Clinical Variability of Cyclosporine Pharmacokinetics in Adult and Pediatric Patients after Renal, Cardiac, Hepatic, and Bone-Marrow Transplants

Christopher W. Clardy,1 Timothy J. Schroeder,2 Steven A. Myr,3 Nand K. Wadhwa,2 Amadeo J. Pecora,2 M. Roy First,2 Paul T. McEnery,1 William F. Ballantrey,1 Richard E. Harris,1 and David B. Melvin2

The most important limitation associated with the clinical use of cyclosporine is the narrow therapeutic range between its efficacy and toxicity. Effective treatment is further complicated by significant variation in intrapatient and interpatient pharmacokinetics of the drug. We describe a practical approach to pharmacokinetic analysis that does not interfere with the cyclosporine dosage regimen or with clinical management of the patient. To optimize therapy, we individualized patient management by using noncompartmental pharmacokinetic analysis. Mean residence time (MRT) and volume of distribution at steady-state were calculated from data on concentration vs time after dose. We applied this approach to 24 kidney, 12 heart, 8 bone-marrow, 7 liver, and 5 pancreas transplant recipients. Individualized requirements for cyclosporine dose and dosage interval can be predicted from these parameters. MRT is the most useful pharmacokinetic parameter, because it allows prediction of the optimal dosage interval.

Cyclosporine is a lipid-soluble cyclic polypeptide, first isolated from fungal fermentation broth in 1972. Soon thereafter it was found that cyclosporine specifically inhibits T-lymphocyte function, thereby blunting the immune response to a foreign antigen.

In 1978, cyclosporine was first used to prevent renal allograft rejection in humans (1). Since then it has been used extensively in kidney, liver, heart, and bone-marrow transplantation (2–4). In the original report, it was noted that cyclosporine was frequently associated with nephrotoxicity. This finding has been confirmed by other investigators, and it appears to be related to the cyclosporine concentration in the circulation (5–14).

Appropriate dosing of cyclosporine in the transplant recipient is made even more difficult because absorption, distribution, metabolism, and excretion vary widely, even among normal individuals, and are affected by, for example, altered gastrointestinal or liver function, which are not uncommon in the transplant population (15). To optimize therapy, we developed a method of individualized cyclosporine pharmacokinetic analysis that can be easily incorporated into the clinical care of the transplant recipient.

Methods

We obtained 73 cyclosporine pharmacokinetic profiles for patients at the University of Cincinnati Medical Center and the Children's Hospital Medical Center. Our subjects included 24 kidney, 12 heart, 8 bone-marrow, 7 liver, and 5 pancreas transplant recipients. Whole-blood cyclosporine concentrations were determined by HPLC (16).

Cyclosporine pharmacokinetics were determined after intravenous dosing in all of the bone-marrow transplant recipients and in seven of the renal transplant recipients. Bone-marrow transplant recipients were given cyclosporine as an intravenous infusion administered during 1 h, the average dose being 1.9 (SD 0.6) mg/kg. Pharmacokinetics were usually determined during the initial dosing interval from data on blood sampled at the end of the infusion and approximately hourly thereafter until the next dose. A pre-infusion "trough" blood sample (i.e., one taken just before a next dose) was obtained if a previous dose had been given. An average of 9.0 (SD 1.1) samples were obtained during 10.4 (SD 0.8) h. Pediatric cadaver-kidney-transplant recipients were treated with cyclosporine via constant-rate intravenous infusion (4 mg/kg per day) for the first three to four days after the transplant. At the discontinuation of this therapy, cyclosporine kinetics were determined from data on blood samples that were taken hourly, obtained from the time the cyclosporine infusion ended to the time of the first oral dose. An average of 10.4 (SD 2.2) samples were obtained over 10.3 (SD 2.0) h in this group of patients.

The rest of the pharmacokinetic profiles were based on data obtained after the initial oral dose in the heart transplant recipients, and at a steady-state (after at least seven days of therapy) in other subjects. In each case, blood was sampled just before the regular dose of oral cyclosporine and approximately hourly thereafter until the next regularly scheduled dose. The average dose of cyclosporine was 4.6 (SD 1.6) mg/kg. In these subjects, we obtained an average of 8.4 (SD 2.0) blood samples during 9.6 (SD 1.2) h after an oral dose.

