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Variable effect of ursodeoxycholic acid on cyclosporin absorption after orthotopic liver transplantation

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Abstract The acute effects of administering a single dose of ursodeoxycholic acid (UDCA) on cyclosporin pharmacokinetics were recorded during paired studies in twelve liver transplant recipients, six of whom were cholestatic. Cyclosporin was measured using monoclonal selective antibodies (for parent drug) and non-selective antibodies (for cyclosporin plus metabolites). UDCA resulted in more rapid absorption of cyclosporin in 8 of 12 cases (67 %) but had no effect in two patients with and two patients without cholestasis. Median t_{max} did not change significantly after UDCA (3.0 vs 4.0 h without UDCA) and only 7 of 12 patients (58 %) showed a rise in the amount of cyclosporin absorbed over 24 h with the AUC not having changed significantly (median 4527 vs 4979 $\mu g \cdot h \cdot l^{-1}$ without UDCA). Median C_{max} and C_{24} also increased only marginally following UDCA administration (616 vs 587 $\mu g \cdot l^{-1}$ and 87 vs 58 $\mu g \cdot l^{-1}$ without UDCA, respectively). In the cholestatic patients, median AUC was 50 % smaller (3223 vs 6439 $\mu g \cdot h \cdot l^{-1}$) and median t½a was 100 % longer (1.58 vs 0.8 h) than in patients without cholestasis. There was no consistent improvement in cyclosporin pharmacokinetics in the cholestatic patients following UDCA, although the significantly elevated ratio of non-selective: selective AUC measurements (median 4.8 vs 2.7) fell markedly in the two most severely affected, possibly as a result of an increased clearance of cyclosporin metabolites by choleresis.

Key words Cyclosporin A, liver transplantation, ursodeoxycholic acid

Introduction

Oral cyclosporin has a low and variable bioavailability – between 10 % and 50 % [10, 13, 16] – which is further reduced by cholestatic liver disease [1, 5, 8, 13, 25]. If severe cholestasis develops, it may be necessary to revert to intravenous administration of cyclosporin to maintain adequate immunosuppression, although this may lead to a longer period in hospital and a greater risk of side effects [2, 15]. Bile refeeding [12] was shown to be an effective alternative to parenteral regimens following reports of improved cyclosporin absorption in liver allograft recipients after the complete internalization of bile flow by biliary T-tube clamping [13]. In dogs, the bile acid chenodeoxycholic acid improves cyclosporin absorption when administered together with lecithin [4]. Ursodeoxycholic acid (UDCA) is a naturally occurring bile acid used mainly in gallstone dissolution and it has been shown to be well tolerated in the treatment of chronic cholestatic liver disease [11, 14, 17]. In this study we examined whether UDCA influenced cyclosporin pharmacokinetics and improved its absorption in liver allograft recipients with both normal and cholestatic liver function.

Table 1 Demographic variables and liver function tests [*Dia* diagnosis, *Tx* time after transplantation (weeks), *HBV* fulminant hepatitis B, *PBC* primary biliary cirrhosis, *CAR* carcinoid syndrome, *CF* cystic fibrosis, *SC* sclerosing cholangitis, *FW* fulminant Wilson's Disease, *CAH* chronic active hepatitis, *CC* cryptogenic cirrhosis, *Bil* serum bilirubin ($\mu mol \cdot l^{-1}$), *AST* serum aspartate aminotransferase ($IU \cdot l^{-1}$), *ALP* alkaline phosphatase ($IU \cdot l^{-1}$), *GGT* gamma glutamyl transpeptidase ($IU \cdot l^{-1}$)]

[a] With Roux-en-Y enterostomy at the time of study

Case no	Sex	Age	Dia	Tx	Dose (mg)		BIL	AST	ALP	GGT
					CyA	UDCA				
1	M	43	HBV	50	125	750	24	16	213	306
2	M	67	PBC	8	250	600	16	45	244	212
3	M	52	CAR	150	600	750	8	23	107	102
4[a]	M	65	PBC	3	100	600	47	26	148	93
5[a]	M	52	PBC	5	200	450	33	236	313	259
6	F	16	CF	100	600	450	9	56	411	283
7	F	35	HBV	40	700	750	382	579	240	52
8[a]	M	19	SC	4	300	450	407	329	526	108
9[a]	F	16	FW	8	300	600	269	312	555	768
10	F	63	PBC	12	250	450	202	131	948	442
11	M	41	CAH	10	500	600	563	39	1023	894
12[a]	M	49	CC	4	400	750	115	50	460	272

