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Pharmacokinetics of oral cyclosporine (Neoral) in heart transplant recipients during the immediate period after surgery

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Abstract Neoral cyclosporine has better absorption characteristics than the original Sandimmun formulation. This has allowed Neoral to be administered orally in circumstances where Sandimmun had been ineffective, including the postoperative phase of liver transplantation. Sampling strategies, such as the measurement of drug concentration 2 h after oral administration, have been used in a variety of settings to estimate systemic exposure to Neoral (measured as the area under the blood concentration curve (AUC) of the drug) in blood. We conducted a pilot study to determine whether Neoral could be administered orally immediately after heart transplantation and to determine which pharmacokinetic parameters reflect systemic drug exposure in this setting. Eight male patients (mean age 50 years) undergoing a first heart transplant were studied. Neoral was administered orally before surgery and at 12-h intervals via a nasogastric tube after surgery. Twelve-hour pharmacokinetic profiles were obtained on postoperative days 1, 3 and 5. Cyclosporine concentrations were measured with the Dade Behring Emit assay, which is specific for the parent drug. Drug concentrations were dose-normalised and drug exposure was measured by the AUC. Drug exposure following administration (AUC_{0-12}) was low on day 1 but increased by 99% between postoperative day 1 and day 5 ($P < 0.05$), indicating more complete absorption of cyclosporine; exposure in the first 4 h post-dose (AUC_{0-4}) increased by 126% ($P < 0.01$), reflecting more rapid cyclosporine absorption, and the maximum blood concentration observed increased by 137% ($P < 0.05$) during the same period. The correlation between the cyclosporine trough concentration and AUC_{0-12} was low on all days. Due to the changing pattern of cyclosporine absorption, concentration measurements at a single time point could not accurately predict 12-h exposure to the drug on all study days. However, the drug concentration at 2 h post-dose had a high correlation with drug exposure during the first 4 h (correlation of C_2 to AUC_{0-4}: $r^2 > 0.93$ on all days). Absorption of Neoral was low immediately after heart transplantation but improved substantially during the first 5 days after surgery. No single timed measurement of drug concentration reflected cyclosporine exposure; however, the 2-h concentration did provide an accurate measure of the early phase of drug absorption (AUC_{0-4}). Oral administration of Neoral may result in inadequate immunosuppression immediately after heart transplantation unless it

is supplemented either by intravenous cyclosporine or by the use of an induction agent.

Keywords Heart transplant · Cyclosporine · Pharmacokinetics · Therapeutic drug monitoring

Introduction

The introduction of cyclosporine as an immunosuppressive agent [4] was a crucial step in making cardiac transplantation a clinically effective treatment for severe heart failure [25]. Although cyclosporine is a potent immunosuppressive agent whose immunological action is specific for T cells, it has dose-limiting non-immunological toxicity and consequently has a narrow therapeutic range [16]. While cyclosporine remains a cornerstone of the immunosuppressive therapy used in most heart transplant centres, much of the information available about its clinical use has been extrapolated from data obtained in other types of organ transplantation.

The original oral formulation of cyclosporine (Sandimmun) was absorbed in an inconsistent manner and its bioavailability varied significantly both between and within individuals. The consequent variation in systemic exposure to the drug was found to be a factor influencing the incidence of acute rejection in kidney transplant patients [20, 29]. This led to the introduction of a new oral formulation of cyclosporine (Neoral, Novartis Pharmaceuticals, Basle, Switzerland) which had better absorption characteristics and less-variable pharmacokinetics [2, 17, 18]. This preparation has allowed the oral administration of cyclosporine in situations where Sandimmun was ineffective, such as the early postoperative phase of liver transplantation [27, 31].

Although Neoral has a more predictable bioavailability than Sandimmun, significant variation still exists which may influence its efficacy and toxicity. Studies relating systemic exposure to cyclosporine (measured as the area under the blood concentration curve (AUC) of the drug) to clinical outcome have found that an adequate AUC is essential for the optimum therapeutic effect [10, 20]. The pharmacokinetics (PKs) of Neoral have been studied in stable long-term recipients of heart transplants [5], but its PKs in the immediate postoperative period have not been investigated.

