# Four-Hour Versus 24-Hour Intravenous Infusion of FK 506 in Liver Transplantation

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IN AN earlier study, intravenous (IV) FK 506 appeared to be less well tolerated than the oral drug for two reasons.[1] One was the selection of a starting IV dose that was too high. The other may have been the use of pulse infusion therapy (over 2 to 4 hours) with consequent high peak plasma concentrations. In patients with unsatisfactory liver graft function, these peak values were sustained for long periods.

In the present study, we compared the perioperative use of constant IV infusion of FK 506 to 4-hour pulse infusion in a total of 238 consecutive primary liver recipients. The therapeutic efficacy and adverse effects of the drug were compared.

## MATERIALS AND METHODS

### Case Material

Two hundred thirty-eight patients received primary liver grafts under FK 506 between Feb 16 and Dec 2, 1990. A starting total daily IV dose of 0.15 mg/kg FK 506 was given as a constant infusion to 151 patients. The other 87 were given a 4-hour infusion of 0.075 mg/kg every 12 hours. The age, sex, and other clinical features of the two study groups were similar (Table 1). In both groups, the IV FK 506 was started 2 to 4 hours after complete revascularization of the liver graft. Liver and kidney functions, FK 506 plasma levels, and doses and drug side effects were monitored through the 2-month study period in all survivors.

**Table 1. Characteristics of Patients with Each Infusion Method***

| | Infusion | |
|---|---|---|
| | 24-h | 4-h |
| No. of patients | 151 | 87 |
| Age (yrs, mean ± SD) | 46 ± 14 | 49 ± 13 |
| Sex | | |
| Male | 91 | 54 |
| Female | 60 | 33 |
| Liver disease | | |
| Alcoholic | 32 (21%) | 23 (26.4%) |
| Viral | 26 (17%) | 23 (26.4%) |
| Cholestatic | 24 (16%) | 13 (14.9%) |
| Malignant | 20 (13%) | 9 (10.3%) |
| Miscellaneous | 49 (33%) | 19 (22%) |
| UNOS Score | | |
| II | 4 (3%) | 0 (0%) |
| III | 55 (36%) | 26 (30%) |
| IV | 92 (61%) | 61 (70%) |
| Serum creatinine (mg %) | 1.4 ± 1.6 | 1.3 ± 1.5 |
| Positive cytotoxic cross-match | 16 (11%) | 11 (13%) |

*$P > .05$.

FK 506 plasma levels were determined with the enzyme immunoassay technique of Tamura et al.[2] Doses were promptly reduced if the preceding day's plasma levels were higher than 5 ng/mL, if the patient had evidence of rapidly deteriorating renal function, or if there was evidence of neurotoxicity and/or life-threatening infections. Upward dose adjustments usually were prompted by a clinical suspicion and/or the histopathologic diagnosis of rejection or by low plasma levels.

During IV therapy, the FK 506 plasma levels reflected a 12-hour trough when the 4-hour infusion technique was used and a steady-state concentration when continuous infusion was used. After oral therapy was begun, plasma levels usually were 12-hour trough values because dosing was twice a day in most of the patients. However, in patients with significant graft dysfunction and/or high plasma levels of FK 506, the drug was given once per day or even every other day. Here, the FK 506 levels were 24- or 48-hour troughs.

In 22 of the patients (13 with 4-hour infusion and 9 with continuous infusion), the FK 506 plasma levels were determined at 30- to 60-minute intervals to obtain pharmacokinetic curves.

Prednisone usually was started at a daily dose of 20 mg. By the end of the study period, 55% of all patients were completely weaned from steroids. Rejection episodes were treated initially in some patients with an increase in the doses of FK 506. Alternatively, daily steroid doses were increased or steroid boluses were given. In 26 patients (10.9%) with an unsatisfactory response, a 3- to 5-day course of OKT3 therapy was required.

### Statistical Analyses

The liver recipients in each group were further stratified according to graft function into two subgroups: (1) those with adequate or excellent liver function as defined by return of the bilirubin to less than 2 mg % within 10 days; and (2) patients with dysfunctional livers from the time of operation in that the bilirubin had not fallen to less than 2 mg % in this interval.

