Cancer Chemother Pharmacol (1985) 15: 76–81

Cancer Chemotherapy and Pharmacology



# Clinical pharmacokinetics of ciclosporin A in bone marrow transplantation patients*

**Pierre Bertault-Pérès[1], Dominique Maraninchi[2], Yves Carcassonne[2], Jean-Paul Cano[1], and Jacques Barbet[1]**

[1] Groupe de Recherche en Immunologie et Pharmacologie des Anticancéreux, INSERM U-278, 232 Bd de Sainte Marguerite, F-13273 Marseille Cedex 9, France
[2] Institut Paoli-Calmettes, 232 Bd de Sainte Marguerite, F-13273 Marseille Cedex 9, France

**Summary.** Ciclosporin A (CsA) plasma concentrations were monitored by radioimmunoassay after administration IV and PO to 15 patients before allogeneic bone marrow transplantation. The clearance (10.4 ± 5.4 l/h), half-life (26.4 ± 14.6 h), and bioavailability (16% ± 10%) calculated directly from experimental data showed wide inter-individual variations. The kinetics after IV infusion, monitored over 2–5 days, appeared to be triphasic. A three-compartment open mamillary model was thus used to simulate the distribution and elimination kinetics of CsA. The distributive delay between administration PO and absorption in the plasma was approximated using a series of six additional compartments connected with a single transfer rate constant. Then, for each patient, the experimental data corresponding to both IV and PO administration were fitted using a single set of rate constants. Clearance and bioavailability calculated from model parameters correlated well with direct estimations obtained from the areas under the concentration time curves. Drug monitoring and linear modeling will be used in an attempt to achieve stable predetermined plasma concentrations of CsA in bone marrow transplantation patients receiving the drug either IV or PO.

## Introduction

Ciclosporin A (CsA) is a fungal cyclic polypeptide with great potential as an immunosuppressive agent [4]. Its efficiency in organ transplantation has been characterized for kidney [6, 23], liver [24], heart [13], and pancreas [25]. Potential activity in allogeneic bone marrow transplantation has been reported in several studies [2, 10, 21]. Various acute toxic effects of CsA have been described [11, 16]. A plasma concentration range of 50–200 μg/l seems optimal for both therapeutic efficacy and prevention of renal toxicity [14, 15]. This optimal plasma concentration is generally obtained by empirical dose adjustments, but individualization of the dosage regimen by the so-called "test dose method", which consists in estimation of the patient's kinetic parameters using data from a preliminary single-dose administration [12, 19], would probably be possible [18]. This approach could be extended to the switch from IV to PO treatment if good evaluations of oral CsA bioavailability can be obtained.

Before bone marrow transplantation and preventive treatments for graft-versus-host disease, CsA was given to 15 patients as a single IV injection, followed by an oral dose 3–5 days later. Plasma concentrations of CsA were monitored by radioimmunoassay [8]. The results of this clinical study are reported here, and a three-compartment mamillary model is proposed to describe the distribution and elimination of CsA following both IV and PO dosage, the lag time observed between the administration and the peak of plasma concentration being simulated with a series of compartments.

## Materials and methods

*Patients.* The patients were entered in this clinical study just before allogeneic bone marrow transplantation. There were 14 with various hematologic malignancies and 1 (AL 15) with severe aplastic anemia. They were not given any other therapy during the study. The median age was 16.1 years (range 2–32). The sex ratio was 11 males to 4 females. The mean body weight was 45.3 kg, ranging from 13.5 to 75 kg. All patients presented normal hepatic and renal functions (serum glutamic-pyruvic and glutamic-oxaloacetic transaminases $<30$ units/l, bilirubin $<20\ \mu M$, creatinine $<120\ \mu M$). Clinical data relevant to the pharmacokinetic study are reported in Table 1.

*CsA administration and plasma sample collection.* All patients received a single dose of CsA (4 mg/kg) IV, five as a direct injection in about 2 min and ten as a 1 h infusion. Blood samples were collected at the following times: 0, 5, 15 and 30 min, then 1, 2, 4, 6, 12, 24, 36, 48, 72, 96 and 120 h up to the time of oral dosage. At 2–5 days after the IV injection, each patient received a single oral dose of CsA (12.5 mg/kg) as a drinking solution diluted 10-fold with a chocolate drink. Blood samples were then collected at 0, 1, 2, 3, 4, 5, 6, 12, 24, 36, 48, 72 and 96 h. Blood was collected in heparinized tubes and kept at 37° C until centrifugation [9]. Plasma was then stored at −20 °C.