The traditional trough (pre-dose) measurement of cyclosporine blood concentration (C_0) has only a moderate correlation with drug exposure (AUC). However, determination of the AUC requires a series of blood samples to be obtained throughout the interval between doses, and this procedure is impracticable for routine clinical management. Therefore, attempts have been made to estimate the AUC from one or more timed blood samples after drug administration [13, 14]. Measurements such as the concentration at 2 h post-dose (C_2) have a much higher correlation with AUC and have been proposed as surrogate measures of AUC [3, 15]. Although studies of the use of C_2 monitoring early after surgery have been performed in renal [6, 21] and liver [19] transplantation, and data are available for stable long-term heart transplant patients [5], the period early after surgery has not been investigated in heart transplantation.

We hypothesised that the better absorption characteristics of Neoral might allow cyclosporine to be administered effectively via the oral route, from the time of heart transplantation. We conducted a pilot study to test this hypothesis and determine which PK parameters reflect systemic drug exposure during this period.

Patients and methods

We studied eight patients undergoing their first orthotopic heart transplantation; patient characteristics are shown in Table 1. The study protocol was approved by the district ethics committee and the study was performed in accordance with the Declaration of Helsinki; informed consent was obtained from each patient.

The commercially available Neoral liquid formulation of cyclosporine (Novartis Pharmaceuticals) was administered by mouth immediately prior to surgery and via a nasogastric tube at 12-h intervals after surgery until the patient could tolerate the drug by mouth. Neoral is a micro-emulsion formulation of cyclosporine. The pre-operative dose was determined by the physician managing the patient's care in the light of the patient's clinical condition and renal function; the mean pre-operative dose administered was 2.7 mg/kg (range 2–4 mg/kg). The postoperative dose was determined by the physician in the light of both the previous trough blood level (C_0) and the patient's clinical condition, including renal function. The aim was to achieve a pre-dose level of approximately 300 ng/ml by day 5. Concomitant immunosuppressive agents used were methylprednisolone followed by prednisolone ($n=8$), azathioprine ($n=8$) and rabbit antithymocyte globulin (ATG; $n=4$). Other postoperative drugs included furosemide (five patients), nystatin (eight), sucralfate (eight), aciclovir (eight), co-trimoxazole (eight), dopamine (two), adrenaline (one), noradrenaline (one), enoximone (one), allopurinol (one), insulin (one), and low-dose aspirin (one). On days 1, 3 and 5 after surgery, a PK study was performed by obtaining a blood sample immediately before the administration of Neoral and a further 14

Table 1 Patient characteristics. Continuous variables are described by their mean value (range)

Characteristic	
Age (years)	50 (21–58)
Gender (*n*)	Male (8)
Weight (kg)	78 (62–99)
Race (*n*)	Caucasian (7), Indo-Asian (1)
Organ ischaemia time (min)	175 (140–210)
Indication for transplantation (*n*)	Ischaemic heart disease (5) Dilated cardiomyopathy (2) Valvar heart disease (1)
Serum creatinine (μmol/l)	116 (95–179)

timed samples, which were obtained during the subsequent 12-h period.

Cyclosporine assay

EDTA whole-blood specimens were stored at −20 °C until the day of analysis. Cyclosporine analysis was performed by Emit 2000 cyclosporine assay (Dade Behring, USA) on a COBAS MIRA analyser (Roche Diagnostic Systems, USA). All specimens were extracted with pre-treatment reagent, thoroughly vortex mixed and centrifuged at 16,000 *g* prior to being loaded on the analyser according to the product insert. All analyses were performed with three levels of Lyphochek Whole Blood Controls (Bio-Rad Laboratories, USA) in each batch. Where results were higher than the 500-ng/ml calibrator, the whole-blood specimen was diluted 1 + 3 with zero calibrator and re-extracted. We validated these dilutions by diluting a high control and 500-ng/ml calibrator in the same way and analysing all dilutions as a batch. The Emit 2000 cyclosporine method measures parent compound in whole blood with minimal cross-reactivity with cyclosporine metabolites and produces results equivalent to high-performance liquid chromatography [7, 22, 24, 30].