Patients and methods

Patients

Twelve orthotopic liver transplant recipients (four female, eight male) with a median age of 46 years (range 16–67 years) participated in a cross-over study of the effects of UDCA at a median time of 9 weeks (range 3–150 weeks) post-transplantation. All twelve patients had stable liver function test results in the 4 days before the study with six of them (cases 1–6) showing a serum bilirubin below 50 µmol/l and the remaining six (cases 7–12) exhibiting cholestatic liver dysfunction judged by a serum bilirubin above 100 µmol/l (Table 1). Cholestasis was due to chronic rejection in cases 10 and 11, to recurrent hepatitis B infection in case 7 and to early post-transplant cholestasis in cases 8, 9 and 12. Bile flow was fully internalized in all cases including five studied less than 8 weeks post-operatively with Roux-en-Y enterostomy. Cyclosporin doses remained unchanged for a minimum of 3 days before the study. Patients received the same breakfast and lunch and there were no changes in other medications on the 2 days on which the study was performed.

To prevent carry-over effects, the cross-over was uni-directional with cyclosporin (Sandimmun capsules, Sandoz Pharmaceuticals, Frimley, Surrey, UK) given alone on day 1 and together with UDCA (10 mg/kg Destolit, Merrell Dow Pharmaceuticals, Uxbridge, Middlesex, UK) on day 2. Cyclosporin (125–700 mg) was given in the morning 24 h after the previous dose and 2 h before breakfast.

Methods

On both study days, blood (3 ml) was taken in EDTA from an in-dwelling cannula prior to and 1, 2, 3, 4, 5, 6, 8, 10, 20 and 24 h after cyclosporin. Samples were frozen at −20 °C until analyzed using the parent drug selective Cyclotrac SP radioimmunoassay (Incstar, Maidenhead, Berkshire, UK) as described previously [22] but with additional standards of 800 and 1200 µg cyclosporin $\cdot l^{-1}$. Cyclosporin and a cross-section of its metabolites were assayed using the Cyclotrac NS radioimmunoassay (Incstar) according to the package insert but using two additional standards (of 800 and 1800 µg cyclosporin $\cdot l^{-1}$) and adding 1 ml of phosphate-buffered saline before centrifugation at 4 °C.

The pharmacokinetic parameters t_{max} (time of maximum drug concentration: C_{max}), C_{24} (trough cyclosporin concentration at 24 h after dosing), AUC (area under the drug blood concentration versus time curve) and t½a (absorption half-life) were calculated during a single dosing interval (24 h) using the Strip curve fitting program provided by Dr. Atholl Johnston, Analytical Unit, St. Bartholomew's Hospital, London, UK [7]. Absorption half-lives were calculated assuming first order kinetics [21] because high correlation coefficients (> 0.9) applied in the majority of cases. Statistical analysis of the effects of UDCA was made using the Wilcoxon paired, signed, ranks test and results between study groups were compared with the Mann-Whitney U-test. The SPSS-PC package (SPSS, Chertsey, Surrey, UK) was used and significance assigned when P was less than 0.05.

Results

Baseline pharmacokinetic variables (no UDCA) ranged more widely in the six patients with cholestasis (e.g. 6.2, 50 and 21-fold for C_{24}, C_{max} and AUC determined from selective assay results, respectively) than in those with bilirubin below 50 µmol/l (3.5, 3.8 and 5.5-fold, respectively; Table 2). Data from non-selective assay results also showed greater variability in the cholestatic patients (Table 3). UDCA was well tolerated in 11 of 12 cases, but one patient (case 8) developed headache and hypertension 6 h after UDCA and at a time corresponding with an increased cyclosporin C_{max}.

