

PHARMACOKINETICS OF CARVEDILOL IN CHILDREN WITH CONGESTIVE HEART FAILURE

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Abstract

In order to study the pharmacokinetics of carvedilol (CVD) in children with congestive heart failure, multiple per os doses of 0.05-0.1-0.2-0.4-0.8 mg/kg body weight were administered to 5 children, with at least one week wash-out time among doses. Plasma concentrations of CVD were determined during a 24 hours period following drug administration. Pharmacokinetic parameters of CVD were calculated using non-compartmental analysis. Following administration of CVD doses between 0.05-0.8 mg/kg bw, the mean normalized peak plasma level (C_{max}) was 5.13 ± 2.89 ng/mL. The time taken to reach C_{max} , t_{max} , was 0.93 ± 0.39 h and the total area under the curve ($AUC_{0-\infty}$) normalized to dose was 20.4 ± 12.89 (ng/mL)·h. The mean half-life of CVD was 3.12 ± 1.37 h. Although there is a large inter- and intra-subject variability, the pharmacokinetics of CVD in children with congestive heart failure is linear and some pharmacokinetic parameters (half-life, mean residence time) have different values in comparison with those registered in healthy adult population.

Rezumat

În vederea studierii farmacocineticii carvedilolului (CVD) la 5 copii cu insuficiență cardiacă congestivă, s-au administrat doze multiple pe cale orală (0,05-0,1-0,2-0,4-0,8 mg/kg corp), păstrând cel puțin o săptămână de *wash-out* între două doze succesive. Concentrațiile plasmatice ale CVD au fost determinate pe o perioadă de 24 de ore după fiecare administrare. Parametrii farmacocinetici ai CVD au fost obținuți utilizând analiza farmacocinetică non-compartimentală. După administrarea unor doze de CVD între 0,05 și 0,8 mg/kg corp, concentrația maximă (C_{max}) normalizată la doză a fost de $5,13 \pm 2,89$ (ng/mL)·h. Timpul de atingere a C_{max} , t_{max} , a fost de $0,93 \pm 0,39$ ore iar aria de sub curbă normalizată la doza ($AUC_{0-\infty}$) a fost de $20,4 \pm 12,89$ ng·oră/mL. Timpul de înjumătățire mediu al CVD a fost de $3,12 \pm 1,37$ ore. Deși există variabilitate inter- și intra-individuală mare, farmacocinetica CVD la copiii cu insuficiență cardiacă congestivă este liniară, iar unii parametrii farmacocinetici (timpul de înjumătățire, timpul mediu de rezidență) au valori diferite de cele ale adulților sănătoși.

Keywords: carvedilol, pharmacokinetics, congestive heart failure

Introduction

Carvedilol (CVD) is a non-cardioselective β/α_1 -adrenoreceptor blocker and is used as an antihypertensive and an antiangina drug, being

recognized as an effective agent for the treatment of congestive heart failure (CHF) [1]. CVD is well absorbed after oral administration but its absolute bioavailability is low, about 25–30% due to an extensive first-pass metabolism. The peak concentrations in plasma occur about 1–2 h and the plasma levels are linearly related to the administered dose, up to 0.3 mg/L. The half-life of CVD in plasma is of 4–8 hours. Only 1% of CVD is excreted unchanged in urine [2, 3].

Congestive heart failure (CHF) is rather frequent in childhood and assumes high material costs and a significant death rate. CHF in children presents important characteristics features from the adult congestive failure, from a physiopathological, etiopathogenical and therapeutical point of view. While the CHF at adult age is due to ischemia in 60–70% of cases, CHF at children is, in most cases, a consequence of either congenital heart diseases (CHD) which remained unoperated, undergone a palliative operation or presented postsurgery complications, or of a cardiomyopathy. We underline the fact that the incidence of the CHD is of 8/1000 alive new-born children and that, in Romania, there are born, annually, between 800 and 1300 children having a CHD. Out of these, more than 50% develop at least once congestive cardiac failure during their first childhood, in accordance to our information [4].

