Pharmacokinetics and haemodynamics of candesartan cilexetil in hypertensive patients on regular haemodialysis

Marc Pfister, Franziska Schaedeli, Felix J. Frey & Dominik E. Uehlinger

Division of Nephrology, Department of Medicine, University of Berne, Switzerland

Aims The pharmacokinetic profile of candesartan cilexetil might be altered in patients with end-stage renal disease (ESRD). No data are available about the pharmacokinetics and haemodynamics of the angiotensin II receptor antagonist candesartan cilexetil in ESRD patients on regular haemodialysis (HD).

Methods We performed a repeated dose study (8 mg candesartan cilexetil once daily) in eight male HD patients over a treatment period of 5 days with an additional observation period of 3 days.

Results Pharmacokinetic analysis with nonlinear mixed effects modeling (NONMEM) over the whole treatment period revealed a dependency of the volume of distribution on body weight and of the metabolic clearance on age and body weight in the studied population. No significant drug elimination by HD was observed. The estimated metabolic and intercompartmental clearances were 83 ml min^{-1} (CV 39%) and 9.9 ml min^{-1}, respectively. The unexplained random variability of the final two compartment model was 30%. In one patient with adult polycystic kidney disease oral clearance decreased during the observation period, attributable to a significant increase in bioavailability. Maximum observed changes in blood pressure were $-50/-27 \pm 14/8$ mmHg on day 5 with haemodialysis therapy as compared with changes in blood pressure of $-14/-12 \pm 14/8$ mmHg on day 1 without haemodialysis treatment. The observed maximum decrease in systolic blood pressure correlated with the amount of ultrafiltration during the HD session on day 5 ($r=0.70$, $P<0.05$). In two patients, one of whom was binephrectomized, severe hypotensive episodes were observed during this HD session.

Conclusions HD does not influence the elimination kinetics of candesartan. The observed inter- and intraindividual variability of oral clearance and the pronounced influence of HD-induced volume contraction on the haemodynamic effects of candesartan makes it mandatory to carefully monitor HD patients treated with candesartan cilexetil.

Keywords: candesartan cilexetil, hypertension, haemodialysis, NONMEM

Introduction

Angiotensin II receptor antagonists have recently been introduced as a new therapeutic class for the treatment of arterial hypertension. Candesartan, one of the currently available angiotensin II receptor antagonists, is a benzimidazole carboxylic acid derivative with a long-lasting antagonism of the angiotensin II type I receptor. Since candesartan itself is poorly absorbed after oral administration the ester prodrug candesartan cilexetil [(±)-1-(cyclohexyloxycarbonyloxy)-ethyl-2-ethoxy-1-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]-1H-benzimidazole-7-carboxylate] was synthesised [1, 2]. This prodrug is rapidly and completely converted to the active compound candesartan during gastrointestinal absorption [3–5]. In healthy subjects 67% of an oral dose of candesartan is excreted in faeces [6] and only about 5% to 10% of the administered dose is excreted unchanged in the urine in 24 h [7, 8]. Studies with candesartan cilexetil in healthy volunteers and patients with hypertension have shown a significant and long lasting decrease of systolic and diastolic blood pressure [7, 9–11]. Despite compensatory increase in plasma renin activity and plasma angiotensin II levels, the relationship between the time-

Correspondence: Dominik E. Uehlinger, M.D., Division of Nephrology, Department of Medicine, University of Berne, Freiburgstrasse 3, 3010 Bern, Switzerland.

Received 5 August 1998, accepted 27 January 1999.

integrated systolic blood pressure response to angiotensin II and the time-integrated levels of candesartan is consistent [12].

