

Pharmacokinetic monitoring of intravenous cyclosporine A in pediatric stem-cell transplant recipients. The trough level is not enough

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Abstract: In order to monitor CsA serum levels after SCT, trough levels (C₀) are widely used. The aim of this study was to estimate the population and individual PK parameters for patients receiving intravenous CsA after SCT. In 27 pediatric patients after SCT receiving CsA (3 mg/kg/day) every 12 h, a total of 289 CsA concentrations was obtained. To describe the PK parameters of CsA, a two-compartment model with first order elimination was used. Covariate analysis identified body weight, age, and the co-administration with itraconazole and tobramycin as factors influencing the Cl. The statistical comparison of AUC, trough level, and C₂ indicates a correlation between AUC and C₂, but no correlation between the AUC and C₀, $r = 0.24$ ($p = 0.146$) vs. $r = 0.526$ ($p = 0.000692$), respectively. Our results underscore the fact that CsA trough levels do not reflect the drug exposure in patients receiving intravenous CsA after SCT. By contrast, CsA blood levels measured 2–6 h after CsA infusion showed a better correlation with the AUC. Our data provide new information to optimize the balancing act between GvHD-prophylaxis, graft vs. leukemia effect, and CsA side-effects after SCT.

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GvHD is a major complication after haematopoietic SCT. There are multiple strategies to prevent GvHD, which depend on the underlying disease, HLA disparity between donor and recipient and local conventions (1). Most pediatric SCT centers use CsA together with MTX for the prevention of GvHD in patients with malignant hematologic diseases. Alternative

strategies such as T-cell depletion might result in increased rates of graft failure and reduced graft -vs. leukemia effects.

However, there is an ongoing controversy with regard to the CsA dosage, duration of prophylaxis, and mode of drug monitoring (1–4). In pediatric patients with acute leukemia, a prospective trial comparing low-dose CsA (1 mg/kg/day) with high-dose CsA (3 mg/kg/day) found significantly more relapse-free survival using low-dose CsA (4). In addition, monitoring of CsA serum levels is necessary because of the narrow therapeutic window and relevant toxicity of the drug (5–7). With regard to relapse – in patients with malignant disease – a PK monitoring might be relevant, too (8). The issue of drug interactions in patients receiving CsA and azole-antimycotics resulting in relevant variations of

Abbreviations: AUC, area under the time-concentration curve; Cl, clearance; CsA, cyclosporine A; GVHD, graft-vs.-host disease; HLA, human leukocyte antigen; IOV, interoccasion variability; MTX, methotrexate; OBF, objective function; PD, pharmacodynamic; PK, pharmacokinetic; Q, the intercompartmental Cl; SCT, stem-cell transplantation; TDM, therapeutic drug monitoring; V₁, volume of distribution into the central compartment; V₂, volume of distribution of the peripheral compartment.

CsA serum levels is also important for many patients receiving an allogeneic graft (9).

Despite the wide-spread use of CsA as GvHD prophylaxis, the best strategy to perform TDM in CsA remains yet to be defined. Most centers do CsA monitoring using CsA trough levels (C0), although data from solid organ transplant recipients have shown that CsA trough levels do not reflect the CsA exposure (10–14). By contrast, monitoring of CsA levels two h after infusion (C2) correlated much better with drug exposure, and, even more importantly, with graft function in kidney and liver transplant recipients.

As a consequence the current study was initiated, and complete PK profiles of CsA blood levels were performed in 27 children after allogeneic SCT, by collecting blood at 7 time points after CsA infusion.

This study aims to develop a population PK model for children receiving CsA after HCT to estimate the PK parameters of CsA, and to determine the drug exposure for each patient. The second aim was to identify the individual factors influencing the PK parameters in this population. Thirdly, to identify the optimal sampling time points for therapeutic CsA monitoring, the correlation of CsA blood levels at various time points after infusion, and the AUC was investigated. Our data underline the hypothesis that in SCT, PK monitoring may add to the results.

