Population pharmacokinetics and dose simulation of carvedilol in paediatric patients with congestive heart failure

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Applying *in silico* tools such as population pharmacokinetic analysis and simulation will help to find adequate dosing strategies and increase the probability of success for a randomized controlled trial.
- Up to now, for carvedilol in paediatric patients with congestive heart failure (CHF) the dose has been linearly extrapolated from adults, but the results with this dosing strategy are ambiguous.
- Further trials are necessary to establish carvedilol for paediatric patients with CHF.

WHAT THIS STUDY ADDS

- Carvedilol pharmacokinetics in paediatric patients with CHF depends on the weight and age of the patient.
- Therefore, the drug exposure differs substantially between patients of different ages receiving the same dose with respect to body weight.
- Simulations revealed that an age-adjusted carvedilol dosing strategy with higher doses for younger patients with respect to body weight is preferable to a uniform one.

AIMS

To investigate the ontogeny of carvedilol pharmacokinetics and to develop an age-appropriate carvedilol dosing strategy for paediatric patients.

METHODS

Data were derived from a prospective, nonplacebo-controlled study of carvedilol for the treatment of paediatric patients with congestive heart failure and analysed using a nonlinear mixed-effects modelling approach (NONMEM, Version V 1.1). The population pharmacokinetic model was further utilized for simulations of different carvedilol dosing strategies.

RESULTS

Four hundred and eighty carvedilol plasma concentrations of 41 patients (0.1–19.3 years; median 3.5) were included in the analysis. A two-compartment model with first-order absorption and absorption lag served as structural model. Weight and age were the most important covariates for carvedilol pharmacokinetics. The weight-adjusted clearance was highest for the younger patients with $2.7 \text{ l h}^{-1} \text{ kg}^{-1}$ for a 1-year-old patient compared with $0.7 \text{ l h}^{-1} \text{ kg}^{-1}$ for a 19.3-year-old patient. Dose simulations revealed that the area under the plasma concentration–time curve (AUC) as a measure of drug exposure increased with age despite constant doses with respect to body weight. For infants (28 days to 23 months), children (2–11 years) and adolescents (12–15 years) daily doses of 3, 2 and 1 mg kg^{-1} , administered in two or three discrete doses, were necessary to reach an exposure comparable to adults receiving $0.7 \text{ mg kg}^{-1} \text{ day}^{-1}$.

CONCLUSION

The ontogeny of carvedilol pharmacokinetics in paediatric patients depends on age and weight. Dose simulations revealed that younger patients have to be treated with higher doses with respect to body weight to reach the same exposure as adults.

Introduction

Carvedilol is a nonselective β -blocker with additional vasodilating and antioxidative properties. The drug is used for the treatment of hypertension and stable angina pectoris, and was the first β -blocker to be approved for the treatment of congestive heart failure (CHF) in adults [1]. For paediatric patients with CHF, several retrospective [2–4] and prospective [5, 6] investigations have reported an improvement in cardiac function under carvedilol treatment. However, preliminary results of a recently conducted prospective, placebo-controlled trial for children with CHF have shown no significant difference between carvedilol and placebo [7]. Up to now, the carvedilol dosing strategy for children has been linearly extrapolated from adults and is uniform for all age groups, but age-dependent differences for elimination half-life and weight-adjusted clearance have already been found in a small paediatric patient population [6]. These results suggest that an age-based carvedilol dosing strategy for children instead of a uniform one might be advantageous.

Carvedilol is a lipophilic drug with an oral bioavailability of about 25%, and 98–99% of the drug is bound to plasma proteins [8]. Elimination of the drug is mainly hepatic; only 2% is excreted unchanged [9]. For adults the total clearance is 590 ml min^{-1} and can be ascribed to about 50% of the polymorphically expressed enzyme cytochrome P 450 (CYP) 2D6 [10]. Genetically determined impaired CYP2D6 metabolic activity results in increased plasma concentrations for carvedilol [10]. In addition to CYP2D6, mainly CYP2C9 and 1A2, and to a lower extent also 3A4, 2C19 and 2E1, are involved in the metabolism of carvedilol [11]. Carvedilol is also a substrate of the drug transporter P-glycoprotein (P-gp) [12, 13].

Liver blood flow is a direct determinate of carvedilol clearance and is reduced in patients with CHF due to their limited cardiac function [14]. Additionally, limited cardiac function can also result in congestion of the liver and thereby in reduced liver function. Therefore, the left ventricular ejection fraction (LVEF) may be a relevant covariate for carvedilol clearance in addition to CYP2D6 metabolic activity. Adult patients with CHF have shown 30–40% higher carvedilol plasma concentrations than healthy adults [15].

Further randomized controlled trials (RCT) are necessary to establish a safe and effective use of carvedilol in paediatric patients with CHF. Using *in silico* tools such as population pharmacokinetic analysis and simulation during the design of clinical trials will increase the probability of success for such an RCT; potential bias due, for example, to inadequate dosing and systemic exposure can be reduced. Therefore, the aim of the current study was to investigate the ontogeny of carvedilol pharmacokinetics by population pharmacokinetic analysis. Data for this analysis were derived from a prospective, nonplacebo-controlled investigation of carvedilol for the therapy of

paediatric patients with CHF. The population pharmacokinetic model was then used to perform dose simulations to confirm or, if necessary, adjust the current carvedilol dosing strategy for paediatric patients in an upcoming RCT.

