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Pharmacokinetics of FK 506 in Transplant Patients

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FK 506 has been in clinical use at the University of Pittsburgh Medical center since March 1989. Currently, it is used as the primary immunosuppressant in liver, kidney, and heart transplant patients. Use of FK 506 has resulted in a significant reduction in the dose of steroid used and is associated with a lower incidence of hypertension in transplant patients. At the present time there are nearly 1,600 patients receiving FK 506 therapy at this institution. Various pharmacokinetic aspects and factors affecting the pharmacokinetics of FK 506 in transplant patients will be discussed here.

DOSAGE FORMS OF FK 506

FK 506 is available for clinical use as an IV formulation. Since the aqueous solubility of FK 506 is less than 100 ng/mL, the IV formulation contains a nonionic surfactant to solubilize FK 506 in aqueous medium. The IV formulation must be diluted with 5% dextrose or normal saline and administered as an infusion to patients. FK 506 in 5% dextrose for injection is most stable and completely available from poly olefin bags or glass containers.[1] FK 506 solution in normal saline is also completely stable and available from poly olefin bags or plastic syringes.

Initially, FK 506 was administered at a dose of 0.15 mg/kg/d, as an IV infusion over 2 to 4 hours, twice a day. To minimize the potential side effects related to high peak concentrations of FK 506 at the end of a 2- or 4-hour infusion, it is administered as a continuous infusion over 24 hours at the present time. The current practice is to administer a dose of 0.1 mg/kg/d as a continuous infusion over 24 hours, until the patient is able to tolerate oral intake. Patients normally receive an oral dose of 0.3 mg/kg (as a solid dispersion of FK 506 in hard gelatin capsule) and further dosing adjustments are made based on the clinical status of the patient, the functional status of the liver and kidney, and the trough plasma FK 506 concentrations.

ANALYTICAL METHODS

The therapeutic plasma concentration of FK 506 appears to be approximately 0.5 to 2 ng/mL. At such low concentrations, FK 506 cannot be measured by high pressure liquid chromatography (HPLC) with ultraviolet (UV) detection. Attempts to derivatize FK 506 to increase the detection limits have not been very successful. FK 506 blood and plasma concentrations are currently measured by enzyme-linked immunoassay (ELISA),[2] which involves minor modifications of the assay method published by Tamura et al.3 While the ELISA assay is specific enough not to cross-react with several other drugs coadministered to transplant patients, it appears to cross-react with some of the metabolites of FK 506. The relative concentrations of these metabolites in blood or plasma and the extent of cross-reactivity of these metabolites with FK 506 monoclonal antibody have not been completely characterized.

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PHARMACOKINETIC STUDIES

Pharmacokinetic studies have been carried out after short IV infusion (2 to 4 hours), continuous IV infusion, or oral administration of FK 506. Multiple blood samples were collected over a 12- or 24-hour dosing interval. Blood samples were incubated at 37°C for 30 minutes to 1 hour and centrifuged at 37°C. Plasma samples were immediately frozen at −70°C, until analyzed for FK 506 by ELISA. In certain studies whole blood samples kept frozen at −70°C were also assayed by a modified procedure.[2] In three patients receiving twice a week FK 506 dosing, blood samples were collected for up to 72 hours after IV infusion of FK 506.

Following IV infusion, peak plasma concentrations are reached at the end of infusion. The drug concentration declines rapidly immediately after the end of infusion indicating rapid distribution of the drug outside the plasma compartment. Once distribution equilibrium is reached, FK 506 concentrations decline at a slower rate corresponding to the disposition of the drug (Fig 1).[4–6] The behavior of the drug can be adequately described by a two compartment model in most of the patients. The half life of FK 506 based on plasma concentrations ranges from 3.5 to 40.5 hours, while the clearance ranges from 7 to 103 mL/min/kg (Table 1). In three patients who were studied for 72 hours, the half lives were 22, 34, and 36 hours. The volume of distribution at steady state ranges from 5.6 to 65 L/kg. These observations indicate a large interindividual variability in the pharmacokinetics of FK 506 in transplant patients.