Mean residence time (MRT) and volume of distribution at steady-state (Vdss) were used to describe the data on cyclosporine concentration vs time. These were calculated from the area under the curve (AUC) and the area under the first moment curve (AUMC) of the concentration vs time data. In all profiles, the effective MRT was calculated with equation 1:

\[
MRT = \frac{AUMC}{AUC}
\]

The cyclosporine concentration when the constant-rate intravenous infusion was terminated was considered to be

4 Nonstandard abbreviations: AUC, area under the concentration vs time curve; AUMC, area under the moment curve; \([\text{CyA}_I]\), last cyclosporine concentration; \([\text{CyA}_0]\), cyclosporine concentration in compartment i at a given time; \([\text{CyA}]_0\), initial cyclosporine concentration; \([\text{CyA}]_i\), cyclosporine concentration at steady-state; \([\text{CyA}]_i\), cyclosporine concentration at a given time; \([\text{Kg}]_i\), absorption rate constant; \([\text{Kg}]_i\), terminal elimination rate constant; \([\text{Kg}]_i\), elimination rate constant for compartment i; MRT, mean residence time; \([\text{T}^\text{F}]\), final time point in kinetic profile; \([\text{T}^\text{F}]/\text{AUC}\), volume of distribution at steady-state; \([\text{Cmax}]/\text{AUC}\), maximum cyclosporine concentration; \([\text{ Tmax}]/\text{AUC}\), time to maximum cyclosporine concentration; and \([\%\text{ F}]\), fractional absorption of cyclosporine.
at steady-state. Equations 2 and 3 were used to calculate the $V_{\text{des}}$ in subjects who received the drug by either constant-rate infusion or intravenous bolus, respectively.

$$V_{\text{des}} = \frac{(\text{infusion rate}) \cdot \text{MRT}}{(\text{CyA})}$$  \(2\)

$$V_{\text{des}} = \frac{\text{dose} \cdot \text{AUMC}}{\text{AUC}^2} - \frac{\text{dose} \cdot \text{infusion time}}{2 \cdot \text{AUC}}$$  \(3\)

In subjects receiving cyclosporine orally, the volume of distribution and the degree of bioavailability could not be resolved from each other. Therefore, an effective volume of distribution was calculated with equation 4:

$$V_{\text{des}}/\%F = (\text{dose} \cdot \text{AUMC}/\text{AUC}^2) - (\text{dose}/(K_a \cdot \text{AUC}))$$  \(4\)

The AUC (equation 5) and the AUMC (equation 6) were calculated from the concentration vs time data by the trapezoidal method (17). Here, we use the convention that brackets symbolize "concentration."

$$\text{AUC} = [\text{CyA}]_0 \cdot \text{dt} + [\text{CyA}]_i/n$$  \(5\)

$$\text{AUMC} = [\text{CyA}]_0 \cdot t \cdot \text{dt} + (T_f \cdot [\text{CyA}]_n) + ([\text{CyA}]_i/n^2)$$  \(6\)

The method of superposition was used to convert steady-state data to first-dose conditions (18). We fitted the concentration vs time data to equation 7 by using the Nelder–Mead algorithm of nonlinear regression analysis (19).

$$[\text{CyA}]_k = ([\text{CyA}]_0 \cdot e^{-xt}) + ([\text{CyA}]_0 \cdot e^{-nt})$$  \(7\)

Initial estimates of the parameters were determined by breakpoint analysis of the curve for log concentration vs time (20). We determined the appropriate exponential equation required for the best fit of the data by using the F-statistic to compare the sums of the squared residuals for the different values of i in equation 7 (21). We made statistical comparisons of pharmacokinetic parameters between different groups of transplant recipients with the two-tailed Student's t-test and with one-way analysis of variance.

**Results**

Table 1 summarizes our data for cyclosporine pharmacokinetic profiles. Statistical comparisons of the $V_{\text{des}}$ and the MRT showed no significant difference between transplant groups after either intravenous or oral dosing. A series of curves for whole-blood concentration vs time, representing several commonly observed pharmacokinetic patterns, are presented in Figures 1–4. Figure 1 illustrates a typical curve for cyclosporine concentration vs time after an oral dose, with a peak concentration at 4 h. In some patients, we observed concentration vs time profiles that lacked an obvious peak after an oral dose, indicating inadequate or delayed absorption of cyclosporine (Figure 2). Such curves were common for kidney, liver, and pancreas transplant recipients, but were not observed for cardiac transplant recipients (Table 2).

