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Research Article

Age-Related Distribution of Cyclosporine Concentrations in Liver Transplant Patients - Comparative Population Pharmacokinetic Retrospective Observation

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Abstract

Immunosuppression following solid organ transplantation is important therapy for the survival of both allograft and patient. After Orthotopic Liver Transplantation (OLT) many patients are treated by emulsified cyclosporine (Neoral®). 20 patients (8 adults and 12 children) who were on Neoral® postorthotopic liver transplantation over a 5 year period were studied (2004-2009). All patients received Neoral® twice daily orally at 08:00 AM and at 08:00 PM. C_0 drug concentrations were recorded in morning (C_0AM) and in evening before each dosing (C_0PM) and C_2 concentrations - in morning and in evening 2 hours post-dosing (C_2AM and C_2PM). A total of 323 CsA C_0 in children group and 242 C_0 in adult group and a set of 117 CsA C_2 in children group and a set of 133 C_2 in adult group were analyzed. Population Pharmacokinetic (PK) analysis was performed with dose normalized to 1 mg/kg cyclosporine concentrations in order to avoid Body Weight (BW) differences between the two age groups. Statistical distributions of CsA blood concentrations at the end of each dose interval and 2 hrs after each oral dose are characterized by non-Gaussian distributions skewed to the right. Normalized $C_{0(trough)}$ and C_2 CsA concentrations were significantly lower in liver transplant children than in adults. The probit analysis confirmed the non-Gaussian distributions and revealed well-distinguishable subgroups of CsA $C_{0(trough)}$ and C_2 levels deviating from linearity and suggestive of non-Gaussian clearance distributions in both age groups of liver transplant patients. Blood concentrations of CsA at the end of each dose interval and 2 hours after each oral dose demonstrated significantly higher variability in liver transplant children, which identifies them as a higher risk group when using standardized dose regimens and draws attention to the need for strictly individualized CsA therapy in this age population. Statistically significant correlation was observed between serum creatinine(Scr) and the normalized CsA $C_{0(trough)}$ concentrations measured on the second day after liver transplantationin adult patients. The applicability of C_2 monitoring to paediatric patients is still being debated given the age-specific properties of CsA. While C_0 monitoring frequently results in overdosing and renal dysfunction, C_2 monitoring may lead to episodes of under dosing and rejection. Therefore better ways of monitoring cyclosporine dosing need to be devised. The statistically significant correlation between Scr and the normalized CsA $C_{0(trough)}$ concentrations in adult patients on the second day after liver transplantation, if confirmed on a larger sample of liver transplanted patients, points to the possibility of Scr being used as a biomarker for individualization of CsA therapy in these transplanted patients.

Keywords: **Liver Transplantation; Cyclosporine; TDM; C_0 And C_2 Cyclsporine Concentrations; Serum Creatinine**

Introduction

Immunosuppression following solid organ transplantation is important therapy for the survival of both allograft and patient. After Orthotopic Liver Transplantation (OLT) many patients are treated by emulsified cyclosporine (Neoral®). Cyclosporine is a narrow therapeutic window drug widely used as Calcineurin Iinhibitor (CNI) during 2004-2009 in the treatment of liver transplant patients in Bulgaria. Too low systemic exposure of the drug results in allograft rejections, where as too high systemic exposure leads to adverse effects such as renal insufficiency and elevated blood pressure [7]. Usually Neoral® is given twice daily. Data showed that blood levels 2 hours post dosing (C_2) were better than trough (C_0) levels in predicting drug systemic exposure over a 12 hr dosing interval. However, limited data are published on clinical outcomes of C_2 monitoring in liver transplant patients. We have investigated age-related variations in C_0 and C_2 cyclosporine concentrations in liver transplant patients in two different recipient age groups. The aim of this retrospective observation by population pharmacokinetic analysis is a comparative investigation of normalized blood $C_{0(trough)}$ and C_2 concentrations of cyclosporine (CsA) in children and adults early after liver transplantation period during the first month after the orthotopic LT.