Following oral administration, the drug is absorbed very rapidly in certain patients with peak plasma concentrations being reached within 0.5 hours after oral dose, while in other patients the drug appears to be absorbed continuously over a prolonged time period yielding essentially a flat oral absorption profile (Fig 2).[5] While the reasons for such an observation are not completely understood, poor dissolution of FK 506 in gastric fluids due to low aqueous solubility and alterations in gastric motility in transplant patients are likely to be partially responsible for this observation. The oral bioavailability of FK 506 ranges from 5% to 67%, with a mean value of approximately 27%. FK 506 appears to be absorbed well from the transplanted small bowel. Small bowel transplant patients require FK 506 oral maintenance doses similar to that used in liver transplant patients in order to maintain adequate immunosuppression. Adequate absorption of FK 506 by the transplanted gut has made small bowel transplantation more feasible with the use of oral FK 506 treatment.

In blood, FK 506 is primarily associated with red blood cells (RBCs). Intracellular contents appear to be responsible for the extensive binding of FK 506 to RBCs (unpublished observations). It is possible that RBCs may contain large amounts of FK binding protein (FKBP). The blood to plasma ratio of FK 506 in normal subjects at a total FK 506 concentration of 10 ng/mL is 12. The trough blood to plasma concentration ratio of FK 506 in transplant patients ranges from 3.6 to 39 with a mean of 10. In plasma, FK 506 is primarily associated with α1 acid glycoprotein (unpublished observations). This is in contrast to cyclosporine (CyA), which is primarily associated with lipoproteins in plasma.7 Outside the vascular system. FK 506 appears to be distributed in the heart, lung, spleen, kidney, and pancreas.4 No FK 506 can be detected in the cerebrospinal fluid of patients with neurotoxicity, suspected to be related to FK 506 therapy. The concentration of FK 506 in placental tissue is greater than that in plasma indicating the potential transfer of FK 506 to the fetus (unpublished observations).

FK 506 is primarily eliminated by metabolism.[4,6] Most of the metabolites are excreted in the bile. We have isolated several metabolites of FK 506 from bile samples obtained from rats and humans. FK 506 metabolites have also been generated by incubation of FK 506 with rat liver microsomes (unpublished observations). FK 506 appears to undergo monodemethylation, didemethylation, hydroxylation, and a combination of monodemethylation and hydroxylation. These metabolites are similar to the FK 506 metabolites isolated from human small bowel and

liver microsomes.[8] In addition, there is preliminary evidence to suggest the presence of conjugates of FK 506 and its metabolites in human bile. However, less than 5% of the dose is excreted in the bile as FK 506 or its conjugates. Less than 1% of the IV dose is excreted in the urine as unchanged FK 506. Small amounts of FK 506 conjugates are also excreted in the urine.

FACTORS AFFECTING FK 506 PLASMA CONCENTRATIONS

Several factors contribute to the observed inter and intra-individual variability in FK 506 plasma concentrations in transplant patients. These include factors that alter the absorption, distribution, and elimination of FK 506.

Studies in dogs indicate that the absorption of FK 506 is significantly increased in experimentally induced cholestasis, presumably due to decreased presystemic metabolism.[9] In addition, biliary diversion or addition of exogenous bile salts in the presence or absence of endogenous bile did not significantly alter the extent of FK 506 absorption.[9] These observations indicate that in contrast to CyA, the absorption of FK 506 is less dependent on the availability of bile. From a practical point of view, there is no need to decrease the dose of FK 506 when the t-tube is clamped in liver transplant patients.[5,10] Preliminary studies indicate that food does not alter the extent of absorption of FK 506 in liver transplant patients. In vitro studies indicate a significant loss of FK 506 from simulated gastric fluid in the presence of magnesium oxide and aluminum hydroxide gel. Until further in vivo data become available it is prudent to dose FK 506 and antacids separately.[11] The distribution of FK 506 within blood is influenced by hematocrit, FK 506 concentrations, temperature of the blood sample, and the concentration of plasma proteins. Changes in one or more of these factors may contribute to the variability in the relative distribution of FK 506 in blood from transplant patients. It is well known that hematocrit increases with time after renal transplantation and that α1 acid glycoprotein concentrations are significantly increased in transplant patients when compared with normal subjects.[12]

