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Pharmacokinetics of Mycophenolic Acid in Live Donor Liver Transplant Patients vs Deceased Donor Liver Transplant Patients

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The exposure of mycophenolic acid in live donor liver transplant patients (those receiving a partial hepatic volume) in comparison to deceased donor liver transplant patients (those receiving the whole hepatic volume) after administration of mycophenolate mofetil has not been reported earlier. The aim of the present study is to compare the pharmacokinetics parameters of mycophenolic acid and mycophenolic acid glucuronide in live donor liver transplant patients versus deceased donor liver transplant patients. Twelve live donor liver transplant and 12 deceased donor liver transplant recipients were studied over a dosing interval after intravenous administration of mycophenolate mofetil. The maximum concentration (C_{max}) and the area under the plasma concentration versus time curve (AUC) for mycophenolic acid in live donor liver transplant patients were significantly higher than in deceased donor liver transplant patients (C_{max}/AUC: live donor liver transplant patients: 16.1 ± 6.6 μg/mL/43.9 ± 12.6 μg/mL·h vs deceased donor liver transplant patients: 10.7 ± 2.0 μg/mL/28.9 ± 7.1 μg/mL·h; P = .046/.002). The volume of distribution was higher in the deceased donor liver transplant patients compared with live donor liver transplant patients. However, the mean plasma concentration at 12 hours (C_{last}), drug disposition rate constant, half-life ($t_{1/2}$), and mean residence time were similar in both groups. The mean plasma concentration of mycophenolic acid glucuronide was 1.4 to 2.0 times higher in deceased donor liver transplant patients compared with live donor liver transplant patients. These observations point to the need to use a lower dosage (approximately 30%) of mycophenolate mofetil in live donor liver transplant patients compared with deceased donor liver transplant patients.

Keywords: *Liver transplantation; live donor; deceased donor; pharmacokinetics; mycophenolate mofetil; mycophenolic acid*

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Mycophenolic acid (MPA) is a noncompetitive inhibitor of inosine monophosphate (IMP) dehydrogenase, which prevents de novo synthesis of purine nucleotides in proliferating T and B lymphocytes. The morpholino ester derivative of MPA, mycophenolate mofetil (MMF), is a non-nephrotoxic immunosuppressive agent, which is increasingly being used with calcineurin inhibitors in solid organ transplant patients.[1-4] Mycophenolate mofetil has been used to reduce the incidence of acute rejection, preserve deterioration in renal function, and spare the use of steroids in deceased donor liver transplantation (DDLT).[5-11]

Most of the pharmacokinetic studies of MMF have been performed in healthy volunteers; kidney, heart, or lung patients; or DDLT patients.[11-14] Wide variations in the kinetic parameters between patients and within a patient over time, as well as between patients with different organs transplanted, have been recognized.[15-21] With the shortage of DDLTs, an increasing number of live donor liver transplants (LDLT) have been performed all over the world.[22-25] The DDLT recipients receive the full volume of liver, but the LDLT recipients receive only about 55% to 60% of normal hepatic volume. The impact of receiving a partial hepatic volume with LDLT on the tacrolimus dose-concentration relationship has already been reported.[26,27] However, such information on MMF kinetics changes has not been reported.

Given that MPA is glucuronidated in the liver to mycophenolic acid glucuronide (MPAG) and that the glucuronidation process is impaired in rats with partial hepatic allograft,[25] it is important to evaluate the pharmacokinetics of MPA in LDLT patients.

AIM

The aim of the present study is to examine the differences in the plasma MPA and MPAG concentration versus time profile in LDLT and DDLT after intravenous (IV) administration of MMF.

