Pharmacokinetics of cyclosporin: influence of rate of constant intravenous infusion in renal transplant patients

S. K. GUPTA¹, B. LEGG¹, L. R. SOLOMON², R. W. G. JOHNSON² & M. ROWLAND¹

¹Department of Pharmacy, University of Manchester, Manchester M13 9PL and ²Renal Transplant Unit, Manchester Royal Infirmary, Manchester M13 9WL

- 1 The pharmacokinetics of cyclosporin were studied in 12 renal transplant patients. Five patients received a constant rate ($7 \text{ mg kg}^{-1} \text{ day}^{-1}$) intravenous infusion over 72 h and the remainder received rates of 7, 4 and $10 \text{ mg kg}^{-1} \text{ day}^{-1}$, consecutively each for at least 24 h.
- 2 Plasma, separated at 37°C , was analysed by h.p.l.c.
- 3 The data were best described by a biexponential model.
- 4 Following the 72 h infusion, a plateau was reached by 24 h and clearance was $0.60 \text{ l h}^{-1} \text{ kg}^{-1}$.
- 5 Clearance associated with the $10 \text{ mg kg}^{-1} \text{ day}^{-1}$ infusion rate ($0.43 \text{ l h}^{-1} \text{ kg}^{-1}$) was estimated to be lower than that following the 4 and $7 \text{ mg kg}^{-1} \text{ day}^{-1}$ rates (0.52 and $0.54 \text{ l h}^{-1} \text{ kg}^{-1}$ respectively) but the difference is unlikely to be of clinical significance.

Keywords cyclosporin pharmacokinetics clearance dose dependency renal transplant patients

Introduction

Cyclosporin, a fungal undecapeptide, is a potent immunosuppressant which is widely used in the inhibition of the graft rejection in organ transplantation. To date the pharmacokinetics of cyclosporin have been generally assumed to be linear in humans and dosage regimens have been adjusted accordingly. Some general concern regarding this assumption has been expressed however, by Bowers & Canafax (1984), Kahan (1985) and Ptachcinski *et al.* (1986), all of whom reported some possibility of dose-dependent pharmacokinetic behaviour of cyclosporin in man, but this concern does not appear to be based on any data in man.

The aim of the present study was to investigate, in renal transplant patients, the influence of the intravenous dosing rate of cyclosporin on its clearance (CL). Interpretation has been based on measurement of cyclosporin concentration in plasma samples using high performance liquid chromatography (h.p.l.c.).

Methods

Clinical

Study 1 Constant rate infusion study Cyclosporin was administered to five renal transplant patients (two male, three female) between 25 and 39 years of age, body weight ranging from 50 to 71 kg. Each patient received a continuous infusion of cyclosporin ($7 \text{ mg kg}^{-1} \text{ day}^{-1}$) in normal saline solution, for 72 h. Cyclosporin infusion was given via a central venous line, using a calibrated pump (IMED 365). The infusion was started 6 h after the transplant operation was completed and all patients had a good urine flow. Blood samples (12 ml) were collected, in the tubes containing potassium EDTA as the anticoagulant at 0, 2, 4, 8, 12, 18, 24, 36, 48, 51, 54, 57, 60 and 72 h after starting the cyclosporin infusion. Patients received no other medication during the study.

Study 2 Variable rate infusion study Seven renal transplant patients (five male, two female) between 14 and 51 years of age, body weight ranging from 35 to 71 kg, were studied. Each received a continuous infusion of cyclosporin in normal saline for 84 h via a central venous line, using a calibrated pump (IMED 365). The infusion was started 6 h after the transplantation was completed and all the patients had good urine flow. Cyclosporin was infused at a rate of $7 \text{ mg kg}^{-1} \text{ day}^{-1}$ for the first 36 h, followed by a rate of $4 \text{ mg kg}^{-1} \text{ day}^{-1}$ for the next 24 h and, over the final 24 h the rate was increased to $10 \text{ mg kg}^{-1} \text{ day}^{-1}$. Blood samples (12 ml) were collected, in tubes containing potassium EDTA as anticoagulant, at 0, 33, 34.5, 36, 57, 58.5, 60, 81, 82.5, 84, 84.5, 85, 85.5, 86, 87, 89, 92, 96 and 108 h after starting the infusion. No other medication was given to the patients while they were on the study.

