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BRIEF REPORT

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Influence of bile on cyclosporin absorption from microemulsion formulation in primary liver transplant recipients

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Abstract We analysed the absorption, after oral application, of a new galenic form of cyclosporin A (CyA-NOF) in liver-grafted patients ($n = 12$) during the 1st week (days 2–4) after transplantation. Pharmacokinetic profiling was performed with an open or clamped T tube in situ or with the T tube absent. The pharmacokinetic parameters of CyA-NOF were influenced by T tube clamping and bile diversion. The highest AUC, C_{max} and earliest T_{max} values were found in patients without a T tube in situ, indicating that absorption of CyA-NOF in patients during the early course after liver transplantation is not bile-independent. CyA-NOF, at a dose of 7.5 mg/kg, was enterally absorbed with appropriate AUC and C_{max} levels. Patients receiving a starting dose of 7.5 mg/kg were successfully maintained on CyA-NOF during the subsequent clinical course.

Key words Sandimmun Neoral, liver transplantation · Liver transplantation, Sandimmun Neoral · Bile, liver transplantation, Sandimmun Neoral

Introduction

Cyclosporin New-Oral-Formulation (CyA-NOF; Sandimmun Neoral) is a new oral formulation of CyA (Sandimmun) based on the concept of microemulsion; its rate of absorption and its bioavailability are higher and more reliable than that of CyA [5]. Data obtained in stable liver-grafted (LTX) patients [2] indicate that the oral absorption of CyA-NOF might be relatively bile-independent. Such a resorption pattern would allow early oral CyA treatment in LTX patients despite external bile diversion via a T tube. As part of a phase II trial investigating the suitability of CyA-NOF for baseline immunosuppression in LTX patients, we have performed pharmacokinetic analysis of CyA dosing in LTX patients during the early phase after LTX.

Patients and methods

We report on 12 consecutive adult liver graft recipients included in the study. Initial immunosuppression consisted of ATG, low-dose steroids, and i.v. CyA (0.5–1 mg/kg per day b.i.d.). No exclusions were made for pretransplant status or early transplant dysfunction. Table 1 depicts the demographic characteristics of the patients as well as their clinical state at the time of the first CyA-NOF dosing. The study was approved by the local Ethics Committee of the Hannover Medical School.

CyA-NOF therapy was initiated between post-transplant day 1 and day 3. CyA-NOF was administered in the liquid form in all patients. Intravenous CyA was stopped the day before initiation of CyA-NOF. Patients were divided into four groups. In group 1 ($n = 2$) a starting dose of 2.5 mg/kg CyA-NOF was used. In group 2 ($n = 4$) CyA-NOF was administered at a dose of 5 mg/kg. In group 3 ($n = 3$) CyA-NOF was given at a dose of 7.5 mg/kg. In all patients in groups 1, 2, and 3, a T tube had been inserted at the time of transplantation for external bile diversion. In group 4

Table 1 Patient characteristics and clinical state at first CyA-NOF dose (*POD* postoperative day, *PBC* primary hiliary cirrhosis, *PK* pharmacokinetics)

Patient no.	Treatment group	Age	Sex	Etiology of liver failure	Circulatory status	Graft function	Postoperative day of 1st PK	CyA level at 1st PK
1	1	61	F	PBC	On adrenergics[a]	Good	POD 1	45
2	1	55	F	Hepatitis B	Stable	Good	POD 2	45
3	4	31	F	*Echinococcus* cyst	Stable	Good	POD 2	32
4	4	53	F	PBC	Stable	Good	POD 2	171
5	4	50	F	Caroli's disease	Stable	Good	POD 2	71
6	2	39	F	Acute liver failure of unknown origin	On adrenergics[a]	Initial dysfunction	POD 1	66
7	2	45	M	Hepatitis B	Stable	Good	POD 2	76
8	2	47	F	Ethyltoxic liver cirrhosis	Stable	Initial dysfunction	POD 2	66
9	2	18	M	Hepatitis B	Stable	Good	POD 3	76
10	3	53	F	Cryptogenic liver cirrhosis	Stable	Initial dysfunction	POD 2	50
11	3	51	F	Hepatitis C	Stable	Good	POD 2	59
12	3	42	M	Acute liver failure of unknown origin	On adrenergics[a]	Initial dysfunction	POD 2	125

[a] Suprarenin, arterenol

Table 2 Pharmacokinetics of CyA-NOF absorption in patients with an open T tube during the early phase after LTX. Data are given as mean ± standard deviation

Group	CyA-NOF dose	*n*	Day after transplant	AUC	C_{max}	C_{min}	T_{max}	Patients maintained on CyA-NOF
1	2.5 mg/kg	2	2–3	888 ± 308	102 ± 35	45 ± 12	3.8 ± 0.4	0/2
2	5.0 mg/kg	4	2–4	2658 ± 508	358 ± 107	115 ± 58	4.3 ± 2.1	2/4
3	7.5 mg/kg	3	2–3	3639 ± 950	449 ± 74	188 ± 69	4.5 ± 0.8	3/3

($n = 3$) liver grafting was performed without inserting a T tube; in these patients CyA-NOF was started at a dose of 5.0 mg/kg at day 2 or 3 after liver transplantation.

Pharmacokinetic profiling was performed after the first dose of CyA-NOF. In patients in groups 1, 2, and 3, pharmacokinetic profiling was performed with the T tube closed 12 h before the first dosing. In addition, on the next day, a second pharmacokinetic profile was done with the T tube opened 12 h before.

