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Intravenous, Oral Pharmacokinetics, and Oral Dosing of FK 506 in Small Bowel Transplant Patients

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FK 506 is a new macrolide with potent immunosuppressive activity. Use of this drug is associated with reduced incidence of rejection following liver, kidney, and heart transplantation.[1-4] Recently, FK 506 has been shown to be effective in small bowel transplantation.[5] It is known that FK 506 absorption is not influenced by the presence or absence of bile.[6-8] The aims of this study are to: (1) determine pharmacokinetics of FK 506 after intravenous (IV) dose in small bowel transplant patients; and (2) to determine the absorption of FK 506 following oral administration.

MATERIALS AND METHODS

Five patients (3 male and 2 female; ages 31, 2, 27, 4, and 3 years) underwent small bowel transplantation between May 1990 and March 1991. The first patient received only a small bowel transplantation, while the other four patients had a liver and small bowel transplanted simultaneously. FK 506 was administered at a dose of 0.1 to 0.15 mg/kg per day as a 4-hour IV infusion or as a continuous infusion in all the patients. Subsequent dose adjustments were made depending on the clinical situation of the patient, the plasma FK 506 concentration, renal function, liver function, and rejection episodes. Oral FK 506 therapy was initiated when patients could tolerate oral intake. Pharmacokinetic studies were carried out over a dosing interval of 12 or 24 hours. Multiple blood samples were obtained over the dosing intervals, and plasma was separated at 37°C and analyzed for FK 506 concentrations by ELISA.[9,10]

Table 1. Pharmacokinetics of FK 506 in Small Bowel Transplant Patients

Patient #	Study #	Clearance (nL/min per kilogram)	Half-Life (hours)	Absorption %	Peak Time (Hours)
1	1	12.7	11.5	25	4
	2	13.2	6.9	10*	2
	3	—		29	3
2	1	25.2			
	2	21.4		31	5
3	1	21		5*	0.5
	2	17		51	2
	3	21		17	2
4	1	27		89	3
	2	28.3		93	4
5	1	53		—	—
	2	25		—	—
	3	29		16	2

*Proximal stoma was open at this time.

Table 2. Mean Oral FK 506 Dosage Requirements (mg/kg per day) and Mean FK 506 Trough Plasma Concentration (mg/mL)

Patient	FK 506	2 Months	4 Months	6 Months	8 Months	12 Months
Children	Dosage	0.087	0.22	0.3	0.15	0.08*
	Level	0.3	0.9	0.4	0.9	0.4*
Adults	Dosage	0.32*	0.28	0.18	0.14	0.15
	Level	2.3*	2.2	2.0	1.4	0.6

*n = 1 Patient.

RESULTS

As shown in Table 1, the plasma clearance of the FK 506 ranged from 12.7 to 53 mL/min per kilogram. The oral absorption of FK 506 was low (5% to 10%) when the proximal stoma was open in two patients. The oral bioavailability ranged from 16% to 93% (mean 43%) when the stoma was closed. The time to peak plasma concentrations after oral dose was 30 minutes to 5 hours (mean 2.8 hours). The oral maintenance dose (mg/kg per day) of FK 506 in adults (n = 2) and children (n = 3) at 2, 4, 6, 8, and 12 months posttransplant and the corresponding trough concentration of FK 506 in plasma are shown in Table 2. The dose of FK 506 and the plasma concentrations achieved in small bowel transplant patients are comparable to those observed in pediatric and adult liver transplant patients.[11]

CONCLUSIONS

The pharmacokinetic parameters of FK 506 in small bowel transplant patients are similar to our observations in other organ transplant patients. FK 506 is well absorbed from transplanted small bowel. FK 506 dosing regimen similar to that used in liver transplant patients can be used effectively in small bowel transplant patients.

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