*CsA concentration measurements.* Reagents for CsA radioimmunoassay were kindly provided by Sandoz Ltd and

* This work was supported by a grant from the Comité Départemental des Bouches du Rhône de la Ligue Nationale Française contre le Cancer and by institutional grants from INSERM and CNRS

*Offprint requests to:* Laboratory of Mathematical Biology, NCI, NIH, Bldg 10, Room 4B56, Bethesda Md 20205, USA

*Abbreviation:* CsA, ciclosporin A

**Table 1.** Patient data

| UPN[a] | Sex[b] | Age (year) | Weight (kg) | Diagnosis and status |
|---|---|---|---|---|
| AL 14 | M | 16 | 60 | Acute lymphoblastic leukemia, first complete remission |
| AL 15 | F | 29 | 54 | Severe aplastic anemia |
| AL 18 | F | 32 | 46 | Chronic myelocytic leukemia, first acute phase |
| AL 19 | F | 10 | 35 | Chronic myelocytic leukemia, first acute phase |
| AL 20 | M | 10 | 46 | Acute lymphoblastic leukemia, second complete remission |
| AL 26 | M | 8 | 26 | Acute lymphoblastic leukemia, third complete remission |
| AL 27 | M | 17 | 58 | Acute lymphoblastic leukemia, relapse |
| AL 29 | M | 28 | 66 | Secondary acute leukemia |
| AL 31 | M | 13 | 40 | Acute lymphoblastic leukemia, second complete remission |
| AL 35 | M | 17 | 42 | Acute lymphoblastic leukemia, relapse |
| AL 37 | F | 7 | 23 | Acute lymphoblastic leukemia, first complete remission |
| AL 38 | M | 7 | 35 | Acute lymphoblastic leukemia, second complete remission |
| AL 39 | M | 2 | 13.5 | Acute lymphoblastic leukemia, first complete remission |
| AL 40 | M | 20 | 60 | Hodgkin's disease, relapse |
| AL 41 | M | 26 | 75 | Acute lymphoblastic leukemia, relapse |

[a] UPN, unique patient number
[b] M, male, F, female

used as described [8]. In particular, plasma samples were diluted 10-, 50- and 500-fold in 50 m*M* Tris HCl, 0.03% Tween 20, pH 8.5 (buffer B). Reaction mixtures containing 100 µl diluted plasma, 100 µl rabbit antiserum (diluted 1/2000 in 50 m*M* Tris HCl, ph 8.5), 100 µl tritiated dihydrociclosporin A (diluted in an 8-to-1 mixutre of buffer B and normal human plasma) and 700 µl buffer B were incubated for 2 h at 20 °C. They were then transferred into a 4 °C water bath prior to the addition of 500 µl of a suspension of deactivated charcoal (1% charcoal from Merck, 0.5% normal human serum in water). After vortexing and a 12-min incubation, the mixture was centrifuged for 5-min at 2000 *g*. The supernatant was then transferred into 9 ml aqueous scintillation liquid (EP from Beckman) and counted for 1 min. The assay was performed on duplicate tubes and CsA concentrations were calculated by interpolation on linearized (logit-log) standard reference curves using a Casio fx 702 P programmable calculator. The sensitivity was better than 10 µg/l and reproducibilities were 4% (intra-assay, $n=10$) and 9% (interassay, $n=5$) in the range 62–2000 µg/l. All samples from one test of kinetics were measured in a single assay together with standards to avoid interassay variations.

*Pharmacokinetic analyses.* Preliminary estimations of several parameters were obtained graphically. Systemic clearance (Cl) and bioavailability (F) were calculated from the area under the concentration-time curve (AUC) according to the well-known equations:

$$Cl = \text{dose} / AUC \quad (1)$$

and

$$F = (AUC_{PO} \times dose_{IV}) / (AUC_{IV} \times dose_{PO}) \quad (2)$$

Log-linear regression was used to determine the half-life of the apparent phase of elimination ($T_{1/2}$) from termi-