Both studies received the approval of the ethics committee of Manchester Royal Infirmary, Manchester; and all patients gave their informed consent. In all cases the infusion rate was monitored by periodic observations of the pump reading and the weight of the infusion bag.

Chemical

Cyclosporin was measured in plasma (separated from blood at 37°C , 3500 rev min^{-1} for 4 min) by h.p.l.c. using a method based on that of Carruthers *et al.* (1983).

The sample (1 ml) was extracted with diethyl ether after addition of cyclosporin D as internal standard and acidification with hydrochloric acid. The ether extract was washed with sodium hydroxide solution and then blown to dryness with oxygen-free nitrogen. The residue was reconstituted in 200 μl of mobile phase and injected onto the h.p.l.c. system with the following characteristics.

Column: 25 cm $\times$ 0.4 cm packed with Zorbax ODS, 5 μm , in a water bath at 70°C .

Mobile phase: Methanol/acetonitrile/water in the volume ratio 48:54:35. Flow rate = 1.5 ml min^{-1} . (Beckman model 110A)

Detection: 214 nm (Waters absorbance detector, model 441)

Retention times: Cyclosporin A = 16 min, Cyclosporin D = 21 min.

Standard curves (6 points, 0–2000 $\mu\text{g l}^{-1}$) were run concurrently with each batch of samples. The minimum detection limit was $30 \mu\text{g l}^{-1}$ and the coefficient of variation in peak height ratio was less than 5%.

The concentrations of cyclosporin in a test sample was determined by calculation of the

peak height ratio [Cyclosporin A/Cyclosporin D] and referenced against a calibration graph constructed using the peak height ratios determined for the standards. Each patient's sample set was assayed on the same occasion.

Data analysis

Clearance (CL) was calculated using the equation

$$\text{CL} = \frac{\text{rate of infusion}}{\text{steady-state concentration}} \quad (1)$$

The steady-state concentration was taken as the average of the three values taken over the last 3 h of any infusion.

The following equation was fitted to the entire plasma cyclosporin concentration-time data, using a non-linear extended least squares regression analysis (Sheiner & Beal, 1980).

$$C(t) = \sum_{i=1}^n \frac{R_i}{V_1} \left[\frac{A' (1 - e^{-\lambda_1 t_i}) e^{-\lambda_1 t_i}}{-\lambda_1} + \frac{(1 - A') (1 - e^{-\lambda_2 t_i}) e^{-\lambda_2 t_i}}{-\lambda_2} \right] \quad (2)$$

where $C(t)$ is the plasma concentration at time t since starting the first infusion, R_i is the i^{th} infusion rate, V_1 is the initial volume of distribution, A' is the fraction of the initial (zero time) plasma concentration associated with the first exponential term, had an i.v. bolus dose been given, and λ_1, λ_2 are the exponential coefficients associated with the first and second exponential terms, respectively. The value t_i is the time since the i^{th} infusion and θ assumes the value t_i during the infusion and τ_i , the duration of the i^{th} infusion, after stopping that infusion.

In addition, the following biexponential equation was fitted to the post-infusion data after stopping the final (third) infusion.

$$C(t_{\text{post}}) = \frac{R_i}{V_1} \left[\frac{A'}{\lambda_1} e^{-\lambda_1 t_{\text{post}}} + \frac{1 - A'}{\lambda_2} e^{-\lambda_2 t_{\text{post}}} \right] \quad (3)$$

where t_{post} is the time elapsed since stopping the last infusion. It should be noted that at $t_{\text{post}} = 0$ the concentration is that just upon stopping the infusion.

For each phase, the half-life ($t_{1/2}$) is given by

$$t_{1/2} = \frac{0.693}{\lambda} \quad (4)$$

The volume of distribution at steady state (V_{ss}) and the volume of distribution during the terminal phase (V) were estimated from the disposition parameters in the standard manner (Gibaldi & Perrier, 1982).

Two-way analysis of variance was performed, to see if clearance varies significantly with variation in dosing rate and among patients. The choice of the exponential model to fit the data was based on the F -ratio test, and an examination of the residuals. A value of $P < 0.05$ was taken as being statistically significant.

