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ORIGINAL ARTICLE

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A pharmacokinetic comparison of cyclosporin oral solution and cyclosporin capsules in heart and lung transplant recipients

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Abstract Pharmacokinetic profiles were obtained for 16 heart or lung recipients following the administration of identical doses of cyclosporin as oral solution and capsules on consecutive days. A comparison of pharmacokinetic parameters (AUC, C_{max}, C_{min} and t_{max}) showed that there were no significant differences between the two formulations except for the t_{max}, which was significantly longer for the capsules. The mean variation in day-to-day trough levels produced by the two different forms was 25.6 %. A retrospective study was carried out of consecutive cyclosporin levels in patients at steady state on oral solution. The mean variation in day-to-day trough levels was 32.3 %. This was not significantly different from the variation in consecutive trough levels seen in the oral solution/capsule comparison. This study shows that cyclosporin capsules can be substituted for oral solution without causing acute changes in cyclosporin blood levels, and that the pharmacokinetics of the two formulations are similar.

Key words Cyclosporin, pharmacokinetics · Heart transplantation, cyclosporin, pharmacokinetics · Lung transplantation, cyclosporin, pharmacokinetics

Introduction

Cyclosporin is an immunosuppressive agent used to prevent rejection following transplantation and must be taken by transplant recipients for the remainder of their life. Cyclosporin has a narrow therapeutic index and blood levels must be maintained within a specified range. Cyclosporin for oral administration is currently available in two dosage forms: as an oral solution or as a soft gelatin capsule. The oral solution is an oil-based formulation that is unpalatable and each dose must be measured with an oral syringe. This method of administration leads to wastage of the solution of the order of 2 % and accurate measurement of the dose is difficult:

in one study patients measured their dose incorrectly by as much as 20 % [12]. The capsules mask the taste of the solution and allow easier measurement of the dose by patients. They are more portable and convenient for patients and lead to less wastage.

Previous studies comparing the pharmacokinetic parameters of the oral solution and capsules in healthy volunteers and renal transplant patients have shown there to be no difference between the two formulations [1, 6, 17]. However, at Harefield, there has been reluctance to use the capsules in heart and lung transplant recipients since no comparative pharmacokinetic data for the two formulations is available in this group of patients. Moreover, it has been suggested that the type of transplant may have a bearing on the pharmacokinetic parameters of cyclosporin [5, 7, 15]. These pharmacokinetic differences between patient groups may be due to several factors, such as the different doses used in different types of transplantation (e.g. heart transplant recipients receive higher doses of cyclosporin than renal transplant recipients), the fact that the cardio-pulmonary bypass necessary during heart transplantation may alter gut perfusion post-surgery and, hence, drug absorption and the fact that the post-operative recovery period, long-term recovery and ensuing disease processes (e.g. the nature and site of cytomegalovirus infections) are different following different types of transplantation.

The aim of this study was to compare the pharmacokinetic parameters produced by administration of equal doses of cyclosporin oral solution and capsules to heart and lung transplant recipients, and to identify whether changing patients to capsules causes acute changes in cyclosporin trough levels. A retrospective study was also carried out, the aim of which was to assess the day-to-day variation in trough levels seen when patients are receiving a constant dose of cyclosporin as oral solution.

Patients and methods

Patients

Three female and 13 male patients completed the study. The mean age of the patients was 45.2 years (SD 12.4). Nine patients had received orthotopic cardiac transplants, two had received heterotopic cardiac transplants, there were four single lung transplant recipients and one double lung transplant recipient. All patients were at least 10 days post-transplant with a median time since transplantation of 15.5 days (range 10 days to 4 years).

Doses of cyclosporin ranged from 4 mg/kg actual body weight per day to 28 mg/kg actual body weight per day (mean 11 mg/kg per day, SD 5.92). All patients were receiving other drugs concurrently but only minor changes were made to any patient's medication over the 2-day study period.

Patients with known pre-existing gastro-intestinal disease (including cystic fibrosis) or who were unable to swallow the capsules intact were excluded from the study.

The study was approved by the Hillingdon District Ethics Committee and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients gave written informed consent.

Protocol

Patients were on a stable dose of cyclosporin that had not been altered for 2.5 days (five doses) and were therefore assumed to be at steady state. The dose of cyclosporin was divisible by 25 mg, enabling the same dose to be given as oral solution and capsules. Patients were studied on 2 consecutive days and the dose of cyclosporin remained constant over these 2 days.

Day 1

A 2 ml venous blood sample was taken from an indwelling cannula in the patient's arm. The patient then took the prescribed 10 a.m. dose of cyclosporin as the oral solution. Two-milliliter venous blood samples were then collected from the cannula at 30 min, 1 h and 30 min, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h post dose. Patients then took their 10 p.m. dose of cyclosporin as oral solution.