**Table 2.** Noncompartmental pharmacokinetic analysis

| UPN | IV injection (4 mg/kg) AUC (h × mg/l) | Clearance (l/h) | $T_{1/2}$ (h) | PO administration (12.5 mg/kg) T max[a] (h) | C max[b] (mg/l) | AUC (h × mg/l) | $T_{1/2}$ (h) | F |
|---|---|---|---|---|---|---|---|---|
| AL 14[c] | 10.3 | 23.3 | 25 | 4 | 0.62 | 4.8 | 23.5 | 0.15 |
| AL 15[c] | 15.5 | 13.9 | 24 | 3 | 0.99 | 6.2 | 16 | 0.13 |
| AL 18[c] | 20.0 | 9.2 | 59 | 4 | 0.84 | 11.4 | 37 | 0.18 |
| AL 19[c] | 19.5 | 7.2 | 36 | 3 | 0.75 | 5.8 | 11 | 0.10 |
| AL 20[c] | 26.1 | 7.1 | 20 | 3 | 2.10 | 13.4 | 19 | 0.16 |
| AL 26 | 7.3 | 14.2 | 14 | 2 | 0.62 | 6.7 | 6 | 0.29 |
| AL 27 | 16.1 | 14.4 | 15 | 5 | 0.47 | 3.5 | 25 | 0.07 |
| AL 29 | 27.7 | 9.5 | 22 | 3 | 0.59 | 7.0 | 21 | 0.08 |
| AL 31 | 14.8 | 10.8 | 9 | 3 | 1.35 | 9.0 | 7 | 0.19 |
| AL 35 | 15.6 | 10.8 | 29 | 3 | 1.03 | 10.5 | 8 | 0.21 |
| AL 37 | 39.8 | 2.3 | 26 | 6 | 0.20 | 2.7 | 5 | 0.02 |
| AL 38 | 8.9 | 15.7 | 8 | 4 | 0.70 | 4.4 | 7 | 0.16 |
| AL 39 | 33.5 | 1.6 | 28 | 4 | 0.15 | 2.2 | 13 | 0.02 |
| AL 40 | 33.2 | 7.2 | 26 | 2 | 2.56 | 42.6 | 16.5 | 0.41 |
| AL 41 | 31.9 | 9.4 | 55 | 6 | 1.67 | 24.7 | 37 | 0.25 |

[a] T max, maximum plasma concentration time
[b] C max, maximum plasma concentration
[c] Direct IV injection (duration <2 min). The other patients were given CsA as a 1 h IV infusion

nal data points and to obtain a rough estimate of the central compartment volume (Vc) using the 5-, 15- and 30-min data points for the patients given the direct injection.

Details about modeling are given in *Results*. The modeling program CONSAM [5] was used to calculate best estimates of the rate constants of the system. The program was run on the Digital Equipment Corporation VAX 11/780 computer of the Laboratory of Mathematical Biology of the National Cancer Institute, using Tektronix 4025 graphic terminals.

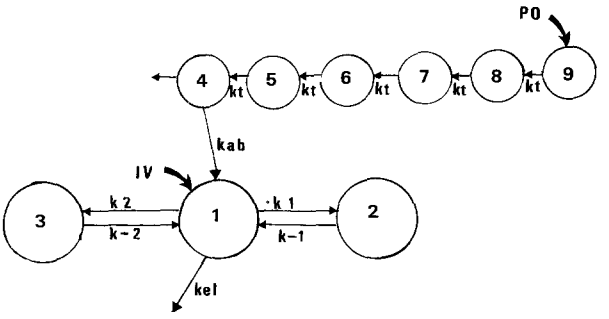


**Fig. 1.** Model description: compartments are represented by *circles*, with *arrows* for CsA linear transfers. Compartment 1 is assumed in fast equilibrium with plasma in which measurements are made. Inputs are either in compartment 1 (IV administration) or in compartment 9 (PO administration)

## Results

### *Noncompartmental analysis*

Pharmacokinetic parameters estimated graphically from individual kinetic data are reported in Table 2. All parameters showed marked individual variations: total systemic clearance ranged from 1.6 to 23.3 l/h, and $T_{1/2}$ ranged from 8 to 59 h. After administration PO (12.5 mg/kg), the maximum plasma level (1.0±0.7 mg/l) was reached after 3.6±1.2 h. Individual variations were also observed after oral administration: half-lives ranged from 6 to 37 h and the estimated bioavailability varied between 2% and 41%.