Materials and Methods

20 patients (8 adults and 12 children) who were on Neoral® postorthotopic Liver Transplantation (LT) over a 5 year period were studied (2004-2009). All patients received Neoral® twice daily orally at 08:00 AM and at 08:00 PM. Whole blood CsA concentrations were measured by FPIA (Abbott Diagnostics). C_0 drug concentrations were recorded in morning (C_0AM) and in evening before each dosing

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(C_0PM) and C_2 concentrations - in morning and in evening 2 hrs post-dosing (C_2AM and C_2PM). A total of 323 CsA C_0 in children group and 242 C_0 in adult group and a set of 117 CsA C_2 in children group and a set of 133 C_2 in adult group were analyzed. Population pharmacokinetic (PK) analysis was performed with dose normalized to 1 mg/kg cyclosporine concentrations in order to avoid Body Weight (BW) differences between the two age groups. Within and between differences of drug concentrations in the adults and children groups for C_0AM, C_0PM and C_2AM and C_2PM were statistically analyzed. Statistical analysis was performed with Graph Pad Prism 5.0 program and Origin 5.0. As classical statistical tests for normality (Kolmogorov Smirnov, D'Agostino& Pearson and Shapiro-Wilk) showed non-Gaussian skewed to the right distributions of concentrations of CsA in both age groups, the results were presented as medians (Me) with corresponding 95% Confidence Intervals (CI) generated by the 2.5th to 97.5th percentile . The differences in median values were tested for statistical significance by the non-parametric Mann Whitney test and $p \leq 0.05$ was considered as statistically significant.

Theoretical considerations

The Steady State (SS) of blood (plasma) drug concentrations is achieved when the quantity of drug input in the body for a given dosage interval equals the quantity of drug output for the same dosage interval *(τ,T)*.

The maintenance drug dose in steady state is calculated as:

$(F)D = C_{target}$ .CL.T (1)

Where C_{target} are usually C_{min} and C_{max}, which determine the fluctuations of plasma drug concentrations in SS, with C_{min} usually referred to as "$C_{(trough)}$s". Specifically, in the case of our study, the symbol is $C_{0(trough)}$ for trough levels and C_2 as a substitute for C_{max}, as it was assumed that the maximum CsA concentrations are observed about 2 hours after oral administration (US, B. B. (n.d.). Neoral Prescribing Information. Retrieved July 12, 2018, from https://www.pharma.us.novartis.com/product-list). CL stays for CsA blood clearance and T is the dosing interval. From (1) follows that

$C_{target} = [(F)D/T]/CL$ (2)

Taking into consideration that both target concentrations are normalized to a CsA dose of 1 mg/kg and T=12 hours, it follows that the term [(F)D/T] is a constant and when replacing it with the factor "a" in (2)

$C_{target} = a.CL^{-1}$(3)

It follows from (3) that the CsA normalized $C_{0(trough)}$ and C_2 levels can be considered as biomarkers for its CL and their statistical distribution will represent the distribution of CL^{-1}.

Results

On Tables 1 and 2 are presented the demographic characteristics of adults and paediatric patients. Statistical distributions of CsA blood concentrations at the end of each dose interval and 2 hrs after each oral dose are characterized by non-Gaussian distributions skewed to the right. The Mann Whitney test revealed highly significant difference between the medians (Me) of the distributions of CsA normalized $C_{0(trough)}$ sin the two groups of liver transplant patients ($p<0.0001$) (Figure 1). The comparison between the median estimates of normalized CsA C_2 distributions by Mann Whitney test indicated statistically significant difference ($p< 0.044$).

Table 1: Demographic characteristics of adults LT patients.

Patient #	Gender*	Age (years)	Diagnosis*	LT	Weight (kg)	Height (cm)
1	F	26	PBC, LC	OLT	64	160
2	F	22	LC(Genesis Autoimmunity)	OLT	75	172
3	F	37	PBC, LF	OLT	61	163
4	M	58	LC	OLT	65	165
5	M	18	LC	OLT	72	183
6	M	43	LC	OLT	70	178
7	M	53	LC	OLT	105	182
8	M	34	LC (cryptogenic)	OLT	62	180

*F: Female; M: Male; PBC: Primary Biliary Cirrhosis; LC: Liver Cirrhosis; LF: Liver Failure; OLT: Orthotopic Liver Transplantation.

Table 2: Demographic characteristics of paediatric LT patients.