Methods

Study design and patient population

A prospective, nonplacebo-controlled study was conducted for the therapy of paediatric patients with CHF from 1997 to 2003 at the Department of Paediatric Cardiology, University Hospital of Hamburg, Germany. Approval was given by the local ethics committee in accordance with the declaration of Helsinki. Patients of both sexes aged between 0 and 20 years were included if they (i) had a diagnosis of CHF, (ii) were on the maximal heart failure therapy consisting of an angiotensin-converting enzyme (ACE)-inhibitor, diuretics and cardiac glycosides, and (iii) had been in a stable clinical situation for ≥ 4 weeks. Exclusion criteria were: premature infants or hypotrophic neonates, acute myocarditis, bradycardia, hypertension, terminal renal or hepatic insufficiency, cardiac block, acute infections, concomitant therapy with α - and/or β -blockers, calcium channel blockers or class I antiarrhythmics, known allergic reactions to the drug, no continuous support and survey at home, and other diseases than CHF limiting the survival of the patient. Patients were enrolled after age-appropriate written informed consent/assent was obtained from the patients and, if appropriate, consent of their parents/guardians. The therapy was initiated with a first dose (test dose) of 0.09 mg kg^{-1} carvedilol (qd). If tolerated, the dose was increased to 0.09 mg kg^{-1} administered twice daily (bid) on the second day, and then weekly uptitrated to the target dose of 0.35 mg kg^{-1} carvedilol bid. The drug was administered orally. For this purpose, capsules were produced from the original tablets (Dilatrend®; Hoffmann-La-Roche, Grenzach-Wyhlen, Germany) by the respective hospital pharmacy using a standardized procedure. The capsule content was given in a glass of water for drug administration. Patients were surveyed while taking their dose. Clinical parameters (ejection fraction, fractional shortening, modified Ross score) were assessed before initiation of treatment and monthly for 6 months.

Carvedilol sampling procedure and analytical methods

A series of blood samples was collected on the day of the first dose and after being at the target dose for at least 3 days. For several patients, additional samples during the uptitration phase could be collected. Patients abstained from food for 1 h before to 2 h (patients ≤ 2 years) or 4 h (patients > 2 years) after drug intake. Blood samples were collected via a permanent venous catheter before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 h after the

ingestion. Plasma was separated by centrifugation at 2700 g and 4°C. Aliquots were stored at –80°C. Carvedilol concentrations were determined with a validated high-performance liquid chromatography (HPLC) assay and fluorescence detection with naftopidil as internal standard [16]. Three hundred microlitres of plasma are required for this analysis. Carvedilol plasma concentrations from 0.40 to 242.0 µg/l are within the validated range. At the lower limit of quantification (0.40 µg l⁻¹), the coefficients of variation for accuracy and precision were <18%.

Phenotyping for CYP2D6

Patients >6 months old were investigated for their CYP2D6 metabolic activity with the test drug dextromethorphan (DM) contained in the antitussive NeoTussan® (Novartis Consumer Health, Munich, Germany). Urine samples were taken before and were collected for 8 h after the intake of an age-appropriate dose of DM. DM and its main metabolite dextrorphan (DR) were determined by HPLC and fluorescence detection with verapamil as internal standard [17]. The metabolic capacity for CYP2D6 was calculated from the ratio between DM and DR urine concentrations.

Population pharmacokinetic analysis

The population pharmacokinetic analysis was performed with the nonlinear mixed-effect modelling software program NONMEM version V, level 1.1 (GloboMax, Hanover, MD, USA) [18] using the Digital Visual Fortran compiler version 5.0.A (Hewlett-Packard, Palo Alto, CA, USA). All plasma concentration data were log-transformed prior to analysis. Using the first-order conditional estimation (FOCE) method with η - ϵ interaction during model development, the minimization step was not successful in most cases. Therefore, we decided to use the first-order (FO) method during model development and reran the final model with FOCE with η - ϵ interaction to refine the parameter estimates, as done by others [19]. Goodness of fit was evaluated by (i) the change in the objective function (OF), (ii) the change in the residual and between-subject variability, and (iii) comparing observed (DV) with population predicted (PRED) concentrations and PRED with weighted residuals (WRES). The bioavailability entered the model as unknown factor (F) because it could not be determined based on the available data.

Initially, the structural model was built. One- and two-compartment models with first-order absorption and elimination with and without absorption lag were tested. For the log-transformed data an additive error model was used to model residual variability. Exponential error models were used to allow for between-subject variability in pharmacokinetic parameters. Nondiagonal elements of the variance-covariance matrix were tested for model improvement.

Before starting the covariate model building, body weight (WT) was added to the structural model following the principles of allometry. Clearances and volume of dis-

tribution parameters are related to indices of body mass (e.g. body weight or body surface area) [20, 21]. Using body weight, an exponent value of 0.75 for clearances and 1.0 for volume of distribution parameters have proven to describe these parameters adequately over a broad range of body weights. Therefore, the body weight was included as follows:

$$TV = \theta \times (WT/WT_{MEDIAN})^x \quad (1)$$

where TV represents the typical value of clearances and volume of distribution parameters, which depends on the population mean (θ) and the WT of the individual normalized for the median WT (WT_{Med}). The exponent (x) was fixed to 0.75 for clearances and 1.0 for volume of distribution parameters. The allometrically scaled model was the base model for further covariate model building.