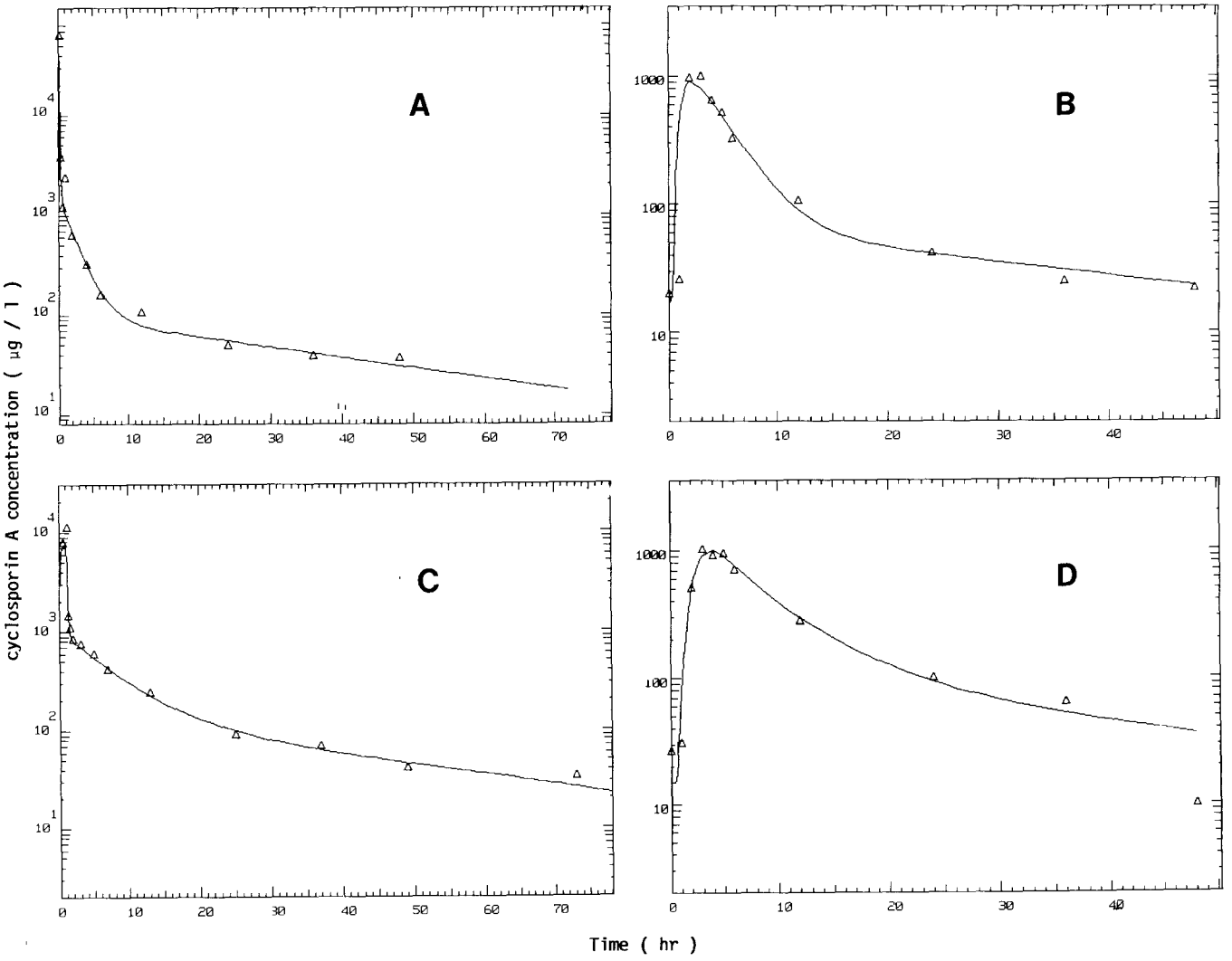


**Fig. 2. A–D.** Plasma concentration kinetics: drug concentration in plasma was measured by radioimmunoassay after IV and PO administration at time intervals shown and plotted on a log-linear scale versus time. The *solide line* represents the best fit obtained using CONSAM simulation of the model shown in Fig. 1. **A** patient AL 15, IV bolus injection; **B** PO administration; **C** patient AL 35, IV 1-h infusion; **D** oral administration

