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Absorption of cyclosporin from conventional and new microemulsion oral formulations in liver transplant recipients with external biliary diversion

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1 Less than 5% of a dose of the conventional oral formulation of cyclosporin, Sandimmun®, is absorbed in liver transplant recipients with external biliary drainage, necessitating intravenous administration of the drug and exposing the patient to increased risk of severe side-effects.

2 We compared the pharmacokinetics of the conventional oral formulation of cyclosporin with that of the new microemulsion formulation, Neoral®, in eight liver transplant recipients with external biliary diversion. Patients were maintained on a continuous infusion of cyclosporin until steady-state conditions had been achieved. They were then given a test dose (10 mg kg^{-1}) of either the conventional or microemulsion formulation (randomised order) followed by the same dose of the other formulation. Parent cyclosporin concentrations were measured in whole blood samples collected at timed intervals over the 24 h after the oral doses and pharmacokinetic parameters calculated.

3 The bioavailability of cyclosporin from the microemulsion formulation was, on average, 6.5-fold (95% C.I. 1.9 to 11.1-fold) greater than that of the conventional formulation, indicating the improved absorption characteristics of the new oral microemulsion formulation during external bile drainage.

4 A significant negative correlation was found between the external bile drainage volume and bioavailability of cyclosporin from the microemulsion formulation ($r = -0.8$; $P = 0.016$), suggesting that variability in cyclosporin absorption from the microemulsion formulation may still be at least partly attributable to bile-dependence. Paradoxically, no relationship was found between bile volume and the very low cyclosporin bioavailability from the conventional formulation, perhaps because the volume of bile reaching the gut was below a threshold required for *any* consistent degree of cyclosporin absorption from this formulation to occur.

5 In conclusion, the use of the new oral microemulsion formulation of cyclosporin should help to minimise the problems of cyclosporin malabsorption in most patients with external biliary drainage following liver transplantation. This will reduce requirements for the initial use of the i.v. formulation with its attendant side-effects and so may also reduce hospital stay.

Keywords cyclosporin microemulsion liver transplantation bile

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Introduction

In the immediate post-operative period following human liver transplantation the absorption of cyclosporin from the conventional oral formulation, Sandimmun®, is extremely poor and highly variable. In some transplant centres this problem is avoided by parenteral administration of the drug for several days in the early post-operative period while the external bile drainage 'T'-tube is open and the reintroduction or continuation of parenteral cyclosporin when episodes of liver dysfunction occur. The low bioavailability of cyclosporin from the conventional formulation has largely been attributed to the poor aqueous solubility of cyclosporin, slow absorption by passive diffusion and a narrow absorption window in the proximal small intestine [1]. Studies in both animals and man have demonstrated the importance of bile and bile salts for the effective absorption of orally administered cyclosporin [2, 3].

The use of intravenous cyclosporin in transplant recipients has been associated with the development of severe side-effects, such as neurotoxicity, attributable either to the drug itself [4] or, more likely, to the polyoxyethylated castor oil vehicle—Cremophor EL [5]. The requirement for intravenous cyclosporin in the early post-operative period exposes the liver transplant recipient to an increased risk of severe side-effects, at a time when these patients are particularly vulnerable to such toxicity. The occurence of side-effects may necessitate cyclosporin withdrawal and increase the risk of early allograft rejection due to inadequate immunosuppression. The use of a dedicated intravenous cannula for the slow cyclosporin infusion is also very inconvenient at a time when there is competition for peripheral venous access. Alternative therapeutic options to reduce the need for parenteral cyclosporin in the early post-operative period would, therefore, be desirable. Anti-lymphocyte products (polyclonal and monoclonal) are effective but they can only be used prophylactically for a limited period of time and also expose the patient to a greater risk of serious infectious complications, particularly viral infections. Therefore, in many centres, these preparations are reserved for the treatment of steroid-resistant rejection.