Day 2

A 2 ml venous blood sample was taken and the patient then took the prescribed 10 a.m. dose of cyclosporin as capsules. Two-milliliter venous blood samples were then collected as on day 1. Patients then took their 10 p.m. dose of cyclosporin as oral solution.

Patients ate identical breakfasts on the 2 days and then received their 10 a.m. dose of cyclosporin, after which they fasted for 2 h (although non-milky drinks were allowed). Lunch was served at 12 p.m. and was of a similar size and composition on the 2 study days. Both oral solution and capsule doses of cyclosporin were taken with a drink of identical volume and composition by each patient.

Blood samples were collected in EDTA tubes, gently shaken and stored at 4 °C until assayed.

RIA assay

Whole blood concentrations of cyclosporin parent compound were assayed using the CYCLO-Trac SP-Whole Blood radioimmunoassay for cyclosporin (Incstar, Minn., USA) by a Tecan RSP 5032 robot sampler.

Analytical error

The intra-assay coefficient of variation was measured at the midpoint of the assay range using three or more samples of a control in each of 11 assay runs. The inter-assay coefficient of variation was measured at seven points covering the entire range of the assay in each of 12 assay runs.

Data analysis

The cyclosporin concentration-time data for each patient was plotted using Fig.P (Biosoft, Cambridge) and the area under the curve (AUC_{0-12}) was determined using the linear trapezoidal

Table 1 Summary of patients' pharmacokinetic parameters (*os* oral solution, *c* capsules)

Patient	AUC os	AUC c	C_{max} os	C_{max} c	T_{max} os	T_{max} c	C_{min} os	C_{min} c
	(ng/ml min)		(ng/ml)		(min)		(ng/ml)	
1	383895	361415	860	795	240	365	354	319
2	436932	455450	975	999	366	365	477	428
3	465890	481442	1626	1596	126	120	316	317
4	528234	634292	1154	1426	130	250	412	562
5	660140	706937	1794	1244	185	490	708	847
6	586210	511090	1752	1224	125	185	359	336
7	378625	637377	1215	1842	130	188	242	381
8	250577	125285	951	334	180	245	94	104
9	576022	491205	1502	1050	195	245	333	341
10	492280	566242	1159	1456	125	126	500	575
11	568605	563340	1666	1642	90	180	273	137
12	412667	451612	1211	1156	95	125	403	272
13	341377	318302	896	777	185	185	306	228
14	361587	428737	1009	1070	95	155	252	297
15	392894	473105	818	924	130	360	351	422
16	560068	567517	1609	1691	128	185	321	381

method. The maximum concentration (C_{max}), 12-h trough level (C_{min}) and the time to maximum concentration (t_{max}) were determined for both formulations for each patient by visual inspection.

The AUC, C_{max}, C_{min} and t_{max} for the oral solution and capsules were compared using a Wilcoxon signed rank test to determine whether there was any significant difference in these parameters for the two formulations. Significance was defined as a P level below 0.05.

The percentage change between the trough level (C_{min}) obtained after the oral solution and that obtained after the capsule was calculated.

Retrospective study to assess day-to-day variation in cyclosporin levels

To allow interpretation of the results obtained from the comparison of oral solution and capsules it was necessary to know the day-to-day variation in cyclosporin levels that could be expected with cyclosporin oral solution. A retrospective survey was carried out and 54 pairs of levels were identified where the following criteria were fulfilled:

1. The dose of cyclosporin oral solution had remained the same for at least 3 days.
2. Cyclosporin levels were than measured on 2 consecutive days, with no alteration in cyclosporin dose over these 2 days.

The percentage change in day-to-day cyclosporin levels from the retrospective study and those from the prospective capsule study were compared using the Mann-Whitney U-test. A correction was used to account for large samples as n_2 exceeded 20 [16]. Significance was defined as a P level below 0.05.

Results

Analytical error

The intra-assay and inter-assay coefficients of variation (CVs) were all less than 10 %.

Pharmacokinetic comparison and retrospective study

The pharmacokinetic parameters obtained for each patient are summarised in Table 1. Examples of the graphs of cyclosporin blood concentration against time for four patients are shown in Fig. 1. The 16 pairs of pharmacokinetic profiles obtained could be divided into four groups, and these four patients have been selected for illustrative purposes as they demonstrate each of these four types:

1. The two pharmacokinetic profiles were identical in size and shape (patient 3).
2. The two pharmacokinetic profiles obtained were of a similar shape and produced similar trough levels, but there is an obvious difference in the AUC (patient 6).
3. The pharmacokinetic profiles were of a similar shape but have markedly different AUCs, peaks and troughs (patient 7).
4. The pharmacokinetic profiles were of a totally different size and shape for the two formulations – often with multiple peaks for one of the formulations – and with differences in AUCs, peaks and troughs (patient 16).