Patients and methods

Between March 2003 and June 2005, CsA PK profiles were measured after SCT in 27 pediatric patients with hematologic malignancies ($n = 15$) or non-malignant hematologic or metabolic diseases ($n = 12$). In 10 children, the profile was performed during concomitant itraconazole treatment while the remaining children received no antifungal prophylaxis. The median age at SCT was 9.2 yr (range 0.9–20 yr) and the median weight was 32.2 kg (range 8.9–68 kg). Nineteen children received a graft from a fully HLA-matched family donor, six patients a fully HLA-matched unrelated donor, and in two children a mismatched unrelated (9/10 antigen) donor was available. Full details of the patient characteristics are shown in Table 1.

All patients received a standardized regimen for gut decontamination (oral amphotericin, metronidazole, and colistin) and an antibiotic prophylaxis with ciprofloxacin. Cotrimoxazole was given for pneumocystis-jiroveci prophylaxis. All children with busulfan-based conditioning regimen received phenytoin as seizure prophylaxis. For antifungal prophylaxis fluconazole, itraconazole, or a different antimycotic was administered (Table 1).

GvHD prophylaxis

For the prevention of GvHD, 14 children received CsA plus three doses of MTX, 15 mg/m² on day +1; 10 mg/m² on days +3, and +6. Intravenous folinic acid was given 24 h

Table 1. Demographics and transplant characteristics in 27 patients of pharmacokinetic study

Male	17 (63%)
Median age (years)	9.2 (0.9–20)
Median bodyweight (kg, range)	32.2 (8.9–68)
Malignant hematologic diseases*	15
Bone marrow failure syndromes†	10
MFD, MUD	25
MMUD, MMFD	2
GvHD prophylaxis	CsA/MTX $n = 14$ CsA (3 mg/kg/day) $n = 11$ CsA (reduced dosage) $n = 2$

*Acute lymphoblastic leukemia ($n = 3$), acute myeloid leukemia ($n = 1$), matched family donor (MFD), matched unrelated donor (MUD), mismatched unrelated donor (MMUD), mismatched family donor (MMFD).

†Including patients with severe aplastic anemia ($n = 1$), myelodysplastic syndrome ($n = 1$), Shwachmann syndrome ($n = 1$), Fanconi anemia ($n = 1$), chronic granulomatous disease ($n = 1$).

after the MTX. Eleven children received only CsA (3 mg/kg/day) and two children received CsA at a reduced dosage (1 and 2 mg/kg/day, respectively). CsA was administered intravenously as two-h infusion twice-a-day until oral medication became possible.

Ethical considerations

The protocol of this study was approved by the Ethical Committee of the Medical School Hannover, and all patients or/and their legal consultants gave their informed consent for participation in the study.

CsA dosage and monitoring

In all children CsA was started 36 h prior to transplantation at a dosage of 1.5 mg/kg twice-a-day, which was given as a two-h intravenous infusion except for two children who received CsA at a reduced dosage. The intravenous administration was continued until the patients could tolerate oral medications (usually after three wk).

CsA infusion was administered always using the same lumen of a triple-lumen centrally inserted catheter system. CsA levels were monitored daily using a different lumen of the central venous access. The CsA dosage was adjusted to maintain serum trough levels of 120–140 ng/mL.

Measurements of cyclosporine blood concentrations were performed using the EMIT 2000 cyclosporine-specific assay (Dade Behring, Schwalbach, Germany). For levels exceeding 500 ng/mL, dilution with the EMIT 2000 cyclosporine-specific diluent was required (Tris-buffer, tenside, 0.1% sodium azide and 0.005% streptomycin sulphate).

The blood was collected via a central venous catheter and the first 10 mL were discarded. The lumen used for blood sampling was not used to infuse CsA and was at the downstream (distal) end of the catheter (15). Samples were collected at $t = 0$ (trough level) and 1, 2, 2.5, 3, 4, 5, 6, and 12 h after starting the infusion. A total of 289 blood samples was collected. Not all patients included had blood samples taken at all nine time points.

The concentrations of the samples after one h (during the infusion) were later excluded from the PK analysis, because they showed a great variation, which was possibly a

consequence of contamination by CsA from the other lumen of the catheter. In addition, nine other concentrations from C 2.5, and C3 were excluded because of the extreme concentrations of CsA making an artificial contamination likely. The dataset for PK model development consisted finally of 241 concentrations from 27 patients collected between day +7 and +11 after SCT.