The pharmacokinetic profile of candesartan cilexetil might be altered in patients with end-stage renal disease (ESRD). No data are available about the pharmacokinetics of candesartan cilexetil in haemodialysis patients with arterial hypertension. Therefore, the first objective of this study was to characterise and compare the single and multiple dose pharmacokinetics of candesartan following the administration of the prodrug candesartan cilexetil in haemodialysis patients. Since the renin angiotensin system is activated in patients with ESRD during haemodialysis, the antihypertensive effect of candesartan might differ from that observed in patients without ESRD. Hence, the second objective of the present study was to assess the effect of candesartan cilexetil on haemodynamic parameters as well as the general tolerability of this angiotensin II receptor antagonist in hypertensive patients on regular haemodialysis.

Methods

Patients and study design

Eight male haemodialysis patients (mean age 53 years, range 38 to 75 years) were enrolled in this open labeled, repeated dose study. The patients were suffering from the following underlying renal diseases: chronic glomerulonpehritis (4), adult polycystic kidney disease (2), diabetic nephropathy (1) and reflux nephropathy (binephrectomized patient) (1). Four patients were anuric and four patients had a minimal residual renal function with a creatinine clearance in the range of 2 to 5 ml min^{-1}. All patients had been on a regular dialysis scheme of three dialyses per week for at least 3 months prior to the study. They all had arterial hypertension (mean diastolic blood pressure between 90 mmHg and 110 mmHg measured on two occasions during a 3 day wash-out period prior to the first candesartan administration). All patients gave their written informed consent to participate in the study. The study was approved by the Ethics Committee of the University of Berne, Switzerland.

Any of the following conditions excluded a patient from the study: infection of the dialysis shunt, malignant hypertension, unstable non-controlled diabetes, severe cardiac disease (congestive heart failure NYHA III and IV), valvular stenosis and/or a history of myocardial infarction. The following drugs were not allowed as concomitant medications during the study: drugs causing systemic vasodilation or vasoconstriction such as theophylline, papaverine, tricyclic antidepressants, neuroleptics or sympathomimetic nasal drugs, antiarrhythmic drugs with the exception of digoxin, non-steroidal anti-inflammatory drugs with the exception of aspirin, steroids as well as immunosuppressive or cytotoxic drugs.

The study consisted of 3 consecutive periods: (1) a wash-out period of at least 3 days when all antihypertensive drugs were discontinued, (2) a treatment period of 5 days when each patient received 8 mg candesartan cilexetil every morning after an overnight fast and (3) an additional observation period of 3 days, including a post-study check on day 8.

Blood samples for the determination of serum concentrations of candesartan were drawn on study days 1 to 5 immediately before drug administration. Additional blood sampling for pharmacokinetic analyses was performed at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 12 h after drug intake on days 1 and 5. During the observation period (days 6 to 8) samples were drawn at 24, 48 and 72 h after the last drug administration.

Haemodialysis procedures were performed on days 2 or 3 and on days 5 and 7. Haemodialysis machines were calibrated to an exact blood flow at 300, 350 and 400 ml min^{-1} and to a dialysate flow of 500 ml min^{-1} prior to the study. Blood and dialysate flow rates were controlled for stability at the end of the study. Polysulfone hollow-fiber dialysis filter (F8, Fresenius, Germany) were used for all haemodialysis sessions. Dialysis treatment times ranged from 3 to 4 h. Dialysate was collected by sampling from the dialysate line immediately after the haemodialysis filter at 0.5, 1 and 2 h after initiation of haemodialysis and at the end of the haemodialysis session. Furthermore, the total ultrafiltrate of each dialysis session was collected at the outlet of the ultrafiltration pump. Since ultrafiltration of the machine was volumetrically controlled and all patients were on a constant ultrafiltration rate throughout the dialysis session, the collection of all ultrafiltrate provides a representative sample of the total amount of candesartan removed during the dialysis session [13].

Haemodynamic and tolerability parameters

At each study day three consecutive blood pressure and heart rate measurements at 2 min intervals were performed in the sitting position after a rest of at least 10 min. The arithmetic mean of the second and third measurement was recorded. During the wash-out period a standard sphygmomanometer was used for blood pressure measurements. During the treatment period and during the following observation period blood pressure was recorded with an automatic device (Dinamap 9302 XL Monitor, Johnson & Johnson Medical, Norderstedt, Germany).