The combination of UDCA with cyclosporin was associated with a shorter absorption half-life of the immunosuppressive agent in 8 of 12 patients (median t½a: 0.49 vs 0.80 h without UDCA, $P = 0.27$; Table 2). C_{max} was higher and t_{max} earlier in six patients given UDCA, with the latter unchanged in an additional three (median for the entire group was 616 vs 587 µg $\cdot l^{-1}$ without UDCA and 3.0 vs 4.0 h without UDCA, $P = 0.88$ and 0.12, respectively). Trough cyclosporin concentrations (C_{24}) increased in seven cases after UDCA (median 87 vs 58 µg $\cdot l^{-1}$ without UDCA, $P = 0.22$; Table 2). UDCA also increased AUC during one dosage interval (24 h) in 7 of 12 cases (median

Table 2 Influence of ursodeoxycholic acid (UDCA) on pharmacokinetic variable determined by selective cyclosporin measurement. ($t½a$ absorption half-life, C_{24} trough cyclosporin concentration at 24 h after dosing, C_{max} maximum drug concentration at time t_{max}, AUC area under the drug blood concentration versus time curve, – cyclosporin alone, + cyclosporin plus UDCA)

[a] With Roux-en-Y enterostomy

Case no	t½a		C_{24}		C_{max}		t_{max}		AUC	
	–	+	–	+	–	+	–	+	–	+
1	0.9	0.48	77	95	682	920	6	3	5398	6843
2	0.25	0.45	64	79	967	488	4	2	7479	4875
3	0.62	0.50	48	41	387	871	2	2	2981	4179
4[a]	1.1	1.2	122	121	1183	1012	5	5	8338	9575
5[a]	0.7	0.47	129	116	2142	1598	4	3	10299	10021
6	1.0	0.53	37	38	549	482	2	3	2700	3060
7	0.43	0.39	45	42	234	162	1	2	1886	1608
8[a]	2.7	2.4	82	146	625	744	8	6	6306	7703
9[a]	2.9	0.9	52	100	362	328	5	3	4559	3652
10	3.0	4.9	28	38	28	56	24	21	439	817
11	0.28	0.68	20	24	52	69	1	3	625	782
12[a]	0.46	0.25	123	115	1404	1824	1	1	9240	8322

Table 3 Influence of ursodeoxycholic acid (UDCA) on pharmacokinetic variables determined by non-selective cyclosporin measurement. ($t½a$ absorption half-life, C_{24} trough cyclosporin concentration at 24 h after dosing, C_{max} maximum drug concentration at time, t_{max}, AUC area under the drug blood concentration versus time curve, $AUC_{NS/SP}$ ratio of non-selective/selective AUC results, – cyclosporin alone, + cyclosporin plus UDCA)

[a] With Roux-en-Y enterostomy

Case no	C_{24}		C_{max}		t_{max}		AUC		$AUC_{NS/SP}$	
	–	+	–	+	–	+	–	+	–	+
1	405	440	1268	1526	6	3	16805	18549	3.11	2.71
2	382	274	1447	1105	5	5	18863	13959	2.52	2.86
3	177	293	865	1245	3	3	8023	12362	2.69	2.96
4[a]	402	387	2393	2191	5	6	22051	23903	2.64	2.50
5[a]	589	537	2533	2468	5	3	27127	27150	2.63	2.71
6	185	179	698	773	2	3	6902	7929	2.56	2.59
7	328	307	545	419	2	3	8901	8530	4.72	5.30
8[a]	421	509	1049	1467	8	9	16502	19770	2.62	2.57
9[a]	371	800	1191	1154	5	6	22981	20662	5.04	5.66
10	148	230	162	230	21	24	3335	4134	7.60	5.06
11	518	533	729	635	0	6	14357	12027	22.97	15.38
12[a]	741	609	2387	2365	3	2	31432	26703	3.40	3.21

4527 vs 4979 $\mu g \cdot h \cdot l^{-1}$ without UDCA, $P = 0.48$) and in one further case after calculating values during the first 10 h after cyclosporin administration when the effects of UDCA were most pronounced (median 3556 vs 3351 $\mu g \cdot h \cdot l^{-1}$, $P = 0.58$). All twelve patients showed improvements in at least one of these indices of earlier or more complete cyclosporin absorption and all parameters were improved in four patients (cases 8 and 11 with cholestasis and cases 1 and 3 with bilirubin $< 50\ \mu mol \cdot l^{-1}$; Table 2), two of which are shown in Fig. 1. In the five patients with Roux-en-Y enterostomy (three with cholestasis), t½a was shorter in four following UDCA administration and t_{max} was reduced in three (and unchanged in two). However, AUC was increased in only three patients over 10 h and in two over 24 h.