Covariates were included in a stepwise forward inclusion procedure (step-up approach). For continuous covariates (age and CYP2D6 activity), individual values were median-normalized and included using additive, proportional, exponential or power-function models. For categorical covariates, the following ones were investigated: gender, aetiology of the disease, the dose level, a LVEF $\leq 30\%$ and an age-based weight percentile ≤ 25 . A covariate was considered to improve the model significantly if the decline of the OBF was >3.84 ($P < 0.05$). The covariate with the greatest decline in the OBF was added to the base model and the entire procedure was repeated until no further improvement could be obtained. In this way a preliminary final model was built. In the subsequent step-down approach FOCE with η - ϵ interaction was used and each covariate was eliminated separately from the model. In this backward deletion procedure the significance level was set to 0.005, meaning that only covariates with a change in the OBF of ≥ 7.8 remained in the model. In this way, the final covariate model was built.

Model evaluation

The adequacy and performance of the developed population pharmacokinetic model was evaluated by a visual predictive check. Based on the point estimates for the pharmacokinetic model parameters and between-subject and residual variability, carvedilol plasma concentrations for the study population were simulated with 100 replicates. Model adequacy was assessed by comparing the median, the 10th and 90th percentile calculated from the simulated concentrations with the measured concentrations.

The precision of the parameter estimates of the population pharmacokinetic model was assessed by establishing 95% confidence intervals (CI) using a nonparametric bootstrap analysis (Wings for NONMEM; Version 409d) [22, 23]. In principle, from the original dataset patients were selected repeatedly and at random to create a new dataset with the same number but different combination of

patients. The bootstrap resampling was repeated 1000-fold. The 95% CI was calculated for each pharmacokinetic parameter by using the 2.5th and 97.5th percentile from 1000 bootstrap estimates. Additionally, the final population pharmacokinetic parameter estimates were compared with the bootstrap estimates.

Individual pharmacokinetic parameters were also calculated with the software program WinNonlin professional version 4.1 (Pharsight Corporation, Cary, NC, USA) to compare them with the population analysis-based empirical Bayesian post hoc parameter estimates for the individual.

Simulation

The population model and its population pharmacokinetic parameter estimates as well as between-subject and residual variability were used for simulations with NONMEM. Simulations were always performed 100-fold. To simulate steady-state conditions for carvedilol, plasma concentrations were simulated after 120 h of drug intake. First, a carvedilol dose of 0.35 mg kg⁻¹ bid for preferably patients of all ages from the original dataset was simulated. This step should give an impression of the area under the plasma concentration–time curve (AUC) in different ages and thereby enable a reasonable grouping together of patients to derive a feasible carvedilol dosing strategy.

Assuming that an age-based dosing strategy might be more feasible than a weight-based one with regard to clinical practicability, patients should be assigned to different age groups. For a first approach to a new dosing strategy, one patient per group with a middle age in this group was chosen. For these patients different daily doses (0.7, 1.0, 1.5, 2.0 and 3.0 mg kg⁻¹) and dosing intervals, bid and three times a day (tid), were simulated. The AUC was calculated by noncompartmental analysis and the linear-trapezoidal rule over 0–12 h (AUC_{0–12}) after simulated drug intake with the software program WinNonlin.

Log-transformed AUC values were compared by univariate analysis of variance (ANOVA) and Bonferroni post hoc analysis. *P*-values < 0.05 were regarded as statistically significant. Dose recommendations were made by calculating the median, the 10th and 90th percentiles from 100 simulated values for the carvedilol peak plasma concentration (C_{max}) and the AUC_{0–12}. These values were compared with the simulation results for a 19.3-year-old patient. The median AUC_{0–12} for this patient receiving the adult target dose of 0.35 mg kg⁻¹ bid served as target AUC.

Results

Patients

A total of 41 paediatric patients were included for the population pharmacokinetic analysis; 21 patients received the test dose level (0.09 mg kg⁻¹), three received a middle dose level (0.15 mg kg⁻¹) and 17 patients received the

Table 1
Patients' characteristics

Characteristics	n (%)	Median (range)
Total	41 (100)	
Gender		
Male	30 (73.2)	
Female	11 (26.8)	
Diagnosis		
VSD, MI	7 (17.1)	
HLH	3 (7.3)	
DCM	31 (75.6)	
LVEF < 30%	12 (29.3)	
Weight percentile < 25	24 (58.5)	
Age (years)		3.5 (0.07–19.3)
Weight (kg)		13.1 (3.1–98.2)
CYP2D6 activity		–2.4 (–1 to –3.5)

DCM, Dilatative cardiomyopathy; HLH, hypoplastic left heart syndrome; LVEF, left ventricular ejection fraction; MI, mitral insufficiency; VSD, ventricular septal defect.

target dose level (0.35 mg kg⁻¹). On average, 12 ± 2 concentration observations were available per patient; in total, 480 plasma concentrations were determined. Carvedilol plasma concentrations reached up to 193.3 µg/l. With regard to the metabolic capacity for CYP2D6, neither a poor nor an ultrarapid metabolizer was present. Patient characteristics are summarized in Table 1. Clinical results for a part of this population have already been published and are not subject of the current work [6].