Parameters studied were function of the liver graft, kidney function, and evidence of neurotoxicity. Protocol biopsies were done in most of the patients at about day 14 postoperative. Biopsies at a later time were dictated by clinical and/or biochemical suspicions of rejection as defined by an increase in serum

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Aided by research grants from the Veterans Administration and project grant DK 29961 from the National Institutes of Health.

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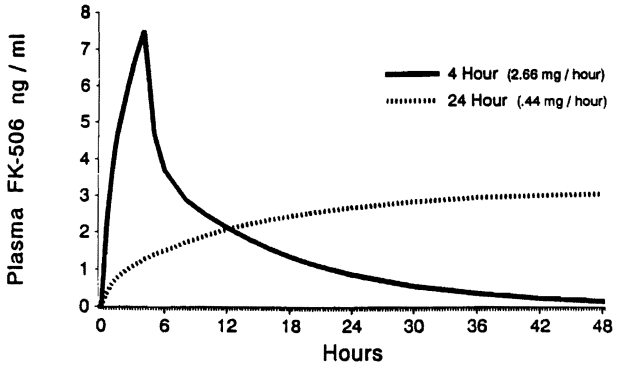


**Fig 1.** Simulation of the mean plasma concentrations of FK 506 after 4- and 24-hour infusion of the first induction dose (0.15 mg/kg) in 13 and 9 patients, respectively.

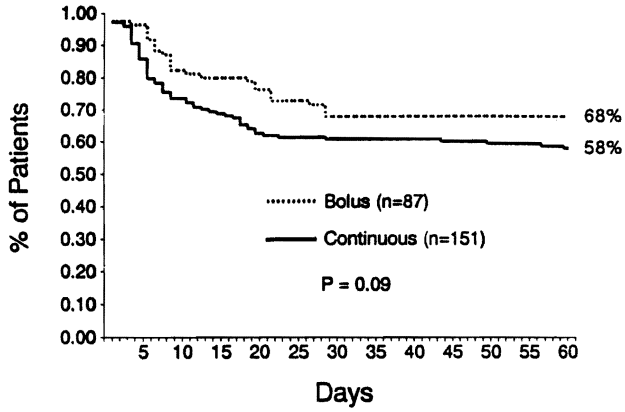


**Fig 2.** The cumulative rejection-free rate after both methods of IV administration of FK 506. There was a trend to *more* rejection using continuous infusion, but the difference was not statistically significant ($P = .09$).

bilirubin, transaminases, and the canalicular enzymes to greater than 50% of the lowest baseline level seen early postoperatively.

Patient, graft, and rejection-free survival were calculated using Kaplan–Meier survival analysis. The comparison was tested by using the log rank test. The rejection, hemodialysis, and neurotoxicity parameters were compared between both groups by using the large sample Z-test, Student's *t* test, and Wilcoxon rank sum tests.

The mean values for all of the biochemical variables and FK 506 dose and levels were calculated for the daily values and averages of the first 10 postoperative days. Changes in blood urea nitrogen (BUN) and creatinine comparing the pretransplant values to the average of the first 10 postoperative days were tested using the sign-rank test with Bonferroni's adjustment. The comparisons between two or more groups for FK 506 plasma levels, drug doses, BUN, and creatinine were done by Wilcoxon rank sum or Kruskal–Wallis chi-square approximation. Spearman correlation analysis was done for all quantitative parameters. All of the statistical analyses were performed using SAS 6.03 (SAS Institute Inc, Cary, NC 27512) and BMDP (BMDP Statistical Software, Cork, Ireland).

## RESULTS

### Pharmacokinetic Data

The mean pharmacokinetic patterns with bolus (4 hour) vs continuous infusion of 0.15 mg/kg FK 506 are shown in Fig 1. The peak concentrations following 4-hour infusion were nearly three times that achieved during continuous infusion.

### Survival

Eleven patients in each group died within the study period. The survival rate was 92.7% for patients with continuous infusion and 87.4% for those in the 4-hour infusion group. Sepsis was the leading cause of death in both groups. Graft survival was also similar in both groups, with a retransplantation rate within 60 days of 10% and 11%, respectively ($P = .8$).

### Graft Rejection

The incidence of graft rejection was similar with both methods of FK 506 IV therapy with a total rate of 43% ($n = 65$) after continuous infusion and 37% ($n = 32$) after 4-hour infusion. The cumulative rejection-free rate over 60 days in those who survived that long was similar ($P = .09$) in both groups with an incidence of 58% and 68%, respectively (Fig 2). The mean onset and frequency of the rejection episodes were also comparable in both groups (Table 2). One patient with the continuous infusion who had a strong positive direct T-lymphocyte cytotoxic crossmatch with 100% PRA required a second graft because of hyperacute rejection. There were no such examples in the bolus group.