PATIENTS AND METHODS

Between January 2005 and November 2005, 12 consenting adult LDLT and 12 adult DDLT recipients were prospectively enrolled in a protocol approved by the institutional review board to study the pharmacokinetics of MPA after intravenous administration of MMF. The institutional review board for the University of Rochester Medical Center approved this study. Patients with a retransplant or multiple organ transplants were excluded from this study. Characteristics of the patients are given in Table I. All patients were initiated with IV MMF at a dose of 1 g twice per day (constant 2-hour infusion using an Alaris pump [Matrix Medical, Minneapolis, Minnesota]) for 2 to 8 days (mean 3.7 ± 1.8; median 3.5 days) and then converted to oral MMF 1 g twice a day, when oral feeds were resumed. Serial blood samples were drawn at 0 (predose) and at 1, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 hours after starting IV MMF on the second or third postoperative day. Blood samples were drawn in BD Vacutainer tubes spray-coated with K_2EDTA (Wilburn, Kernesville, North Carolina) and kept on ice until centrifugation, and the plasma obtained was transferred into a clear tube and frozen at –20°C until analysis. The plasma concentrations of MPA and MPAG were measured using a high-performance liquid chromatography (HPLC) method that has been validated in our laboratory.[28] Various pharmacokinetic parameters were calculated using noncompartmental analysis with WinNonlin software (Version 4.1, Pharsight Corporation, Mountainview, California). The parameters calculated included terminal disposition rate constant (λ_z), terminal disposition half-life ($t_{1/2}$), area under the concentration versus time curve (AUC), systemic clearance (CL), steady-state volume of distribution (V_{ss}) and mean residence time (MRT) after IV administration, the peak plasma concentration (C_{max}) time to reach peak concentration (t_{max}), and last plasma concentration (C_{last} at 12 hours). These parameters are presented as mean ± standard deviation (SD). Statistical comparison of different parameters was made using the *t* test (SPSS software, Version 14.0, Chicago, Illinois). A P value <.05 was considered statistically significant.

All of the study patients also received oral tacrolimus, starting at a dose of 0.05 mg/kg twice a day.

Table I Characteristics of DDLT vs LDLT Patients

	DDLT	LDLT
Male	11	7
Female	1	5
Mean age recipients, y, ± SD	51.5 ± 13.1	51.6 ± 6.7
Mean age donor, y, ± SD	51.3 ± 13.5	38.3 ± 11.6
Mean weight, kg, ± SD	86.9 ± 22.6	88.1 ± 17.2
Mean height, cm, ± SD	174.7 ± 5.3	172.1 ± 10.0
Body mass index, kg/m^2, ± SD	29.11 ± 6.9	30.6 ± 8.1
Mean body surface area, m^2, ± SD	2.06 ± 0.27	2.1 ± 0.20
Diagnosis (n)		
Hepatitis C	5	5
Ethanol	3	4
Cryptogenic	1	2
Primary biliary cirrhosis	0	1
Autoimmune	1	0
Sclerosing cholangitis	1	0
Biliary atresia	1	0
Blood type (n)		
O	5	8
A	3	3
B	1	1
AB	3	0

LDLT, live donor liver transplant; DDLT, deceased donor liver transplant.

Table II Biochemical Parameters (Mean ± SD), DDLT vs LDLT

MMF	WBC	Hct	Plat	BUN	Creat	Alb	T Bili	AST	ALT	ALK	GGT
DDLT	12.2 ± 5.7	29.2 ± 3.6	68.8 ± 40.6	42.5 ± 16.5	1.9 ± 1.2	2.3 ± 0.4	3.5 ± 3.3	916 ± 1146	698 ± 482	84.8 ± 71.1	74.3 ± 51.0
LDLT	15.2 ± 6.9	25.5 ± 5.9	73.8 ± 29.3	29.5 ± 11.0	1.05 ± 0.7	2.1 ± 0.3	2.1 ± 1.0	286 ± 197	299 ± 284	76.6 ± 51.8	66.0 ± 57.2
P value	.89	.68	.72	.02	.14	.14	.06	.13	.41	.47	.5

P < .05 between intravenous and oral study days. DDLT, deceased donor liver transplant; LDLT, live donor liver transplant; WBC, white blood cell count (10^3/mL); Hct, hematocrit %; Plat, platelets (10^3/mL); BUN, blood urea nitrogen (mg/dL); Creat, creatinine (mg/dL); Alb, albumin (g/L); T Bili, total bilirubin (mg/dL); AST, aspartate aminotransferase (U/L); ALT, alanine aminotransferase (U/L); ALK, alkaline phosphate (U/L); GGT, damma glutamyl transpeptidase (U/L).