Median AUC values derived from selective cyclosporin assay were 50% lower in the six cholestatic patients ($P = 0.20$ vs those with bilirubin $< 50\ \mu mol \cdot l^{-1}$) and the lowest AUC value (after UDCA) was associated with the highest bilirubin (563 $\mu mol \cdot l^{-1}$ in case 11). In only three of the six cholestatic patients did AUC values increase after UDCA administration during the 24 h dosing interval (median 2630 vs 3223 $\mu g \cdot h \cdot l^{-1}$ without UDCA, $P = 0.92$) with comparable increases in four of six patients with bilirubin below 50 $\mu mol \cdot l^{-1}$ (median 6859 vs 6439 $\mu g \cdot h \cdot l^{-1}$ without UDCA, $P = 0.82$). Considering only the first 10 h after cyclosporin administration, increases in AUC measurements were again noted in only three cholestatic patients but in five of six without cholestasis. Reductions in median t½a in patients with cholestasis were quantitatively and proportionally greater (1.58 vs 0.79 h with UDCA, $P = 0.75$) than in those with serum bilirubin levels below 50 $\mu mol \cdot l^{-1}$ (0.80 vs 0.49 with UDCA, $P = 0.17$). Median t_{max} was decreased following UDCA only in the patients without cholestasis (by 25%, $P = 0.20$) but median cyclosporin concentrations at 24 h increased in both these and the cholestatic patients after UDCA (by 23% and 46%, $P = 0.64$ and 0.17, respectively). In contrast C_{max} concentrations changed by less than 20% in each group, although there was at least one additional peak in cyclosporin blood concentrations after UDCA treatment for four patients with serum bilirubin levels below 50 $\mu mol \cdot l^{-1}$ and for three with cholestasis.

Results from the non-selective assay (in which cyclosporin metabolites contribute greatly to blood concentrations) showed median AUC values 2.7 times the selective assay results in the patients without cholestasis (17834 vs 6439 $\mu g \cdot h \cdot l^{-1}$, $P = 0.002$) and 4.8-fold higher in those with cholestasis (15430 vs 3223 $\mu g \cdot h \cdot l^{-1}$, $P = 0.002$; Table 3). Median C_{24} concentrations were 5.6 times the se-

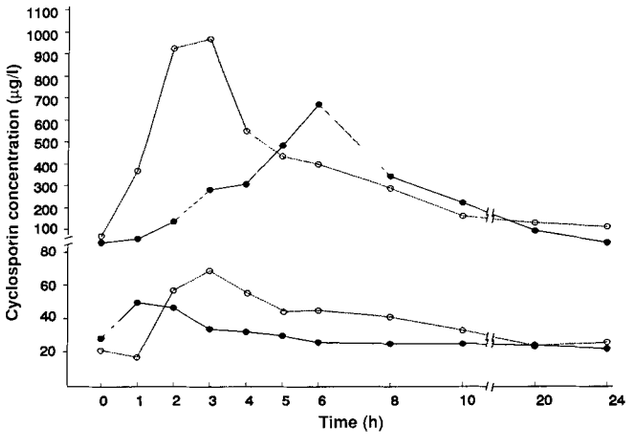

Fig. 1 Influence of ursodeoxycholic acid on cyclosporin blood levels during one dosage interval. Blood levels of cyclosporin are shown for one patient with good liver function (case 1, *upper curves*) and one with cholestasis (case 11, *lower curves*) after cyclosporin alone (●—●) and cyclosporin + ursodeoxycholic acid (○---○)

lective assay result in the former patients ($P = 0.028$) and 8.2-fold higher in those with cholestasis ($P = 0.028$), and corresponding values for C_{max} were 1.65- and 2.98-fold, respectively ($P = 0.028$ in both cases). T_{max} for the non-selective assay (median 5.0 h without vs 4.0 h with UDCA, $P = 0.39$) was later than for the parent drug (median 4.0 h without vs 3.0 h with UDCA, $P = 0.12$) in 11 of the 12 patients on at least one of the occasions it was measured. After UDCA administration, the ratio of AUC results by non-selective to selective assays ($AUC_{NS/SP}$) fell by more than 30% in the two cases (10 and 11) with the most pronounced accumulation of cyclosporin metabolites, but there was no significant change for the cholestatic patients overall (median 5.18 vs 4.88 without UDCA, $P = 0.46$), nor in the median values of non-selective AUC (15900 vs 15430 $\mu g \cdot h \cdot l^{-1}$ without UDCA, $P = 0.46$) or C_{max} (890 vs 895 $\mu g \cdot l^{-1}$, $P = 0.75$). In contrast, UDCA caused disproportionate increases in median trough levels (C_{24} by non-specific assay) in cholestatic patients (+32% vs −13% in those with good liver function) although neither increase achieved significance.