Statistical analysis

We compared cyclosporine bioavailability on each day using 'normalised' cyclosporine blood concentrations, which we adjusted by multiplying by the ratio of the dose administered to that patient on day 1 to the dose administered on the day of the PK profile; all profiles were obtained after the morning dose of Neoral had been given. The mean doses of cyclosporine administered were 2.3 mg/kg (day 1), 2.6 mg/kg (day 3) and 2.8 mg/kg (day 5); the corresponding total daily doses were 4.8 mg/kg per day (day 1), 5.2 mg/kg per day (day 3) and 5.3 mg/kg per day (day 5). Dose-normalised concentrations were used for all PK analysis.

The 12-h AUC (AUC_{0-12}) for each 15-point PK profile was calculated by the linear trapezoidal rule; an AUC for the initial 4 h (AUC_{0-4}) was also calculated. C_{max} was defined as the maximum drug concentration observed in a PK profile. The concentrations at individual time points were designated as with the time (in hours) as a suffix, e.g. C_2 for the concentration measured 2 h post-dose. Linear regression was performed to examine the relationship between drug concentration at specific times and cyclosporine exposure (AUC). Friedman's non-parametric two-way analysis of variance was used to determine if the changes in AUC_{0-12}, AUC_{0-4} and C_{max} with time after transplantation were statistically significant; the two factors used were 'patient' and 'day'.

Results

The speed and extent of cyclosporine absorption increased steadily between days 1 and 5 after surgery (Fig. 1). The AUC_{0-12} increased by 41% from day 1 to day 3 and by a further 40% between days 3 and 5 so that AUC_{0-12} was 99% greater on day 5 than on day 1 ($P < 0.05$). Even larger changes occurred in the AUC_{0-4} and C_{max}, which increased 126% ($P < 0.01$) and 137% ($P < 0.05$), respectively, between days 1 and 5.

The correlation (r^2) between the AUC_{0-12} and the 'trough' concentrations C_0 and C_{12} were low on all three study days (Table 2). The time at which the maximum correlation occurred changed from 5 h (day 1) to 4 h (day 3) and 2.5 h (day 5), reflecting the increased rate of drug absorption. The exposure during the normal absorption period (AUC_{0-4}) was also weakly correlated with the trough concentrations, but it had a strong correlation with C_2 on all 3 days (day 1, $r^2 = 0.96$; day 3, $r^2 = 0.96$; day 5, $r^2 = 0.93$; Table 3 and Fig. 2).

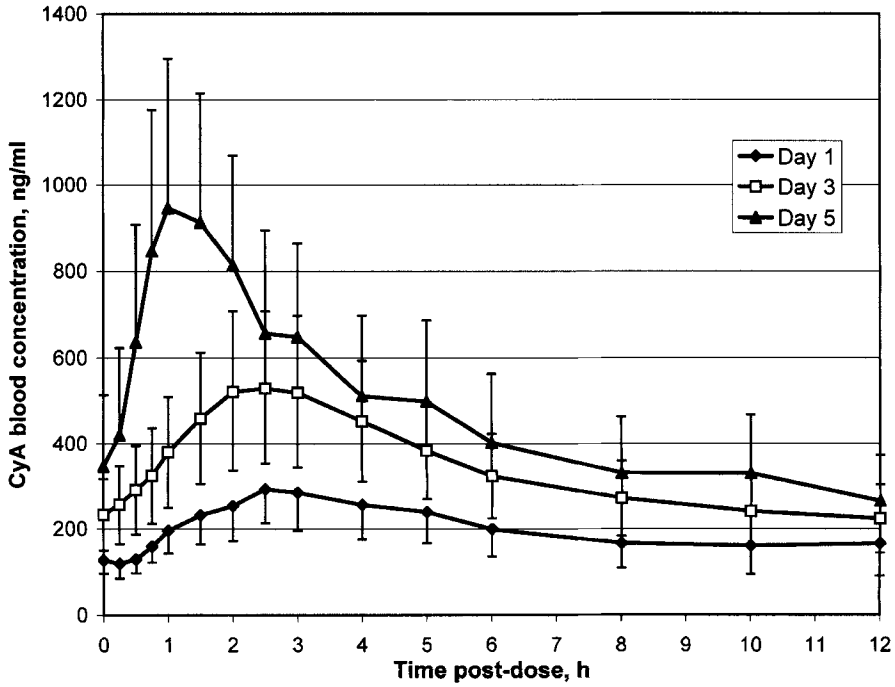

Fig. 1 Mean (standard error) dose-normalised cyclosporine blood concentration following the morning dose of Neoral for eight heart transplant recipients studied on days 1, 3 and 5 after surgery

