], 7.0 (1.9) or 7.6 (3.9) h [9]; Morgan et al. [10] reported a half-life of 5.0 (1.2) or 5.3 (0.7) h, but it is not clear from their paper whether that half-life represents the terminal half-life. The age distribution in the above studies was 61 (6) y [8], 45 (10) y [9], and < 50 y (patient Group 1) or 65–80 y (patient Group 2) [11]. In contrast to the above results, one study reported an AUC of 348 ng·ml·h^{-1} (170–611) and a terminal half-life of 6.4 h

Table 3. Supine systolic (SBP), diastolic blood pressure (DBP), and heart rate (HR) before and 0.5 h, 1 h, 3 h, 6 h, 12 h, and 24 h after a single oral dose of 50 mg carvedilol

		Before	0.5 h	1 h	3 h	6 h	12 h
Group I							
SBP [mm Hg]	155 (13)	137 (6)	130 (10)	127 (23)	135 (9)	140 (26)	153 (25)
DBP [mm Hg]	95 (5)	87 (6)	85 (5)	82 (8)	87 (6)	82 (8)	97 (13)
HR [beats/min]	83 (10)	77 (12)	73 (12)	73 (15)	80 (12)	73 (12)	68 (12)
Group II							
SBP [mm Hg]	170 (26)	152 (22)	143 (25)	134 (25)	138 (23)	148 (23)	156 (24)
DBP [mm Hg]	98 (21)	88 (15)	81 (18)	76 (15)	78 (18)	84 (13)	86 (15)
HR [beats/min]	72 (9)	65 (7)	62 (8)	61 (9)	64 (6)	72 (9)	67 (9)
Group III							
SBP [mm Hg]	177 (26)	163 (24)	150 (27)	144 (29)	140 (27)	159 (28)	163 (37)
DBP [mm Hg]	102 (8)	91 (11)	86 (15)	84 (16)	81 (16)	89 (14)	91 (20)
HR [beats/min]	82 (9)	80 (10)	75 (7)	75 (5)	79 (8)	78 (6)	76 (9)

(4.1–14.6) in 20 healthy male volunteers [6, 7, 11]. However the mean age was 26 (6) y and the healthy controls were of over-average size (height 180 (10) cm; weight 77 (9) kg; body surface 1.96 (0.15) m^2) [6, 7, 11]. Therefore those findings cannot confidently be compared with the above studies [8–10], or with the present investigation. In addition, the results of Morgan et al. [10] appear to suggest that AUC may increase with age. In another study Neugebauer et al. [14] demonstrated an AUC of 292 $ng \cdot h \cdot ml^{-1}$ after oral administration of 50 mg carvedilol to 10 young (mean age 29.5 y) male subjects, confirming their previous results [6, 7, 11].

In accordance with these results, the effects of oral administration of 50 mg carvedilol on blood pressure and heart rate in patients with chronic renal failure seem to be comparable to those in essential hypertensive patients [2–4]. Since a low AUC of carvedilol and concomitant intake of vitamin D_3 derivatives appeared to be associated, the possible interaction of the two drugs should be examined in a further study.

The rate of adverse effects in the present study was low and none was classified as serious, although a rather high dose of carvedilol had been administered.

In conclusion, the main pharmacokinetic parameters after a single oral dose of 50 mg carvedilol did not differ between patients with different degrees of renal failure, despite a decrease in the renal clearance of carvedilol and its metabolites M2, M4, and M5.

Acknowledgements. We thank Dr. K. Reiff, Boehringer Mannheim, for performing the HPLC analysis of carvedilol and metabolites, and Dr. B. Kaufmann, Boehringer Mannheim, for calculating pharmacokinetic parameters. We are indebted to Dr. M. Bihlmaier (Department of Medicine I, University of Ulm), to Dr. C. Piper (Department of Medicine A, Wiesbaden), and to Dr. N. Spannbrucker (Department of Nephrology, University of Bonn) for participating in the present multicentre study. We thank Dr. L. Widmann and Dr. G. Neugebauer, both from Boehringer Mannheim, for helpful discussions in the preparation of the manuscript.

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