*Modeling and data fitting*

For IV injection a classic three-compartment mamillary model (Fig. 1) was used, with input and observations in the central compartment as either a 2-min or a 1 h infusion. Plasma concentration was assigned to this compartment, whose volume ($V_c$) was set equal to 7% of total body weight. This figure was selected for two reasons. First, CsA has been shown to distribute very quickly between plasma and formed elements of the blood in almost equal proportions ([19] and our own unpublished observations). Thus, assigning to the central compartment a total blood volume of 7% of total body weight was physiologically meaningful and merely accounted for the very rapid binding of CsA to circulating cells. Second, when $V_c$ was made an adjustable parameter, the estimations of $V_c$ were variable (from 2.5% to 40% of total body weight) and the standard deviations of $V_c$ or the elimination rate constant ($k_{el}$), or both, were very large. When averaged over all individual kinetics, the weighted mean of estimated $V_c$ was very close to 7% (7.08%) and very close to the means of graphical estimations of $V_c$ for the direct infusions.

CONSAM selected the deconvolution method to solve the system of linear differential equations, and several iterations were performed, using IV data only, from a set of empirically determined initial values ($k_{el}$ was initially set to $Cl/V_c$). For the oral administration, the three-compartment model was completed with six additional compartments connected by a single transfer rate constant $k_t$. This is a calculation trick equivalent to the introduction of a delay of $5/k_t$ with a time resolution of $1/k_t$ preserving the linear structure of the problem [5]. From the last of these dummy compartments a fraction ($F_1$) of the drug diffused into the central compartment with a rate constant of absorption ($k_{ab}$). The rest of it was eliminated with a rate constant equal to $[(1-F_1)/F_1] \times k_{ab}$ (Fig. 1). The oral administration was set at its actual time after IV injection and the concentrations of drug in compartments 1,2 and 3 were *not* reset to 0.

The rate constant of distribution and elimination determined from the IV injection data were used to get a first estimation of $k_t$, $k_{ab}$, and F, then all parameters were made adjustable and more iterations were performed. This final adjustment improved the fit with moderate modifications of previous parameter estimations. Examples of curve fitting are shown in Fig. 2. For all 15 patients, it was possible to fit the IV and the PO administration kinetics simultaneously using a single set of distribution and elimination rate constants. The estimations of the various rate constants and of bioavailability for each patient are reported in Table 3.

## Discussion

The radioimmunoassay specificity has been questioned since some CsA metabolites crossreact with anti-CsA antibodies [8]. CsA is extensively metabolized [26], and accor-