**Table 2. Frequency and Treatment of Rejection Episodes with Both Methods of FK 506 IV Infusion***

| | No. of Patients (%) | | | Onset of First Episode | No. of Episodes | | |
|---|---|---|---|---|---|---|---|
| Infusion | Total | ≤10 d | >10 d | (Mean ± SD) | 1 | 2 | ≥3 |
| 24-h | 65 (43%) | 42 (28%) | 23 (15%) | 12 ± 12 | 33 (50%) | 14 (22%) | 18 (28%) |
| 4-h | 32 (37%) | 19 (22%) | 13 (15%) | 15 ± 18 | 14 (44%) | 12 (37%) | 6 (19%) |

*$P > .05$.

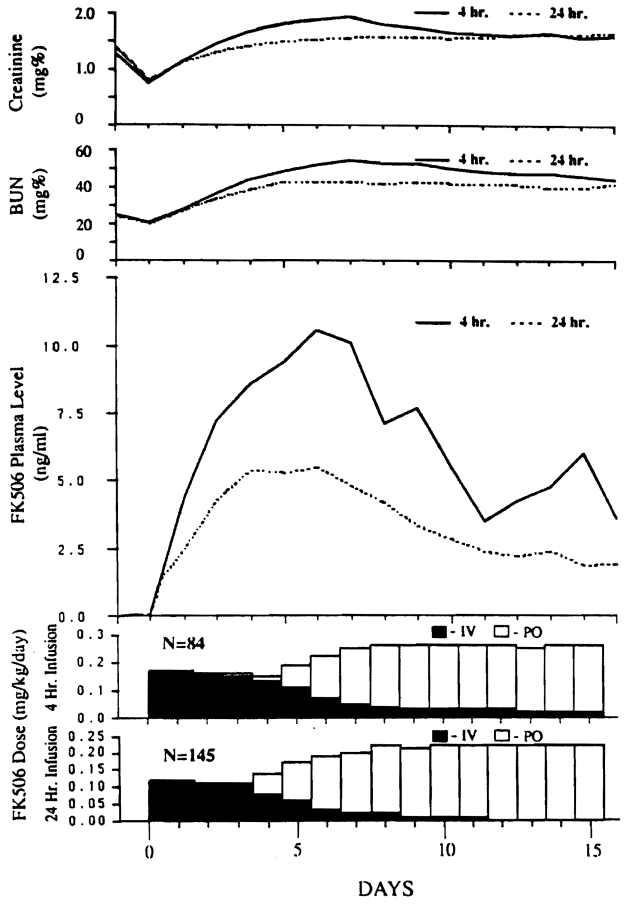


**Fig 3.** The effect of 4-hour (every 12 hours) and continuous IV infusion of FK 506 within the first 15 postoperative days on FK 506 plasma levels and renal function in liver allograft recipients.

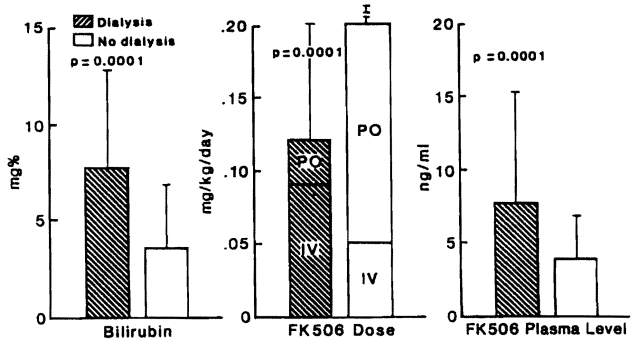


**Fig 4.** The development of posttransplant renal failure and the mean of the average of the first 10-day serum bilirubin, FK 506 dose, and drug plasma level.

### FK 506 Doses and Drug Plasma Levels

The means during the first 15 days of the daily FK 506 doses and plasma levels were plotted in Fig 3, showing the trough levels after bolus administration vs the steady-state levels in patients on continuous infusion. The mean doses as well as the FK 506 plasma levels were significantly higher ($P < .0001$) with 4-hour infusion compared to continuous therapy. The dose differences were due to more aggressive and rapid downward dose adjustments in the constant infusion group.