Results

Study 1

The plasma cyclosporin concentration rose progressively to a steady state by 72 h, with little fluctuation at plateau (Figure 1). The concentration rose rapidly at first, reaching 50 per cent of plateau by 2 to 3 h, but then approached the plateau much more slowly. The plasma cyclosporin concentration-time data were adequately fitted by a biexponential disposition model ($n=1$, Equation 2). A monoexponential disposition model did not describe the data as well and a triexponential model was found unnecessarily complicated.

Table 1 lists the various parameters associated with the biexponential model. The mean clearance was $0.60 \text{ l h}^{-1} \text{ kg}^{-1}$ (range 0.39 to $0.80 \text{ l h}^{-1} \text{ kg}^{-1}$) and varied relatively little among patients. There was wide variation in the estimated initial volume of distribution (V_1), range 0.36 to 1.61 l kg^{-1} (average 0.87 l kg^{-1}) and less, but still substantial variation, in the volume of distribution at steady state (V_{ss}), range 2.3 to 7.8 l kg^{-1} (average 4.6 l kg^{-1}). The mean half-lives for the

Figure 1 Cyclosporin plasma concentration-time profile in a renal transplant patient receiving a $7 \text{ mg kg}^{-1} \text{ day}^{-1}$ infusion for 72 h. Solid line represents the computer prediction associated with a bi-exponential disposition model.

Table 1 Parameters obtained by fitting plasma cyclosporin concentration-time data in patients receiving a 72 h constant rate infusion ($7 \text{ mg kg}^{-1} \text{ day}^{-1}$)

Patient	Weight (kg)	A'	λ_1 (h^{-1})	λ_2 (h^{-1})	V_1 (l kg^{-1})	V_{ss} (l kg^{-1})	V^a (l kg^{-1})	C_{ss} ($\mu\text{g l}^{-1}$)	$t_{1/2}$ (λ_1) ^b (h)	$t_{1/2}$ (λ_2) ^b (h)	CL ($\text{l h}^{-1} \text{ kg}^{-1}$)	Time to reach 90% of 72 h concentration (h)
1	71	0.897	1.01	0.0980	1.06	3.28	5.58	533	0.68	7.1	0.547	18
2	66	0.950	3.79	0.160	0.358	2.27	3.97	459	0.18	4.3	0.635	12
3	50	0.942	2.23	0.0722	0.472	3.56	5.34	755	0.31	9.6	0.386	24
4	59	0.921	5.36	0.0870	0.864	7.75	9.19	365	0.13	8.0	0.799	30
5	54	0.946	0.68	0.0500	1.61	6.26	13.0	447	1.02	13.9	0.652	30
Mean (s.d.)	60 (8.5)	0.931 (0.022)	2.61 (1.75)	0.093 (0.037)	0.87 (0.50)	4.62 (2.29)	7.42 (3.68)	512 (148)	0.26	7.45	0.604 (0.152)	22.8 (7.8)

^a $V = CL/\lambda_2$, ^b Harmonic mean.

first and second exponential terms were 0.26 h and 7.5 h, respectively.

Based on direct observation and using the estimated parameters, it took, on average, 23 h to reach 90% of the steady-state concentration value.

Study 2

Figure 2 shows a typical plasma cyclosporin concentration-time profile during the various infusions. A clear biexponential disposition of the terminal data is seen after stopping the 10 mg kg⁻¹ day⁻¹ infusion (inset, Figure 2). Table 2 lists the average of the three plasma cyclosporin concentration values taken over the last 3 h of each infusion, and the associated plasma cyclosporin clearance values assuming that a steady state had been reached on each occasion. The average concentrations associated with the 4, 7 and 10 mg kg⁻¹ day⁻¹ infusions were 340, 560 and 1010 µg l⁻¹; the corresponding calculated clearance values are 0.52, 0.54 and 0.43 l h⁻¹ kg⁻¹ respectively. ANOVA identified a significant difference in estimated clearance values between the 10 mg kg⁻¹ day⁻¹ and the lower infusion rates but not between the two lowest rates. The clearance values obtained following an infusion rate of 7 mg kg⁻¹ day⁻¹ in Study 2 (0.54 l h⁻¹ kg⁻¹) is similar to the clearance obtained in Study 1 (0.60 l h⁻¹ kg⁻¹).

