Cyclosporin A pharmacokinetics in liver transplant recipients in relation to biliary T-tube clamping and liver dysfunction

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SUMMARY Cyclosporin A pharmacokinetics were studied after oral (4–14 mg/kg body weight) and intravenous dosing (1·5–3·5 mg/kg) in 13 orthotopic liver transplant recipients before and after permanent clamping of the biliary T-tube. After T-tube clamping, cyclosporin A absorption was faster and more complete with the mean time of peak concentration, t\textsubscript{max}, reduced to around three hours from around six hours and mean bioavailability rising from only 16·6% (n=11 after clamping) or to 35% after excluding two patients who developed severe cholestasis after the preclamping study. Bioavailability in these two patients fell below 8% and to around 1% in a further patient with severe graft dysfunction. Clamping reduced the metabolic clearance of cyclosporin A by only 25% from a mean before clamping of 2·9 ml/min/kg to 2·3 ml/min/kg (n=11). Oral cyclosporin A becomes a reliable means of maintaining therapeutic drug concentrations only after bioavailability increases in association with T-tube clamping and in the absence of severe liver dysfunction or cholestasis.

Pharmacokinetic studies have shown that the absorption of cyclosporin A is low, highly variable and influenced by various factors, particularly age, gastric emptying and hepatic and intestinal dysfunction. In liver transplant recipients, there is also evidence that changes in bile flow, associated with insertion, opening and clamping of the biliary T-tube, may affect cyclosporin A absorption. Thus, Andrews et al reported changes in trough cyclosporin A concentrations in three patients and Venkataramanan et al showed a higher profile of blood concentrations after oral cyclosporin A dosing in a single patient after T-tube clamping. While additional studies in dogs showed that diversion of bile flow from the intestine reduced cyclosporin A blood concentrations the absence of intravenous data in all these studies means that decreased drug clearance cannot be excluded as an alternative to increased absorption.

The present study was carried out to document the influence of biliary T-tube clamping in liver transplant recipients on the pharmacokinetic profiles of cyclosporin A administered both orally and intravenously. Particular emphasis was placed on recording changes in the bioavailability and clearance of the drug such that its absorption could be assessed in relation to the appropriate time for commencement of oral therapy.

Methods

PATIENTS

Informed consent was obtained from 13 consecutive recipients of orthotopic liver grafts in the Cambridge/King's College Hospital programme who had no major acute postoperative complications (Table 1). Pharmacokinetic studies commenced when a steady...
Table 1  Patient records

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Values obtained with biliary T-tube unclamped (uc) or clamped (c). BCS–Budd Chiari syndrome; PHM–primary hepatic malignancy; PBC–primary biliary cirrhosis; PSC–primary sclerosing cholangitis; CAH–chronic active hepatitis; AHF–acute hepatic failure; AST–serum aspartate aminotransferase activity (IU/l); BIL–total serum bilirubin concentration (umol/l); ALP–serum alkaline phosphatase activity (IU/l).

The state of cyclosporin A dosing was achieved as judged by stable trough levels and were undertaken both before and after permanent clamping (or removal) of the biliary T-tube. In two patients postclamping data could not be obtained. At the time of the measurements none of the patients had clinically apparent intestinal dysfunction. There were also no significant differences in the types or amounts of drugs coadministered with cyclosporin A before and after T-tube clamping and none received hepatic enzyme inducers – for example, phenobarbitone, rifampicin, or inhibitors such as ketoconazole, and erythromycin.

Cyclosporin A was administered after overnight fasting either as a constant (pumped) intravenous infusion in 100 ml normal saline over two hours or by mouth as Sandimmun oral solution followed by a drink of choice. The study was repeated using the alternative route of administration within 48 hours. Doses were determined by clinical requirements and ranged from 1.5–3.5 mg/kg body weight intra-

venously and 4–14 mg/kg orally. Blood samples (4 ml in EDTA anticoagulant) were taken from an indwelling cannula at 0, 1, 2, 3, 4, 6, 8, 10, and 12 hours (+24 hours during once daily dosing) after oral (po) dosing and additionally at 0-5 and 2-5 hours after intravenous (iv) dosing and samples were stored at 4° prior to analysis.

Whole blood cyclosporin A concentrations were assayed using the cyclosporin A (polyclonal antibody) radioimmunoassay kit (Sandoz) under recommended conditions but including an additional 15 min preincubation with isotope before incubation with antibody at 4°. At 500 µg/l, assay accuracy was 101% and the interassay coefficient of variation was 9-8%. Areas under the blood cyclosporin A concentration versus time curve (AUC) were calculated using the trapezoidal rule. Where steady state could be assumed, calculations were made on the basis that AUC in one dosage interval equalled that for one dose extrapolated to infinity. If steady state did not apply – for example, for oral dosing after sequential intravenous doses, the terminal elimination rate constant was calculated and used to determine residual AUC values prior and subsequent to the sampling interval.