Regarding therapeutical issues in the pediatric CHF, at present, there are no therapeutical guidelines for pediatric CHF and specific research is limited [5]. The therapy is, mainly, based on adult cases data. The angiotensin conversion enzyme inhibitors (ACEI) along with the diuretics represent the first line medication. If needed, digitalics can be associated. Beta-blokors such as CVD are recommended in pediatric CHF which does not improve under conventional therapy with ACEI, diuretics, digitalics. CVD is more frequently used in adult therapy whereas, in pediatrics, there are very few studies which led to disputed conclusions [6].

The aim of our study was to assess the pharmacokinetics of CVD in children with congestive heart failure.

Materials and methods

Subjects

Five children took part in the study. The study was conducted according to the principles of the Declaration of Helsinki (1964) and its amendments (Tokyo 1975, Venice 1983, Hong Kong 1989) and Good Clinical Practice (GCP) rules. The clinical protocol was reviewed and approved by the Ethics Committee of the University of Medicine and Pharmacy “Iuliu Hatieganu”, Cluj-Napoca, Romania. The parents of the

children involved in the research gave their written informed consent prior to study inclusion. The main demographic and pathologic characteristics of the subjects included in the study are presented in Table I.

Table I
The main demographic and pathologic characteristics
of the subjects included in the pharmacokinetic study

Subject cod	Sex	Age (years)	DIAGNOSIS	Score ROSS/ NYHA*	Weight (kg)	Height (cm)	EFLV
DD	F	0.8	DCMP	III	6.000	72	EF<20%,
DMS	M	1.3	sDCMP DORV, GAT	III	8.100	75	EF< 30%
MD	M	6.1	DCMP	IV	22.0	125	EF 15.6%
SGL	M	2	DCMP	III	9.800	79	EF< 30%
MGP	F	2	DCMP	IV	8.300	78	EF 27%.

Abbreviations

F – Female

M – Male

DCMP – Dilated Cardiomyopathy

sDCMP – Secondary Dilated Cardiomyopathy

DORV – Double Outlet Right Ventricle

GAT – Great Arteries Transposition

EFLV – Ejection Fraction of Left Ventricle

EF – Ejection Fraction

*score used for evaluating cardiovascular disfunctions (Ross classification/NYHA; New York Heart Association) classification

Study design

The subjects included in the study had primitive or secondary dilated cardiomyopathies and CHF functional class NYHA/ROSS II-IV. They were treated with conversion enzyme inhibitors (ACEI), diuretics, digitalics, being unresponsive to the conventional therapy, therefore eligible for the carvedilol treatment. The ejection fraction of the left ventricle (measured by echocardiography) was very reduced (more than half of the normal value) despite conventional therapy lasting more than 8 weeks, which represented another eligibility criterion for the carvedilol therapy, respective its pharmacokinetic study. The patients were itemed as follows (code-number-dose): DD1 with 0.05 mg/kgbw; DD2 with 0.2 mg/kgbw; DD3 with 0.4 mg/kgbw, DD4 with 0.8 mg/kgbw; DMS1 with 0.1 mg/kgbw; DMS2 with 0.2 mg/kgbw; MD [1-2-3-4] with doses [0.1-0.2-0.4-0.8], SGL1 with dose 0.1; MGP1, MGP2 and MGP3 with doses 0.1, 0.2 and 0.4 mg/kgbw.

Venous blood (2 mL) was drawn into heparinized tubes, at 0.5, 1, 2, 4, 6, 8, 10 and 24 hours after drug administration and the separated plasma was stored frozen (-20°C) until analysis.

Analysis of plasma samples

CVD plasma concentrations were determined by a validated LC/MS method [7], according to previous established criteria [8-10].