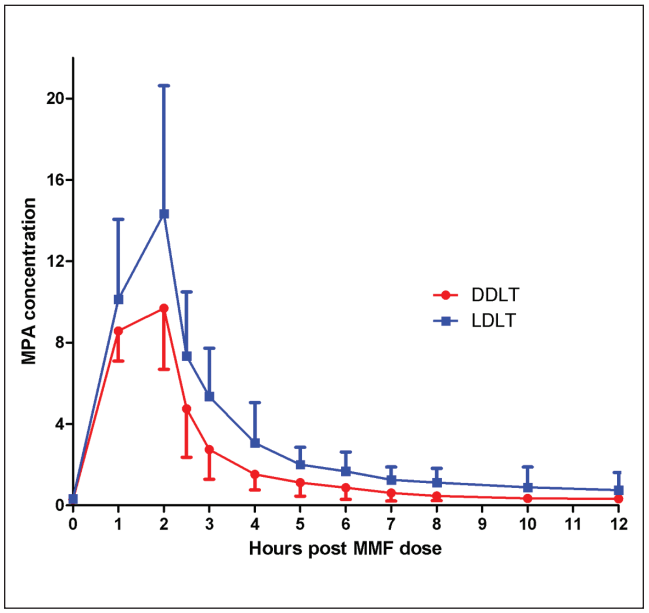

Figure 1. Mean plasma concentrations (with SD) of mycophenolic acid (MPA) over time after initiation of 1 g IV mycophenolate mofetil (MMF) in live donor liver transplants (LDLTs) and deceased donor liver transplants (DDLTs).

The dose of tacrolimus was adjusted as per the clinical conditions, and the target trough levels were normally maintained around 8 to 10 ng/mL. The patients also received 500 mg of methylprednisolone before perfusion of the liver and then a total of 600 mg of methylprednisolone that was tapered over the next 5 days (day 1: 100 mg bid, day 2: 80 mg bid, day 3: 60 mg bid, day 4: 40 mg bid, and day 5: 20 mg bid).

RESULTS

The characteristics of the patients, including the primary diagnosis, age, and gender distribution for both groups of patients, are shown in Table I. Similarly, the laboratory values, including albumin level (LDLT: 2.1 ± 0.4 g/L, DDLT: 2.3 ± 0.5 g/L, *P* = .14) in the patients on the study day, are shown in Table II. The overall mean concentration of MPA over time for DDLT and LDLT is shown in Figure 1, and the pharmacokinetic parameters of MPA after IV administration of MMF are shown in Table II. There was a wide variation in various pharmacokinetic parameters of MPA in LDLT and DDLT patients after intravenous MMF.

The maximum plasma concentration achieved in LDLT recipients was significantly higher than in DDLT recipients (16.1 ± 6.6 μg/mL LDLT vs 10.7 ± 2.0 μg/mL in DDLT; *P* = .046). The AUC was also significantly higher in LDLT recipients compared with DDLT recipients (43.9 ± 12.6 μg/mL·h LDLT vs 28.9 ± 7.1 μg/mL·h in DDLT; *P* = .002). However, the mean concentration at time 0, mean C_{12} concentrations, drug disposition rate constant, half-life, and mean residence time were not significantly different. The volume of distribution and clearance was significantly higher in DDLT compared with LDLT (Table III). The mean MPAG concentration was 1.4 to 2.0 times higher in DDLT compared with LDLT during the kinetics study (Figure 2). The ratio of AUC_{MPAG} to AUC_{MPA} was 47 ± 26 and 18 ± 11 for DDLT and LDLT, respectively. Assuming the fraction of MPA metabolized to MPAG to be close to 1, the elimination clearance of MPAG was 809 ± 458 and 1437 ± 951 mL/hr (*P* < 0.051), respectively.