A new oral microemulsion formulation of cyclosporin, Neoral®, has recently been developed in an attempt to overcome some of the problems associated with malabsorption of cyclosporin from the conventional formulation. The new formulation is a mixture of surfactant and both hydrophilic and lipophilic solvents. An anti-oxidant is added before filling the gelatin capsules with the water-free preconcentrate. Although the active component has not been altered, this formulation undergoes microemulsification in the gastrointestinal tract. Theoretically, this should reduce the requirement for bile salts in the emulsification and solubilisation of lipophilic molecules such as cyclosporin and so potententially improve absorption from the gut. We describe a formal pharmacokinetic study, comparing the absorption of cyclosporin from the new microemulsion with that from the conventional formulation in liver transplant recipients with external biliary diversion during the early post-operative period.

Methods

Subjects

Our pilot studies in two liver transplant recipients with cholestasis indicated that the relative bioavailability of the microemulsion formulation of cyclosporin when compared with the conventional formulation is between 2 and 8 when there is impaired bile flow to the gut. Thus we estimated that no more than eight patients with external biliary diversion would be required to demonstrate a statistically significant difference in the bioavailability of the two formulations. Eight liver transplant recipients (five male), aged between 43 and 63 years (mean 52 years), were studied during the first post-operative month. In all eight patients biliary reconstruction had included placement of a T-tube in the bile duct. They were studied while the T-tube remained unclamped and there was still free drainage of bile into an external collection bag. Patients with evidence of serious infection were excluded. The primary diagnosis was hepatitis C in three cases, primary biliary cirrhosis in two cases, cryptogenic cirrhosis in two cases and one patient had carcinoid syndrome. All patients gave written informed consent prior to inclusion and the protocol was approved by the Cambridge Health Authority Ethics Committee.

Pharmacokinetics

Throughout the study, patients were maintained on a continuous intravenous infusion of cyclosporin; the dose adjusted to maintain reproducible therapeutic blood cyclosporin concentrations within the range 120 to 300 ng ml^{-1} (<20% variation in three or more consecutive samples over a 48 h period). After these steady-state conditions had been achieved, patients were randomised to receive a test dose (10 mg kg^{-1}) of either the conventional or microemulsion formulation the next morning, followed by the same dose of the other formulation within 4 days. Blood samples were collected immediately before both oral doses and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14 and 24 h after the doses for pharmacokinetic analysis. The volume of bile draining from the open T-tube during this 24 h period was measured. In order to minimise the influence of food intake on cyclosporin absorption from the different oral formulations, breakfast times were standardised following administration of both formulations.

Whole blood cyclosporin concentrations were measured by the INCSTAR CYCLO-Trac®SP kit (Stillwater, MN, USA). The calibration range of the method extends from 20 to 1000 ng ml^{-1} and the

inter-assay coefficient of variation is less than 10% across this range. The total area under the blood cyclosporin concentration-time curve, AUC(0, 24h), attributable to both oral and intravenous doses, was calculated by the linear trapezoidal rule when concentrations were increasing and the logarithmic trapezoidal rule when concentrations were decreasing. The AUC(0, 24h) due to the oral dose was then calculated by subtracting the AUC(0, 24h) due to intravenous infusion from the total AUC(0, 24h). The AUC(0, 24h) due to the infusion was calculated from the product of the average steady-state cyclosporin concentration (C_{ss}: measured in three or more consecutive blood samples collected during the infusion in the 36 h prior to the oral doses) and the dosing interval. Bioavailability (F) was then calculated from the equation:

$$F = \frac{\text{infusion rate} \times \text{AUC(0, 24h)}}{C_{ss} \times \text{Dose}} \times 100\%$$

Comparison of pharmacokinetic parameters for the two oral cyclosporin formulations was made by Student's paired t-test. Pearson's product moment correlation coefficient (r) was used for correlation analysis.