CyA levels were determined by specific monoclonal radioimmunoassay (Cyclo-Trac, Incstar, Clearwater, Mass., USA). Patients with appropriate C_{max} levels (> 400 ng/ml specific RIA) while the T tube was open were maintained on CyA-NOF. In these patients subsequent dosing was adjusted to target trough levels between 100 and 200 ng/ml (specific RIA).

Results

The pharmacokinetics of CyA-NOF absorption given at 5.0 mg/kg body weight are shown in Fig. 1. Depending on the initial liver function of the patients, CyA trough levels at the time of the first CyA-NOF dose varied between 30 and 170 ng/ml (Table 1). There was a modifying influence of bile on the absorption pattern of CyA-NOF: compared to patients without a T tube in situ, patients with either an open or closed T tube showed a CyA adsorption pattern with lower AUC, C_{max} and later T_{max}. When, in patients with external bile diversion, the T tube had been clamped before CyA-NOF dosing, the resulting AUC was higher than that recorded with an open T tube. The C_{max} detected was lowest in patients with an open T tube.

The influence of different doses of CyA-NOF given on days 2–4 post-transplant to patients with an open T tube is shown in Table 2. When CyA-NOF was given at a starting dose of 2.5 mg/kg, the resulting AUC as well as C_{min} levels were too low for maintenance therapy. A CyA-NOF dose of 5.0 and 7.5 mg/kg resulted in appropriate AUC and C_{min} levels in two of four patients receiving 5.0 mg/kg CyA-NOF and in all patients receiving 7.5 mg/kg CyA-NOF.

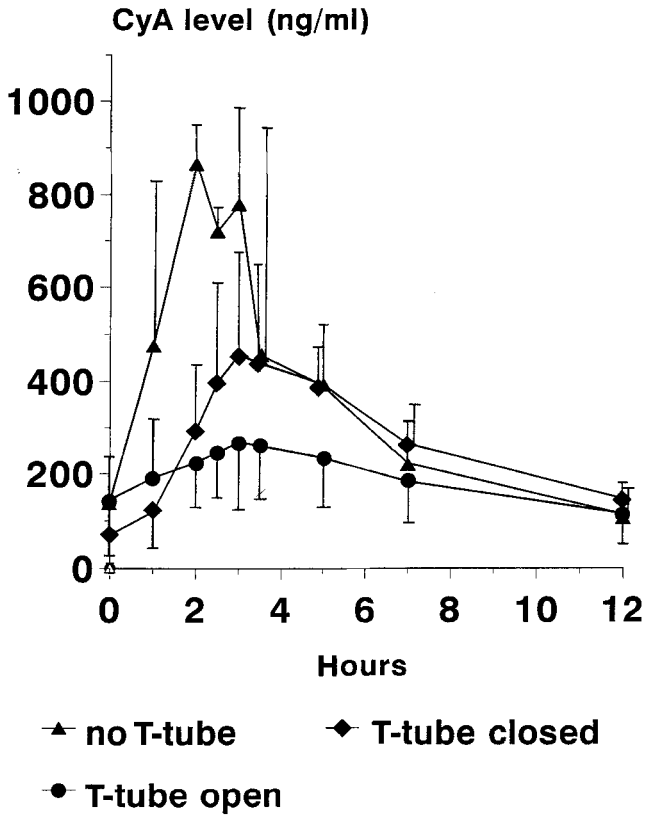

Fig. 1 Pharmacokinetic profile of CyA adsorption from CyA-NOF (5.0 mg/kg body weight) in patients after liver transplantation. Data are given as mean ± standard deviation
(▲ three patients without a T tube in situ, ◆ four patients with a closed T tube, ● the same four patients as in ◆ with an open T tube)

Discussion

The oral absorption of CyA is known to be highly dependent on bile flow [1]. In LTX patients, oral CyA absorption is impaired by initial low bile production of the graft, as well as by bile diversion via T tube drainage [3, 4]. Therefore, to ensure sufficient CyA blood levels in these patients, a prolonged intravenous treatment phase is necessary. That the newly developed, advanced galenic form of CyA (CyA-NOF) might be suitable for oral CyA therapy in these patients is suggested by the clinical course of patients with CyA malabsorption converted from CyA to CyA-NOF on a compassionate use basis [5, 6]. In fact, our data indicate that there is significant CyA-NOF absorption in patients during the early course after liver transplantation, even with external bile diversion via a T tube. However, there is still some bile influence on the adsorption of CyA-NOF. The pharmacokinetic parameters were influenced by T tube clamping and bile diversion. While, in most patients, comparable absorption patterns were observed with an open or clamped T tube, in others clearly lower AUCs were observed with the T tube open. In addition, in patients without T tubes in situ, the highest AUC, C_{max} and earliest T_{max} values were found.

Recent studies on the use of CyA-NOF for baseline immunosuppression in LTX patients showed no influence of T tube clamping on CyA-NOF adsorption, which is in contrast to our results [2]. These studies had been performed during days 10–14 post-transplantation; the T tube had been opened only 12 h before performing pharmacokinetic analysis. It is possible that despite an open T tube, at this time some bile is already present in the gut, improving CyA-NOF adsorption in such a way that no significant difference between an open or closed T tube can be observed. Thus, not only the actual bile excretion but also the overall bile load present in the gut at the time of CyA-NOF dosing might be important for CyA-NOF adsorption. Such a mechanism would explain the superior CyA-NOF adsorption observed at day 2 post-transplantation in patients with no T tube in situ.

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