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Research Article

THERAPEUTIC MONITORING OF CYCLOSPORINE IN RENAL TRANSPLANT PATIENTS

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ABSTRACT

Therapeutic drug monitoring of cyclosporine (CSA) is important to obtain the optimum serum concentration, since CSA has a narrow therapeutic window and it can cause possible life-threatening toxicities, especially in the organ transplant recipients in which the therapy is life-sustaining. The objectives of this study were to identify the proportion of CSA concentrations achieved the therapeutic range at different post transplant durations, and to estimate cyclosporine pharmacokinetic (PK) parameters in renal transplant patients at Penang Hospital, Malaysia.

An observational retrospective cohort design was adopted. A total of 1601 PK profiles were obtained from 156 patients who underwent kidney transplantation in the period from 1988 to 2007. Based on the therapeutic range of both CSA concentrations (before the dose and 2 hours post-dose); these PK profiles were sub-classified. Data were collected from the transplant records at the haemodialysis unit of Penang Hospital.

The results of this study revealed that the majority of the cyclosporine PK profiles (864) were classified under group 6 (one year after transplantation). Majority of cyclosporine PK profiles based on C_0 (before the dose) concentration (six months and above post transplantation) were achieved therapeutic range. At the same time, more than half of these PK profiles based on C_2 (2 hours post-dose) concentration (the first year of transplantation) were achieved the therapeutic range.

The findings of this study showed the importance of the individual monitoring of CSA serum concentrations and their relationship to therapeutic outcomes in renal transplant patients. The obtained PK parameters will assist in the estimation of CSA empiric dose which is necessary to achieve the therapeutic outcomes.

INTRODUCTION

Although therapeutic drug monitoring (TDM) services were started long time ago in Malaysia (1984), very few studies, especially on cyclosporine (CSA), have been performed regarding this service[1,2]. Therapeutic drug monitoring services for immunosuppressant drugs are important to identify the optimum serum concentrations. Cyclosporine without concentration monitoring may has potential to cause life-threatening toxicities, especially in organ transplant recipients in which therapy is life-sustaining[3].

Since the introduction of CSA in 1978 as a cyclic peptide immunosuppressant drug to prevent graft rejection in solid organ transplant recipients, patient and graft survival rates have improved[4,5]. Initially, CSA monitoring in kidney transplant patients at Penang Hospital only involved the pre-dose concentration (C_0). After the introduction of the CSA microemulsion formulation, the 2-hour post-dose concentration (C_2) started to be measured along with the C_0 already implemented for cyclosporine TDM. This is particularly important because the C_2 shows a better correlation with CSA exposure indices and clinical outcomes than the C_0[6]. The therapeutic range of CSA concentrations (both C_0 and C_2) in renal transplant recipients were established according to the post transplant duration (in months)[7]. Although higher CSA concentrations are needed at the early post transplantation stage to prevent the immunological reactions, a decrease in the therapeutic range may be necessary with longer post transplant duration in order to prevent or decrease adverse drug reactions and complications related with CSA use. In tandem with the above, researchers from the School of Pharmaceutical Science, Universiti Sains Malaysia (USM) intended to investigate the proportion of kidney transplanted patients achieved therapeutic concentrations of CSA.

At present, there are no local data on the pharmacokinetic (PK) parameters of CSA. So that, generation such parameters might be necessary to optimize CSA therapy in renal transplant patients[8]. The objectives of this study were to identify the proportion of CSA concentrations achieved the therapeutic range at different post transplant durations, and to estimate cyclosporine PK parameters in renal transplant patients at Penang Hospital.