Results

Pharmacokinetic parameters for the two oral formulations of cyclosporin are shown in Table 1. The AUC(0, 24h) for the conventional formulation could not be calculated in one patient because blood cyclosporin concentrations measured after administration of the oral dose did not increase appreciably above the baseline level due to the cyclosporin infusion. The bioavailability of cyclosporin from the microemulsion was, on average, 6.5-fold (95% C.I. 1.9 to 11.1-fold) greater than that of the conventional formulation. Both bioavailability and the maximum concentration measured in the 24 h following administration of the microemulsion (C_{max}) were consistently greater when compared with the conventional formulation although there was still substantial variability in these parameters between patients (Figure 1). The time to C_{max} (t_{max}) was significantly shorter for the microemulsion when compared with the conventional formulation and was less variable between individuals (Table 1).

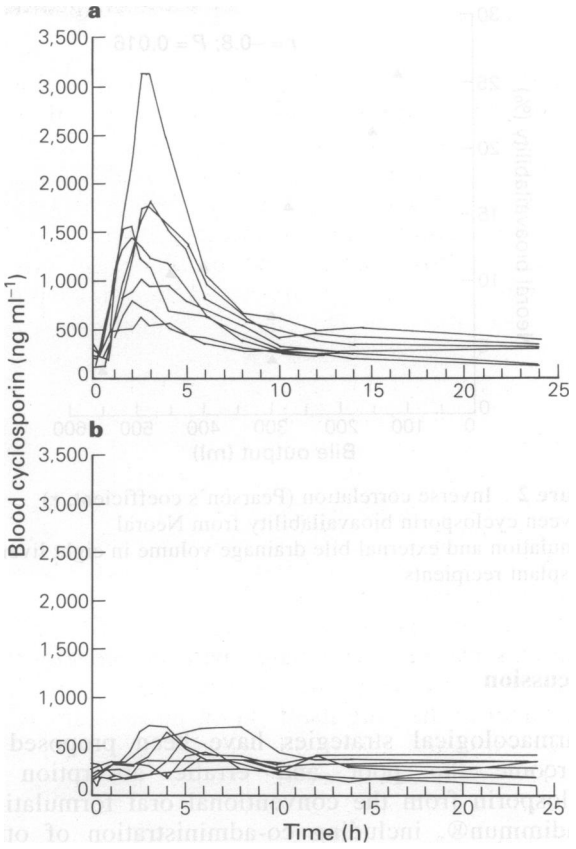

Figure 1 Blood cyclosporin concentration-time curves obtained following single oral doses (10 mg kg^{-1}) of Neoral (a) and Sandimmun (b) in eight liver transplant recipients with external biliary diversion.

The mean (and 95% confidence interval) volume of bile draining from the T-tube during the 24 h following administration of the microemulsion was 317 ml (194–440 ml) and this was not significantly different from the mean volume of 287 ml (130–445 ml), measured following administration of the conventional formulation. However, there was a significant negative correlation between this bile volume and the bioavailability of the microemulsion formulation (r = –0.80, P = 0.016); Figure 2). This analysis indicated that 64% (r^2 = 0.64) of the variation in bioavailability of cyclosporin from the microemulsion formulation could be explained by differences in bile output (assuming a linear model). In contrast, no significant relationship was found between the bile output from the T-tube and the bioavailability of cyclosporin from the conventional formulation.

Table 1 Cyclosporin pharmacokinetic parameters following single oral doses (10 mg kg^{-1}) of Sandimmun and Neoral in eight liver transplant recipients with external biliary diversion

	Mean (± s.d.)		*Mean of difference*	
	Sandimmun	*Neoral*	*(95% C.I.)*	P *value*
Bioavailability (%)	2.3 (1.1)[†]	12.6 (8.0)	10.9 (3.3–18.6)	P = 0.013
C_{max} (ng ml^{-1})	308 (136)	1302 (787)	1070 (338–1803)	P = 0.012
	Median (Range)			
t_{max} (h)	6 (3–8)	2.5 (2–3)	3.1 (1.5–4.8)	P = 0.004

[†]n = 7 (AUC(0, 24h) for Sandimmun unmeasurable in one patient).