The pharmacokinetic parameters obtained by fitting of the post infusion data after stopping the 10 mg kg⁻¹ day⁻¹ infusion are listed in Table 3. There was wide variation in the estimated initial volume of distribution (V_1), range 0.17–1.16 l kg⁻¹

(average 0.47 l kg⁻¹) and in the volume of distribution at steady state (V_{ss}) 0.78 to 4.09 l kg⁻¹ (average 2.34 l kg⁻¹).

The average clearance associated with this final infusion was 0.43 l h⁻¹ kg⁻¹ with relatively little variation among patients (range 0.26 to 0.52 l h⁻¹ kg⁻¹). Also, the average half-lives of the first and second exponential phases were 0.27 h and 7.4 h respectively.

Discussion

The purpose of the study was to obtain definitive information on the intravenous disposition kinetics of cyclosporin in renal transplant patients, with particular attention to clearance, a basic pharmacokinetic parameter and one used, for example, in estimating absolute oral bioavailability. Clearance is estimated best at steady state, but most intravenous disposition studies with cyclosporin have involved short term (1–4 h) infusions (Follath *et al.*, 1983; Bertault-Peres, 1985; Yee *et al.*, 1984; Ptachcinski *et al.*, 1985) in which a steady-state was not reached. On clinical grounds, both the single constant-rate and variable rate infusion studies were limited to a total of approximately 3 days. The usual practice in the hospital is to initiate cyclosporin therapy intravenously and change to oral administration as soon as possible, usually within 24 h.

The first study was designed primarily to investigate how long it takes to reach a steady-state plasma concentration. It is generally regarded that it takes 3.3 half-lives to reach a plateau during a constant-rate infusion, and the

Figure 2 Cyclosporin plasma concentration-time profile in a renal transplant patient receiving the 7, 4 and 10 mg kg⁻¹ day⁻¹ infusion for 36, 24 and 24 h respectively. Solid line is the computer prediction associated with the bi-exponential disposition model. The inset contains a semilogarithmic plot of the post-infusion (10 mg kg⁻¹ day⁻¹) concentration-time data.

Table 2 Steady state concentration and clearance values of cyclosporin, following a variable constant rate infusion regimen

Patient	Weight (kg)	Cyclosporin concentration at steady state ($\mu\text{g l}^{-1}$)				Clearance ($\text{l h}^{-1} \text{kg}^{-1}$)			
		Mean (s.d.)		Dose ($\text{mg kg}^{-1} \text{day}^{-1}$)		Dose ($\text{mg kg}^{-1} \text{day}^{-1}$)			
				7	4	7	4	7	10
			obs	calc ^a			obs	calc ^a	
6	70.0	575 (58)	380 (26)	342 ^b (54)	920 (54)	0.51	0.44	0.48	0.45
7	56.0	430 (30)	306 (20)	276 ^b (52)	840 (52)	0.68	0.59	0.65	0.50
8	35.5	477 (74)	330 (57)	322 (52)	875 (52)	0.61	0.50	0.52	0.48
9	46.0	500 (8)	245 (11)	216 (20)	801 (20)	0.58	0.68	0.77	0.52
10	60.0	572 (26)	367 (12)	320 (80)	932 (80)	0.51	0.45	0.52	0.45
11	51.5	587 (17)	263 (40)	236 (136)	1608 (136)	0.51	0.63	0.71	0.26
12	70.0	781 (44)	486 (47)	400 (86)	1090 (86)	0.37	0.34	0.42	0.38
Mean		560	340	301	1010	0.54	0.52	0.58	0.43
s.d.		(105)	(76)	(64)	(259)	(0.09)	(0.011)	(0.013)	(0.082)

^a Correction made of contribution of previous $7 \text{ mg kg}^{-1} \text{day}^{-1}$ infusion at 24 h following $4 \text{ mg kg}^{-1} \text{day}^{-1}$, based on fitting of $10 \text{ mg kg}^{-1} \text{day}^{-1}$ post infusion data.

^b Correction made assuming that $7 \text{ mg kg}^{-1} \text{day}^{-1}$ infusion contributes 11% to 24 h $4 \text{ mg kg}^{-1} \text{day}^{-1}$ value.