MATERIALS AND METHODS

An observational retrospective cohort design was adopted for this study. A total of 1601 PK profiles were obtained from 156 patients who underwent kidney transplantation in the period from 1988 to 2007 and met the eligibility criteria. These PK profiles were classified into six groups based on the post transplant duration (Table 2). Inclusion criteria were defined as those kidney transplanted patients taking an oral microemulsion formulation of CSA twice daily, aged 18 years old and above, and having data on the both C_0 and C_2 of CSA. Kidney transplanted patients who did not receive CSA or those who received CSA therapy for purposes other than renal transplantation, patients aged less than 18 years old, and patients who did not have the above-mentioned information were excluded from the study. Data were collected from the transplant records at the haemodialysis unit of Penang Hospital. The information extracted from patients medical records included demographic data, post-transplant duration, donor type of transplanted kidney, immunosuppressant therapy, serum creatinine (Srcr), type of CSA product (Neoral® or Gengraf®), and dose of CSA. This study was approved by the Clinical Research Centre (CRC), National Institutes of Health (NIH), Ministry of Health, Malaysia. The TDM Laboratory at the Department of Pharmacy of Penang Hospital analysed drugs by using Abbott AXSYM machine. Blood samples were taken before and 2 hours after the morning dose of CSA.

Population PK analysis was performed by using the Statistical Package for Social Science (SPSS) software program, version 12. The PK parameters of CSA were derived using a one-compartment model with first-order absorption and elimination (Appendix). All analyses used two-tailed statistical tests, and a P-value < 0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the patients are shown in Table 1.

The daily dose of CSA in this study ranged from a minimum of 0.29 mg/kg/day to a maximum of 16.07 mg/kg/day (mean of 3.49 ± 1.8 mg/kg/day) given to the patients in two divided doses. The results of this study revealed that the majority of the cyclosporine PK profiles (864) were classified under group 6 (one year after transplantation), as shown in Table 2.

Table 1: Patients' demographic data

Characteristics	Values
Gender (Male/Female)	(97/59)
Race (Malay/Chinese/Indian)	(17/129/10)
Mean age (years)	43± 11
Mean weight (kg)	63± 13.7
Mean BMI (kg/m^2)	24.05± 4.7
Donor type (Related/Unrelated)	(23/133)
Immunosuppressant therapy (Double/Triple)	(33/123)
Cyclosporine products (Neoral®/Gengraf®)	(125/31)
Mean cyclosporine dose (mg)	208.7± 94.6
Mean Srcr (µmol/L)	137.8± 47.3
Mean CLcr (ml/min)	51.3± 15.5

Table 2: Groups of cyclosporine PK profiles (n= 1601) based on post transplant duration in kidney transplanted patients at Penang Hospital.

Groups	Frequency	percentages
Group 1 (after 1 month)	128	8
Group 2 (after 2 months)	83	5.2
Group 3 (after 3 months)	85	5.3
Group 4 (after 4 – 6 months)	210	13.1
Group 5 (after 7– 12 months)	231	14.4
Group 6 (after 12 months)	864	54
Total	1601	100

Based on the therapeutic range of both CSA concentrations (before the dose and 2 hours post-dose); these PK profiles were sub-classified (Tables 3 and 4).

Table 3: Percentages of C_0 cyclosporine levels achieving the therapeutic range (n=1601)

Time post transplantation (months)	C_0 therapeutic range (ng/ml)	C_0 % (n)		
		Sub therapeutic	Therapeutic	Toxic
< 6*	250-375	28.5 (144)	40.3 (204)	31.2 (158)
> 6**	100-250	21.5 (235)	65.3 (715)	13.2 (145)

* Group1, 2, 3, and 4; ** Group 5 and 6.

Table 4: Percentages of C_2 cyclosporine levels achieving the therapeutic range (n= 1601).

Time post transplantation (months)	C_2 therapeutic range (ng/ml)	C_2 % (n)		
		Sub therapeutic	Therapeutic	Toxic
1	1360- 2070	33.6 (43)	57.8 (74)	8.6 (11)
2	1200-1800	32.5 (27)	50.6 (42)	16.9 (14)
3	1040-1560	22.4 (19)	63.5 (54)	14.1 (12)
4-6	880-1320	21.9 (46)	59 (124)	19 (40)
7-12	720-1080	22.9 (53)	50.2 (116)	26.8 (62)
> 12	640-960	43.2 (373)	44.1 (381)	12.7 (110)

Table 5 depicts the mean ± SD and the range for the PK parameters calculated in this study.

Table 5: Population pharmacokinetic (PK) parameters of cyclosporine in kidney transplanted patients (n= 1601).