Population pharmacokinetic analysis

Carvedilol pharmacokinetics were best described by a two-compartment model with first-order absorption and absorption lag. The following parameters, corrected for bioavailability *F*, were estimated for this model: total clearance (CL), intercompartmental clearance (*Q*), central (*V*₂) and peripheral (*V*₃) volume of distribution, absorption rate constant (*K*_A) and lagtime (*T*_{LAG}). Estimation of covariances between CL, *V*₂, *V*₃ and *Q* on one hand, and between *K*_A and *T*_{LAG} on the other hand significantly improved the model fit (ΔOBF = –69.1 and –4.2, respectively). Variances and covariance for *K*_A and *T*_{LAG} were fixed to their estimated values from a preliminary estimation attempt (ω²_{KA} = 0.06, ω²_{TLAG} = 0.04, ω_{KA, TLAG} = 0.1) to avoid an overparameterization. Following the allometric principles, the patient's body weight normalized to the median was included for CL and *Q* with an exponent of 0.75 and for *V*₂ and *V*₃ with an exponent of 1.0. The allometric scaled model was the base model for further covariate testing (Table 2: Model 1).

During the step-up approach, age as covariate for CL had the most significant influence (ΔOBF = –24.7). The between-subject variability was reduced from 56.6% to 42.4% (Table 2: Model 2). Further covariate testing revealed a significant influence of age as a covariate for *V*₂ [ΔOBF = –24.7; Table 2: Model 3 (FO)]. After this step, no

Table 2

Parameter estimates during model development

Parameter	Model 1 Allometric scaled model	Model 2 Age as covariate for CL	Model 3 (FO) Age as covariate for CL and V ₂	Model 3 (FOCE) Final model
CL/F (l h ⁻¹) [CV (%)]	31.5 (9.2)	40.6 (7.7)	41.3 (7.1)	38.1 (7.1)
V ₂ /F (l) [CV (%)]	18.1 (16.7)	20.1 (16.9)	25.5 (15.6)	22.0 (22.7)
V ₃ /F (l) [CV (%)]	99.2 (18.3)	96.4 (18.5)	96.9 (16.6)	96.5 (22.7)
Q/F (l h ⁻¹) [CV (%)]	16.1 (15.5)	17.1 (16.1)	14.9 (15.4)	13.5 (12.8)
K _A (l h ⁻¹) [CV (%)]	0.55 (8.0)	0.55 (6.5)	0.54 (6.9)	0.62 (5.7)
T _{LAG} (h) [CV (%)]	0.14 (11.9)	0.14 (10.5)	0.14 (12.3)	0.15 (12.5)
θ ₇ [CV (%)]		2.70 (3.1)	2.77 (2.2)	2.70 (2.2)
θ ₈ [CV (%)]			-0.15 (6.0)	-0.13 (18.0)
ω ² _{CL}	0.32	0.18	0.17	0.19
ω ² _{V₂}	2.11	2.17	1.86	1.29
ω ² _{V₃}	1.23	0.98	1.42	1.49
ω ² _Q	0.48	0.49	0.41	0.42
ω _{CL,V₂}	0.42	0.26	0.22	0.23
ω _{CL,V₃}	0.30	0.29	0.34	0.33
ω _{CL,Q}	0.20	0.22	0.21	0.25
ω _{V₂,V₃}	-0.17	-0.19	0.04	-0.22
ω _{V₂,Q}	0.13	0.17	0.14	0.18
ω _{V₃,Q}	0.36	0.35	0.42	0.62
σ ²	0.054	0.055	0.052	0.054
OBF	-429.3	-454.0	-478.7	-483.0

CV, Coefficient of variation; CL, total clearance; F, bioavailability; FO, first-order estimation; FOCE, first-order conditional estimation; K_A, absorption rate constant; OBF, objective function; Q, intercompartmental clearance; θ₇ and θ₈, regression parameters estimated by NONMEM for CL and V₂; σ², variance of residual variability; T_{LAG}, lagtime; V₂ and V₃, central and peripheral volume of distribution; ω, covariance of between-subject variability; ω², variance of between-subject variability.

other covariate could further improve the model fit. The subsequent step-down approach was performed using the FOCE method with η-ε interaction. Backward deletion of each covariate from the full model resulted in a significant decline in the OBF (ΔOBF > 7.8) and confirmed the covariate selection in the forward addition procedure. Therefore all included covariates remained in the final model. This model was rerun with the FOCE method to obtain the final population estimates [Table 2: Model 3 (FOCE)]; Figure 1A,B. The following equations describe the final covariate model [13 (3.5)=median weight (age)]:

$$TVCL[l/h] = CL \times (WT/13)^{0.75} - ((AGE/3.5)^{\theta_7}) \quad (2)$$

$$TVV2[l] = V2 \times (WT/13) \times (1 + (\theta_8 \times AGE/3.5)) \quad (3)$$

$$TVV3[l] = V3 \times (WT/13) \quad (4)$$

$$TVQ[l/h] = Q \times (WT/13)^{0.75} \quad (5)$$

The final model and its parameter estimates include that weight-adjusted CL and V₂ decrease with increasing age. This could be confirmed by correlation analysis of the Win-Nonlin estimates for weight-adjusted CL (Figure 2) and weight-adjusted V₂ with age: age was significantly correlated ($P < 0.05$) with both. For a 1-year-old patient the

weight-adjusted CL was 2.7 l h⁻¹ kg⁻¹ compared with 0.7 l h⁻¹ kg⁻¹ for a 19.3-year-old one.