DISCUSSION

Limited studies on the pharmacokinetics of drugs used in the recipients of LDLT have been performed. These studies have used a small number of patients, or the analysis is limited to trough blood concentrations measured for drugs such as cyclosporine, tacrolimus, and propofol.[26,27,29-32]

Higher tacrolimus blood levels have been reported in LDLT patients compared with deceased donor liver recipients.[26] This has led to the use of reduced doses of tacrolimus in the early postoperative period in LDLT recipients.[27] Based on a population pharmacokinetic analysis immediately after surgery, patients receiving LDLT showed a smaller clearance, and the

Table III Kinetics Parameters: Intravenous MMF DDLT vs LDLT

	C_{max}, μg/mL	t_{max}, h	C_{last}, μg/mL	λ_z, h^{-1}	$t_{1/2}$, h	AUC, μg/mL·h	CL, L/h	V_{ss}, L	MRT, h
DDLT									
Mean	10.73	1.67	0.33	0.15	5.52	28.92	26.89	84.93	3.27
SD	2.05	0.49	0.17	0.08	2.31	7.13	6.16	24.45	1.10
Median	10.84	2.00	0.33	0.12	5.72	25.75	28.70	93.59	3.12
LDLT									
Mean	16.12	1.78	0.48	0.19	4.28	43.86	18.43	54.49	3.08
SD	6.56	0.44	0.23	0.08	1.72	12.57	6.41	19.11	1.13
Median	13.90	2.00	0.55	0.16	4.39	46.07	16.04	64.01	2.97
P value	.046	.37	.11	.38	.16	.002	.002	.01	.52

LDLT, live donor liver transplantation; DDLT, deceased donor liver transplantation; MMF, mycophenolate mofetil; λ_z, terminal disposition rate constant; $t_{1/2}$, terminal disposition half-life; AUC, area under the plasma concentration versus time curve; CL, systemic clearance; V_{ss}, steady-state volume of distribution; MRT, mean residence time after intravenous administration; C_{max}, peak plasma concentrations; t_{max}, time to reach peak concentration; C_{last}, last plasma concentration at 12 hours.

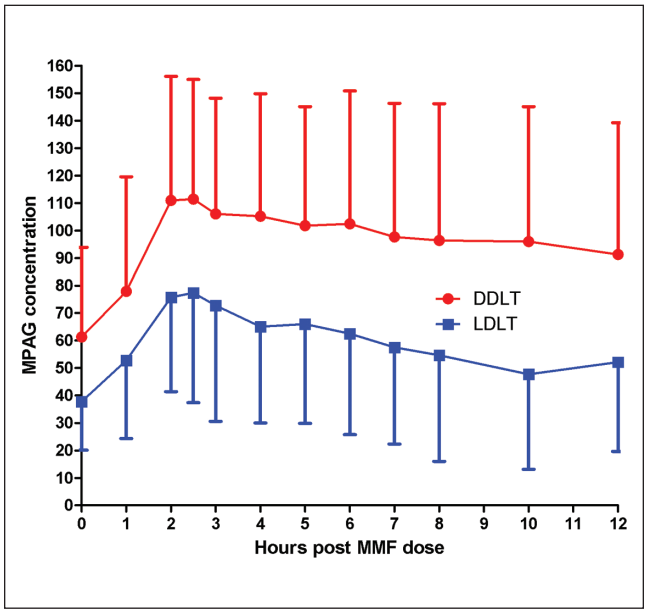

Figure 2. Mean plasma concentrations (with SD) of mycophenolic acid glucuronide (MPAG) over time after initiation of 1 g intravenous mycophenolate mofetil (MMF) in live donor liver transplant (LDLTs) and deceased donor liver transplants (DDLTs).

clearance increased with time after transplantation (1.8% increase per day).[29]

Mycophenolic acid is primarily eliminated as a glucuronide conjugate. Glucuronide conjugation has been shown to be impaired during hepatic regeneration but recovers completely within 2 weeks after partial hepatectomy in rats.[25] In a recent publication, Tian et al[33] have also reported decreased clearance of MPA in partially hepatectomized rats early postsurgery that recovers completely within 2 weeks to normal values.