Table 2 Correlation (r^2) between AUC_{0-12} and concentrations measured at various times following the administration of Neoral on days 1, 3 and 5 after surgery

Sampling time (h)	Day 1	Day 3	Day 5	All days
0	0.51	0.80	0.03	0.44
0.25	0.71	0.81	0.06	0.51
0.5	0.81	0.61	0.59	0.57
0.75	0.80	0.39	0.70	0.49
1	0.75	0.23	0.79	0.46
1.5	0.72	0.21	0.80	0.51
2	0.69	0.48	0.78	0.65
2.5	0.68	0.53	0.91	0.69
3	0.80	0.76	0.80	0.82
4	0.93	0.79	0.84	0.83
5	0.99	0.72	0.84	0.83
6	0.97	0.78	0.52	0.80
8	0.97	0.75	0.54	0.77
10	0.81	0.57	0.22	0.58
12	0.75	0.50	0.23	0.47

Table 3 Correlation (r^2) between AUC_{0-4} and concentrations measured at various times following the administration of Neoral on days 1, 3 and 5 after surgery

Sampling time (h)	Day 1	Day 3	Day 5	All days
0	0.27	0.51	0.01	0.19
0.25	0.44	0.71	0.00	0.29
0.5	0.64	0.76	0.48	0.70
0.75	0.78	0.83	0.66	0.77
1	0.94	0.72	0.91	0.83
1.5	0.97	0.77	0.96	0.90
2	0.96	0.96	0.93	0.96
2.5	0.96	0.96	0.92	0.96
3	0.96	0.91	0.88	0.85
4	0.96	0.52	0.67	0.53

Discussion

This study has examined the absorption of orally administered Neoral cyclosporine in the first 5 days after heart transplantation. Absorption was slow and incomplete on day 1, resulting in a low systemic exposure to the drug, but it had improved considerably by day 5 (Fig. 1). The changing pattern of absorption prevented the drug concentration measured at any one time point from being a useful guide to AUC_{0-12} on all the study days; however, C_2 provided the best estimate of the extent of drug absorption during the first 4 h (AUC_{0-4}) on all 3 days.

Pharmacological immunosuppression for heart transplantation is usually achieved by a combination of agents [1]. Cyclosporine is a cornerstone of the immunosuppression regimen used in most centres, but there is a wide variation between hospitals in the way the drug is administered during the peri-operative period. Options include either intravenous or oral administration of the drug

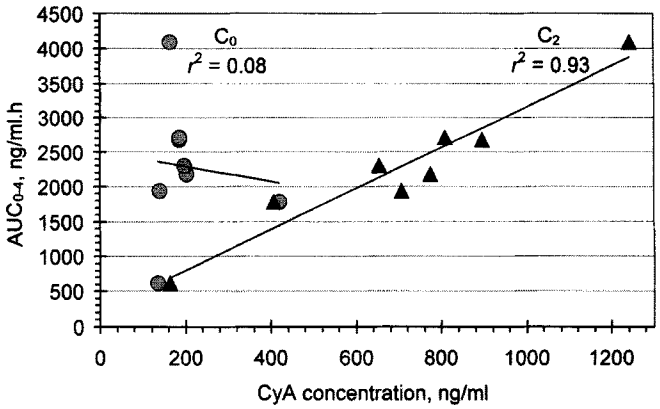

Fig. 2 Correlation between both C_2 and AUC_{0-4} and C_0 and AUC_{0-4} on day 5

with or without the concomitant use of an anti-T-cell induction agent; when induction is used, the introduction of cyclosporine is usually delayed. There is no consensus about how cyclosporine therapy should be monitored and adjusted during the postoperative period.