Table 3 Parameters (mean, s.d.) obtained by fitting a biexponential disposition model to the post $10 \text{ mg kg}^{-1} \text{day}^{-1}$ infusion plasma cyclosporin concentration-time data

Patient ^a	A'	V_1 (l kg^{-1})	λ_1 (h^{-1})	λ_2 (h^{-1})	Concentration predicted 24 h after $7 \text{ mg kg}^{-1} \text{day}^{-1}$	Contribution of $7 \text{ mg kg}^{-1} \text{day}^{-1}$ at 24 h	V_{ss} (l kg^{-1})	V (l kg^{-1})
8	0.940 (0.011)	0.38 (0.08)	2.11 (0.63)	0.151 (0.019)	8	2.4	1.52	3.18
9	0.985 (0.010)	0.17 (0.12)	5.79 (4.41)	0.094 (0.021)	29	11.8	2.70	5.53
10	0.955 (0.013)	0.50 (0.10)	1.53 (0.35)	0.081 (0.017)	47	12.8	2.61	5.56
11	0.989 (0.005)	0.12 (0.02)	3.02 (0.61)	0.098 (0.029)	27	10.3	0.78	2.27
12	0.954 (0.030)	1.16 (0.25)	0.57 (0.16)	0.045 (0.022)	87	17.9	4.09	8.44
Mean (s.d.)	0.965 (0.021)	0.47 (0.42)	2.60 (1.99)	0.094 (0.038)	40 (30)	11.0 (5.61)	2.34 (1.26)	5.08 (2.31)

^a No post infusion data obtained in patients 6 and 7.

literature quotes wide variations in the terminal half-life of cyclosporin ranging from 2.9 h (Newberger & Kahan, 1983) to 16.5 h (Follath *et al.*, 1983) in renal transplant patients, although differences in analytical methodology, such as use of RIA, makes interpretation difficult. A 72 h infusion was therefore thought to be necessary to provide definitive information. Also with a desire to describe the rise to plateau accurately and with the limitations in the total volume of blood that could be taken, blood sampling was restricted to times during the infusion. Such an experiment provides a good estimate of the plateau concentration, and hence of clearance, but relatively poor estimates of other parameters. For example, the terminal half-life and volume of distribution primarily from observations beyond 12 h when the concentration rises gradually to the plateau. Much better estimates of these parameters are gained from declining concentration values after stopping an infusion. Accordingly, the values for all but clearance in Table 1 should be regarded as indicative, whereas much more confidence is provided in the pharmacokinetic parameter listed in Table 3.

Because of the significant biexponential nature of cyclosporin disposition kinetics, the approach to plateau is more complicated than drugs showing monoexponential disposition. The time to achieve 50% of plateau concentration was only 2 to 3 h, much shorter than anticipated based on the terminal half-life, which ranged from 4.3 to 13.9 h, assuming a one-compartment model. Indeed, the early sharp rise is influenced by the first exponential term, with a half life of only 0.26 h. Using the estimated pharmacokinetic parameters the time to reach 90% of plateau is, on average, 23 h (range 12–30 h) and this information was used in the design of the variable infusion rate experiment (Study 2).

The infusion rates chosen to study the concentration-dependence in clearance (4, 7 and 10 mg kg⁻¹ day⁻¹) span the range of daily dosing rates likely to be encountered in clinical practice. The experimental design was a compromise, however, which complicates the interpretation because a true steady state is not reached and the order of dosing rates could not be randomised. For ethical reasons, the initial dosing rate was always 7 mg kg⁻¹ day⁻¹, as this is the daily dosing rate usually employed in the hospital. The final rate was set at the highest value to permit the best description of the events following termination of the infusion, and was limited to 10 mg kg⁻¹ day⁻¹ on safety considerations. To keep the average daily infusion rate over the 3 day study period to 7 mg kg⁻¹ day⁻¹, the lowest, and middle, rate was fixed at 4 mg kg⁻¹ day⁻¹.

