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Effect of Hepatic Dysfunction and T Tube Clamping on FK 506 Pharmacokinetics and Trough Concentrations

A.B. Jain, **R. Venkataramanan**, **E. Cadoff**, **J.J. Fung**, **S. Todo**, **A. Krajack**, and **T.E. Starzl**
Departments of Surgery and The School of Pharmacy, University Health Center of Pittsburgh, University of Pittsburgh; and the Veterans Administration Medical Center, Pittsburgh, PA

In initial clinical trials of organ transplantation, FK 506 has shown remarkable immunosuppressive activity. 1 The drug is very lipophilic, metabolized in the liver, and predominantly eliminated through the bile. 2 Hepatic dysfunction was expected to alter the pharmacokinetics of FK 506. Hepatic dysfunction is also known to alter the absorption of lipid soluble drugs. [3] This is related to the lack of sufficient bile for solubilization of the drug in the gastrointestinal tract. Orthotopic liver transplantation (OLT) commonly reqyires temporary external drainage of bile via T tube. Clamping and unclamping of the T tube allowing bile to be delivered to the gastrointestinal tract or drained externally, respectively, could affect the absorption and bioavailability of lipid soluble FK 506, as it is known to do with CyA.

The objectives of this study were to examine the effect of hepatic dysfunction on the pharmacokinetics of FK 506 following intravenous and oral doses, to study the effect of liver dysfunction on the daily trough concentration of the drugs, and to define the effect of T tube clamping and unclamping following OLT on the absorption and bioavailability of the drug.

MATERIALS AND METHODS

Intravenous pharmacokinetic studies were done in patients with or without hepatic dysfunction. The patients received 0.15 mg/kg of FK 506 as an infusion over 1 to 2 hours. Blood samples were collected for plasma FK 506 concentration measurements at 0, ½, 1, 1½, 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours after starting the infusion. Blood samples were also collected for daily trough FK 506 measurements just prior to the daily morning dose. Pharmacokinetic studies were also done when the patients received their first oral dose of FK 506 (0.15 g kg). Multiple blood samples were obtained over the dosing interval of 12 hours. In one patient, the intravenous pharmacokinetics study was repeated at 1- and 3- month intervals, by which time there had been improvement in hepatic function. Various pharmacokinetic parameters and the trough FK 506 concentrations were compared between patients with normal and abnormal liver function.

The effect of T tube clamping on the oral absorption of FK 506 was studied in five OLT patients with good liver function who had a duct to duct biliary reconstruction with a T tube stent. Multiple blood samples were withdrawn at various time periods after oral administration of FK 506 (0.15 mg. kg) before and after clamping the T tube. The amount of bile drainage was recorded, and the hepatic function was monitored.

All blood samples were centrifuged at 37°C after incubation at 37°C for 1 hour, and the plasma was analyzed for FK 506 concentrations by enzyme-linked radioimmunoassay, as described

Address reprint requests to T.E. Starzl, MD, PhD, Department of Surgery, 3601 Fifth Avenue. Falk Clinic, Pittsburgh, PA 15213.

by Tamura et al4 and modified by Cadoff et al. [5] Various pharmacokinetic parameters (noncompartmental analysis) were calculated according to standard techniques. [6]

RESULTS

Hepatic Function

Intravenous Pharmacokinetics in All Cases—Patients with normal serum bilirubin tended to have low 24-hour trough levels after the first intravenous bolus of 0.15 mg/kg FK 506. In contrast, jaundiced patients had high trough levels (Fig 1).

Intravenous Pharmacokinetics With Liver Dysfunction—Five of the most jaundiced patients, who also had other evidence of hepatic dysfunction, were studied separately (Tables 1 and 2). Their peak and trough FK 506 levels were higher, as shown for a single patient in Fig 2 compared with a patient with good hepatic function. In Fig 3, a change in pharmacokinetics is seen in a single patient as the liver function improved over a 3-month interval. The principal change was a much lower trough level at an earlier time after the liver had recovered, although the same intravenous dose was given.