Neoral is a micro-emulsion formulation of cyclosporine that has a more consistent bioavailability than the previous Sandimmun formulation [2, 17, 18]. Sandimmun was found not to be absorbed in the postoperative phase of liver transplantation because its absorption was dependent on bile flow and gastrointestinal function [23]. Neoral has been used from the time of surgery in liver transplantation [27, 31]. Our present study has shown that, despite the improved characteristics of the Neoral formulation, cyclosporine absorption is poor immediately after heart transplantation (Fig. 1). This is likely to be due to gastrointestinal dysfunction related to the effects of anaesthesia, cardiopulmonary bypass, postoperative haemodynamic instability and the use of inotropic agents as well as opiate analgesia. Similar changes in Neoral absorption were also observed after liver transplantation [27, 31].

C_0 and C_{12} levels correlated poorly with AUC, demonstrating that pre-dose cyclosporine concentrations provide a poor indication of cyclosporine exposure in the postoperative period (Table 2). Due to the changing pattern of cyclosporine absorption, measurements performed at a single time point could not be used to estimate accurately the 12-h exposure to cyclosporine (Table 2). However, the early phase of absorption, which changed most during the recovery period, was accurately assessed by C_2 (Table 3).

Cyclosporine exposure on days 1 and 3 was low. The pharmacodynamic effect of cyclosporine (inhibition of calcineurin) closely parallels cyclosporine concentration, with maximum inhibition occurring at the time of the peak concentration [11]. In stable renal transplant patients low cyclosporine exposure has been linked to an increased risk of acute rejection [20, 29]. Whether a

transiently low cyclosporine exposure immediately after surgery has an adverse effect on the long-term outcome after heart transplantation is unknown. However, this seems likely because, in one study performed after liver transplantation, low exposure in the first 10 days after surgery was associated with an increased incidence of allograft rejection [9] and, in another, patients who achieved target C_2 levels earlier after transplantation had a lower incidence of rejection [19]. Poor initial exposure to cyclosporine could partly explain the results of a post-hoc analysis of the trial comparing the use of Sandimmun and Neoral in de novo heart transplant recipients, which found that, regardless of the cyclosporine formulation used, the addition of an anti-T-cell induction agent during the postoperative period reduced the incidence of subsequent acute rejection [8]. Similar observations were also made in a post-hoc analysis of the European tacrolimus heart pilot study, where acute rejection rates were lower after induction therapy regardless of whether cyclosporine or tacrolimus was used as the calcineurin inhibitor [28]. Concern about the risk of peri-operative renal failure after heart transplantation has led most centres to use cyclosporine doses that are lower than those typically used after renal or liver transplantation [12, 26]. Exposure to cyclosporine after heart transplantation might be increased by the administration of higher doses of Neoral during the early postoperative period; however, the monitoring and rapid correction of the 12-h cyclosporine exposure in the face of changing gastrointestinal function would remain a challenge.

This study was an open-label pilot study and it has limitations. The pre- and postoperative doses of Neoral were determined by the physician managing the patient's care in the light of the patient's clinical condition, renal function and previous trough levels (C_0). The dose administered varied between patients and during the period of the study. Therefore, the cyclosporine concentrations are expressed as dose-normalised results. The study was composed of eight subjects; this small sample size prevented us from carrying out an analysis of variables that could influence cyclosporine absorption or of the relationship of cyclosporine exposure to the subsequent incidence of rejection.

In conclusion, absorption of Neoral cyclosporine was low immediately after heart transplantation but improved substantially during the first 5 days after surgery. No single timed measurement of drug concentration reflected cyclosporine exposure on all study days; however, the 2-h concentration (C_2) did provide an accurate measure of the early phase of drug absorption (AUC_{0-4}). These findings suggest that the oral administration of Neoral might result in inadequate immunosuppression on day 1 unless it is supplemented either by intravenous cyclosporine or by the use of an induction agent such as ATG, muromonab-CD3 or an anti-IL-2 receptor antibody such as basiliximab.

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