Discussion

Ursodeoxycholic acid (UDCA) increased the rate of cyclosporin absorption in this group of twelve liver transplant recipients as evidenced by a shorter absorption half-life and earlier t_{max}. However, cyclosporin relative bioavailability was not increased by UDCA on the basis of changes in AUC measurements during one dosage interval (24 h in all patients), although in the first 10 h after UDCA administration AUC values were increased in five of six patients without cholestasis. Nine of the 12 patients studied did show additional peaks in cyclosporin absorption 6–10 h after UDCA and this is at the late limit of the period (< 8 h) during which the effects of UDCA on bile acid absorption are said to prevail [19]. Recently, Gutzler and colleagues [6] reported a decrease in t_{max} associated with an increase in cyclosporin bioavailability of around 30% during the 12 h after two liver allograft recipients were given UDCA. An increase in bioavailability of more than 100% was also noted for a heart transplant recipient with a short bowel, but the dose of UDCA used was approximately 50% greater than in the present study. This dosage difference may explain the more pronounced benefits of UDCA reported by Gutzler et al. [6], but their patients were also studied during a twice daily dosage regimen and the effects of UDCA were greater over 10 h than the 24 h in our study.

Decreased bile production and excretion [5, 13] probably underlie the poor absorption and low bioavailability of cyclosporin in patients with cholestasis, and it is known that the proportion of parent drug to metabolites in blood correlates with serum bilirubin, but less strongly with elevated alkaline phosphatase or γ-glutamyltranspeptidase results [20]. The metabolism of cyclosporin by enterocytic cytochrome P450IIIA may also contribute to reduced cyclosporin bioavailability [9], especially during cholestasis [21]. Bile salt refeeding [12] and chenodeoxycholic acid supplementation [4] have been shown to increase cyclosporin absorption in cholestatic patients, but the enhancement by UDCA noted in this study was small and variable, and possibly weaker than in the patients with good liver function. UDCA administration also induced no significant improvements in relative cyclosporin bioavailability in the five patients with Roux-en-Y enterostomy in this series. Such interventions reduce cyclosporin absorption because of the reduced length of bowel available for absorption [24], and recent experimental studies suggest that bile improves cyclosporin absorption in both the proximal and distal small intestine [3], so benefit with UDCA may have been expected. Chenodeoxycholate has been suggested to improve cyclosporin absorption by promoting micelle formation [4] and the weaker micelle-forming properties of UDCA [19] may underlie its lesser potency. Benefit from UDCA may be greater at higher doses or after prolonged administration, and twice daily administration of UDCA may be optimal, particularly if combined with 12-hourly dosing with neoral, the microemulsion formulation of cyclosporin that appears to be absorbed better than conventional Sandimmun preparations [23]. No side effects were encountered that would contraindicate such regimens. Additional benefit with UDCA may be obtained from the hypercholeresis it induces [18], leading to enhanced biliary excretion of cyclosporin metabolites accumulated during cholestasis [20, 21]. This was demonstrated from the ratio of selective to non-selective cyclosporin assay results in the two patients with the greatest impairment of cyclosporin absorption and most pronounced metabolite accumulation.