**Table 3.** Model-dependent pharmacokinetic parameters

| UPN | $k_1$ | $k_{-1}$ | $k_2$ | $k_{-2}$ | $k_{el}$ | $k_{ab}$ | $k_t$ | $F_1$ |
|---|---|---|---|---|---|---|---|---|
| AL 14[a] | 12.41 | 3.07 | 1.19 | 0.033 | 5.59 | 0.021 | 3.75 | 0.189 |
| | (1.76)[b] | (0.37) | (0.10) | (0.004) | (0.20) | (0.003) | (0.23) | (0.010) |
| AL 15[a] | 4.57 | 0.76 | 2.34 | 0.036 | 4.83 | 0.077 | 4.34 | 0.170 |
| | (0.44) | (0.07) | (0.15) | (0.004) | (0.13) | (0.009) | (1.55) | (0.012) |
| AL 18[a] | 1.74 | 0.71 | 1.87 | 0.010 | 2.97 | 0.024 | 4.15 | 0.240 |
| | (0.18) | (0.06) | (0.13) | (0.001) | (0.13) | (0.002) | (0.97) | (0.012) |
| AL 19[a] | 2.71 | 0.56 | 1.27 | 0.017 | 4.52 | 0.034 | 4.69 | 0.168 |
| | (0.22) | (0.05) | (0.07) | (0.002) | (0.12) | (0.003) | (0.31) | (0.008) |
| AL 20[a] | 10.49 | 3.55 | 2.30 | 0.056 | 3.70 | 0.180 | 2.21 | 0.154 |
| | (1.47) | (0.49) | (0.15) | (0.003) | (0.10) | (0.118) | (0.59) | (0.009) |
| AL 26 | 17.12 | 0.80 | 1.27 | 0.021 | 6.61 | 0.072 | 8.90 | 0.217 |
| | (1.96) | (0.07) | (0.15) | (0.008) | (0.29) | (0.008) | (2.76) | (0.012) |
| AL 27 | 3.84 | 0.88 | 0.88 | 0.040 | 2.91 | 0.013 | 5.63 | 0.047 |
| | (0.55) | (0.08) | (0.18) | (0.001) | (0.20) | (0.001) | (0.47) | (0.003) |
| AL 29 | 2.64 | 0.19 | 0.43 | 0.021 | 1.91 | 0.023 | 2.44 | 0.057 |
| | (0.15) | (0.01) | (0.07) | (0.003) | (0.04) | (0.004) | (0.26) | (0.004) |
| AL 31 | 2.99 | 0.39 | 0.30 | 0.017 | 3.28 | 0.163 | 1.58 | 0.139 |
| | (0.29) | (0.04) | (0.03) | (0.005) | (0.12) | (0.053) | (0.32) | (0.009) |
| AL 35 | 3.75 | 0.28 | 1.24 | 0.034 | 3.14 | 0.074 | 2.08 | 0.192 |
| | (0.18) | (0.03) | (0.18) | (0.004) | (0.08) | (0.010) | (0.15) | (0.010) |
| AL 37 | 8.61 | 1.26 | 0.34 | 0.028 | 1.60 | 0.021 | 0.85 | 0.021 |
| | (1.31) | (0.16) | (0.03) | (0.002) | (0.05) | (0.074) | (1.00) | (0.002) |
| AL 38 | 4.23 | 0.54 | 0.82 | 0.015 | 5.20 | 0.055 | 2.30 | 0.151 |
| | (0.47) | (0.05) | (0.08) | (0.004) | (0.21) | (0.007) | (0.20) | (0.009) |
| AL 39 | 0.59 | 0.48 | 1.61 | 0.003 | 0.93 | 0.004 | 1.76 | 0.012 |
| | (0.08) | (0.05) | (0.84) | (0.002) | (0.84) | (0.001) | (0.28) | (0.001) |
| AL 40 | 2.01 | 0.29 | 1.45 | 0.022 | 1.47 | 0.066 | 8.15 | 0.206 |
| | (0.31) | (0.03) | (0.02) | (0.004) | (0.11) | (0.008) | (0.09) | (0.018) |
| AL 41 | 2.10 | 0.38 | 0.62 | 0.011 | 1.67 | 0.041 | 2.58 | 0.220 |
| | (0.26) | (0.04) | (0.04) | (0.002) | (0.06) | (0.003) | (0.13) | (0.011) |
| Mean | 5.3 | 0.94 | 1.19 | 0.024 | 3.35 | 0.058 | 3.69 | 0.145 |

[a] Direct IV injection (duration $<2$ min)

[b] Numbers in parentheses are standard deviations on the estimation of the parameter

dingly systematic comparisons showed that radioimmunoassay yielded higher results for CsA concentration measurements in blood or plasma than high-pressure liquid chromatography [1, 7, 22]. Results given by the two methods are nevertheless correlated, and Robinson et al. [22] concluded that both techniques are appropriate for clinical monitoring. In addition, radioimmunoassay data have been used so far in many clinical studies to provide information about therapeutic and toxic concentrations [14, 16]. These concentrations should be measured in whole blood or, as in our tests, without allowing blood samples to cool down before plasma separation [9]. Insofar as pharmacokinetics and modeling are concerned, quantitative differences in parameter estimates, such as smaller clearances and distribution volumes or longer half-lives, may be caused by the fact that data represent CsA concentration plus a fraction of the crossreactive metabolite concentrations, and not only CsA concentration. However, the overall profiles of the concentration-time curves and their pharmacokinetic interpretations would not be fundamentally altered [9, 22]. This question should be directly addressed, but the time required to measure CsA concentrations by high-pressure liquid chromatography in such a large set of experimental samples is a major limitation.

Previous studies [3, 20] have presented CsA kinetics as biphasic. The kinetics we observed after IV injection appeared to be triphasic and better represented by a three-compartment mamillary model, as reported earlier for patients with renal failure [9]. The mean clearance normalized to body weight (0.24 l/h/kg) [9, 18] and terminal half-life (26.4 h) [3, 9, 20, 26] were comparable to that reported in the literature. Interindividual variations of clearance were large (1–21 between patients AL 14 and AL 39), and bioavailability was poor, with large interindividual variations (2.2%–41%, mean 16% ± 10%). These two pharmacokinetic parameters varied independently (correlation coefficient = 0.21), indicating that calculation of doses from body weight would give wide differences in plasma concentrations, especially for administration PO. The lag between oral administration and maximum plasma concentration was relatively long (3.7 ± 1.2 h). These parameters agree closely with those found in the literature [3, 14, 26].