FK 506 is primarily eliminated by metabolism. Several factors known to alter drug metabolism also alter the elimination of FK 506. Following IV administration of 0.15 mg/kg/d, 24-hour trough plasma FK 506 concentrations are normally higher in patients with liver dysfunction when compared with patients with normal liver function.[10,13] Correspondingly, patients with liver dysfunction tend to have longer half-lives and smaller clearance values.[10] With an improvement in liver function the half-life decreases to normal values. Cold ischemia and reperfusion injury to the liver may also alter the clearance of FK 506. Impairment in the elimination of FK 506 due to ischemic damage of the liver is expected to resolve with time.

Increase in FK 506 concentrations is also seen when FK 506 is coadministered with clotrimazole, ketoconazole, erythromycin, fluconazole, diltiazam, and cimetidine in rats. Erythromycin, fluconazole, methylprednisolone, and clotrimazole-mediated increases in FK 506 concentration have also been observed in transplant patients. In patients who simultaneously receive hepatic drug metabolizing enzyme inducers or inhibitors. FK 506 should be used with caution. Another drug interaction that is of some importance is the interaction between FK 506 and cyclosporine (CyA). Combined use of these two agents results in synergistic immunosuppression[14] and increased nephrotoxicity.15 FK 506 inhibits CyA metabolism in vitro.16 However, in liver transplant patients, short-term treatment with FK 506 does not appear to alter CyA clearance.17 Studies in dogs indicate that while FK 506 does not alter CyA clearance, it may increase FK 506 oral bioavailability, presumably due to inhibition of presystemic metabolism.18 This interaction is similar to the reported interaction between CyA and erythromycin in patients.[19] Pediatric patients in general tolerate FK 506 better than adults. This may be related to the higher clearance of FK 506 from pediatric patients when compared with adult transplant patients (unpublished observations). Pediatric and adult

patients appear to absorb FK 506 similarly. On an average, pediatric patients require nearly twice the FK 506 dosage (mg/kg) given to adults in order to maintain similar therapeutic plasma concentrations.[20]

FK 506 is not dialyzable. This may be related to the extensive binding of FK 506 to blood proteins and the large volume of distribution of this drug. Dialysis will be of limited use in FK 506 overdosing.

THERAPEUTIC MONITORING

FK 506 doses of 2 to 24 mg/d are required in order to maintain therapeutic plasma trough concentrations in the range of 0.5 to 2 ng/mL in clinically stable liver and kidney transplant patients (Fig 3). This indicates that even in patients with normally functioning liver and kidney, there is wide variability in the kinetics of FK 506. In addition, it has been shown that nephrotoxicity is the principal side effect of FK 506. It is therefore essential to monitor the blood or plasma concentration of FK 506 in patients to minimize incidence of the rejection and toxicity. In adopting an analytical procedure for routine therapeutic monitoring, one should consider the specificity, sensitivity, rapid turnaround time, and the precision of the method used. While immunologic monitoring is the ideal method for optimal immunosuppression, current status of this technology does not permit routine use of this procedure. Bioassay as proposed recently is an attractive tool but its routine use is limited by the long time necessary for conducting this assay.[21] Studies are also currently underway to determine the right choice of biologic matrix (blood or plasma) that should be used for FK 506 monitoring, based on the relationship between blood or plasma concentrations and toxicity or rejection episodes.