References

1. Andrews W, Iwatsuki S, Shaw BW, Starzl TE (1985) Letter to the editor. Transplantation 39: 338
2. Berden JHM, Hoitsma AJ, Merx JL, Keyser A (1985) Severe central nervous system toxicity associated with Cyclosporine. Lancet I: 219–220
3. Cakaloglu Y, Marinos G, Marsden J, Peters TJ, Williams R, Tredger JM (1993) Localization of cyclosporin A absorption in rat small bowel and the effect of bile. Clin Sci 84: 675–679
4. Ericzon BG, Todo S, Lynch S, Kam I, Ptachcinski RJ, Burchart GJ, Thiel DH van, Starzl TE, Venkataramanan R (1987) Role of bile and bile salts on cyclosporine absorption in dogs. Transplant Proc 19: 1248–1249
5. Groen PC de (1990) Cyclosporine and the liver: how one affects the other. Transplant Proc 22: 1197–1202
6. Gutzler F, Fischer G, Sauer P, Zimmerman R, Theilmann L, Weber E, Kommerell B, Stiehl A (1992) Improved bioavailability of cyclosporin by coadministration of ursodeoxycholic acid (abstract). Gastroenterology 102: A816
7. Johnston A, Woolard RC (1983) Strip: an interactive computer program for the analysis of drug pharmacokinetics. J Pharmacol Methods 9: 193–200
8. Kahan BD, Kramer WG, Wideman C, Flecher SM, Lobert MI, Buren CT van (1986) Demographic factors affecting the pharmacokinetics of cyclosporine estimated by radioimmunoassay. Transplantation 41: 459–464
9. Kolars JC, Awni WD, Merion RM, Watkins PB (1991) First-pass metabolism of cyclosporin by the gut. Lancet 338: 1488–1490
10. Lemaire M, Fahr A, Maurer G (1990) Pharmacokinetics of cyclosporine: inter- and intra-individual variations and metabolic pathways. Transplant Proc 22: 1110–1112
11. Makino J, Shinizaki K, Nakagawa K, Yoshino K (1975) Dissolution of cholesterol gallstones by long-term administration of ursodeoxycholic acid. Jpn J Gastroenterol 72: 690–702
12. Merion RM, Gorski GH, Burtch GD, Turcotte JG, Colletti LM, Campbell DA (1989) Bile refeeding after liver transplantation and avoidance of intravenous cyclosporine. Surgery 106: 604–610
13. Naoumov NV, Tredger JM, Steward CM, O'Grady JG, Grevel J, Niven A, Whiting B, Williams R (1989) Cyclosporin A pharmacokinetics in liver transplant recipients in relation to biliary T-tube clamping and liver dysfunction. Gut 30: 391–396
14. Podda M, Ghezzi C, Battezzati PM, Bertolini E, Croienania A, Petroni ML, Zuin M (1989) Effect of different doses of ursodeoxycholic acid in chronic liver disease. Dig Dis Sci 34 [Suppl 12]: 59S–65S
15. Powell-Jackson PR, Young B, Calne RY, Williams R (1983) Nephrotoxicity of parenterally administered cyclosporine after orthotopic liver transplantation. Transplantation 36: 506–508
16. Ptachcinski RJ, Venkataramanan R, Burckart GJ (1986) Clinical pharmacokinetics of cyclosporin. Clin Pharmacokinet 11: 107–132
17. Sackmann M, Paulezki J, Aydemir U, Holl J, Sauerbruch T, Hasford J, Paumgartner G (1991) Efficacy and safety of ursodeoxycholic acid for dissolution of gallstone fragments: comparison with the combination of ursodeoxycholic acid and chenodeoxycholic acid. Hepatology 14: 1136–1141
18. Scharschmidt BF, Lake JR (1991) Hepatocellular bile acid transport and ursodeoxycholic acid hypercholeresis. Dig Dis Sci 34 [Suppl 12]: 5S–15S
19. Stiehl A, Raedsch R, Rudolph G (1992) Acute effects of ursodeoxycholic and chenodeoxycholic acid on the small intestinal absorption of bile acids. Gastroenterology 98: 424–428
20. Tredger JM, Steward CM, Williams R (1988) Cyclosporine blood levels – an evaluation of radioimmunoassay with selective monoclonal or polyclonal antibodies and high performance liquid chromatography in liver transplant recipients. Transplantation 46: 681–686
21. Tredger JM, Grevel J, Naoumov NV, Steward CM, Niven AA, Whiting B, Williams R (1991) Cyclosporine pharmacokinetics in liver transplant recipients: evaluation of results using both polyclonal radioimmunoassay and liquid chromatographic analysis. Eur J Clin Pharamcol 40: 513–519
22. Tredger JM, Gonde CE, Williams R (1992) Monitoring cyclosporine in liver transplant recipients: effects of clinical status on the performance of two monoclonal antibody-based methods. Clin Chem 38: 108–113
23. Trull AK, Tan KKC, Uttridge J, Bauer T, Alexander GJM, Jamieson NV (1993) Cyclosporin absorption from microemulsion formulation in liver transplant recipient. Lancet 341: 433
24. Whitington PF, Kehrer BH, Whitington SH, Shneider B, Black DD (1989) The effect of biliary enteroenterostomy on the pharmacokinetics of enterally administered cyclosporine in rats. Hepatology 9: 393–397
25. Yee GC (1990) Pharmacokinetic interaction between cyclosporine and other drugs. Transplant Proc 22: 1203–1207