Tolerability parameters obtained before and after treatment with candesartan cilexetil included electrocardiogram, whole blood count, serum electrolytes, creatinine, albumin, liver enzymes, plasma protein, blood urea

nitrogen (BUN), urine analyses as well as a complete physical examination.

Analytical procedures

Blood samples for the measurement of serum candesartan concentrations were collected into polypropylene tubes without an anticoagulant and were centrifuged within 30 min. Additional blood samples for the determination of protein binding of candesartan were collected into polypropylene tubes with Li-heparin as an anticoagulant before haemodialysis, at 0.5, 1 and 2 h after initiation of haemodialysis, as well as at the end of the haemodialysis session on day 5. All serum and dialysate samples were stored at -20° C until further analysis. Serum and dialysate concentrations of candesartan were measured in all eight study patients by high performance liquid chromatography (h.p.l.c.) at Bio-Research Laboratories B.V. (Zuidlaren, the Netherlands). In addition, the inactive metabolite CV-15959 were measured in three out of the eight study patients by the same method (h.p.l.c.). Protein binding was determined by equilibrium dialysis technique with ^{14}C-labeled candesartan. Laboratory safety tests were performed at the laboratory of the Inselspital, University of Berne, Switzerland using standard methods.

Pharmacokinetics and data analysis

Individual dialysis clearances of candesartan and of the inactive metabolite CV-15959 were estimated from the total amount of drug recovered in the dialysate [14] as well as from the serum extraction rate [14, 15], calculated from the serum concentration measured at the dialyzer inlet and at the dialyzer outlet (see Appendix). A two–compartment model was used to describe the disposition of candesartan. With only oral data available, bioavailability was assumed to be 1 and therefore estimated clearances of candesartan correspond to oral clearances. The pharmacokinetic models describing drug disposition over the whole observation period of 8 days were calculated with the computer program NONMEM (nonlinear mixed effects modelling, NONMEM Project Group, University of California at San Francisco) [16, 17] on a DEC Alpha 3000-400 computer running Digital Unix Version 4.0b. Proportional errors were used for all models. Expanded models were selected over reduced models by using the likelihood ratio test, referred to a chi-square distribution, with the degrees of freedom corresponding to the number of fixed parameters in the reduced model [18]. Models with the same number of free (modelled) parameters were discriminated by choosing the model with the better fit [18]. Descriptive statistical analyses were performed with the software package SYSTAT (Systat 6.01, SSPS Inc., Evanston, USA). Data are given as mean values standard deviation (s.d.).

Results

Haemodynamic effects

A baseline blood pressure of $155/93 \pm 39/16$ mmHg was measured immediately before starting candesartan administration. Blood pressure was unchanged 24 h after the administration of the first dose of candesartan ($151/91 \pm 24/14$ mmHg) but decreased to $140/89 \pm 26/10$ mmHg ($P<0.05$) 24 h after the final fifth dose of candesartan. Corresponding measurements of heart rate were 77 ± 13 beats min^{-1} at baseline, 84 ± 13 beats min^{-1} after the first dose and 87 ± 15 beats min^{-1} after the final dose, respectively. Maximal observed changes in blood pressure were $-14/-12 \pm 14/8$ mmHg ($P<0.05/0.01$) 2 to 6 h after the first dose on study day 1 without a haemodialysis session and $-50/-27 \pm 14/8$ mmHg ($P<0.001$) after the final dose on day 5 with a hemodialysis session (Figure 1). The changes in heart rate were negligible on day 1, whereas a maximum increase in heart rate of $+14 \pm 7$ beats min^{-1} ($P<0.001$) was observed 2 to 6 h after the final dose on day 5 (Figure 1).