Moreover, based on the 72 h single infusion rate study, the infusion time at each rate must be at least 24 h to approach a plateau, but this was virtually the maximum permitted time, given a total limit of around 3 days. As patients are expected to be under light anaesthesia for some time during the first part of the initial infusion, which began approximately 6 h after surgery, and anaesthesia may affect cyclosporin pharmacokinetics, it was decided to extend the first infusion to 36 h. Furthermore, as the emphasis was on the measurement of clearance, blood sampling was kept to times close to the end of each infusion period and was intensive after the 10 mg kg⁻¹ day⁻¹ infusion, to define as accurately as possible the disposition kinetics to cyclosporin.

The principal problem that this design created was the estimation of steady-state plasma cyclosporin concentration following the 4 mg kg⁻¹ day⁻¹ infusion. At 24 h into this infusion rate there was some residual concentration associated with the previous 7 mg kg⁻¹ day⁻¹ rate; the effect of the 4 mg kg⁻¹ day⁻¹ rate on the 24 h 10 mg kg⁻¹ day⁻¹ rate value was negligible. The only means of estimating the contribution of the 7 mg kg⁻¹ day⁻¹ rate to the 4 mg kg⁻¹ day⁻¹ infusion is based on pharmacokinetic information gained from the post-10 mg kg⁻¹ day⁻¹ data, assuming linearity. With this assumption the contribution at 24 h has been calculated to be between 8–87 µg l⁻¹ (average 40 µg l⁻¹) or 11% of the 4 mg kg⁻¹ h⁻¹ plateau value (Table 3). Making this correction, the estimated plateau concentration associated with the 4 mg kg⁻¹ day⁻¹ rate is 301 µg l⁻¹ instead of the observed 340 µg l⁻¹, and the corresponding estimated clearance value is 0.58 l h⁻¹ kg⁻¹, compared to estimated values of 0.54 and 0.43 l h⁻¹ kg⁻¹ associated with the 7 mg and 10 mg kg⁻¹ day⁻¹ infusion rates respectively. ANOVA now indicated a statistically significant lower clearance value between the 10 mg and both 4 and 7 mg kg⁻¹ day⁻¹ rates, with no difference between the two lowest rates. The % decrease in clearance (25%) over the 2.5 fold range of infusion rates studied is however relatively small and unlikely to be clinically significant, although it does tend to support the earlier suggestion that part of the difference in clearance values reported here and in the literature may be associated with saturable kinetics. Even at the highest constant rate infusion of 10 mg kg⁻¹ day⁻¹, the plateau concentration was around 1000 µg l⁻¹ (Table 2), yet when, for example, a daily dose of only 3.5 mg kg⁻¹ is infused over 2 h the maximum blood cyclosporin concentration (h.p.l.c.) is in the order of 4000 µg l⁻¹ (Ptachcinski *et al.*, 1985).

Further evidence of some dose-dependency in clearance is shown for one patient in Figure 2, in which the solid line corresponds to that predicted by fitting equation 2 ($n=3$) to all the concentration-time data assuming linearity. As can be seen, there is a tendency to predict higher-than-observed concentrations associated with the 4 and 7 mg kg⁻¹ day⁻¹ infusion rates, the estimated parameters being dominated by the 10 mg kg⁻¹ day infusion data, which form the majority of the observations. A similar observation was made in other subjects.

Animal data also point to the possibility of dose-dependency in the pharmacokinetics of cyclosporin. Awni & Sawchuk (1985) observed, in rabbits, an increase in both volume of distribution and clearance following an increase in the cyclosporin intravenous dosing rate, from 5 to 20 mg kg⁻¹. Nooter *et al.* (1985) noted a 25-fold increase in the whole blood AUC (RIA) in rats when the oral dose was increased from 20 to 80 mg kg⁻¹. Ueda *et al.* (1984) also reported a dose dependent oral absorption of cyclosporin in rats.