Model evaluation

The simulation-based visual predictive check for the final population pharmacokinetic model indicates that the model adequately describes the measured data. The comparison between simulated and measured carvedilol concentrations for the target dose 0.35 mg kg⁻¹ bid is shown in Figure 3. A total of 215 plasma concentrations from 17 patients receiving the target dose level were available for this comparison. About 90% of the measured data are within the 90th percentile of the simulated plasma concentrations.

The results of the nonparametric bootstrap analysis are shown in Table 3. The final population pharmacokinetic parameter estimates were very similar to the bootstrap estimates ($n = 1000$). Furthermore, for the pharmacokinetic parameters CL, Q, K_A, T_{LAG} and θ₇ the 95% CIs were narrow. The density distribution for all parameters approximated a Gaussian distribution.

In addition, the population analysis-based pharmacokinetic parameters were in good agreement with previous reports for select age groups. For example, a 19.3-year-old patient with a body weight of 98.0 kg had a weight-adjusted CL of 10 ml min⁻¹ kg⁻¹ and weight-adjusted

Figure 1

Goodness-of-fit plot for the final model. (A) Observed concentration (DV) vs. population predicted (PRED). (B) Population predicted concentration (PRED) vs. weighted residuals (WRES)

steady-state volume of distribution of 2.3 l kg^{-1} compared with $8.4 \text{ ml min}^{-1} \text{ kg}^{-1}$ [9] and $1.5\text{--}2.0 \text{ l kg}^{-1}$ [8] previously reported for a 70-kg adult.

Simulation

Simulations were performed to evaluate and if necessary improve the carvedilol dosing strategy for paediatric patients. Estimates for the pharmacokinetic parameters, the between-subject and residual variability from the final population model were used for the simulations. Initially, a dose of $0.35 \text{ mg kg}^{-1} \text{ bid}$ was simulated for patients of all ages. This simulation revealed that the AUC_{0-12} as a measure of drug exposure increases significantly with increasing age ($P < 0.05$). The median AUC_{0-12} from 100 simulations for this dose level was $78.6 \mu\text{g h}^{-1} \text{ l}^{-1}$ for a 0.1-year-old patient compared with $495.4 \mu\text{g h}^{-1} \text{ l}^{-1}$ for a 19.3-

Figure 2

Measured weight-adjusted carvedilol clearance in the paediatric population. Clearance (CL) with respect to body weight is significantly correlated with age ($P < 0.05$)

Figure 3

Visual predictive check for the target dose $0.35 \text{ mg kg}^{-1} \text{ bid}$. For $n = 17$ patients plasma concentrations on the target dose level were observed ($\square$) and compared with the median, the 10th and 90th percentile of 100 simulations for this dose

year-old patient. Concerning the pairwise comparison, the differences between an 8.3 and a 10.7-year-old patient, and an 11.9 and 14.5-year-old patient, respectively, were significant probably due to the age difference of >2.4 years. Additionally, the AUC_{0-12} for a 16.2-year-old patient was significantly different from a 14.5-year-old, but not from a 17.5-year-old patient.

These results suggest an age classification of the patients according to the International Conference on Harmonization [24] with few modifications: neonates (0–27 days), infants (28 days to 23 months), children (2–11 years), adolescents (12–15 years) and adults (>16 years). One patient per group with a middle age in this group was now chosen as an example to simulate different doses and dosing intervals. The chosen patients were 1.0, 7.5 and 14.5 years old. No patient from the neonate group

Table 3

Population pharmacokinetic (Pop-PK) parameter estimates and the corresponding bootstrap results

Parameter	Pop-PK estimate	Bootstrap Mean	95% CI (%) [*]
CL/F (l h ⁻¹)	38.1	37.6	31.6, 43.7 (84.0–116.2)
V ₂ /F (l)	22.0	21.8	13.4, 32.1 (61.5–147.2)
V ₃ /F (l)	96.5	103.7	62.6, 170.0 (60.4–163.9)
Q/F (l h ⁻¹)	13.5	13.6	10.3, 17.8 (75.7–130.9)
K _A (l h ⁻¹)	0.62	0.62	0.55, 0.72 (88.7–116.1)
T _{LAG} (h)	0.15	0.15	0.11, 0.19 (73.3–126.7)
θ ₇	2.70	2.67	2.44, 2.82 (91.4–105.6)
θ ₈	−0.13	−0.12	−0.17, −0.04 (141.7–33.3)

^{*}Percent from bootstrap mean. CI, Confidence interval; CL, total clearance; F, bioavailability; K_A, absorption rate constant; Q, intercompartmental clearance; θ₇ and θ₈, regression parameters estimated by NONMEM for CL and V₂; T_{LAG}, lagtime; V₂ and V₃, central and peripheral volume of distribution.

was chosen because the youngest patient was 23 days old and thereby nearly at the threshold to the infant group. An extrapolation for younger patients does not seem justifiable at this point. To compare the results with adults, simulations were also done for a 19.3-year-old patient.