Patient #	Gender	Age	Weight (kg)	Height (cm)	Diagnosis*
AEM	F	5 m/o	5.6	60	CBA, LC, A
ASA	F	1 y/o	7.6	71	LC
ATT	F	6 m/o	6.7	64	CBA
BAC	M	6 m/o	5.6	62	CBA, LF
EEM	F	9 m/o	6.4	65	CBA, CBC
ISG	M	3 y/o	11.8	88	LC
JMM	F	4 y 7 m/o	20	104	CBA
PPV	F	7 m/o	7.4	67	CBA, LC, A
SZA	F	8 m/o	7.7	69	CBA
SZS	F	12 y/o	50	154	APV, HA, LC
TFB	F	7 m/o	6	64	CBA, CBC, CLF
VStI	F	8 y/o	18	110	CBA, LC

*CBA: Congenital Biliary Artesia; LC: Liver Cirrhosis; A: Ascites, LF: Liver Failure; CBC: Congenital Biliary Cirrhosis; APV: Artesia of the Portal Vein; HA: Hepatic Adenomatosis; CLF: Chronic Liver Failure

Normalized $C_{0(trough)}$ and C_2 CsA concentrations were significantly lower in liver transplant children than in adults.

The probitanalysis confirmed the non-Gaussian distributions and revealed well-distinguishable subgroups of CsA $C_{0(trough)}$ and C_2levels deviating from linearity and suggestive of clearance not belonging to the Gaussian population in both age groups of liver transplant patients (Figure 2).

Blood concentrations of CsA at the end of each dose interval and 2 hrs after each oral dose demonstrated significantly higher variability in liver transplant children, which identifies them as a higher risk group when using standardized dose regimens and draws attention to the need for strictly individualized CsA therapy in this age population (Table 3).

Statistically significant correlation was observed between Serum Creatinine (Scr) and the normalized CsA $C_{0(trough)}$ concentrations measured on the second day after liver transplantationin adult patients (Figure 3).

Discussion

A body of clinical investigations have confirmed the superiority of C_2 monitoring when using the CsA micro emulsion Neoral® in preventing of acute rejection in *de novo* liver transplant recipients without detrimental effects on renal function and the importance of monitoring of maintenance trough CsA levels for avoiding the unexpected over- or under-exposure to CsA [1,2]. The applicability of C_2 monitoring to paediatric patients is still being debated given the age-specific properties of CsA. Since there are two unique features to consider regarding the pharmacokinetics of CsA in paediatric patients: 1) the bioavailability of CsA correlates with age, being lower in younger patients, and 2) paediatric patients have a higher rate of metabolism [3,4], the guidelines established in adult patients may not apply to paediatric patients.

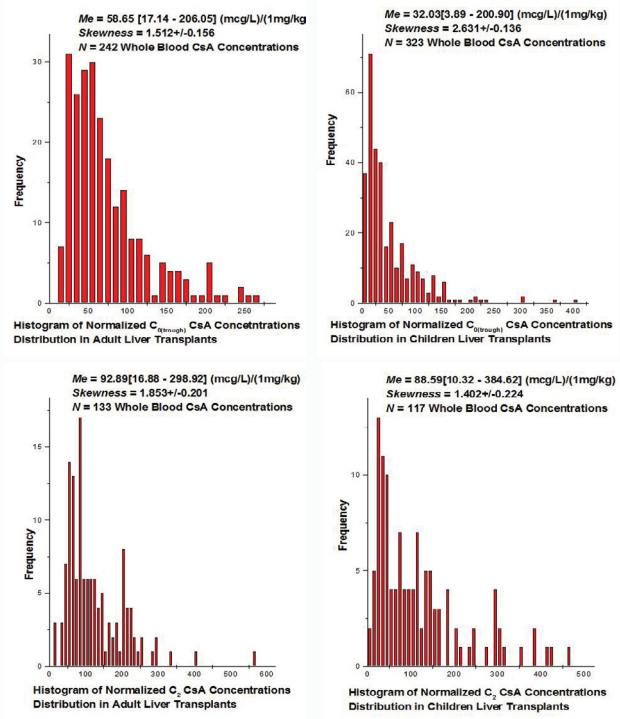

Figure 1: Comparison between the distributions of normalized CsAC0(trough) and C2 concentrations in adult and children liver transplants. Mann Whitney test revealed significant difference of median estimates between the two groups of liver transplant patients.

