Selected Topics on FK 506, With Special References to Rescue of Extrahepatic Whole Organ Grafts, Transplantation of "Forbidden Organs," Side Effects, Mechanisms, and Practical Pharmacokinetics

T.E. Starzl, K. Abu-Elmagd, A. Tzakis, J.J. Fung, K.A. Porter, and S. Todo

EXPERIMENTAL and clinical studies of FK 506 during the last 3 years have positioned this powerful drug in a very favorable light. Rather than summarizing these studies, we will comment on several issues that will not be covered in other presentations.

RESCUE OF REJECTING WHOLE ORGAN GRAFTS

FK 506 was first tested clinically and shown to be effective for rescuing failing liver grafts.[1,2] Armitage reported a follow-up about heart grafts that have been salvaged with this drug.[3,4]

Kidney rescue attempts have been limited by the cumulative toxicity of cyclosporine (CyA) and FK 506 at the time of switch.[1,5] However, such trials are starting. The kidney recipient whose course is summarized in Table 1 had developed a posttransplant nephrotic syndrome and was excreting about 10 g/d albumin 13 months after cadaveric transplantation. His serum creatinine and clearance still were adequate. After changing to FK 506 and stopping CyA, azathioprine, and steroids, the proteinuria was dramatically reduced along with normalization of serum cholesterol and albumin levels. The response was similar to that recently reported in nontransplant nephrotic patients,[6] for example, the 30-month-old child depicted in Table 2. The child's albumin excretion was almost completely shut off within 2 weeks of therapy while depressed serum albumin and elevated serum cholesterol levels were restored to normal. Here also, previous steroid treatment was stopped.

TRANSPLANTATION OF FORBIDDEN ORGANS

FK 506 will be used principally as primary therapy in transplantation; trials for livers, hearts, lungs, and kidneys[1,3,7,8] are summarized separately. Using FK 506, it may be possible to perform procedures that until now have been impractical or impossible. For example, intestinal and multivisceral allotransplantation in rats can be accomplished easily with rather small doses of FK 506 for only 2 postoperative weeks, and with permanent survival.[9] Clinically, a patient who lost his small bowel and colon after a gunshot wound to the superior mesenteric artery received a complete small bowel transplant on May 2, 1990 (Fig 1). He is now on an unrestricted oral diet and is being treated with 0.2 mg/kg oral FK 506 and 10 mg prednisone/d. He has good intestinal absorption, and a normal mucosal pattern on his gastrointestinal (GI) series (Fig 2). Shown also in Fig 2 is his preoperative condition with only a stomach and a blind sac of duodenum. Two more patients have had successful complete intestinal grafts in continuity with liver grafts. Grant et al[10] reported on hepaticoenteric grafts under (CyA) earlier this year. The prospect of transplanting a variety of hollow viscus organs is good.

Pancreatic islet graft transplantation also has been successfully performed under FK 506 in patients who are now insulin independent more than 6 months after upper abdominal cluster resections (including total pancreatectomy) and liver plus intraportal islet transplantation. These

Table 1. Nephrosis in 49-Year-Old Cadaveric Kidney Recipient (Switch 13 Months Postoperative)

		FK 506	
	CyA	1 mo	5 mo
Urinary protein (mg 24°)	9768	1697	100
Serum creatinine (mg dL)	1.5	1.7	1.6
Serum cholesterol (mg dL)	289*	183	173
Serum albumin (g dL)	3.7	3.8	4.5
Prednisone (mg d)	15	0	0
Azathioprine (mg d)	150	0	0

*While on anticholesterolemic drug

Table 2. Focal Sclerosing Glomerulonephritis

	Before FK 506	3 mo	6 mo
Urinary protein (mg/24°)	1406	63	0
Serum creatinine (mg/dL)	0.3	0.1	0.3
Creatinine clearance (mL/min/1.73 m²)	82.0	86.0	ND
Serum cholesterol (mg/dL)	630	169	146
Serum albumin (g/dL)	1.7	3.7	3.9
Prednisone (mg/d)	175-35	0	0

Note: 30-month-old boy, 14.8 kg.

From the Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pennsylvania; the Department of Pathology, St Mary's Hospital and Medical School, London, England.

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

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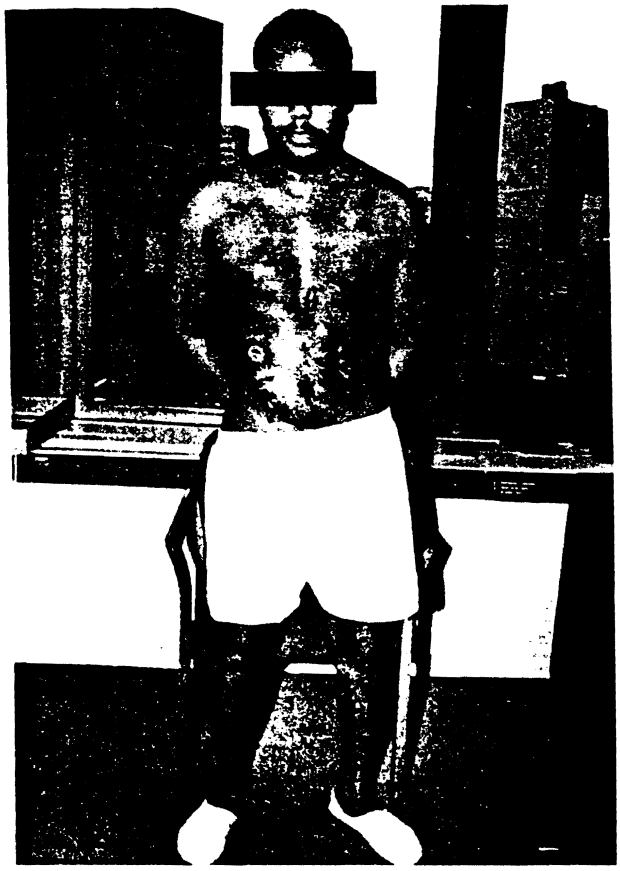