Overall there was no significant difference between the AUC_{0-12}, C_{max} or C_{min} for the oral solution and capsules. However, the t_{max} of the capsules was greater than that of the oral solution. This difference was significant at the $P < 0.01$ level ($n = 16$, t = 4.5, two-tailed hypothesis, Wilcoxon signed rank test). The mean day-to-day variation in trough cyclosporin levels produced by the two forms was 25.6 % (SD 25.3 %).

The mean day-to-day change in trough cyclosporin levels identified in the retrospective study was 32.3 % (SD 41.2 %). A comparison of this figure with the oral solution/capsule result showed that there was no signifi-

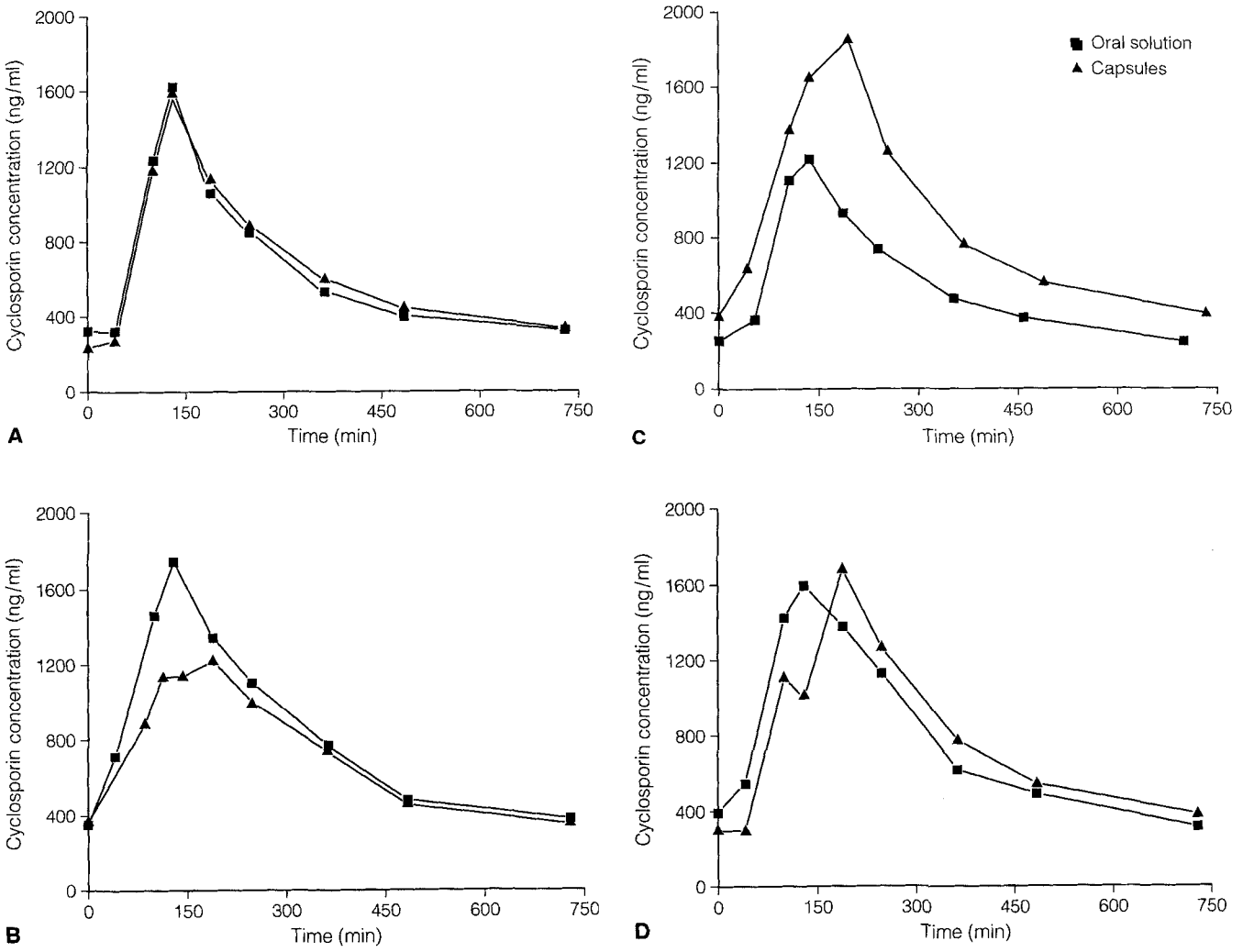

Fig. 1 A–D Cyclosporin blood concentration against time for cyclosporin oral solution (■) and cyclosporin capsules (▲) in patients 3, 6, 7 and 16

cant difference between the percentage changes in trough levels for the two groups (U = 485.5, z = 0.748, n_1 = 16, n_2 = 54, Mann-Whitney U-test).