One of the five patients with hepatic dysfunction developed fulminant hepatic failure due to recurrence of hepatitis B (Fig 4). The serum bilirubin increased from 2.2 on day 1 to 25.7 mg/dl on day 11. The daily trough plasma FK 506 concentration increased from 3.4 to 8.2 ng/ml in 5 days. FK 506 was discontinued after the morning dose on day 5. Even 72 hours after discontinuation of the drug, trough plasma concentrations were still 3 ng/ml.

The mean half-life of FK 506 was 38.5 hours (22.4 to 61.5 hours), and the mean clearance was 39.8 (12.9 to 70) L/h in the five patients with abnormal liver function. The normal half-life is less than 10 hours and the normal clearance is about 120 L/h. [2]

Oral Kinetics in the Five Patients With Liver Dysfunction—The serum bilirubin on the day of oral study ranged from 8.1 to 17.6 mg/dl (Table 2). The predose FK 506 level ranged from 2.4 to 12.4 ng/ml. The time to reach peak plasma concentrations ranged from 0.5 to 2 hours. Two patients failed to show any peak. The mean bioavailability calculated was 36% (21 to 51%). Thus, the bioavailability was increased because of the greatly reduced intrinsic clearance. [2]

Effect of T Tube Clamping and Unclamping

In the five patients, bile drainage was from 210 to 500 ml/d prior to clamping the T tube (Tables 3 and 4). There was no significant increase in the mean peak FK 506 concentration (1.2 to 1.5 ng/ml) or the mean trough FK 506 concentrations (0.5 to 0.7 ng/ml) in the patients before and after T tube clamping (Table 3). Three patients showed a small increase in the dose-normalized area under the plasma concentration time curve (AUC), whereas in two patients there was a reduction in the AUC following clamping of the T tube (Table 4). The AUC is the index of bioavailability. Overall, there was no significant change in the AUC values.

DISCUSSION

The pathway of hepatic metabolism for FK 506 is not known precisely. The degree of jaundice (serum bilirubin concentration) is one of the most sensitive parameters reflecting hepatic damage, although it does not represent the overall function of the liver. Our results indicate how profoundly hepatic dysfunction affects the rate of metabolism and elimination of FK 506.

The increased half-life and the lower clearance of FK 506 in patients with hepatic dysfunction is striking. The mean half-life of the drug was many times higher and the clearance of the drug was about one third or less of normal, depending on the severity of the liver dysfunction.

The practical consequence is that dose adjustment must be made in patients when there are serious hepatic functional abnormalities in order to maintain the appropriate plasma concentrations. These adjustments are needed with oral as well as with the intravenous methods of administration. FK 506 is a high-clearance drug, and any change in the intrinsic clearance of the drug in the presence of liver dysfunction is expected to increase the bioavailability after oral administration. Additional studies should be done to characterize the changes in first-pass effect in patients with hepatic dysfunction.

The T tube studies were also of practical importance. In patients with a T tube, a considerable amount of bile is diverted from the gastrointestinal tract, and this variable factor greatly influences the absorption of CyA. [7] The lack of any significant change in the trough, peak, and bioavailability of FK 506 in the presence or absence of biliary diversion is an important management advantage.

CONCLUSION

Following intravenous FK 506 in the presence of moderate-to-severe hepatic dysfunction (serum bilirubin > 2 mg/dl). the metabolism of the drug was affected. The half-life of the drug after the distribution phase was prolonged, and the clearance was reduced. The daily trough concentrations were increased. Following oral administration of the drug, the bioavailability also is increased. Clamping of the T tube does not alter the absorption of FK 506.