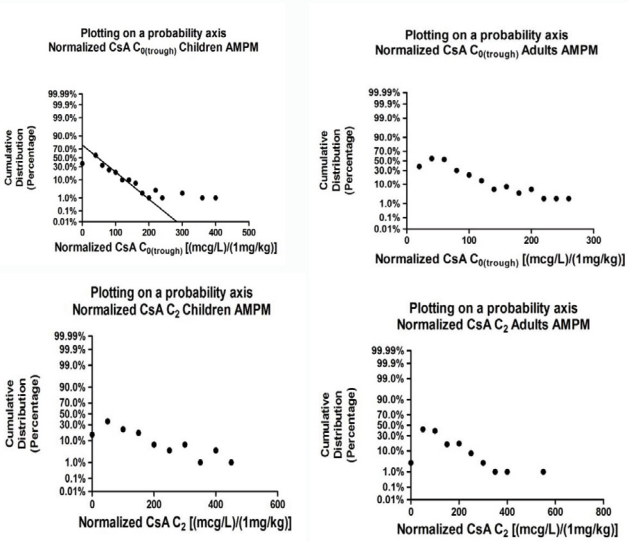

Figure 2: Probit analysis of the cumulative frequency distributions of normalized CsAC0(trough) and C2 concentrations in both groups of liver transplant patients [AMPM stays for morning (AM) and evening (PM) CsA blood sampling].

Table 3: Comparative variability of CsA normalized $C_{0(trough)}$ and C_2 concentrations in liver transplanted children and adults.

	CV (%) ($C_{0\ (trough)}$))	CV (%) (C_2)
Children	107.26	88.28
Adults	68.57	66.82
Differences	1.56 times	1.32 times

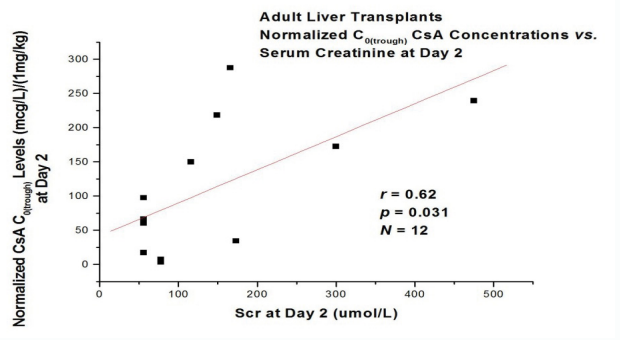

Figure 3: Relationship between Scr and normalized C0(trough) CsA concentrations in adult patients after liver transplantation (Day 2).

We observed that normalized CsA $C_{0(trough)}$ and C_2 concentrations are significantly lower in liver transplanted children than in adults. Frauca et al. [5] concluded that poor CsA exposure cannot be estimated by single C_0 and C_2 determinations in the early post-transplant period. While C_0 monitoring frequently results in overdosing and more renal dysfunction, C_2 monitoring may lead to episodes of under dosing and rejection. Therefore better ways of monitoring cyclosporine dosing need to be devised [6]. Assessment of AUC by multi-linear regression equations or Bayesian estimation is another solution. Measurement of $AUC_{0\text{-}4h}$ that requires only two or three samples has been proposed but is no longer used [8]. The difficult interpretation of the results in drug monitoring, which interfere with the precise dosing is also the variability (1.56 times) for $C_{0(trough)}$ and (1.32 times) for C_2 in adults and children.The therapeutic range of CsA for C_0 and C_2 varies with the type of indication, the period of prescription, the clinical state, the emplyoyed analytical technique. In all cases therapeutic index is low. In previous investigation we found no significant association between measured $CsAC_2$ concentrations and serum creatinine levels in adult transplanted patients [9]. The statistically significant correlation between Scr and the normalized CsA $C_{0(trough)}$ concentrations in adult patients on the second day after liver transplantation, if confirmed on a larger sample of liver transplanted patients, points to the possibility of Scr being used as a biomarker for individualization of CsA therapy in these transplanted patients. Moreover, similar to aminoglycosides, CsA nephrotoxicity is predominantly associated with inadequate drug levels at the end of each dosing interval.

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