Pharmacokinetics

Model building

In our study, sampling was performed under steady-state conditions. All 241 concentrations were included in the model development. The PK analysis was performed using the non-linear mixed effect approach as implemented in NONMEM version V (GloboMax LLC, Hanover, MD, USA) (the NONMEM software is concerned with the development of data analysis techniques for fitting nonlinear mixed effects (statistical regression-type) models. These techniques are useful when the data are population PK/PD data, and when there are only a few PK/PD measurements from some individuals sampled from the population, or when the number of samples varies considerably between individuals). Different compartment models were tested to describe the PK of CsA (16–22). Additive, proportional and combined error model were implied to account for the residual error. We finally choose the two-compartment model (ADVAN3, TRANS4) and a combined error model.

Population estimates of the following PK details were obtained: Cl, V1, Q, and V2.

A number of evaluation criteria were used to select the most appropriate PK model, including: (i) a low value of the OBF, a parameter for the quality of fit decreasing by the improvement of the model; (ii) a low estimate of the residual error term comprising the assay error and the model misspecification error; (iii) a low estimation of interindividual variability in the PK parameter; and (iv) good correlation between model-predicted and observed CsA concentrations.

The accuracy of the population estimates was evaluated by the calculation of percentage relative standard error (the standard error of the population PK parameter estimate divided by the population estimate, multiplied by 100). IOV, i.e., variability of the PK parameters in a single patient from one administration to the other, was introduced to the model as described by Karlsson et al. (23).

Covariate analysis

We studied the influence of the weight, age, co-medication on the PK parameters. The influence of individual candidate covariates on specific PK parameters was also assessed by adding these to the basic population PK model, and analysing the changes in OBF, residual error, and the interindividual variability. A covariate was considered as relevant if it decreased the OBF value to at least 6.6 (21). Precision of the parameter estimates and decrease of residual error or interindividual variability were also taken into account. All covariates that were found to be relevant during the initial screening procedure were cumulatively added to the population PK model in order of their contribution to the reduction of the residual error and the OBF. A backward elimination step in NONMEM was then performed in which each covariate was removed from the model in descending order of its contribution to the change in the OBF. The final model included only the significant covariates.

Results

A two-compartment model with first order elimination adequately fit the data. Introduction of a third compartment did not improve the fit and led to imprecise parameter estimates. For the residual error a combined error model gave the best fit and was therefore kept in the final model. The covariates were tested for their ability to improve the model, to reduce the residual error, and the interindividual variability in the PK parameters. There was a good correlation between the weight and Cl ($r = 0.713$; $p = 0.00003$) while no relationship was found between body weight and V1 ($r = 0.043$; $p = 0.83$). However, a better correlation ($r = 0.67$; $p = 0.00013$) was found between the age and Cl. No improvement of the dataset was obtained after inclusion of age as covariate on V1.

IOV, i.e., variability in the PK parameters from one administration to the next was tested for its power to improve the model. Introducing IOV on Cl (IOV = 36%) improved the model by reducing the OBF and the residual error whereas no improvement was observed when IOV was tested for V1.

The impact of the co-medication was studied for those drugs administered to more than 10 patients. The effects of these drugs were tested on the Cl showing that itraconazole and tobramycin reduced the Cl of CsA with factors of 0.72 and 0.73, respectively. Introducing co-medication resulted in the best model with regard to the OBF, interindividual variability, and the residual error.

This model can estimate the CsA concentrations for each desired point in time. As an example, Fig. 1 shows the blood concentrations measured and the predicted concentrations for three patients. It can be depicted from the model that it estimates the CsA concentrations sufficiently. The parameter estimates, their interindividual variability, and the standard error of the final model are shown in Table 2. The mean Cl in this population is 15.3 L/h with a high interindividual variability of 57%. The IOV of the Cl is also substantial (48%). Patients treated with itraconazole show a Cl reduced to 72% in comparison to patients not receiving itraconazole. Likewise, the Cl of CsA in patients receiving tobramycin is diminished to 73%. Interindividual variability in the mean volume of the central compartment (12.9 L) was 63%. The standard errors of all mean population parameters are not higher than 27% indicating that the model provides reliable estimates (Table 2).