Acknowledgments

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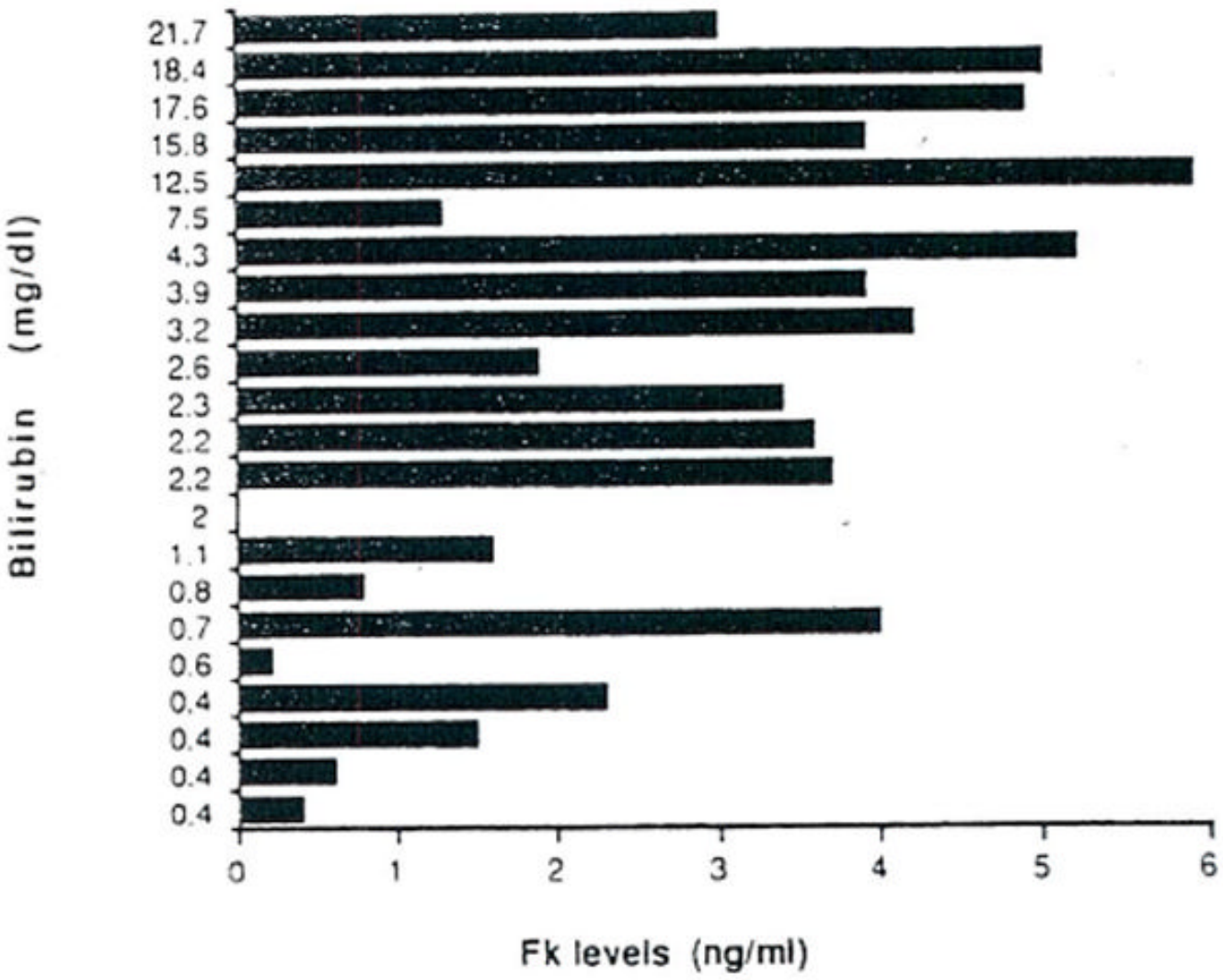

Fig 1.

Twenty-four hour trough plasma concentrations of FK 506 in relation to serum bilirubin following the first intravenous dose. Trough values tended to be higher when serum bilirubin was > 2 mg/dl.