We have previously shown that the bioavailability of MPA is only about 50% after oral administration of MMF in the perioperative period in DDLT patients.[34] In this study, we evaluated the pharmacokinetics of MMF after IV administration in LDLT and DDLT patients. When comparing our observations in recipients of DDLT versus LDLT, there were several noteworthy observations. Generally, after an identical dosage regimen, the plasma concentrations were significantly higher during the IV therapy in LDLT patients compared with DDLT patients. There was no significant difference in the plasma concentration of MPA at time 0 and at the end of the dosing interval after IV administration of MMF, indicating achievement of steady state in each subject. When MMF was administered intravenously, there were no significant differences in the disposition rate constant, disposition half-life, and mean residence time, but C_{max} and AUC were significantly higher and CL and V_{ss} were significantly lower in the LDLT patients compared with DDLT patients. Based on previous studies, serum albumin levels appear to have an effect on the plasma concentration of MPA.[11] In the present series, mean albumin level in LDLT recipients was not significantly different from DDLT recipients. The observed differences in V_{SS} may be related to the decreased plasma protein binding of MPA in DDLT compared to LDLT, due to higher bilirubin concentrations.

These observations are consistent with the expectation that a reduced-size liver will clear the drug less readily. The observations are also consistent with the report in the rat study, indicating that the loss of the ability to clear the drug is lower than what is expected based on the reduced liver mass and the decreased activity of glucuronide-conjugating enzymes during the hepatic regeneration process.

During the IV infusion of MMF, glucuronidation of MPA to MPAG in LDLT (smaller size of the liver) is somewhat inefficient compared with DDLT (larger hepatic mass). This results in higher plasma concentration of MPA during, and several hours after completion of MMF infusion in LDLT patients (Figure 2). The MPAG concentration was higher in DDLT recipients compared with LDLT recipients at all the time points examined. MPAG clearance is dependant on renal function. Higher MPAG concentrations have been reported in patients with renal dysfunction.[35] Given that DDLT patients had a decreased renal function compared with LDLT patients, the higher concentration and the lower clearance of MPAG may also be due to the impaired elimination of MPAG in DDLT compared with LDLT patients.

Given that the oral bioavailability is low during the early post–liver transplant (LTx) period, it may be prudent to use IV MMF in these patients during the first few days after transplantation.[34] The benefit of this regime on the reduced rate of rejection has been reported previously from our center.[36] Independent of the mechanism involved, LDLT patients will require lower doses of MMF (approximately 30% lower dose) compared with deceased donor livers to achieve similar therapeutic exposure to MPA during the early postoperative period. In addition, a better exposure of MPA in LDLT with the currently used dosing regimen of MMF may allow a reduction in tacrolimus dose or a delay in the introduction of tacrolimus to prevent the calcineurin-related nephrotoxicity and neurotoxicity. It may also allow a reduction in the induction dose of steroid bolus. Further studies with immunomodulation markers may be helpful to optimize overall immunosuppression.

CONCLUSION

After a fixed intravenous dose of MMF, a significantly higher exposure of MPA is observed compared with DDLT. To achieve comparable AUC in LDLT patients and DDLT patients, a mean reduction in dose of MMF by approximately 30% may be prudent. On the other hand, a higher exposure of the current dosing regimen in LDLT patients may facilitate the use of a lower dose/concentration range of calcineurin inhibitors or a delay in the introduction of calcineurin inhibitors to preserve renal function. This reasoning may also facilitate use of a reduced dose of steroids for induction in these patients.

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REFERENCES

1. Alessiani M, Kusne S, Martin M, et al. Infections in adult liver transplant patients under FK 506 immunosuppression. *Transplant Proc*. 1991;23(pt 2):1501.