The relationship between the AUC and the C₀, C₂, C₃, and C₆ can be seen in Fig. 2. Correlation

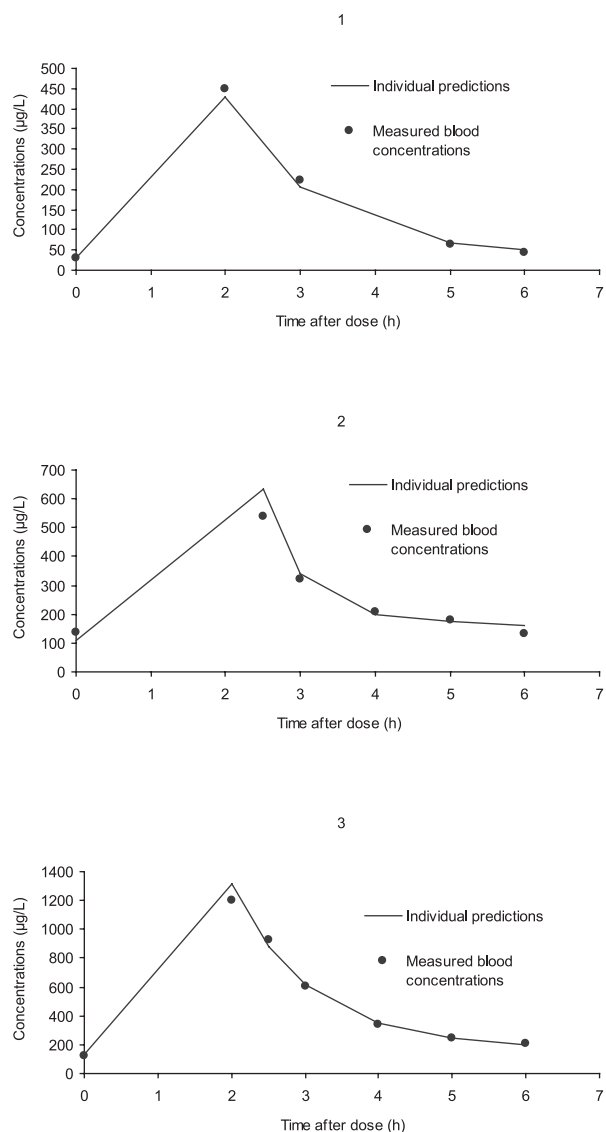


Fig. 1. Blood concentrations measured vs. individual predictions of the final model for three representative patients.

Table 2. Parameters of the pharmacokinetic model

Parameter	Mean	s.e. (%)	IV (%)	s.e. (%)
Cl, L/h	15.3	17	57	70
Interoccasion variability in Cl %	48	17	n.a.	n.a.
V1, L	12.9	26	63	35
V2, L	83.3	17	n.s.	n.a.
Q, L/h	6.28	27	89	31
AUC, mg/h/L	4.22	n.a.	n.a.	n.a.
Residual error				
Proportional error (%)	53	23	n.a.	n.a.
Additive error (µg/L)	21	16	n.a.	n.a.

Cl, clearance; V1, volume of distribution into the central compartment; Q, the inter compartment rate constant; V2, volume of distribution of the peripheral compartment; AUC, area under the curve; s.e., standard error of the estimates; IV, interindividual variability; n.s., not significant; n.a., not applicable.

coefficients between the calculated AUC and the different concentration were performed using the software SIGMASTAT 3.1 (Statcon B Schaefer, Witzenhausen, Germany). The correlation coefficients between AUC and C0, C2 were 0.24 ($p = 0.146$), 0.526 ($p = 0.000692$), respectively. In our patient group, there is no significant relationship between AUC and CsA trough level concentrations, and C0 does not reflect the drug exposure. However, in the population under investigation the correlation coefficient between AUC and C3, C6 were $r = 0.56$ ($p = 0.00204$) and $r = 0.705$ ($p = 0.00017$) respectively (Fig. 2). The results indicate that the blood concentration at the end of the infusion (C2) provides better information for the TDM rather than the trough level (C0). According to our results, C6 would be the best predictor for the AUC after intravenous infusion of CsA.