Bioavailability and metabolic clearance were calculated from equations 1 and 2, respectively.

\[
\text{Bioavailability (%) } = \frac{\text{po AUC}}{\text{iv AUC}} \times \frac{\text{iv dose}}{\text{po dose}} \times 100
\]

\[
\text{Clearance (ml/min/kg) } = \frac{\text{DOSE (nmol/kg)}}{\text{iv AUC (nmol.min/ml)}}
\]

The results were compared by non-parametric statistical analysis using Wilcoxon’s test for paired samples.

Results

Figure 1 shows the profile of cyclosporin A blood concentrations after intravenous and oral administration both before and after T-tube clamping (one week apart) in a representative patient (OL 313). Whilst the T-tube was draining freely, cyclosporin A blood concentrations increased only slightly after oral dosing (Fig. 1: unclamped) and the low area under the blood cyclosporin A concentration versus time curve (AUC) was reflected in a low level of bioavailability (14-5%). With clamping and restoration of the entire bile flow to the intestine there was a rapid rise in cyclosporin A blood concentrations after oral dosing (Fig. 1: clamped) and AUC increased nearly 3-fold (3007 versus 1164 nmol.l/l per 100 mg drug) while bioavailability rose to 32%.

Table 2 summarises the results obtained in the 13 patients, 11 of whom were studied both before and
Cyclosporin A pharmacokinetics in liver transplant recipients in relation to biliary T-tube clamping

Table 2  Cyclosporin A pharmacokinetics before and after biliary T-tube clamping

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Mean    9590 11470 2020 3200 18-8 29-9 2-94 2-28
(SD)    (3470) (3810) (1410) (1740) (11-0) (15-9) (1-42) (0-67)
(n=11)

Mean    8840 10980 1460 3730* 14-8 35-1* 3-25 2-44*
(SD)    (2970) (3850) (750) (1430) (6-1) (12-0) (1-39) (0-64)
(n=9)

T-tube status is shown as unclamped (uc) or clamped (c). AUC values were calculated per 100 mg cyclosporin A administered. Where n=11, cases OL 283 and 291 were excluded; where n=9, OL 307 and 311 were additionally excluded (see text).

*Significant difference from unclamped (p<0.05; Wilcoxon’s paired-rank).

Fig. 1  Profile of cyclosporin A blood concentrations before and after biliary T-tube clamping. Cyclosporin A blood concentrations (determined by radioimmunoassay) are shown in a representative patient after intravenous (●...●) and oral (○...○) dosing.

Mean bioavailability (n=11) increased substantially from 18-8 (11-0)% before to 29-9 (15-9)% (0-1>p>0-05) after clamping of the T-tube. Bioavailability was highest (56%) in the patient (OL 314) studied at the longest interval after transplantation (162/3 days) but this was only marginally greater than the value of 53% found at 25/26 days in case OL 308. Bioavailability was lowest (~1%) in patient OL 283 in whom hepatic artery thrombosis was diagnosed immediately after the investigations were completed and the minimal absorption of cyclosporin A in this patient is shown in Figure 2. The dose normalised AUC after oral cyclosporin A was higher after clamping in all but two cases (OL 307 and 311). In these patients, AUC was high before clamping because of a pronounced late absorption peak but it was substantially reduced after clamping (by around 80%) and there were corresponding marked decreases in cyclosporin A bioavailability (from 29 and 44% to 8 and 5%, respectively). These two subjects differed from the remainder in that their graft function was deteriorating at the time of the second study (Table 1) with severe cholestasis (serum bilirubin 390 and 593 μmol/l) caused by chronic rejection. The reduction in cyclosporin A bioavailability seen in association with the deteriorating liver function is shown in Figure 3 for one of these patients (OL 311). On the basis of this dysfunction.
clearance and metabolic breakdown. Therefore, our present findings after biliary T-tube clamping, showing a 2.4-fold increase in bioavailability with only a 25% decrease in clearance, indicate that a substantial increase in cyclosporin A absorption occurred which could only be inferred from previous studies in which no determinations of clearance were made.148 Our results from paired intravenous and oral pharmacokinetics studies also permitted exclusion of two possible alternative explanations for the increased area under the curve of cyclosporin A blood concentrations with time (AUC) after T-tube clamping. Thus, increases in the enterohepatic recirculation of the small amounts of biliary cyclosporin A79 or its metabolites are unlikely because no substantial increase in the postclamping intravenous AUC was noted. Increased bioavailability, caused by decreases in renal excretion or extrahepatic metabolism, is also inconsistent with the small reduction in cyclosporin A clearance observed.