Tolerability parameters and adverse events

None of the safety parameters including laboratory values, electrocardiography and/or physical examination showed any alterations during the course of candesartan cilexetil applications.

Eight adverse events in five patients were observed during the study: headache (2), dizziness (1), warm feeling in both legs (1), leg cramps (2), and severe hypotension (2). In two patients severe hypotensive episodes were observed during the haemodialysis sessions on day 5. Blood pressure dropped to a minimum of 78/54 mmHg and 68/47 mmHg, respectively in these two patients, whereas heart rate increased from 85 beats min^{-1} to 99 beats min^{-1} and from 75 beats min^{-1} to 97 beats min^{-1}, respectively.

Pharmacokinetic analyses

Measured peak serum candesartan concentrations were 87 ± 26 ng ml^{-1} on day 1 and 128 ± 36 ng ml^{-1} on day 5. The estimated half-life of the inactive metabolite CV-15959, determined in three patients, was longer than that of candesartan (73 ± 39 h *vs* 9.9 ± 3.2 h, respectively).

Plasma protein binding of candesartan was $>99\%$ determined on day 5 of the study. Serum extraction rates of candesartan and CV-15959, determined from serum

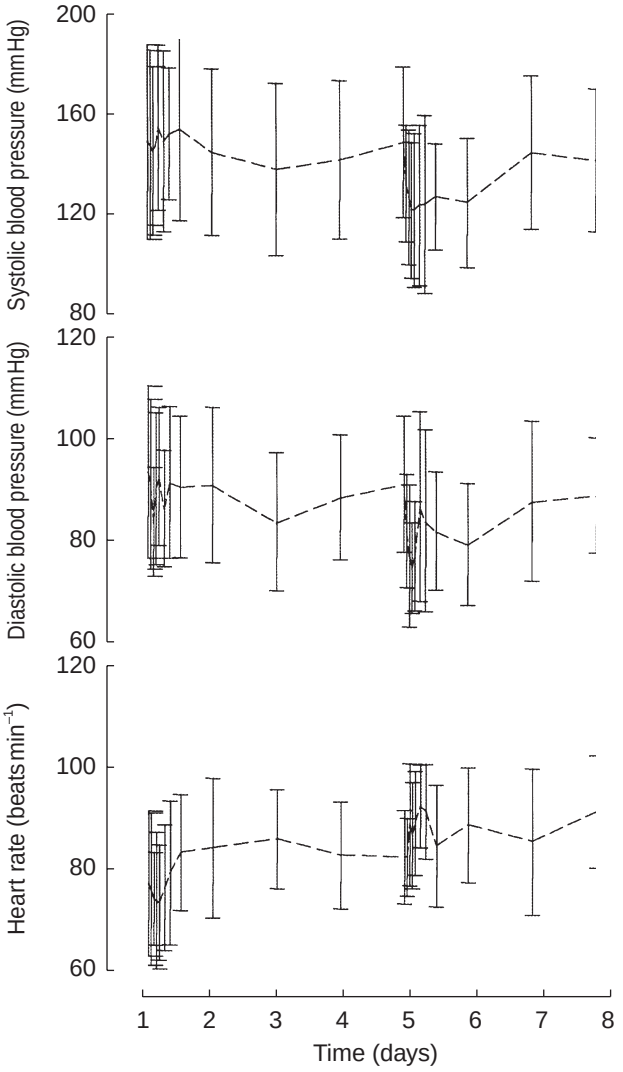

Figure 1 Observed changes in blood pressure and heart rate over the whole observation period of 8 days. A haemodialysis procedure was performed on days 2 or 3 and on days 5 and 7. The dotted lines represent the mean values of the measured blood pressures and heart rates, respectively. The error bars denote the corresponding standard deviations.

concentration differences at the dialyzer inlet and outlet (see Appendix), were negligible during haemodialysis sessions (range -0.05 to 0.09 and -0.03 to 0.12, respectively). Estimated candesartan dialysis clearances were in the range of 1 to 2 ml min^{-1} and only $0.2 \pm 0.1\%$ of an 8 mg dose of candesartan cilexetil was recovered unchanged in the dialysate.