When uswing CONSAM, there are two ways to simulate a lag time. One is to introduce a time delay and a zero-order input of the drug into a compartment from which absorption occurs, and the other is to use a series of compartments connected with a single transfer rate constant, the drug being absorbed from the last one or eliminated [5]. We have used the second solution, as shown in Fig. 1. The number of the delay compartments was set empirically at six, since this influences only the time resolution of the absorption. This should be understood as a mere trick to generate a smooth input curve with adjustable delay, without using nonlinear equations. Then, fairly good fit could be achieved for both routes of administration using a single set of parameters for each patient. The different rate constants reflected the interindividual variations. The fast distribution component corresponded to a compartment whose volume was about 7 times that of the blood. The slow component corresponded to a volume approximately equal to 50 times the blood volume. This is consistent with extensive distribution and binding to cells in various organs and agrees with previous reports [9]. Clearances ($V_c \times k_{el}$) and bioavailabilities ($F_1$) were close to the estimates made directly from experimental AUC measurements (Table 4).

**Table 4.** Clearance and bioavailability: comparison of model-dependent and noncompartmental estimations

| UPN | Clearance | | Bioavailability | |
|---|---|---|---|---|
| | Dose/AUC (l/h) | $V_c \times k_{el}$ (l/h) | F (%) | $F_1$ (%) |
| AL 14 | 23.3 | 23.5 | 15 | 19 |
| AL 15 | 13.9 | 18.2 | 13 | 17 |
| AL 18 | 9.2 | 9.6 | 18 | 24 |
| AL 19 | 7.2 | 11.1 | 10 | 17 |
| AL 20 | 7.1 | 11.9 | 16 | 15 |
| AL 26 | 14.2 | 12.0 | 29 | 22 |
| AL 27 | 14.4 | 11.8 | 7 | 5 |
| AL 29 | 9.5 | 8.8 | 8 | 6 |
| AL 31 | 10.8 | 9.2 | 19 | 14 |
| AL 35 | 10.8 | 9.5 | 21 | 19 |
| AL 37 | 2.3 | 2.6 | 2 | 2 |
| AL 38 | 15.7 | 12.7 | 16 | 15 |
| AL 39 | 1.6 | 1.0 | 2 | 1 |
| AL 40 | 7.2 | 6.2 | 41 | 21 |
| AL 41 | 9.4 | 8.8 | 25 | 22 |

This suggests that a simple linear compartmental model might represent CsA kinetics as measured by radioimmunoassay accurately (at least in the range of therapeutic doses). Several assumptions contained in the model, such as linearity or elimination from the central compartment only, should be independently verified and the metabolism of CsA should be further studied to assess the biological relevance of radioimmunoassay measurements and of their modeling. However, the large interindividual variations of CsA disposition and absorption (Table 3) have prompted us to attach more importance to the initiation of the treatments with intensive drug monitoring. The linear model presented here will then be used to test the possibility of calculating individual IV and PO doses on the basis of pretreatment pharmacokinetic identifications (test dose) in a larger number of allogeneic bone marrow transplantation patients.

## References


1. Abisch, E, Beveridge T, Gratwohl A, Niederberger W, Nussbaumer K, Schaub P, Speck B, Trapp M (1982) Cyclosporin A: correlation between HPLC and RIA serum levels. Pharm Weekbl [Sci] 4: 84
2. Atkinson K, Biggs JC, Ting A, Concannon AJ, Dodds AJ, Pun A (1983) Cyclosporin A is associated with faster engraftment and less mucositis than methotrexate after allogeneic bone marrow transplantation. Br J Haematol 53: 265
3. Beveridge T, Gratwohl A, Michot F, Niederberger W, Nüesch E, Nussbaumer K, Schaub P, Speck B (1981) Cyclosporine A pharmacokinetics after a single dose in man and serum levels after multiple dosing in recipients of allogeneic bone marrow grafts. Curr Ther Res 30: 5
4. Borel JF, Feurer C, Gubler HU, Stähelin H (1976) Biological effects of Cyclosporin A: a new antilymphocytic agent. Agents Actions 6: 468
5. Boston RC, Greif PC, Berman M (1981) Conversational-SAAM – an interactive program for kinetic analysis of biological systems. Comp Prog Biomed 13: 111

