Population Pharmacokinetics and Dose Simulation of Carvedilol in Pediatric Patients with Congestive Heart Failure

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1 Introduction and Objective

The nonselective β-blocker carvedilol is typically administered with a dose linearly delineated from adults for the treatment of pediatric patients with congestive heart failure (CHF). The results with this dosing strategy are ambiguous[1-3] and challenge the well established and successful adult gold standard of ß-blocker therapy in patients with CHF.

Applying in-silico tools like population pharmacokinetics (POP-PK) and simulation analyses will help to find adequate dosing strategies. This may increase the probability of success for randomized controlled trials (RCT) aiming at efficacy.

Therefore, our objective was to investigate the ontogeny of carvedilol pharmacokinetics by POP-PK analysis. Dose simulations were performed to investigate the carvedilol dosing strategy for pediatric patients.

2 Study Design and Patient Population

Prospective, open-label study of carvedilol for the treatment of pediatric patients with CHF:

Inclusion criteria:
- both sexes
- diagnosed CHF
- max. heart failure therapy
- stable clinical situation

Exclusion criteria: e.g.
- hypertension,
- bradycardia
- acute myocarditis
- terminal renal or hepatic insufficiency etc.

Patients Characteristics		n (%)
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)

	Median (Range)
Age [years]	3.5 (0.1 - 19.3)
Weight [kg]	13.1 (3.1 - 98.2)
CYP2D6-activity	-2.4 (-1 - (-3.5))

VSD = Ventricular septal defect; MI = Mitral insufficiency; HLH = Hypoplastic left heart syndrome; DCM = Dilatative cardiomyopathy; LVEF = Left ventricular ejection fraction

- Uptitration from 0.09 mg/kg to 2 x 0.35 mg/kg (BID) oral carvedilol
- Determination of up to 13 plasma concentrations during one dosing interval using a validated HPLC-assay[4]
- Determination of CYP2D6-activity for patients > 6 months

3 Population Pharmacokinetic Model Development

Total log-transformed plasma concentrations were analysed using NONMEM, Version V 1.1:

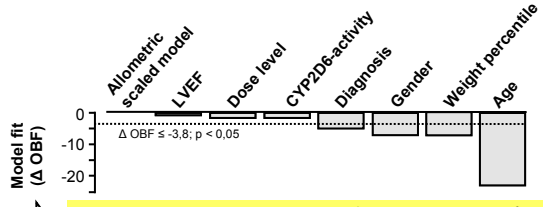
⇨ Structural Model: 2-compartment model with first order absorption and lagtime using ADVAN4 TRANS4 routine and FO estimation method (final model was rerun with FOCE with interaction)

⇨ Exponential error models to allow for between-subject variability; additive error model to model residual variability

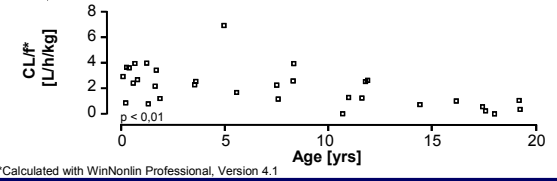
⇨ Allometric weight normalization for clearances and volume of distribution parameters[5]

⇨ ALLOMETRIC SCALED MODEL = BASE MODEL FOR COVARIATE MODEL DEVELOPMENT

4 Covariate Model Development for Clearance (CL): CL/kg Decreases with Age (also Confirmed by the Measured Data)



$CL\ [L/h] = 38.1 \times (weight\ [kg]/13)^{0.75} - ((age\ [yrs]/3.5)^{\theta 7})$



*Calculated with WinNonlin Professional, Version 4.1

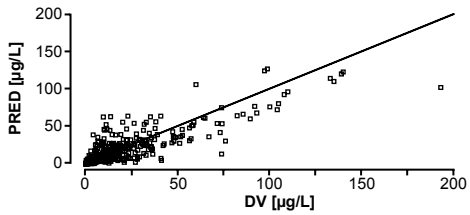
5 Final Model: Age and Weight are the Most Important Covariates for Carvedilol Pharmacokinetics

Parameter	Model	Estimate (CV [%])	Bootstrap Mean*
CL/f [L/h]	θ_1*(weight [kg]/13)$^{0.75}$-((age[yrs]/3.5)$^{\theta 7}$)	38.1 (7.1)	37.6
V2/f [L]	θ_2*(weight [kg]/13)*(1+(θ_8*age [yrs]/3.5))	22.0 (22.7)	21.8
V3/f [L]	θ_3*(weight [kg]/13)	96.5 (22.7)	103.7
Q/f [L/h]	θ_4*(weight [kg]/13)$^{0.75}$	13.5 (12.8)	13.6
KA [1/h]		0.62 (5.7)	0.62
TLAG [h]		0.15 (12.5)	0.15
θ_7		2.70 (2.2)	2.67
θ_8		-0.13 (18.0)	-0.12

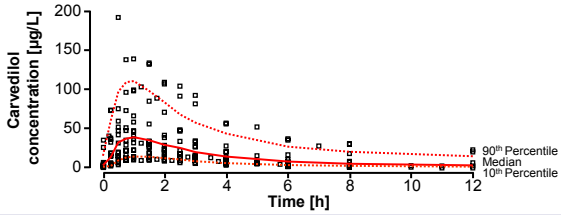
*n = 1000; Wings for NONMEM, Version 409d

6 Model Evaluation and Performance

a) Observed (DV) vs. predicted (PRED) concentrations: r = 0.859

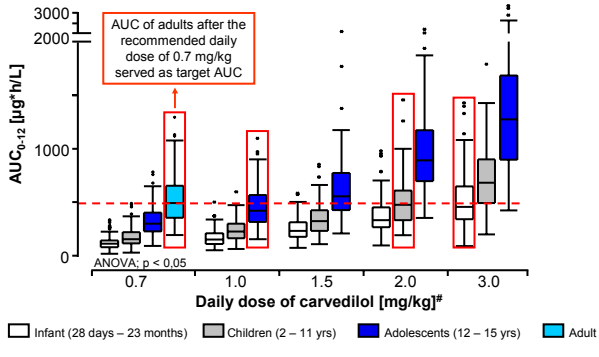


b) Predictive check: about 90% of the measured data (□) are within the 90th percentile of the simulated concentrations (100 replicates)



7 Results for Dose Simulations*

⇨ For infants, children and adolescents daily doses of 3, 2 and 1 mg/kg, administered in two or three doses, are necessary to reach an exposure (AUC) comparable to adults!



*using NONMEM: n = 100 replicates; #administered in two doses

8 Conclusion

For further RCTs investigating the efficacy of carvedilol for pediatric patients with CHF it has to be considered that younger patients have to be treated with higher doses. Otherwise the drug exposure might be ineffective and results might be biased.

References

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