PK parameters	Range	Mean ± SD
K_e (hr $^{-1}$)	0.01 - 0.33 (hr $^{-1}$)	0.149 ± 0.042 (hr $^{-1}$)
t ½ (hr)	2.09 - 55.37 (hr)	5.29 ± 3.44 (hr)
V/F (L)	75.75 - 14563.11 (L)	385.94 ± 538.84 (L)
CL/F (L/hr)	8.14 - 257.02 (L/hr)	48.26 ± 21.93 (L/hr)
AUC (ng/ml/hr)	358.08 - 16116.34 (ng/ml/hr)	4800.72 ± 2309 (ng/ml/hr)
C0 (ng/ ml)	7.60 - 1092.4 (ng/ ml)	219.28 ± 134.87 (ng/ ml)
C2 (ng/ ml)	65.80 - 2842.80 (ng/ ml)	912.48 ± 418.40 (ng/ ml)

DISCUSSION

To the best of our knowledge, this study is the first to estimate cyclosporine PK parameters in kidney transplant patients in Malaysia. The narrow therapeutic index, significant variability in PKs, and severity of adverse effects justify the use of TDM for CSA[4]. Although CSA has been the cornerstone of immunosuppression in organ transplant patients for more than 20 years, no consensus on the correlation between PK parameters and therapeutic response has yet been achieved[6]. The first use of CSA was proposed to be at fixed doses; this was soon abandoned. Recently, monitoring of both concentrations (C_0 and C_2) became an essential part in CSA dosing[9]. The therapeutic range concept is a population-based statistical approach, suggesting that most patients would achieve a desired therapeutic response at specific target concentrations. Furthermore, concentrations below or above this therapeutic range may increase the probability of rejection or other underside outcomes[4].

Pourfarziani et al. 2008 found that their kidney recipients population showed good overall patient and graft survival rates

despite 57% of C_2 levels of their patient population never met the target levels in all their post transplant measurement that were studied[10]. In Germany, Einecke et al. 2004 reported in their study that C_2 values were lower than the recommended range in 68% in the first two months post transplantation and in 55% of their total transplant population at late post transplant period[11].

The discrepancy in results may be explained by different dosage regimens among transplant centres, for example, the mean CSA dose received by kidney transplant patients at one of the transplant centres in China was 200±43 mg in two divided doses[12]. A study conducted in Japan by Tokui et al. illustrated the values of the cyclosporine PK parameters to be 0.547 ± 0.033 hr^{-1} for the mean K_e, 147.1 L for the V/F, and 23.7 L/hr for the oral clearance[13]. Furthermore, two previous studies have documented the values of these cyclosporine PK parameters; the first study[14] found that the CL/F was 28.5 L/hr and the V/F was 133 L, whereas the second study[15] found that the CL/F value was 22.1 L/hr and the V/ F was 147 L for their population. Finally, the values of the PK parameters obtained from these previous studies were somewhat different from the results of this study. Tokui et al. calculated the AUC_{0-4} for all kidney transplant patients and found the mean AUC to be 2290 ± 505 ng/ml/hr, which was lower than the value in the present study[13]. Such variation in the results may be due to different immunosuppressant protocols, different CSA therapeutic ranges, different immunoassays used (HPLC, FPIA, or RIA) in transplant centres worldwide. In addition, non-compliance with medication, irregular visits to the hospital may result in different CSA levels. There are some limitations in this study in which the effect of drug-drug and drug-food interactions on the cyclosporine serum concentrations were not investigated.

In conclusion, majority of CSA pharmacokinetic profiles based on C_0 concentration (six months and above post transplantation) were achieved therapeutic range. At the same time, more than half of these PK profiles based on C_2 concentration (the first year of transplantation) were achieved the therapeutic range. The obtained PK parameters will assist in the estimation of CSA empiric dose which is necessary to achieve the therapeutic outcomes for patients. Individual monitoring of CSA serum concentrations and their relationship to therapeutic outcomes in renal transplant patients is recommended.

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Appendix

Equations for the calculation of cyclosporine PK parameters [13].

$$K_e = \frac{(\ln C_2 - \ln C_0)}{\text{Dosing interval} - 2}$$

$$V/F = \frac{\text{Dose}}{[C_2 - C_0]}$$

$$CL/F = K_e \times V/F$$

$$AUC_{2-\infty} = \frac{\text{Dose}}{[CL/F]}$$