Published in final edited form as:
Transplant Proc. 1994 June ; 26(3): 1609–1610.

FK 506 in Small Bowel Transplant Recipients: Pharmacokinetics and Dosing

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FK 506 is currently used as the primary immunosuppressive drug in several small bowel transplant (SBT) recipients.[1,2] The pharmacokinetics of FK 506 has been previously reported in orthotopic liver transplant (OLT) patients.[3] The kinetics and dosage of FK 506 have been compared to that of cyclosporine (CyA)[4] and differences in the dosage requirements of FK 506 have been reported in adults and children.[5] We have previously reported the IV and oral kinetics of FK 506 in five SBT recipients.[6] The aim of the present study is to further evaluate the kinetic parameters and dosage of FK 506 in pediatric and adult SBT recipients in comparison with OLT recipients.

MATERIALS AND METHODS

Between May 1990 and December 1992. 34 patients received cadaveric SBT with or without liver transplantation. Four patients who died and one patient who was retransplanted in less than 12 months were excluded from the study. The study group consisted of 16 adults (mean age 30.2 ± 8.8 years), 7 men and 9 women, and 13 children (mean age 2.9 ± 2.6 years), 5 boys and 8 girls. Oral dose and trough levels of FK 506 were compared with 20 adults and 20 pediatric OLT recipients. In addition, 21 (11 adults, 10 children) pharmacokinetic studies were carried out during one dosing interval after oral administration of FK 506. Seventeen kinetic studies were performed with IV FK 506 (10 continuous infusions. 7 4-hour infusions: 24 hour kinetic studies). Multiple blood samples were obtained and plasma was separated at 37°C and analyzed for FK 506 concentrations by enzyme-linked immunosorbent assay (ELISA).[7,8]

RESULTS

IV Kinetics

The plasma concentration vs time profile after IV and oral administration is shown in Fig 1. The mean plasma clearance of FK 506 was 21.7 ± 9.0 mL/min/kg in adults (n = 6) and 32.1 ± 12.7 mL/min/kg in children (n = 11). Its half-life was similar (13.7 hours) in seven patients (four adults and three children).

Oral Kinetics

Following an oral dose of FK 506, the mean bioavailability was 19.0 ± 8.7% in adults and 24.5 ± 19.4% in children. The mean time to peak was 2.9 ± 2.2 and 3.4 ± 2.9 hours in adults and children, respectively. The mean peak FK 506 plasma concentration achieved was 2.7 ± 2.2 ng/mL in adults and 2.6 ± 2.2 ng/mL in children. Its mean trough plasma concentration was 0.9 ± 0.6 ng/mL in adults and 1.5 ± 1.1 ng/mL in children.

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Maintenance Dose of FK 506

The mean oral maintenance dose and trough level of FK 506 at 2, 4, 6, 8, and 12 months posttransplant were higher in the SBT recipients compared with the OLT recipients. Pediatric patients appeared to require a higher dose of FK 506 in order to obtain similar plasma concentrations seen in adults (Table 1).

DISCUSSION

Kinetic parameters of FK 506 are comparable between SBT recipients and OLT recipients. Wide variations in its half-life, clearance, time to peak, peak levels, and bioavailability remain a common problem in both OLT and SBT patients. Monitoring of FK 506 concentration, therefore, is very important. Despite these wide variations, however, SBT recipients absorb the drug and achieve adequate drug levels just as well as the OLT recipients. Children appear to require a higher dose of FK 506 based on a mg/kg/d basis to maintain a similar concentration in SBT just as reported for OLT recipients.[5] Because the incidence of rejection episodes in SBT recipients is much higher[9] compared with the incidence of rejection in OLT recipients reported before,[10] currently it is our practice to use a higher dose of FK 506 and maintain a higher FK 506 concentration in SBT recipients compared with OLT recipients.

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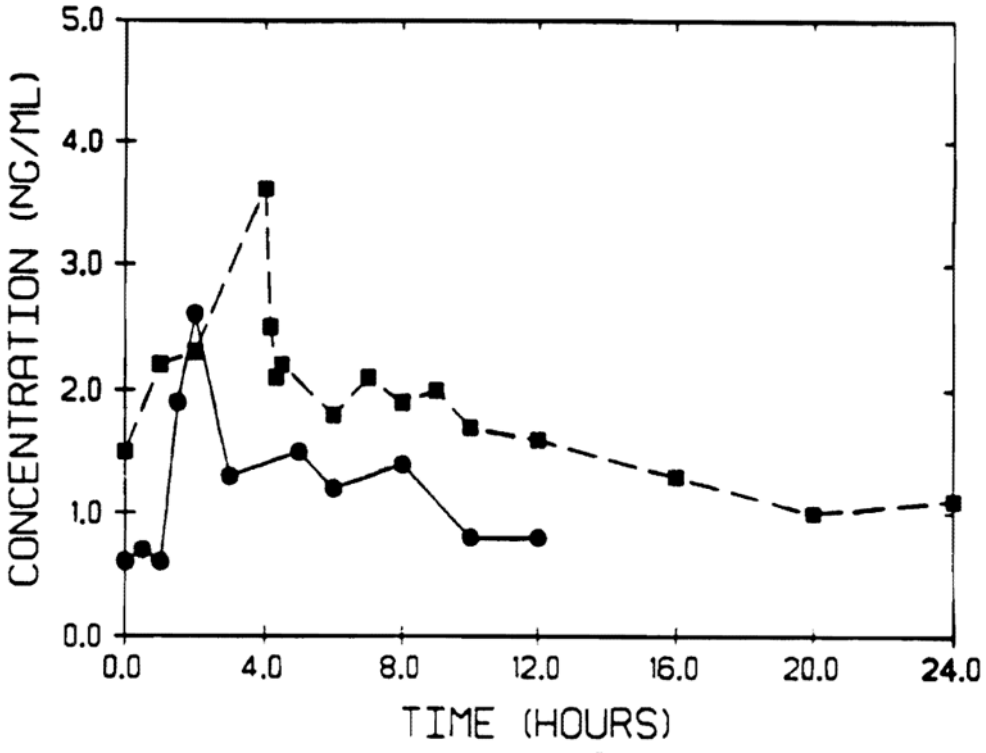

Fig 1.
Plasma concentration vs time course after IV (■) and oral administration (●) of FK 506 in an SBT patient.

Table 1

Posttransplant (mo)	Adults				Children			
	FK 506 Dose (ng/mL/d)		FK 506 Level (ng/mL)		FK 506 Dose (mg/kg/d)		FK 506 Level (ng/mL)	
	SBT	OLT	SBT	OLT	SBT	OLT	SBT	OLT
2	0.30 ± 0.15	0.20 ± 0.08	1.5	0.7	0.46 ± 0.45	0.42 ± 0.19	0.9	0.7
4	0.22 ± 0.14	0.17 ± 0.08	1.1	0.6	0.50 ± 0.50	0.32 ± 0.13	0.9	0.8
6	0.22 ± 0.14	0.13 ± 0.08	1.1	0.6	0.48 ± 0.30	0.27 ± 0.15	0.9	0.6
8	0.20 ± 0.14	0.13 ± 0.08	1.2	0.7	0.50 ± 0.30	0.25 ± 0.13	0.8	0.5
12	0.30 ± 0.32	0.14 ± 0.09	0.9	0.6	0.39 ± 0.19	0.19 ± 0.15	0.8	0.5

Note. Mean ± SD Shown for FK 506 doses. Medians shown for FK 506 levels.