Dose-dependency apart, the data indicate that cyclosporin is a drug of reasonably high clearance distributing significantly into a slowly equilibrating tissue or group of tissues. The existence of a slowly equilibrating tissue is indicated by the pronounced distribution phase on stopping the 10 mg kg⁻¹ day⁻¹ infusion after 24 h, when a steady state has virtually been

attained. For most drugs after stopping an infusion at plateau the distribution phase is shallow. Cyclosporin is highly lipophilic and the likely slowly equilibrating tissue is fat, which is poorly perfused and into which cyclosporin favourably partitions (Niederberger *et al.*, 1983). Calculations show that had cyclosporin been given as a bolus a very pronounced distribution phase (signified by $A' = 0.95$, Tables 1 and 3) would have been seen falling rapidly with a half-life of 0.26 h (Tables 1 and 3). A significant fraction of the dose is eliminated, however, during this phase. This loss is evident by the large discrepancy between the volume of distribution at steady state of 3.5 l kg⁻¹ (estimated from the combined data in Tables 1 and 3), which is a relatively pure measure of distribution, and the volume of distribution during the terminal phase, $V (= CL/\lambda_2$; Gibaldi & Perrier, 1982) of 6.2 l kg⁻¹ (Tables 1 and 3), whose value is influenced by elimination.

In summary, the change in clearance with concentration is small. Accordingly, this study provides no evidence that individual cyclosporin dosage adjustment, based upon constant clearance, is inadequate.

We thank Sandoz Pharmaceuticals for the gifts of cyclosporin A and D. One of us (S. K. Gupta) thanks the University of Manchester, for a Frederick Craven Moore Scholarship.

References

- Awni, W. M. & Sawchuk, R. J. (1985). The pharmacokinetics of cyclosporine. I. Single dose and constant rate infusion studies in the rabbit. *Drug Metab. Disp.*, **13**, 127–132.
- Bertault-Peres, P., Maraninchi, D., Carcassonne, Y., Cano, J. & Barbet, J. (1985). Clinical pharmacokinetics of cyclosporin A in bone marrow transplantation patients. *Cancer Chemother. Pharmacol.*, **15**, 76–81.
- Bowers, L. D. & Canafax, D. M. (1984). Cyclosporine: Experience with therapeutic monitoring. *Ther. Drug Monit.*, **6**, 142–147.
- Carruthers, S. G., Freeman, D. J., Koegler, J. C., Howson, W., Keown, P. A., Laupacis, A. & Stiller, C. R. (1983). Simplified liquid-chromatographic analysis for cyclosporin A, and comparison with radioimmunoassay. *Clin. Chem.*, **29**, 180–183.
- Follath, F., Wenk, M., Vozeh, S., 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**, 638–643.
- Gibaldi, M. & Perrier, D. (1982). *Pharmacokinetics*, 2nd edition. New York: Marcel Dekker Inc.
- Kahan, B. D. (1985). Individualization of cyclosporine therapy using pharmacokinetic and pharmacodynamic parameters. *Transplantation*, **40**, 457–476.
- Newberger, J. & Kahan, B. D. (1983). Cyclosporine pharmacokinetics in man. *Trans. Proc.*, **15**, 2413–2415.
- Niederberger, W., Lemaire, M., Maurer, G., Nussbaumer, K. & Wagner, O. (1983). Distribution and binding of cyclosporine in blood and tissues. *Trans. Proc.*, **15**, 2419–2421.
- Nooter, K., Schultz, F. & Sonnereld, P. (1984). Evidence for a possible dose dependent pharmacokinetics of cyclosporin-A in the rat. *Res. Comm. Chem. Path. Pharmacol.*, **43**, 407–415.
- Ptachcinski, R. J., Venkataramanan, R., Rosenthal, J. T., Burckart, G. J., Taylor, R. J. & Hakala, T. R. (1985). Cyclosporine kinetics in renal transplantation. *Clin. Pharmacol. Ther.*, **38**, 296–300.
- Ptachcinski, R. J., Venkataramanan, R. & Burckart, G. J. (1986). Clinical pharmacokinetics of cyclosporin. *Clin. Pharmacokin.*, **11**, 107–132.
- Sheiner, L. B. & Beal, S. (1981). *Elsfit*, Division of Clinical Pharmacology, University of California, San Francisco.
- Ueda, C. T., Lemaire, M., Gsell, G., Misslin, D. & Nussbaumer, K. (1984). Apparent dose-dependent

oral absorption of cyclosporin-A in rats. *Biopharm. Drug Disp.*, **5**, 141-151.

Yee, G. C., Kennedy, M. S., Storb, R. & Thomas, E. D. (1984). Pharmacokinetics of intravenous cyclosporine in bone marrow transplant patients. *Transplantation*, **38**, 511-513.

(Received 23 December 1986,
accepted 15 June 1987)