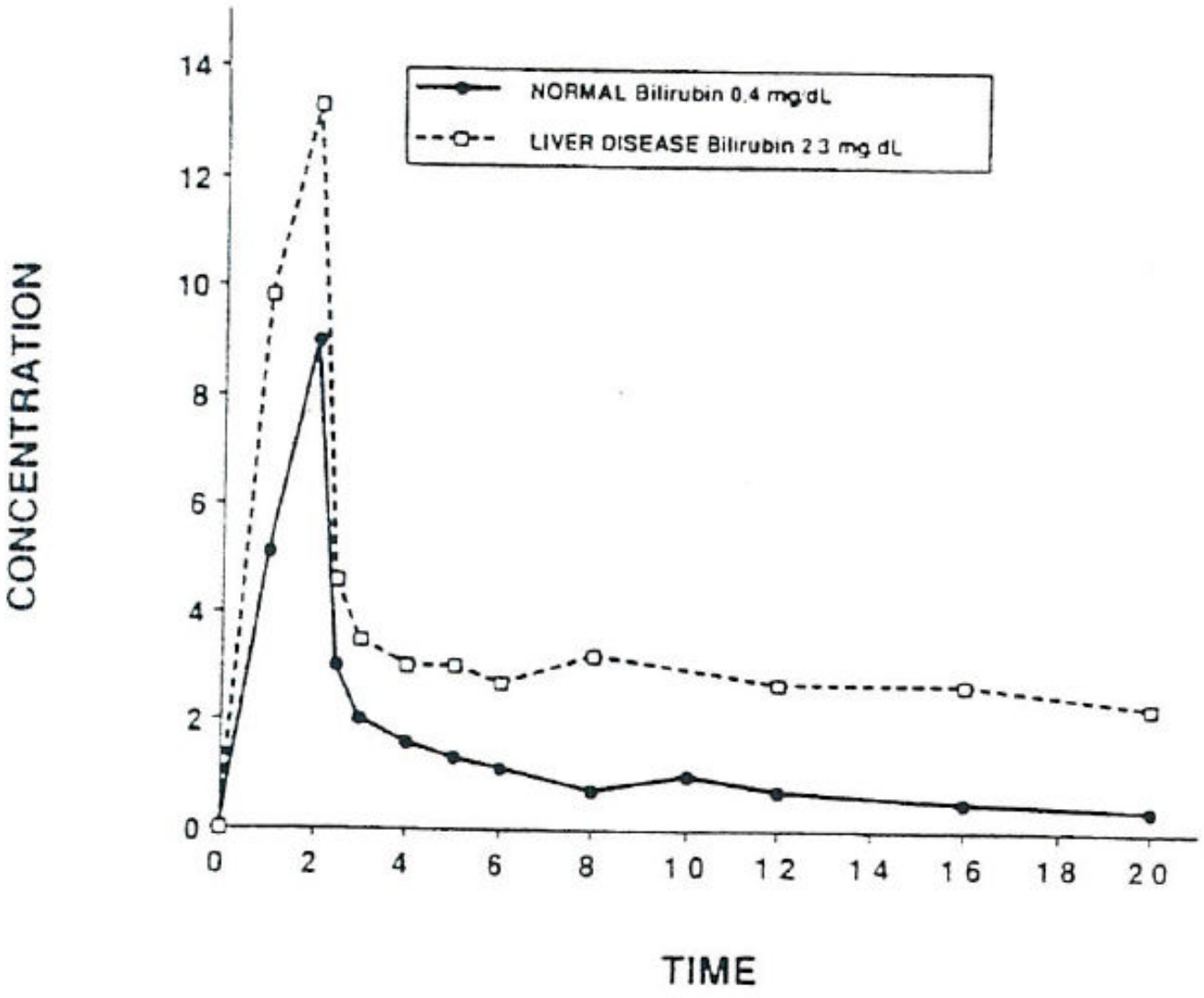

Fig 2.

Typical pharmacokinetic profile following intravenous FK 506 administration in two patients with bilirubin 0.4 and 2.3 mg/dl. A slower fall in plasma concentration is noted after the distribution phase in the jaundiced patient.