DOSING REGIMEN DESIGN FOR FK 506

Studies in renal transplant patients indicate that at a plasma FK 506 concentration of 0.8 ng/mL or greater, more than 90% of the lymphocytes are inhibited in an in vitro test system.[22] Considering 0.8 ng/mL to be the desired steady state concentration, one can calculate the average and maximum infusion rate required based on average and maximum plasma clearance of FK 506 in transplant patients. The average and maximum infusion rate required will be 0.04 and 0.093 mg/kg/d, respectively. The maximum infusion rate derived from this formula is close to the current infusion regimen (0.1 mg/kg/d) used at our institution. Based on an oral bioavailability of 27%, the mean and maximal oral dose required should be 0.15 and 0.35 mg/kg/d, respectively. Further adjustment in dosing regimen should be made based on liver function, kidney function, use of other immunosuppressants, and other drugs known to interact with FK 506. Table 2 summarizes the dosing recommendation for FK 506 as compared with CyA.

In summary, FK 506 is similar to CyA in terms of the extent of absorption and metabolism (Table 3). However, they differ in the requirement of bile for absorption and in their distribution within blood. Liver disease also appears to alter FK 506 kinetics differently as compared with CyA. Improved understanding of the pharmacokinetics, pharmacodynamics, and various factors affecting the pharmacokinetics and pharmacodynamics of FK 506 using specific assay methods will help us to optimize therapy with this novel and potent immunosuppressant.

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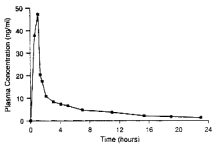

Fig 1.
Plasma concentration time curve after IV administration of 0.15 mg/kg of FK 506 to one patient.

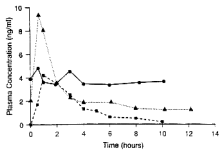

Fig 2.
Plasma concentration time curve after oral administration of 0.3 mg/kg to three different patients.

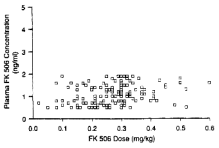

Fig 3.

Relationship between dose (mg/kg/d) and steady state plasma concentration (ng/mL) of FK 506 as measured by ELISA in clinically stable liver and kidney transplant patients.

Table 1

Pharmacokinetics of FK 506

Parameters*	
Time to peak concentrations (ng/mL)	0.5–4 h
Extent of absorption (%)	5–67 (mean 27)
Half life (h)	3.5–40.5
Total body clearance (mL/min/g)	7–103 (mean about 30)
Renal clearance (mL/min)	<1
Volume of distribution (L/kg)	5–65 L/kg

* Based on plasma concentrations analyzed by solid phase extraction and ELISA.

Table 2

Comparison of Kinetics of FK 506 and CyA

Condition	FK 506	CyA
Absorption		
Rate	Variable	Variable
Extent	5%–67%	<5–89%
Bile	Less essential	Very essential
Small bowel Transplant	Good absorption	Poor absorption
Distribution		
Blood: plasma	>12; 4–39	About 2
Depends on	Hematocrit, temperature, drug concentration, plasma protein concentration	Hematocrit, temperature, drug concentration, plasma protein concentration
Major binding protein in plasma	α1 acid glycoprotein	Lipoprotein
Metabolism		
Metabolism	>98%	>98%
Pathways	Hydroxylation, demethylation, conjugation	Hydroxylation, demethylation, conjugation
Excretion		
Parent drug	<2% in urine	<2% in urine
Metabolites	Primarily in bile	Primarily in bile
Activity		
Parent drug	Most active	Most active
Metabolites	A lot less active	Less active

Table 3

Dosing Recommendation for FK 506

Condition	FK506	CyA
Switch from IV to oral therapy	Threefold increase in dose	Threefold increase in dose
T-tube clamping	No change in dose	Decrease dose
Pediatric patients	About two times higher dose compared with adults	About two to three times higher dose compared with adults
Liver dysfunction	Decrease IV dose; decrease oral dose	Decrease IV dose; increase oral dose
Renal dysfunction	Does not affect kinetics	Does not affect kinetics
	Decrease dose to decrease levels if renal dysfunction is related to the drug	Decrease dose to decrease levels if renal dysfunction is related to the drug
Dialysis	Not removed by dialysis	Not removed by dialysis
Inhibitors of hepatic metabolism	Decrease dose	Decrease dose
Inducers of hepatic metabolism	Monitor drug level; increase dose	Monitor drug level; may need to increase dose