Pharmacokinetic analysis

The non-compartmental pharmacokinetic analysis method was employed to determine the pharmacokinetic parameters of CVD [11, 12]. The maximal plasma concentration (C_{max} , ng/mL) and the time to reach the peak concentration (t_{max} , h) were obtained directly by the visual inspection of each subject's plasma concentration-time profile. The area under the concentration-time curve (AUC_{0-t}) has been estimated by integration using trapezoidal rule from time zero to the last measurable concentration at time t . The area was extrapolated to infinity ($AUC_{0-\infty}$) by addition of C_t/k_{el} to AUC_{0-t} where C_t is the last quantifiable drug concentration and k_{el} is the elimination rate constant. The elimination rate constant k_{el} was estimated by the least-square regression of plasma concentration-time data points lying in the terminal region by using semilogarithmic dependence that corresponds to a first-order kinetics. The half-life ($t_{1/2}$) was calculated as $0.693/k_{el}$. The pharmacokinetic analysis was performed using Kinetica 4.0.2 (Thermo Labsystems, U.S.A.).

Results and discussion

The carvedilol study in pediatric pathology started in 1999, and in 2001 the first research results were published, followed, in the next years, by just a few more. Most of them were clinical studies, based on a limited number of cases, represented by patients of very different ages (varying between 6 weeks to 19 years) [7-13]. The results were mostly positive, a quick response to the beta-blockers being associated to an increasing rate of survival and a decreasing rate of cardiac transplant recommendation. In a clinical study conducted by our team, on a limited number of cases, we observed positive effects (in view of the NYHA/ROSS score and of the left ventricle ejection fraction) at pediatric patients having Congestive heart failure (CHF) [15]. The conclusions of the only existing pediatric trial were published by Shaddy in 2007 [16]. They show there is a need of other research and that there are different effects of CVD, depending on ventricular morphology. The pharmacokinetics research on CVD in pediatrics is scant. Laer et al. reported a study in which the traditional therapy failed in the case of 15 children with CHF (aged between 6 weeks and 19 years) observed [17]. They compared CVD's pharmacokinetics in the case of those 15 children with the one found in the case of 9 healthy

adults. The diminishing to half time was significantly shorter at children in comparison with adults (2.9 in contrast with 5.2 hours). By dividing the children in two groups (under and above 3.5 years old), the medium time registered was 2.2 hours at children under 3.5 years and 3.6 hours in the case of those above the mentioned age. According to the actual research studies, the CVD dosing in infants uses 0.05-2 mg /kgbw/day divided in 2 administrations. The mentioned doses can be titrated every 1 or 2 weeks, as needed, there have been used target doses of 0.2-1mg/kgbw/day, with a maximum of 2 mg /kgbw/day [18, 19].

Typical plasma levels of CVD, administered to subjects coded DD and MGP are presented in Fig. 1.

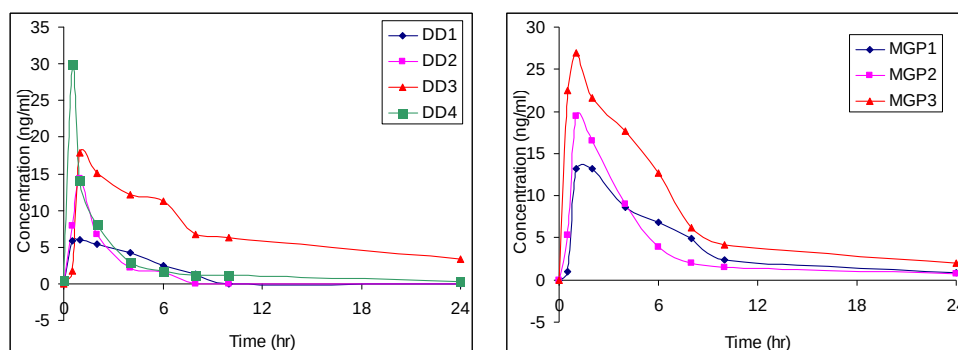


Figure 1

The plasma levels of CVD in two children (coded DD and MGP) with congestive heart failure after administration of different dose levels (DD1 and MGP1 – 0.05 mg/kgbw; DD2 and MGP – 0.2 mg.kgbw, DD3 and MGP3 – 0.4 mg/kgbw, DD4 – 0.8 mg/kgbw)

The calculated pharmacokinetic parameters of CVD for each subject and each dose level are presented in Table II. In order to provide statistics for the parameters having values related to the dose (C_{max} and $AUC_{0-\infty}$), they have been normalized to the smallest dose administered (0.05 mg/kgbw).