Discussion

GvHD, treatment-related mortality, and relapse of the underlying malignant disease are the most important threats for patients after SCT (24): With regard to the role of CsA in this concert, leukemia relapse was observed more frequently in patients receiving 5 mg/kg body weight during the first 10 days after the transplant compared to a second group receiving only 1 mg/kg (2). On the other hand, mortality due to GvHD was more frequent in the low-dosage CsA group. These results were supported by data from Locatelli et al. (4). The Italian group reported on 59 children with acute leukemia who were randomly assigned to receive either 1 mg/kg CsA in two-divided two-h infusions or 3 mg/kg. According to their data, more acute GvHD was seen in the low dosage CsA group (57% vs. 38%, respectively). Even more importantly, in the low dosage CsA group significantly fewer leukemia relapses were seen (four children vs. 11 children). Locatelli et al. (4) speculated that CsA might interfere with the graft vs. leukemia response, and thus influence the relapse rate after SCT. Importantly in this context, the data of our PK study indicate that CsA drug exposure after SCT is not only a function of the dosage administered but also depending upon the co-medication, and individual factors such as drug Cl, which makes close CsA drug monitoring mandatory. Here, the traditional method of trough level monitoring is imprecise according to the results of the data shown, but CsA blood levels collected after the CsA infusion do more significantly reflect the AUC.

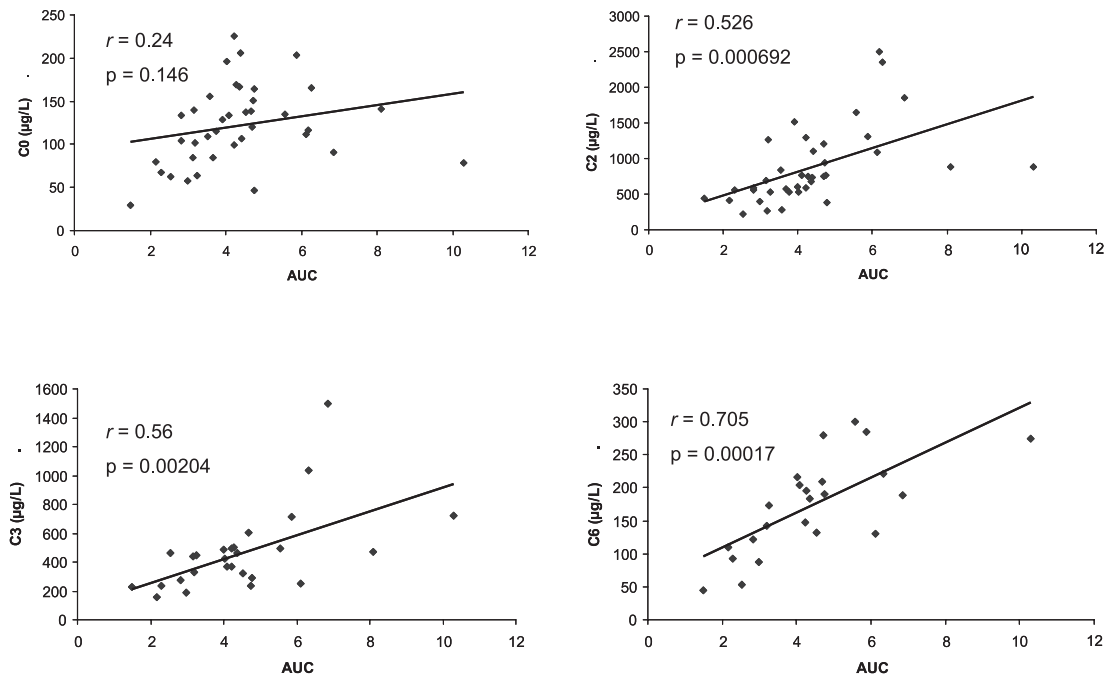


Fig. 2. Relationship between CsA-AUC and C0 (trough level), C2 (top level), C3, and C6.