For further analyses, the pharmacokinetic data of all patients were combined and fitted to a basic two-compartment model using NONMEM (Figure 2a). Analysis of residuals from the basic model revealed a dependency of the peripheral volume of distribution on body weight. Furthermore, the metabolic clearance was related to age and body weight. The basic model was expanded by these relationships and the data were fitted with this expanded model (Figure 2b). The estimated metabolic clearance of candesartan was 83 ml min^{-1}, the intercompartmental clearance was 9.9 ml min^{-1}, and the estimated dialysis clearance was negligible. The mean apparent central and peripheral volumes of distribution were 9.3 and 177.3 l, respectively. All estimated parameters of the expanded model are given on Table 1. The inclusion of additional dialysis treatment parameters did not improve the expanded model.

In one patient much higher serum candesartan concentrations were observed as compared with the other seven patients on days 5 to 8 (maximum serum candesartan concentration on day 5: 228 ng ml^{-1}). Allowing for an individual oral clearance for this patient from days 5 to 8 further improved the expanded model. The calculated oral clearance for this individual was 16.9 ml min^{-1} from days 5 to 8 as compared with a clearance of 50.4 ml min^{-1} during the first 4 study days. Figure 2c shows a plot of the predicted *vs* measured serum candesartan concentrations from this final model.

Discussion

A negligible contribution of haemodialysis to the elimination of candesartan was observed in this study. Measured serum concentrations of candesartan at the dialyzer outlet were not significantly lower than those measured at the dialyzer inlet. Furthermore, only about 0.2% of a dose of 8 mg candesartan cilexetil was recovered as unchanged drug in the dialysate. The minimum serum extraction ratio of candesartan during dialysis is easily explained by the high protein binding of this drug. In accordance with a previously published report [6] the unbound candesartan serum concentration accounted for $<1\%$ of the total candesartan serum concentration in this study.

The pharmacokinetic profile of candesartan was analyzed with NONMEM over the whole observation period assuming a two-compartment drug distribution. The mean central volume of distribution was 9.3 l which is similar to a previously reported central volume of distribution of 9.1 l [Takeda, data on file]. A strong relationship between the peripheral volume of distribution of candesartan and body weight was observed. Expanding the basic pharmacokinetic model to take into account this relationship and relating the metabolic clearance of candesartan to body weight and age [19] significantly improved the model.

The expanded model described above was further improved when it allowed for a decrease in oral clearance in one patient from days 5–8 as compared with the first 4 days of the study. This patient suffered from adult polycystic kidney disease with multiple liver cysts and the following conditions might theoretically have accounted for the observed changes in the oral clearance of