Simulations were performed for daily doses of 0.7, 1.0, 1.5, 2.0 and 3.0 mg kg⁻¹ administered bid and tid. The AUC_{0–12} increased with increasing doses, but the pairwise comparison revealed significant differences between the different patients ($P < 0.05$) (Figure 4; Table 4). Median AUC_{0–12} for the 19.3-year-old patient with 0.35 mg kg⁻¹ bid was 495.4 µg h⁻¹ l⁻¹ compared with 300.1 µg h⁻¹ l⁻¹ for the 14.5-year-old patients receiving the same dose. Compared with the younger patients, the median AUC_{0–12} of the 19.3-year-old patient was 3.2 (4.4)-fold higher than the median AUC_{0–12} of the 7.5 (1.0)-year-old patient. The simulation of the same daily doses administered tid revealed little accumulation of carvedilol. The median AUC_{0–12} for a 1.0-year-old patient after 1.0 mg kg⁻¹ tid was 580.5 µg h⁻¹ l⁻¹ compared with 451.4 µg h⁻¹ l⁻¹ after 1.5 mg kg⁻¹ bid. C_{max} values were higher with the bid dosing strategy (Table 4). Overall, the difference between bid and tid was not sufficient to recommend a reduction of the daily dose with a tid dosing strategy. This means that doses of 3.0, 2.0 and 1.0 mg kg⁻¹ administered in two or three discrete doses per day for infants, children and adolescents are necessary to reach the same drug exposure as an adult receiving 0.7 mg kg⁻¹. This was confirmed by direct comparison of the simulated concentrations for these age-dependent target doses (Figure 5).

Discussion

Carvedilol pharmacokinetics were best described by a two-compartment model with first-order absorption and absorption lag. Weight, used for the allometric scaling approach, and age were the most important covariates. The weight-adjusted clearance decreased continuously with age and was highest for the youngest patients. Similarly, the weight-adjusted central volume of distribution decreased with age. Dose simulations revealed that the AUC as a measure of drug exposure increased with age despite an equal dose with respect to body weight.

We used an allometric scaling approach in terms of body weight to account for the effect of physiological development on pharmacokinetic parameters in the paediatric population. Allometric scaling should be performed before covariate model development, otherwise the effect of other covariates can be obscured [25]. This approach has often been used in trials with paediatric patients [26, 27]. Age was identified as the most important covariate beyond body weight, with a significant influence on the weight-adjusted clearance (CL) and central volume of distribution (V₂). Age-dependent differences for hepatic clearance, body composition, but also bioavailability, which was not determined, have to be discussed.

Many hepatically eliminated drugs show an age-dependent clearance [28–30]. Reasons might be the higher liver mass and higher liver blood flow per unit body weight for younger children [31, 32]. For CYP2D6, the main metabolizing enzyme of carvedilol, some reports have described adult activity levels at the age of 1 year [33], others already at the age of 2 weeks [34]. The latter would be concordant with our results. Age differences for volume of distribution might be due to differences in body composition or protein binding [28]. Because the between-subject variability for V₂ and V₃ is still high, there might be another relevant covariate not detected yet. Hirt *et al.* have investigated the pharmacokinetics of oral nelfinavir in a one-compartment model and also detected age as a significant covariate for clearance and volume of distribution [35]. They have ascribed this effect to age-dependent differences in bioavailability with lower values for younger patients. Because we were not able to delineate bioavailability from clearance and volume terms, an influence of this factor cannot be excluded. In this context, intestinal P-gp activity might also be of relevance. For an animal model, however, intestinal P-gp activity was reduced for younger animals [36]; this would result in higher values for the bioavailability of carvedilol.

The metabolic activity of CYP2D6 had no significant influence on carvedilol clearance. Of 41 patients, 33 were phenotyped for their CYP2D6 activity. Probably because there were no poor and only two intermediate but 31 extensive metabolizers, no influence of CYP2D6 activity on carvedilol clearance could be detected. It is already known from adults that a limited CYP2D6 metabolic activity phe-

Figure 4

Simulated AUC_{0-12} after different doses and dosing intervals. Different doses were administered (A) bid or (B) tid. Box plots represent the median, 25th and 75th percentile (box), lower and upper limit of normal (error bars) and outliers (*). Each dose was simulated for patients of different ages: 1.0 year old (white box), 7.5 years old (light grey box) and 14.5 years old (dark grey box) compared with a 19.3-year-old adult (hatched box). Pairwise comparisons for each dose revealed significant differences between the different patients for AUC_{0-12} (ANOVA; $P < 0.05$)

notype as encountered in poor metabolizers (PM) causes higher carvedilol plasma concentrations; the AUC is about twofold higher in PMs compared with extensive metabolizers [10]. In the paediatric population it is also very likely that PMs have higher plasma concentrations due to a lower clearance. Whether this is to the same extent as for adults should be subject of further investigation. For healthy adults, the metabolic ratio between DM and DR was highly variable, which in part was ascribed to changes in urinary pH [37]. An influence of urine pH in our investi-

gation cannot be excluded, because we did not determine it, but the DM/DR ratio seems to be a good approximation to CYP2D6 activity for children also, as recent results suggest [38].