From the pharmacokinetic analysis results, one can observe that the peak plasma level of CVD (C_{max}) is increasing with the dose. However, that increase is not always linear, probably due to a large intra-subject variability. The exposure to the drug, given by the area under the curve ($AUC_{0-\infty}$) is also increasing linearly with the dose. For example, in subject coded DMS, the exposure is increasing from 32.87 (ng/mL)·h to 64.13 (ng/mL)·h, for a dose increase from 0.1 to 0.2 mg/kgbw. The time for reaching peak plasma level, T_{max} , is about the same for all subjects included in the study, 0.93 ± 0.39 hours. The mean residence time (MRT) of

CVD in the body is about 4.50 ± 1.44 hours and the mean half-life is about 3.12 ± 1.37 hours, with a median of 2.73 hours (table II).

Table II
The mean pharmacokinetic parameters of CVD administered at multiple dose levels in children with congestive heart failure

	Dose	Cmax	Cmax	Tmax	AUC _{0-∞}	AUC _{0-∞}	t _{1/2}	MRT*
Subject code	mg/kgbw	ng/mL	(normalized to dose)	h	ng/mL*h	(normalized to dose)	h	h
DD1	0.05	6.04	6.04	1.00	34.29	34.29	2.29	4.25
DD2	0.20	14.37	3.59	1.00	33.56	8.39	2.00	2.94
DD3	0.40	17.80	2.23	1.00	142.30	17.79	4.75	7.97
DD4	0.80	29.94	1.87	0.50	60.24	3.77	7.05	5.79
DMS1	0.10	10.66	5.33	1.00	32.87	16.44	1.84	3.25
DMS2	0.20	13.54	3.39	1.00	64.13	16.03	3.84	5.82
MD1	0.10	7.82	3.91	2.00	36.76	18.38	2.40	4.20
MD2	0.20	8.52	2.13	0.50	22.03	5.51	2.45	2.76
MD3	0.40	68.49	8.56	0.50	158.33	19.79	2.71	3.48
MD4	0.80	192.72	12.05	1.00	765.99	47.87	2.81	4.59
SGL1	0.10	15.78	7.89	0.50	31.90	15.95	3.13	3.49
MGP1	0.10	13.23	6.62	1.00	85.59	42.80	3.28	5.79
MGP2	0.20	19.49	4.87	1.00	76.11	19.03	2.30	3.84
MGP3	0.40	26.96	3.37	1.00	156.64	19.58	2.75	4.83
N	-	14	14	14	14	14	14	14
Mean	-	-	5.13	0.93	-	20.40	3.12	4.50
Geometric mean	-	-	4.45	0.86	-	16.63	2.91	4.31
SD	-	-	2.89	0.39	-	12.89	1.37	1.44
Median	-	-	4.39	1.00	-	18.08	2.73	4.23

*MRT= mean residence time

Our results are in good agreement with literature data [18,21,22] and with some other personal research on CVD's pharmacokinetics on healthy adult population (unpublished data), where the findings show that CVD has a shorter half-life in children than in adults. In literature data, half-life values between 2.5 and 3 hours were reported for CVD in children [18,21,22]. In a pharmacokinetic study of CVD in healthy adult volunteers, we found a mean half-life of 5.46 ± 2.12 for CVD (unpublished data), about 75% higher than the value in children with congestive heart failure ($p=0.0218$, t test for non-paired values). The differences between children and adults regarding the volume of hydro-compartments and renal/hepatic clearance could explain the differences observed in the half-life of CVD.

Conclusions

The pharmacokinetics of CVD in children with congestive heart failure (CHF) was studied using the non-compartmental pharmacokinetic analysis method. The main pharmacokinetic parameters of CVD were calculated. Generally the peak plasma level of CVD ($C_{\max}$) and the exposure to the drug, ($AUC_{0-\infty}$) are increasing with the dose. The mean residence time of CVD in the body is about 4.50 ± 1.44 hours and the mean half-life is about 3.12 ± 1.37 hours. Significant differences of the half-life between healthy adults (values from other papers) and children with congestive heart failure were observed.

Acknowledgements

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