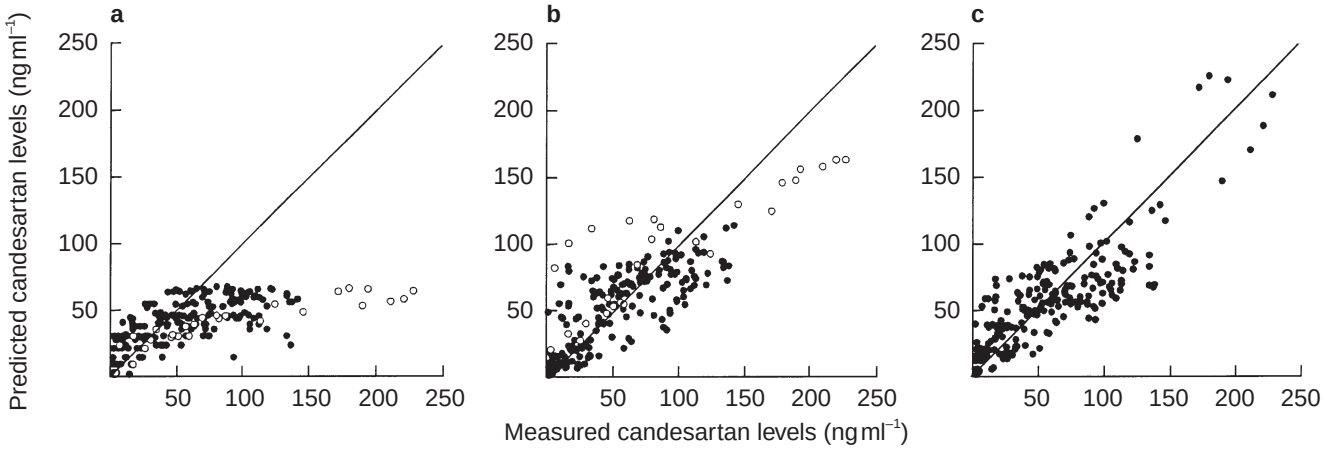

Figure 2 Relationship between predicted and measured candesartan serum levels. Open circles represent the data of the patient with much higher candesartan levels on day 5 to 8 as compared with the other seven patients (black circles). The line represents the identity line. a) A basic two-compartment model is assumed. b) Expansion of the basic two-compartment model (panel a) by relating the peripheral volume of distribution to body weight and by relating the metabolic clearance to age and body weight (see Appendix). c) Improvement of the expanded two-compartment model (panel b) by allowing for an individual oral clearance for the patient with increased candesartan levels from days 5 to 8.

Table 1 Estimated pharmacokinetic parameters for candesartan.

	Expanded model	
Parameter[a]	*Mean*	*Range*
k_a (10^{-3} min^{-1})	1.75	1.06–2.48
Q (ml min^{-1})	9.9	
K_{12} (10^{-3} min^{-1})	1.39	0.63–3.99
K_{21} (10^{-3} min^{-1})	0.14	0.01–0.30
V_c (l[1])	9.3	2.5–15.6
V_p (l)	177.3	33.0–802.0
CL_m (ml min^{-1})	83.4	50.4–129.0

[a]k_a, absorption coefficient; Q, intercompartmental clearance; K_{12}, coefficient of transfer from compartment 1 to 2; K_{21}, coefficient of transfer from compartment 2 to 1; V_c, volume of distribution in the central compartment (compartment 1); V_p, volume of distribution in the peripheral compartment (compartment 2); CL_m, metabolic clearance.

candesartan during the study: relevant intraindividual variability of the bioavailability induced by alterations of presystemic intestinal elimination and/or changes in conversion of the prodrug candesartan cilexetil to the active metabolite candesartan during gastrointestinal absorption. Furthermore, transient occurrence of entero-hepatic recirculation or variations of the metabolic clearance due to alterations of the hepatic blood flow and/or the metabolic capacity of the liver might have influenced the oral clearance. Only few data are available from the literature about drug metabolism in patients with polycystic kidney/liver disease. Possible alterations of hepatic clearance of antipyrine by loss of active liver mass (reduction in biotransformation of antipyrine) and/or by the formation of arterio-venous shunts (delayed availability of antipyrine to the liver) in patients with polycystic liver disease has previously been discussed [20]. On the other hand, no significant alterations in the key pharmacokinetic parameters of candesartan in patients with mild to moderate liver dysfunction was found as compared with healthy volunteers [21]. Therefore, the most likely explanation for the observed decrease in oral clearance in our patient is an increase in bioavailability during the observation period. Possible explanations for an observed increase in bioavailability include illness related reduction of presystemic intestinal elimination, reduction of protein intake in relation to carbohydrate and fat ingestion and/or a decrease of energy supply below the individual needs [22]. To the best of our knowledge, a significant alteration in bioavailability of candesartan by food intake has been reported in animals [Takeda, data on file] but not in healthy men [8]. However, variations in diet composition in haemodialysis patients are frequently observed and may lead to alteration in bioavailability even within days.