2. Jain A, Khanna A, Molmenti EP, Rishi N, Fung JJ. Immunosuppressive therapy. *Surg Clin North Am*. 1999;79:59-76.

3. Sollinger HW, Deierhoi MH, Belzer FO, Diethelm AG, Kauffman RS. RS-61443: a phase I clinical trial and pilot rescue study. *Transplantation*. 1992;53:428-432.

4. Allison AC, Almquist SJ, Muller CD, Eugui EM. In vitro immunosuppressive effects of mycophenolic acid and an ester pro-drug, RS-61443. *Transplant Proc*. 1991;23(suppl 2):10-14.

5. Eckhoff DE, McGuire BM, Frenette LR, Contreras JL, Hudson SL, Bynon JS. Tacrolimus (FK506) and mycophenolate mofetil combination therapy versus tacrolimus in adult liver transplantation. *Transplantation*. 1998;65:180-187.

6. Fisher RA, Stone JJ, Wolfe LG, et al. Four-year follow-up of a prospective randomized trial of mycophenolate mofetil with cyclosporine microemulsion or tacrolimus following liver transplantation. *Clin Transplant*. 2004;18:463-472.

7. Jain A, Kashyap R, Dodson F, et al. A prospective randomized trial of tacrolimus and prednisone versus tacrolimus, prednisone and mycophenolate mofetil in primary adult liver transplantation: a single center report. *Transplantation*. 2001;72:1091.

8. Jain A, Vekatramanan R, Eghtesad B, et al. Long-term outcome of adding mycophenolate mofetil to tacrolimus for nephrotoxicity following liver transplantation. *Transplantation*. 2005;80: 859-864.

9. Klupp J, Bechstein WO, Platz KP, et al. Mycophenolate mofetil added to immunosuppression after liver transplantation: first results. *Transplant Int*. 1997;10:223.

10. Klupp J, Glanemann M, Bechstein WO, et al. Mycophenolate mofetil in combination with tacrolimus versus Neoral after liver transplantation. *Transplant Proc*. 1999;31:1113-114.

11. Pisupati J, Jain A, Burckart G, et al. Intraindividual and interindividual variations in the pharmacokinetics of mycophenolic acid in liver transplant patients. *J Clin Pharmacol*. 2005; 45:34.

12. Armstrong VW, Tenderich G, Shipkova M, et al. Pharmacokinetics and bioavailability of mycophenolic acid after intravenous administration and oral administration of mycophenolate mofetil to heart transplant recipients. *Ther Drug Monit*. 2005;27:315.

13. Bullingham R, Monroe S, Nicholls A, Hale M. Pharmacokinetics and bioavailability of mycophenolate mofetil in healthy subjects after single-dose oral and intravenous administration. *J Clin Pharmacol*. 1996;36:315.

14. Ensom MH, Partovi N, Decarie D, Ignaszewski AP, Fradet GJ, Levy RD. Mycophenolate pharmacokinetics in early period following lung or heart transplantation. *Ann Pharmacother*. 2003;37:1761-1767.

15. Brusa P, Ceruti M, Casullo R, et al. Pharmacokinetic monitoring of mycophenolate mofetil in kidney transplanted patients. *Farmaco*. 2000;55:270.

16. Cattaneo D, Gaspari F, Ferrari S, et al. Pharmacokinetics help optimizing mycophenolate mofetil dosing in kidney transplant patients. *Clin Transplant*. 2001;15:402-409.

17. Gonzalez-Roncero FM, Gentil MA, Brunet M, et al. Pharmacokinetics of mycophenolate mofetil in kidney transplant patients with renal insufficiency. *Transplant Proc*. 2005;37:3749-3751.

18. Johnson AG, Rigby RJ, Taylor PJ, et al. The kinetics of mycophenolic acid and its glucuronide metabolite in adult kidney transplant recipients. *Clin Pharmacol Ther*. 1999;66:492.