Radioimmunoassay (with a polyclonal antibody) was used to monitor the changes in cyclosporin A blood concentrations in this study because, at that time, dosage was adjusted on the results of this method. While radioimmunoassay measurements are useful in studies of the clinical pharmacokinetics of cyclosporin A,19-20 they will overestimate drug concentrations because of cross-reactivity of the polyclonal antibody with metabolites of cyclosporin A.21 This could lead to an overestimation of bioavailability, particularly before clamping when cyclosporin A values by radioimmunoassay are especially high due to liver dysfunction,11 and to an underestimation of metabolic clearance after clamping because of an increased biliary recirculation of cyclosporin A metabolites. Therefore, it is of note that the same 25% decrease in clearance and a 2.7-fold increase in bioavailability were noted after clamping when cyclosporin A was assayed by high performance liquid chromatography (unpublished observations). While increased cyclosporin A absorption underlies the increase in bioavailability of the drug after T-tube clamping, the decreased clearance is less obviously explained. As already discussed, reductions in the renal excretion or extrahepatic metabolism of cyclosporin A or increases in its enterohepatic recirculation seem unlikely and there was no evidence for a deterioration in liver function or liver blood flow. Alternative explanations include changes related to other pharmacokinetic parameters, such as the volume of distribution, but seem an unlikely consequence of T-tube clamping.

Before clamping of the biliary T-tube, and with an undetermined variable proportion of the biliary drainage externalized, the absorption of cyclosporin

does not allow discrimination between these patients and those excluded from the analysis. In the remainder both the mean bioavailability and the dose normalised AUC after oral dosing showed significant increases (p<0.01) after T-tube clamping (14.8 (6.1)% to 35.1 (12.0)% and 1464 (747) to 3733 (1429) nmol/l), respectively; n=9).

The rate of cyclosporin A absorption was also faster after T-tube clamping with the time of mean maximal blood concentrations after oral dosing reduced from 6-1 to 3-3 hours (n=11). In nine of these 11 patients mean dose normalised AUC after intravenous dosing rose following clamping (0.1>p>0.05). The metabolic clearance of cyclosporin A (dose/AUC) ranged from 1.18 to 6.17 ml/min/kg before clamping and from 1.23 to 3.22 ml/min/kg afterwards. Values in the two patients who developed severe cholestasis were low both before (1.18 and 2.06 ml/min/kg) and after clamping (1.83 and 1.33 ml/min/kg) and changed in parallel with serum bilirubin levels. When these two cases were excluded from the analysis mean clearance fell significantly after clamping (p=0.05).

Discussion

Bioavailability, the proportion of an orally administered drug reaching the peripheral circulation intact, reflects the amount of drug absorbed minus that irreversibly removed as a result of first pass hepatic

Fig. 2 Minimal bioavailability of cyclosporin A associated with severe liver dysfunction as a result of hepatic artery thrombosis. Cyclosporin A blood concentrations (by radioimmunoassay) are shown after intravenous (●...●) or oral dosing (○...○) on consecutive days in OL 283 in whom bioavailability was calculated as approximately 1%.

these patients were excluded from the analysis and in the remainder both the mean bioavailability and the dose normalised AUC after oral dosing showed significant increases (p<0.01) after T-tube clamping (14.8 (6.1)% to 35.1 (12.0)% and 1464 (747) to 3733 (1429) nmol/l), respectively; n=9).

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Discussion

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Cyclosporin A pharmacokinetics in liver transplant recipients in relation to biliary T-tube clamping

Fig. 3  Reduced cyclosporin A absorption in a patient with severe cholestasis. Cyclosporin A blood concentrations (by liquid chromatography) are shown after intravenous (●...●) or oral dosing (○...○) in a patient (OL.311) who developed severe cholestasis related to the vanishing bile duct syndrome after the first (a) and before the second study (b).

A was poor, slow and, in some cases, prolonged. As early as one week after total diversion of bile flow to the intestine, cyclosporin A absorption was faster and more complete in individuals with good graft function and mean bioavailability values after clamping (35%) were comparable with those noted in recipients of bone marrow (34%), heart (35%), and kidney (29%) grafts. In contrast, bioavailability deteriorated below the mean preclamping value for the entire series in two patients who developed severe cholestasis. In the same two patients, cyclosporin A clearance fell after clamping to values reported in patients with liver failure, while in the remainder with good graft function clearance values were similar to those reported in healthy volunteers.

The enhanced absorption of cyclosporin A in liver transplant recipients with good internalised bile flow is consistent with the conclusion drawn from experiments in dogs that bile salts are necessary for the dispersion and uptake of this non-polar drug. This role for bile explains previous suggestions that cyclosporin A is poorly and variably absorbed in liver transplant recipients and that trough blood levels and the relative bioavailability of the drug (derived without intravenous data) rose after biliary T-tube clamping. The major clinical implication of our present findings is that the administration of conventional oral preparations of cyclosporin A can provide neither reliable nor economic therapy until the biliary T-tube is clamped. In the presence of severe liver dysfunction and cholestasis, it is essential to use intravenous cyclosporin A if therapeutic drug concentrations are to be maintained.

The transplant operations on these patients were performed by Professor Sir Roy Calne and his surgical team. We also thank the Wellcome Trust for the award of a fellowship to NVN and Sandoz Pharmaceuticals for their support and interest.

References


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