The LVEF as a surrogate for liver blood flow had also no significant influence on carvedilol clearance. This influence may only be present when patients with normal and limited cardiac function are compared, but not when patients with limited cardiac function are compared against each other. During model development the LVEF

Table 4

Simulation results* for different doses and dosing intervals

Patient (years)	Simulation results for the bid dosing regimen			Simulation results for the tid dosing regimen		
	Dose (mg kg ⁻¹)	AUC (μg h ⁻¹ l ⁻¹) (10th–90th)	C _{max} (μg l ⁻¹) (10th–90th)	Dose (mg kg ⁻¹)	AUC (μg h ⁻¹ l ⁻¹) (10th–90th)	C _{max} (μg l ⁻¹) (10th–90th)
1.0	0.35	113.2 (62.5–223.0)	37.6 (17.0–73.7)	0.25	136.5 (70.7–220.9)	25.3 (11.2–48.0)
	0.5	153.6 (88.7–265.5)	47.7 (21.4–102.2)	0.35	213.9 (122.6–326.8)	41.7 (20.5–72.7)
	0.7	231.4 (143.8–388.6)	80.1 (37.8–163.0)	0.5	309.5 (162.0–551.5)	60.0 (27.1–117.3)
	1.0	332.5 (206.2–640.4)	117.1 (50.8–214.0)	0.7	378.3 (233.9–655.8)	76.8 (41.7–150.9)
	1.5	451.4 (255.2–896.6)	131.9 (56.8–293.6)	1.0	580.5 (321.8–1030.9)	118.4 (52.2–237.7)
7.5	0.35	153.9 (86.9–298.8)	43.7 (18.9–97.1)	0.25	222.0 (115.1–369.6)	39.5 (18.5–76.6)
	0.5	227.5 (131.2–393.2)	72.3 (30.0–150.3)	0.35	303.9 (170.8–524.7)	59.2 (27.1–113.9)
	0.7	322.7 (184.4–514.1)	108.8 (53.3–208.9)	0.5	398.5 (220.1–701.1)	79.9 (39.6–154.7)
	1.0	474.4 (257.2–762.6)	147.3 (60.2–313.4)	0.7	621.7 (321.1–1133.8)	120.6 (53.4–246.8)
	1.5	682.5 (393.8–1179.5)	216.8 (89.9–451.0)	1.0	792.9 (459.2–1504.7)	159.6 (77.2–323.5)
14.5	0.35	300.1 (167.6–504.1)	87.0 (38.8–172.6)	0.25	384.3 (209.7–749.4)	74.2 (33.2–143.0)
	0.5	421.9 (269.5–726.0)	117.1 (54.6–290.2)	0.35	526.1 (292.7–918.0)	92.4 (45.3–181.7)
	0.7	556.7 (338.8–942.6)	158.5 (70.9–282.9)	0.5	721.2 (388.3–1329.2)	138.1 (66.5–282.6)
	1.0	891.7 (439.2–1656.9)	242.0 (117.3–546.0)	0.7	1029.2 (543.1–1859.1)	184.3 (88.0–450.5)
	1.5	1272.6 (731.9–2041.5)	384.2 (189.6–743.1)	1.0	1553.1 (802.7–2575.0)	285.0 (139.4–543.3)
19.3	0.35	495.4 (260.3–903.3)	133.5 (66.4–285.6)			

*Simulation results are presented as median, 10th and 90th percentile from 100 simulations. AUC, Area under the plasma–concentration time curve; bid, bis in die; C_{max}, carvedilol peak plasma concentration; tid, ter in die; recommended target doses for each age group are highlighted.

had an influence on V_3 , but in the final model this effect was not significant.

The number of concentration measurements during the absorption phase is often not sufficient to describe adequately the parameters related to the absorption phase such as K_A and T_{LAG} . Concerning this, and the number of parameters to be estimated, we fixed the variances and covariance for K_A and T_{LAG} by using preliminary estimated values before fixing them. This model could be used successfully during covariate model development and therefore no further restrictions in terms of fixing the THETAs for K_A and T_{LAG} were made. Model evaluation revealed that the final population model was appropriate to describe the pharmacokinetics of carvedilol in the paediatric population. Additionally, the comparison of population model-based Bayesian post hoc pharmacokinetic parameters and individual ones (calculated with WinNonlin) confirmed that. Nevertheless, there might be other covariates, not yet detected, which influence the pharmacokinetics of carvedilol, because the DV vs. PRED and WRES vs. PRED plots still show some deviations. For the WRES vs. PRED plot, the most deviating points could basically be ascribed to four patients; up to now, no correlations between them have been identified.

Because of age-dependent differences for CL, the AUC as a measure of drug exposure differs substantially between different age groups, with lower values for younger patients. To increase the exposure, either the dose level can be increased or the dosing interval can be shortened. Both options were tested during simulation. The median AUC_{0–12} of a 19.3-year-old patient calculated from 100 simulations with 0.35 mg kg⁻¹ bid served as target