Our study was designed for PK evaluations, but not for clinical end-points such as acute or chronic GvHD, and leukemia-free survival. However, using the results of this study, a multicenter study is under way to evaluate the clinical end-points, such as GvHD and leukemia-free survival in the context of a PK CsA study.

With regard to the pivotal role of CsA in the setting of SCT it is not surprising that there is an ongoing controversy among pediatric SCT specialists how to schedule, and perform monitoring of CsA after transplantation. According to a survey performed by Peters et al. (1), most pediatric SCT centers administer CsA in the early phase after SCT intravenously twice-a-day. According to these data, adjustments of CsA dosage were made according to trough levels (1). In kidney transplant recipients after oral CsA exposure; however, an estimate of the total drug exposure as measured by AUC was considered to be more valuable for CsA drug monitoring than measurements of trough level (13, 25). After intravenous application of CsA in liver transplant recipients it was demonstrated that trough level (=C0) measurements were not indicative for CsA drug exposure (12). In contrast, CsA peak level concentrations correlated with CsA exposure in these patients. These data are supported by other investigations, reflecting that CsA AUC monitoring affords better control of drug exposure of an individual patient to CsA with regard to organ

function, rejection, and toxicity (10, 12, 14). Whether this holds also true for SCT recipients has not been investigated yet. Clinically, the poor correlation of CsA trough levels is reflected in reports from patients with neurotoxic symptoms despite CsA blood trough concentrations within the so-called therapeutic range underscoring that trough-level monitoring of CsA did not prevent the occurrence of toxic side effects (6).

To our knowledge, this is the first investigation where population PK methods are applied to CsA data in pediatric HCT patients. This model provides precise population parameters as well as accurate estimates of all forms of variability, i.e., inter and intraindividual variability in the PK parameters as well as estimates for residual variability.

In our study, only a weak correlation between the AUC and trough levels was observed (Fig. 1) supporting results in the literature from solid organ transplant recipients. While the correlation coefficient r is highly dependent on the absolute values, the level of significance p is an estimate how significant the correlation between these two values is. To overcome the problem of determining the CsA drug exposure in pediatric patients with one blood sample our results indicate and we therefore recommend that blood sampling 2–6 h (C2–C6) after initiation of the infusion allowed the best correlation to the AUC and could be used for monitoring. This should be an

good alternative compared to the “traditional” trough level monitoring.

In view of the implications that CsA carries for SCT recipients, drug interactions are important: CsA is metabolized by the CYP3A4 isoenzyme system, and co-medication with azoles will result in increased CsA trough levels and/or increased toxicity (9). The same holds true for calcium channel blockers whereas a co-medication with phenytoin will result in decreased CsA trough levels. Incorporation of itraconazole and tobramycin to the PK model of the presented study resulted in better parameter estimations. The reduction in CsA Cl with both drugs was about 30% indicating that a moderate dose reduction of CsA should be considered when patients are treated with one or both of these drugs. Cl showed a significant increase with age and body weight. The correlation between age and Cl was very high and inclusion of age into the model as a covariate for Cl resulted in an even better model compared to the model based on with body weight. However, with an age range between 0.9 and 20 yr in this study there is a strong correlation between age and body weight and the low number of patients do not allow drawing final conclusions in this respect.

One work published by Martin et al. showed conflicting results: According to their data on childhood SCT patients the CsA trough blood concentration, but not the peak blood concentration correlated to acute GvHD. In this study, CsA was applied as an eight h infusion, and without complete PK monitoring but extrapolating the AUC which might account for the differing results (26).

Given the strong correlation between CsA (dosage) and GvHD, and pivotal role of CsA as a risk factor for relapse in malignant disease known from former studies (7, 26, 27, 28), optimal PK monitoring of CsA should be mandatory. Our data underscore the lack of correlation between CsA trough level and the CsA–AUC, but show by contrast a strong correlation between C2 and C6 blood levels with the CsA–AUC (=the “real” drug exposure) in SCT patients after a two-h infusion. Future studies addressing clinical end-points will answer the question whether our PK model will help to improve the management in pediatric SCT patients.

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