6. Calne RY, White DJ, Thiru S, Evans DB, McMaster P, Dunn DC, Craddock GN, Pentlow BD, Rolles K (1978) Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet II: 1323
7. Carruthers SG, Freeman DJ, Koegler JC, Howson W, Keown PA, Laupacis A, Stiller CR (1983) Simplified liquid-chromatographic analysis for cyclosporin A, and comparison with radioimmunoassay. Clin Chem 29: 180
8. Donatsch P, Abisch E, Homberger M, Traber R, Trapp M, Voges R (1981) A radioimmunoassay to measure cyclosporin A in plasma and serum samples. J Immunoassay 2: 19
9. Follath F, Wenk M, Vozeh F, Thiel G, Brunner F, Loertscher R, Lemaire M, Nussbaumer K, Niederberger W, Wood A (1983) Intravenous cyclosporine kinetics in renal failure. Clin Pharmacol Ther 34: 638
10. Gluckman E, Arcese W, Devergie A, Boiron M (1981) Cyclosporin-A prophylactic treatment of graft-versus-host disease in human allogeneic bone marrow transplantaton: preliminary results. Transplant Proc 13: 368
11. Gratwohl A, Speck B, Wenk M, Forster I, Müller M, Osterwalder B, Nissen C, Follath F (1983) Cyclosporine in human bone marrow transplantation. Serum concentration, graft-versus-host disease, and nephrotoxicity. Transplantation 36: 40
12. Greenblatt DJ (1979) Predicting steady-state serum concentrations of drugs. Annu Rev Pharmacol Toxicol 19: 347
13. Griffith BP, Hardesty RL, Deeb GM, Starzl TE, Bahnson HT (1982) Cardiac transplantation with Cyclosporin A and prednisone. Ann Surg 196: 324
14. Keown PA, Stiller CR, Laupacis AL, Howson W, Coles R, Stawecki M, Koegler J, Carruthers G, McKenzie N, Sinclair NR (1982) The effects of cyclosporine: relationship to drug pharmacokinetics. Transplant Proc 14: 659
15. Keown PA, Stiller CR, Sinclair NR, Carruthers G, Howson W, Stawecki M, McMichael J, Koegler J, McKenzie N, Wall W (1983) The clinical relevance of cyclosporine blood levels as measured by radioimmunoassay. Transplant Proc 15: 2438
16. Klintmalm GB, Iwatsuki S, Starzl TE (1981) Nephrotoxicity of cyclosporin A in liver and kidney transplant patients. Lancet I: 470
17. Lemaire M, Tillement JP (1982) Role of lipoproteins and erythrocytes in the in vitro binding and distribution of cyclosporin A in the blood. J Pharm Pharmacol 34: 715
18. Lokiec F, Devergie A, Poirier O, Gluckman E (1983) Pharmacologic monitoring in the clinical use of cyclosporine. Transplant Proc 15: 2442
19. Monjanel S, Rigault J, Cano JP, Carcassonne Y, Favre R (1979) High dose methotrexate: preliminary evaluation of a pharmacokinetic approach. Cancer Chemother Pharmacol 3: 189
20. Newburger J, Kahan BD (1983) Cyclosporine pharmacokinetics in man. Transplant Proc 15: 2413
21. Powles RL, Barret AJ, Clink H, Kay HE, Sloane J, McElwain TJ (1978) Cyclosporin A for the treatment of graft-versus-host disease in man. Lancet II: 1327
22. Robinson WT, Schran HF, Barry EP (1983) Methods to measure cyclosporine levels-high pressure liquid chromatography, radioimmunoassay, and correlation. Transplant Proc 15: 2403
23. Starzl TE, Weil R III, Iwatsuki S, Klintmalm G, Schröter GP, Koep LJ, Iwaki Y, Terasaki PI, Porter KA (1980) The use of cyclosporin A and prednisone in cadaver kidney transplantation. Surg Gynecol Obstet 151: 17
24. Starzl TE, Klintmalm GB, Porter KA, Iwatsuki S, Schröter GP (1981) Liver transplantation with use of cyclosporin A and prednisone. N Engl J Med 30: 266
25. Sutherland DE, Goetz FC, Elick BA, Najarian JS (1982) Experience with 49 segmental pancreas transplants in 45 diabetic patients. Transplantation 34: 330
26. Wood AJ, Maurer G, Niederberger W, Beveridge T (1983) Cyclosporine: pharmacokinetics, metabolism, and drug interactions. Transplant Proc 15: 2409

Received October 15, 1984/Accepted January 2, 1985