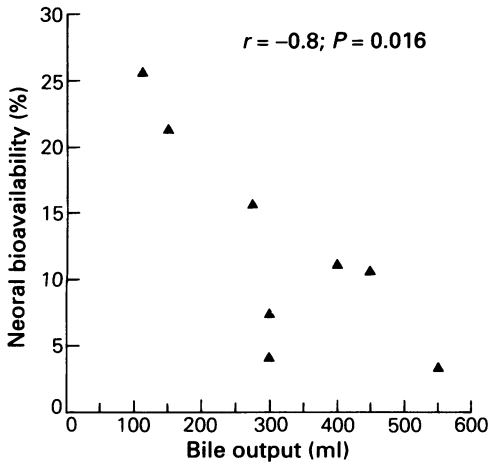

Figure 2 Inverse correlation (Pearson's coefficient, *r*) between cyclosporin bioavailability from Neoral formulation and external bile drainage volume in eight liver transplant recipients.

Discussion

Pharmacological strategies have been proposed to overcome the poor and erratic absorption of cyclosporin from the conventional oral formulation, Sandimmun®, including co-administration of other interacting drugs [6, 7] and the use of an alternative vehicle [8]. Bile refeeding has also been used to improve the absorption of cyclosporin and reduce the requirement for the intravenous formulation in liver transplant recipients with external biliary diversion [9]. However, none of these strategies has been widely adopted. Solid micellar and faster releasing microemulsion oral formulations of cyclosporin have been found to increase the extent of absorption by 45 and 49% respectively when compared with the standard soft gelatine preparation [10]. This strategy may prove the most clinically acceptable. Our preliminary pharmacokinetic study of the new microemulsion formulation, Neoral®, in a liver transplant recipient with cholestasis and associated cyclosporin malabsorption was also encouraging [11].

We have now further shown that the rate and extent of cyclosporin absorption from the microemulsion formulation is significantly greater than that from the conventional formulation in eight liver transplant recipients with external biliary drainage during the early post-operative period. Thus, the median t_{max} occurred 3.5 h earlier and, on average, C_{max} was over 4-fold higher. The bioavailability of cyclosporin from the microemulsion formulation was, on average, 6.5-fold greater when compared with the conventional formulation. Although this is compatible with a reduction in the bile-dependence of cyclosporin absorption from the microemulsion formulation, there was indirect evidence to suggest that variation in bioavailability of cyclosporin from the microemulsion formulation is still partly attributable to differences in bile flow to the gut. Thus, a significant negative correlation was found between the bioavailability of cyclosporin from the microemulsion formulation and the volume of bile draining freely from the T-tube. Assuming that the collected bile volume diverted via the T-tube is inversely related to the volume of bile flowing into the gastrointestinal tract, it is likely that poor absorption of cyclosporin from the microemulsion formulation is at least partly due to a limiting supply of bile in the small intestine.

The failure to show any relationship between cyclosporin bioavailability from the conventional formulation and bile volume may, paradoxically, be attributable to the greater bile-dependence of this formulation and its consistently extremely low bioavailability (<4%). Thus, the volume of bile reaching the gut during external biliary diversion may be below a threshold required for *any* consistent degree of cyclosporin absorption from the conventional formulation to occur but above such a threshold for cyclosporin absorption from the microemulsion. More direct evidence for the bile-dependence of cyclosporin absorption from the microemulsion formulation is still required and could be obtained by carrying out pharmacokinetic studies both before and after T-tube clamping. The rediversion of bile into the gut should result in an improvement in cyclosporin absorption.

In conclusion, this study has demonstrated the improved absorption characteristics of the new oral microemulsion formulation of cyclosporin in patients with external biliary diversion. Although the extent of cyclosporin absorption from the microemulsion is still relatively unpredictable in these patients, it is anticipated that early introduction of the microemulsion formulation will allow therapeutic blood cyclosporin concentrations to be achieved without the use of the parenteral preparation with a concomitant decrease in the incidence of adverse effects. In this way, the use of the microemulsion formulation should simplify the management of immunosuppression and help to reduce hospital stay.

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