Unexpected alterations in serum drug concentrations are most likely observed in drugs with low bioavailability. According to previous studies in animals [5] and men [6], candesartan cilexetil has a low bioavailability in the range of 5-30% and 42%, respectively, comparable with the other currently available angiotensin II receptor antagonists such as valsartan [23], losartan [24, 25] with the exception of irbesartan (bioavailability 60 to 80%) [26].

The blood pressure lowering effect of candesartan observed after the first dose on day 1 of the study (no haemodialysis session) was similar to the one observed in previous studies with hypertensive patients without end-stage renal disease. The decrease in systolic and diastolic

pressure was significantly more pronounced after five doses of candesartan cilexetil. Severe hypotensive episodes were observed in two patients during haemodialysis sessions on day 5. Individual total ultrafiltrations during haemodialysis sessions were in the range between 0 and 4 l. Changes in systolic blood pressure during haemodialysis sessions correlated with the observed changes in body weight during these session ($r=0.70$, $P<0.05$). No objective data about the absolute pre- and postdialysis volume state are available in the studied patients. The strong influence of haemodialysis induced volume contraction on angiotensin II receptor antagonism most likely corresponds to the observed pronounced hypotensive effect when angiotensin II receptor antagonists are combined with diuretics. The successful reversal of the two hypotensive episodes with plasma volume expanders underlines the importance of the hydration state during angiotensin II receptor antagonism.

One of the two patients in whom a severe hypotensive episode was observed during haemodialysis was binephrectomized 7 years prior to the study. It has been shown that cardiovascular tissue renin completely disappears after binephrectomy [27] and that circulating angiotensin I and II can no longer be detected in circulating blood after binephrectomy in the rat [28]. The pronounced effect of candesartan cilexetil in our binephrectomized patient might nevertheless be explained by highly upregulated local/tissue angiotensin II receptors. Furthermore, non-renin-angiotensin mediated mechanisms might have accounted for the observed decrease in blood pressure in our binephrectomized patient.

In conclusion, haemodialysis does not influence the elimination kinetics of candesartan cilexetil. The haemodynamic effects of candesartan cilexetil might be pronounced during haemodialysis due to volume contraction. The rather low bioavailability of candesartan cilexetil and the observed high interindividual and especially intraindividual variability makes it crucial to carefully monitor haemodialysis patients who are treated with candesartan cilexetil.

This study was supported in part by grant no. 32-49585.96 from the Swiss National Science Foundation and by Takeda Euro R&D Centre GmbH, Germany.
The authors thank Mrs M. Fernandez for her invaluable technical assistance.

Appendix

Dialysis clearance calculated from serum extraction rate

$$E=(C_a-C_v)/C_a$$

$$CL_e=Q_b\cdot E$$

where C_a is the arterial serum concentration of candesartan and of the inactive metabolite (CV-15959), respectively (at dialyzer inlet) and C_v is the venous serum concentration of candesartan and CV-15959 (at dialyzer outlet). E is the extraction rate, Q_b is blood flow and CL_e denotes dialysis clearance from serum extraction rate.

Dialysis clearance calculated from drug recovery in dialysate

$$CL_d=A/AUC$$

where A is the total amount of candesartan recovered in the dialysate and AUC is area under the serum candesartan concentrations curve during dialysis, calculated by the standard trapezoidal rule [14] from the concentrations in the arterial serum (at dialyzer inlet).

Expansion of the basic two-compartment model of candesartan disposition

$$V_p=a\cdot WT$$

$$CL_m=b\cdot WT+c\cdot(100-Y)/100$$

where V_p is the peripheral volume of distribution (l), CL_m is the metabolic clearance (ml min^{-1}), WT is the body weight before dialysis (kg) and Y denotes age (years). a, b, c and d are regression coefficients.

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