A secondary peak was apparent in 27 of 58 (47%) subjects studied. The presence of this second cyclosporine concentration peak strongly suggests enterohepatic recirculation of cyclosporine (Figure 3).

The distribution of cyclosporine after intravenous infusion was clearly multicompartmental in 8 of the 15 subjects; in the remaining 7 patients this was not apparent. Figure 4 shows an initial rapid decrease in concentrations in the blood (distribution phase) followed by a slower decrease (elimination phase).

**Discussion**

The pharmacokinetics of cyclosporine are complex, because of variable absorption, multicompartmental distribution, and individual differences in metabolism and excretion. Appropriate dosing of cyclosporine is often based solely on monitoring of trough concentrations. Such values alone do not allow one to distinguish inadequate cyclosporine absorption (Figure 2) from a normal pattern of absorption (Figure 1). A complete classical pharmacokinetic analysis is not practicable in the transplant recipient, however, because it would require many blood samplings during a long interval, which would interfere with our standard 12-h dosing interval. To overcome these limitations, we used a more practicable approach to individualized cyclosporine therapy, which is based on noncompartmental pharmacokinetic analysis and does not interfere with the normal dosing interval.

This approach has its limitations in the precise characterization of cyclosporine absorption. The clinical restriction on the number of blood samples that could be obtained per profile, as well as the deviation of the concentration vs time data from that predicted with simple pharmacokinetic models, did not permit the calculation of $K_a$, $T_{\text{max}}$, or $C_{\text{max}}$. Hence, we could not precisely characterize cyclosporine absorption after an oral dose. Another quantitative assessment of the degree of absorption is given by the fractional absorption ($\%F$), which is included in the effective volume of distribution ($V_{\text{des}}$) and varies markedly between individuals (Table 1). The $V_{\text{des}}$ and the $\%F$ could not be resolved without data on both intravenous and oral dosing on the same subject. They do have a parallel clinical effect such that the dose of cyclosporine required to attain a given concentration will vary directly with the effective volume of distribution. As can be seen from the data in Table 1, the effective volume of distribution shows a wide individual variation but no obvious difference in this term between the different types of transplant recipients. A comparison of the geometric mean volumes of distribution at steady-state for the subjects receiving intravenous cyclosporine vs the effective volume of distribution in those receiving the drug orally gives a predicted mean fractional absorption of 38%, which is similar to that reported in simultaneous oral/intravenous studies.
The rate of removal of active, un-metabolized cyclosporine is reflected in the MRT, which is the average interval during which a molecule of cyclosporine resides in the body. Calculation of the MRT is not impaired if the %F is unknown. Variations in MRT as described in Table 1 will directly affect the ideal dosage interval for cyclosporine. There were wide individual variations in MRT, with the longest times being in recipients of liver and heart transplants (Table 1). We use an approximation to estimate the appropriate cyclosporine oral dosing schedule: dosing interval equals approximately two times the MRT. With use of this approach, our cyclosporine dosing regimens are individualized for each patient, and the drug may be given once, twice, or three times a day. In our experience, patients with a large proportion of body fat initially clear cyclosporine from the blood rapidly, because of redistribution. Calculation of the dosing interval with the MRT should be done cautiously in these patients.

The reciprocal of the MRT is the terminal elimination rate constant (n). We attempted, in each subject, to resolve this single rate constant into various intracompartmental

| Table 2. Frequency of Inadequate Absorption of Cyclosporine after Various Transplants |
|---------------------------------|--------|------|
| Kidney                          | 12/29  | 41%  |
| Pancreas                        | 2/9    | 22%  |
| Liver                           | 3/8    | 38%  |
| Cardiac                         | 0/12   | 0%   |
| Total                           | 17/58  | 29%  |

In conclusion, there is wide and unpredictable individual variation in the pharmacokinetics of cyclosporine. In our experience, the use of noncompartmental pharmacokinetic analysis allows one to obtain useful information regarding the correct dosage of cyclosporine in an individual patient while maintaining the standard clinical care. The MRT appears to be a very useful pharmacokinetic parameter and, at our institution, calculation of the oral dosage of cyclosporine is based on it.

References