### Kidney Function

*Hemodialysis.* Renal failure severe enough to necessitate hemodialysis developed in the postoperative period in a total of 35 patients (14.7%). Nineteen of these patients received continuous infusion (13%) and 16 were treated with 4-hour infusion (18%). The onset of posttransplant renal failure was similar in both groups with mean values of 13 ± 10 days (24-hour) and 12 ± 10 days (4-hour). Prolonged posttransplant liver graft dysfunction was concomitant with renal failure in 89% and 75% of the morbid cases in the respective groups. Recovery of the kidney function occurred in all but one of the continuous infusion and all but three of the 4-hour infusion morbid cases who died within the study period.

The means of the average of the first 10-day values of FK 506 doses, plasma levels, and serum bilirubin for patients who required hemodialysis vs those who maintained their renal function are depicted in Fig 4. Patients with good liver function were given more FK 506, but had lower plasma FK 506 levels and less need for dialysis ($P < .0001$).

*BUN and Serum Creatinine.* Blood urea nitrogen and serum creatinine were significantly increased postoperatively with both methods of FK 506 infusion (Fig 3). The maximal rises occurred within the first 10 days after transplantation. The average values during that period were significantly ($P = .04$) higher with the 4-hour infusion compared to the continuous therapy. In all patients, a significant correlation was observed between the simultaneously measured FK 506 plasma level and serum creatinine ($r = .49$, $P = .001$).

### Neurotoxicity

Acute neurologic dysfunctions in the form of confusion, paranoid illusion, seizure, and akinetic mutism developed in a total of 14 patients: 9 after 4-hour infusion (10.3%) and 5 after continuous (3.3%) therapy. The difference was statistically significant ($P = .04$). The time of onset was similar in both groups with a mean of 12 ± 11 and 15 ± 12 days, respectively. At the time of neurotoxic symptoms, the serum bilirubin level was high with a mean value of 4 ± 4 mg % (4-hour) and 3 ± 3 mg % (24-hour). The FK 506 12-hour trough plasma levels were also high in both groups, with a mean value of 2.5 ± 2 ng/mL with the 4-hour infusion and 3.4 ± 4 ng/mL with the 24-hour infusion. Prolonged IV therapy was in effect for most patients who developed neurotoxicity.

### Effect of Graft Function

With each infusion method, patients with significant graft dysfunction (class II) had higher FK 506 plasma levels and

lower IV doses compared to those with good functioning liver grafts (class I) with $P$ values of .0001 and .009, respectively. A significant positive correlation was also noticed between serum bilirubin and FK 506 plasma level at all points during the study period ($r = .5$, $P = .001$). BUN and creatinine were significantly ($P < .04$) increased in class II compared to class I patients.

## DISCUSSION

These studies suggest that continuous vs bolus dosing of FK 506 can reduce the incidence of renal failure, which requires dialysis, and the incidence of neurologic complications. Both renal failure and neurotoxicity appear to be correlated positively with the plasma concentration of FK 506, and in turn the plasma concentration was a function of the height of the serum bilirubin. This was not surprising because the profound effect of hepatic dysfunction on the elimination of FK 506 was emphasized in earlier publications.[1,3–6]

The seeming advantage of continuous vs bolus infusion could be illusory and more the consequence of the total dose given than the rate of administration. The patients treated with continuous infusion had more aggressive dose adjustment at the first sign of drug toxicity and more quickly available results from the plasma monitoring. Consequently, their doses were cut at an earlier time with the result that the mean daily dosages were significantly less than in the bolus group. Nevertheless, that may have been an advantage to avoiding the peak FK 506 plasma concentration that occurred soon after completion of the bolus. It was of interest that therapeutic levels from a single bolus were maintained throughout the full 24-hour period.

Our recommendation, based on this experience, is that FK 506 should be given by constant infusion with very close attention to the steady-state plasma levels of the drugs. During the critical perioperative period, it is probable that the plasma FK 506 levels should be kept in the 2–3 ng/mL range, but the optimal therapeutic zone has not yet been determined. The technique presented at this meeting by McMichael et al[7] for algorithmic dose adjustment should help in more accurately defining the ideal therapeutic range.

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