AUC. This is the usual dose for an adult, and the median AUC_{0–12} for this patient (495.4 μg h⁻¹ l⁻¹) was comparable to known adult values (554 ± 485 μg h⁻¹ l⁻¹; $n = 20$) [15]. The median C_{max} of 100 simulations for this patient (133.5 μg l⁻¹) was also comparable (108 ± 68.7 μg l⁻¹) [15]. For the bid dosing strategy, daily doses of 3, 2 and 1 mg kg⁻¹ for infants, children and adolescents were necessary to reach a similar median AUC_{0–12} and not to exceed the 90th percentile of the 19.3-year-old patient. The same daily doses administered tid reached little higher values for the median AUC and the 90th percentile because of accumulation. Therefore, one might suggest lower daily doses with the tid dosing strategy. As expected, C_{max} values were higher with the bid compared with the tid dosing strategy, but overall comparable with the values for the 19.3-year-old patient. Considering the clinical approach of initiating β-blocker therapy, it seemed reasonable to accept a higher drug exposure than a lower one: β-blockers are slowly uptitrated to the individual tolerated target dose. Target doses are recommended, but not obligatory to reach, unlike, for example, therapy with antibiotics. It should be decided individually whether the bid or tid dosing strategy is preferable. For patients reacting with a pronounced decrease in blood pressure after β-blocker uptake, the tid dosing strategy with lower single doses and peak plasma concentrations might be preferable. Adolescents might be more compliant with the bid dosing strategy. The recommended doses are far removed from the no-observed-effect dose level for overt toxicity and impairment of fertility, which is 60 mg kg⁻¹ day⁻¹ in rats [39].

Up to now, the carvedilol dosing strategy for paediatric patients has been uniform for all age groups. However, the

Figure 5

Simulated concentrations for each age group receiving the recommended age dependent target dose. (A) 1.0-year-old patient receiving 1.5 mg bid. (B) 7.5-year-old patient receiving 1.0 mg bid. (C) 14.5-year-old patient receiving 0.5 mg bid. (D) 19.3-year-old patient receiving 0.35 mg bid. The simulated concentrations (grey squares), their median (continuous line), 10th and 90th percentile (dotted line) were compared with the measured concentrations (!) for the target dose level of the study (0.35 mg bid); in case there were no measured concentrations available for this dose level the median of the simulated concentrations was used (A + D)

target dose has differed substantially in different investigations. Azeka *et al.* have investigated prospectively the treatment with carvedilol against placebo and included 22 patients from 3.2 months to 10 years; the mean age was 2.1 years and all patients had an LVEF <30% [5]. The target dose was $0.2 \text{ mg kg}^{-1} \text{ day}^{-1}$. After 6 months the LVEF was significantly improved for the carvedilol group, but not for the placebo group. Shaddy *et al.* included 161 children aged between 3 months and 17 years in their recent investigation [7]; 45% percent of patients were <2 years old. Patients were assigned to $0.4 \text{ mg kg}^{-1} \text{ day}^{-1}$, $0.8 \text{ mg kg}^{-1} \text{ day}^{-1}$ carvedilol or to placebo. Concerning the primary end-point, carvedilol was not superior to placebo.

The authors discussed an unexpectedly high placebo effect and a large number of patients of heart failure class II (71%) as potential reasons for their negative findings. With regard to the results of the current work, one can assume that the young patients from the study by Shaddy *et al.* were treated with too low doses of carvedilol. The patient population from Azeka *et al.* was different regarding their cardiac function and smaller than the population of Shaddy *et al.* This might be one reason why the carvedilol treatment was successful in the study by Azeka *et al.* despite the low target dose. In general, however, higher doses of carvedilol are probably required for younger patients.

For the dose simulations, we assumed that reaching the same drug exposure is desirable for all patients. Pharmacodynamic aspects have so far not been included in these simulations. Carvedilol might have a higher potency in younger patients with regard to heart rate reduction, as earlier results from our group with a smaller population suggest [40]. Additionally, genetic polymorphisms have been described for the β_1 - and β_2 -receptor, but little is known about their relevance to β -blocker therapy [41]. Pharmacodynamic aspects should be further investigated. The influence of comedication on the pharmacokinetic parameters of carvedilol was not investigated during model development. For all patients the cardiac comedication was the same, consisting of an ACE-inhibitor, diuretics and cardiac glycosides. There is a known interaction between carvedilol and digoxin, as both are substrates of P-gp. Administered simultaneously, carvedilol acts as a competitive inhibitor of P-gp, resulting in increased digoxin plasma concentration, but no change in carvedilol plasma concentration [13]. For thiazides and loop diuretics, no pharmacokinetic interactions with carvedilol have yet been described [39]. ACE-inhibitors interact at the pharmacodynamic level, but again no pharmacokinetic interaction has yet been described [42]. Therefore, an influence of cardiac comedication on the pharmacokinetic parameters of carvedilol is unlikely for the investigated population. It should also be noted that our recommended dosing strategy is based on the oral administration of a suspension. The bioavailability for capsules or tablets might be slightly lower, as known from adults, where the bioavailability of capsules is 93% of that of a suspension [8]. Therefore, even higher doses might be necessary for paediatric patients using capsules or tablets.

In conclusion, a population pharmacokinetic model has been developed for carvedilol in paediatric patients. Age and weight were the most important covariates. Simulations revealed that for infants (28 days to 23 months), children (2–11 years) and adolescents (12–15 years) daily doses of 3, 2 and 1 mg kg⁻¹, administered in two or three discrete doses, were necessary to reach an exposure comparable to adults receiving 0.7 mg kg⁻¹ day⁻¹. These age-dependent differences have to be considered for further RCTs investigating the efficacy of carvedilol in order to prevent ineffective therapy and potentially biased RCT results.

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