19. Johnson HJ, Swan SK, Heim-Duthoy KL, Nicholls AJ, Tsina I, Tarnowski T. The pharmacokinetics of a single oral dose of mycophenolate mofetil in patients with varying degrees of renal function. *Clin Pharmacol Ther*. 1998;63:512-518.

20. Shaw LM, Korecka M, Venkataramanan R, Goldberg L, Bloom R, Brayman KL. Mycophenolic acid pharmacodynamics and pharmacokinetics provide a basis for rational monitoring strategies. *Am J Transplant*. 2003;3:534-542.

21. Shaw LM, Mick R, Nowak I, Korecka M, Brayman KL. Pharmacokinetics of mycophenolic acid in renal transplant patients with delayed graft function. *J Clin Pharmacol*. 1998; 38:268.

22. Settmacher U, Theruvath T, Pascher A, Neuhaus P. Living-donor liver transplantation: European experiences. *Nephrol Dial Transplant*. 2004;19(suppl 4):iv16-21.

23. Testa G, Malago M, Broelsch CE. Living-donor liver transplantation in adults. *Langenbecks Arch Surg*. 1999;384:536-543.

24. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med*. 2002;346:1074-1082.

25. Tian H, Ou J, Strom SC, Venkataramanan R. Activity and expression of various isoforms of uridine diphosphate glucuronosyltransferase are differentially regulated during hepatic regeneration in rats. *Pharm Res*. 2005;22:2007-2015.

26. Charco R, Rimola A, Garcia-Valdecasas JC, et al. Steroids and living liver donation increase tacrolimus blood levels in living donor liver transplantation. *Transplant Proc*. 2005;37:3930-3931.

27. Troisi R, Militerno G, Hoste E, et al. Are reduced tacrolimus dosages needed in the early postoperative period following living donor liver transplantation in adults? *Transplant Proc*. 2002; 34:1531.

28. Shipkova M, Niedmann PD, Armstrong VW, et al. Simultaneous determination of mycophenolic acid and its glucuronide in human plasma using a simple high-performance liquid chromatography procedure. *Clin Chem*. 1998;44:1481-1488.

29. Fukudo M, Yano I, Masuda S, et al. Pharmacodynamic analysis of tacrolimus and cyclosporine in living-donor liver transplant patients. *Clin Pharmacol Ther*. 2005;78:168-181.

30. Fukudo M, Yano I, Masuda S, et al. Cyclosporine exposure and calcineurin phosphatase activity in living-donor liver transplant patients: twice daily vs. once daily dosing. *Liver Transplant*. 2006;12:292-300.

31. Takizawa D, Hiraoka H, Nakamura K, Yamamoto K, Horiuchi R. Propofol concentrations during the anhepatic phase of living-related donor liver transplantation. *Clin Pharmacol Ther*. 2004;76:648-649.

32. Takizawa D, Sato E, Hiraoka H, et al. Changes in apparent systemic clearance of propofol during transplantation of living related donor liver. *Br J Anaesth*. 2005;95:643-647.

33. Tian H, Ou J, Strom SC, Venkataramanan R. Pharmacokinetics of tacrolimus and mycophenolic acid are altered, but recover at different times during hepatic regeneration in rats. *Drug Metab Dispos*. 2005;33:329.

34. Jain A, Venkataramanan R, Kwong T, et al. Pharmacokinetics of mycophenolic acid in liver transplant patients after intravenous and oral administration of mycophenolate mofetil. *Liver Transplant*. 2007;13:791.

35. Jain A, Venkataramanan R, Hamad IS, et al. Pharmacokinetics of mycophenolic acid after mycophenolate mofetil administration in liver transplant patients treated with tacrolimus. *J Clin Pharmacol*. 2001;41:268.

36. Jain A, Mohanka R, Orloff M, et al. Intravenous mycophenolate mofetil with low-dose oral tacrolimus and steroid induction for live donor liver transplantation. *Exp Clin Transplant*. 2005;3:361.