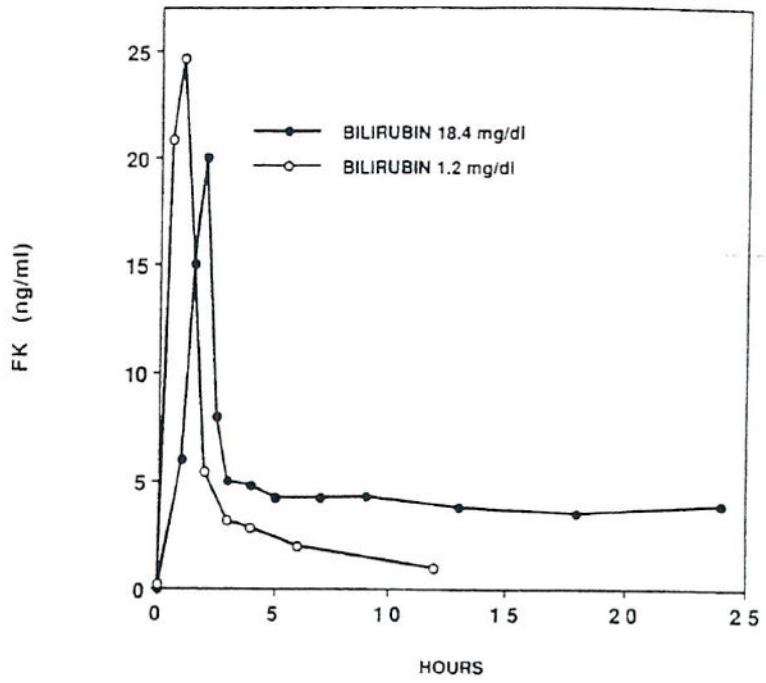

Fig 3.

Pharmacokinetic profile of FK 506 after intravenous dosing on two separate occasions in the same patient. A rapid fall was noticed after the distribution phase as the liver function improved.

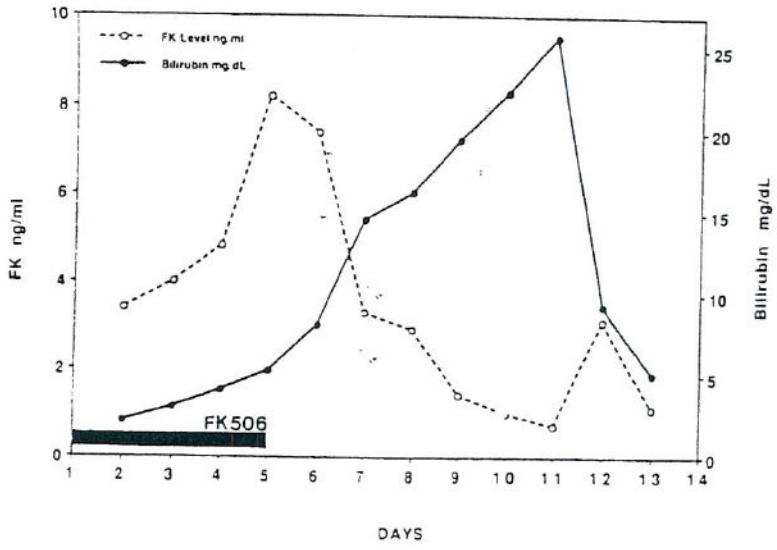

Fig 4.

Rise in daily trough levels of FK 506 as the hepatic function deteriorated. Three days after stopping FK 506, there was still a significant drug level in the blood plasma.

Table 1

Pharmacokinetics of FK 506 Administered Intravenously in Five Patients

Patient	Bilirubin (mg/dl)	Half-Life (h)	Clearance (L/h)
J.G.	17.6	22.4	70.2
A.N.	2.3	29.9	49.3
H.W.	12.5	40.1	35.9
D.S.	18.4	38.8	30.7
H.M.	21.7	61.5	12.9
Mean		38.5	39.8

Table 2

Pharmacokinetics of FK 506 Administered Orally

Bilirubin (mg/dl)	Trough (ng/ml)	C Max* (ng/ml)	Bioavailability (%)
8.1	7.4	8.0	47
8.5	7.1	8.7	56
13.5	4.0	4.0	—
17.3	12.4	14.6	21
17.6	2.4	2.4	21
Mean	7.5		36

* C Max. maximum plasma concentration.

Table 3

Effect of T Tube Clamping on FK 506 Absorption

	Peak(ng/ml)		Trough (ng/ml)	
Bile Volume	**Open**	**Closed**	**Open**	**Closed**
475	0.4	1.3	0.4	0.6
500	0.8	0.6	0.5	0.3
220	1.8	2.0	0.8	1.0
490	0.5	0.7	0.2	0.4
210	2.5	2.8	0.7	1.1
Mean	1.2	1.5	0.5	0.7

Table 4

AUC* With T Tube Open and Closed

	T Tube	
Subject	**Open**	**Closed**
B.D.	0.34	0.8
R.S.	0.65	0.63
S.H.	0.96	0.76
H.T.	0.16	0.39
J.S.	2.1	2.9
Mean	0.84	1.1

*Normalized to 1 mg.