Power calculation

In order to detect a difference in AUCs of 20% (A = 0.05, B = 0.20), 14 patients would have been needed. Since the data from 16 patients was used, this study would have had the power to detect this difference, if one existed [8].

Discussion

The blood concentration-time profiles for each patient were plotted using a simple graphing package. The data was not fitted to a particular pharmacokinetic model as the large variations in pharmacokinetic profiles seen with cyclosporin mean that no model is generally considered suitable. Modelling the data would result in over-fitting of the data and could distort the results. This procedure of not fitting the data to a model corresponds with that adopted in previous studies [1, 17], although smooth curves have been used [6].

On comparison of the pharmacokinetic parameters (C_{max}, C_{min}, AUC_{0-12} and t_{max}) derived from the data for the two formulations, it was found that only the t_{max} was significantly different. This is in contrast to previous studies comparing oral solution and capsules in this

way that have found no significant difference between any of the parameters, including t_{max} [1, 6, 17]. The fact that the C_{max} is unaffected suggests that the rate of absorption is not altered but that there is a lag time before absorption begins. This longer t_{max} with the capsule form is to be expected since there is an additional disintegration step that must occur with the capsules before the cyclosporin can be made available for absorption [14]. The lag time between ingestion of cyclosporin oral solution and its appearance in the blood has been reported to range from 0.2 to 0.8 h [9, 13] and this lag time is presumably greater for the capsules. However, insufficient blood samples were taken in the 1st hour after administration of the dose to allow an estimation of the lag time seen in this study. Likewise, the absolute value of t_{max} for the capsules cannot be derived from this data since the limited number of sampling points means that the t_{max} can only be approximated to the nearest sampling time.

The site of absorption of cyclosporin is the upper small intestine [9, 11] and absorption is a saturable process [3, 4, 13]. Thus, if the capsules release the cyclosporin more slowly, the bioavailability would be expected to increase as the absorption mechanism would not be so likely to be saturated. One study has found a relative capsule bioavailability of 111 % [17], and one long-term study found that a smaller dose of cyclosporin was required when the capsules were used [2]. However, other studies have found the opposite, with the relative bioavailability of the capsules being 91 % and a larger dose being necessary when the capsules are used [10]. A calculation of relative bioavailability of the capsules cannot be performed on the results given here as the patients were only switched over to the capsules for one dose and, therefore, did not achieve steady state. It would have been desirable to have switched the patients over to the same dose of cyclosporin as capsules and to repeat the pharmacokinetic profile after 3 or more days, allowing them to reach a new steady state on the capsule formulation. However, due to the lack of comparative pharmacokinetic data in this specific group of patients (and reluctance, for reasons already mentioned, to extrapolate data from other groups of patients), it was felt that this initial study should only switch patients over to capsules for one dose and look at whether this caused any acute changes in pharmacokinetic parameters. If no major changes were detected following such a switch, further studies that switched patients over for longer periods and allowed them to reach steady state on the capsules could then be performed.

For most patients the two cyclosporin concentration-time profiles were similar shapes, although five patients showed two peaks with one of the formulations. A second peak is generally believed to coincide with the release of bile, leading to the solubilisation of previously unabsorbed drug [5, 13].

The retrospective study showed that the mean day-to-day variation in cyclosporin levels in patients at steady state on oral solution is 32.3 % (SD 41.2 %). This is comparable with published intra-individual variations in AUCs of 200 % [9]. The mean day-to-day variation in trough levels between the oral solution and the capsules was found to be 25.6 % (SD 25.3 %) and this was not significantly different from that seen with the oral solution. This confirms the lack of acute changes in trough levels caused by the switch from oral solution to capsules. However, as has already been discussed, the pharmacokinetic parameters for the capsules were not obtained under steady state conditions. In order to confirm whether the switch from oral solution to capsules caused changes in steady state trough levels, the trough level comparison would have to be repeated with trough levels obtained when the patient had reached steady state on the capsules.

To summarise, in this study, cyclosporin capsules produced concentration-time curves similar to those produced by cyclosporin oral solution in individual heart-lung recipients. This indicates that cyclosporin capsules can be substituted for the oral solution without causing acute alterations in cyclosporin blood levels and that there is no significant difference in the AUC_{0-12}, C_{max} or C_{min} of the two formulations after such a substitution.

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