Fig 1. Patient who received a complete small bowel transplant from a cadaveric donor on May 2, 1990. The ileostomy is seen in the right lower quadrant. The oval skin defect in the right upper quadrant was the site of a jejunostomy that was brought out as a "chimney," and later closed when the patient was able to eat.

are the first unambiguously successful islet transplants in humans.[11]

AUTOIMMUNE DISEASES

The impact of FK 506 and presumably other new generation immunosuppressants will go beyond transplantation, and may reduce the number of whole organ candidates who suffer from autoimmune diseases. Four autoimmune diseases already have been treated: hemolytic uremic syndrome (one case), nephrotic syndrome as mentioned earlier (five cases), psoriasis (four cases), and pyoderma gangrenosum (two cases). With the skin disorders, the rapidity of response has been particularly easy to document graphically.[12] Within 2 or 3 days after starting FK 506, an effect can be seen and after 2 to 4 weeks, the skin lesions of these disorders were healed. The list of candidate autoimmune diseases is long, and in many instances there are animal analogue diseases that permit exact preclinical testing. For example, Murase et al[13] have provided from BB rat experiments strong support for trials in insulin-dependent diabetes mellitus.

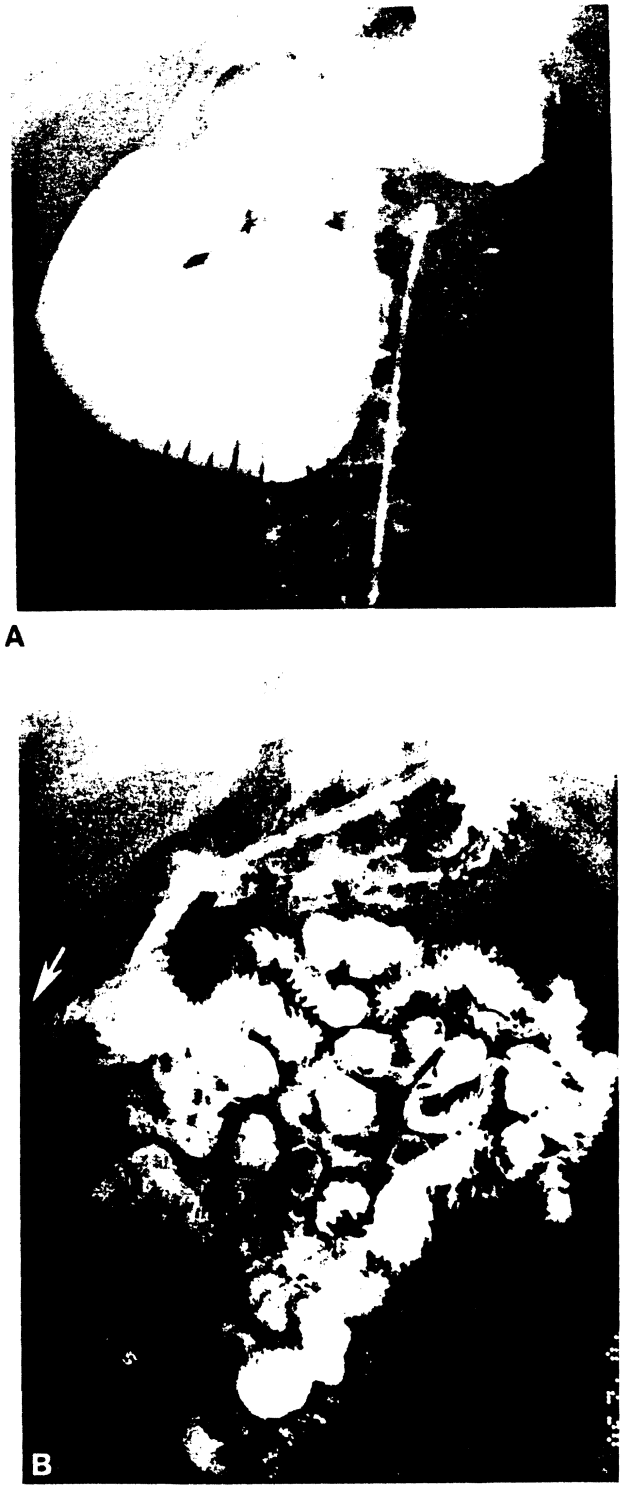

Fig 2. GI series of same patient as Fig 1. He is a 31-year-old patient who lost his small bowel and colon in early November 1989, after a gunshot wound to the superior mesenteric artery. **(A)** Residual GI tract that consisted of the stomach and the duodenal loop that ended blindly. **(B)** GI series with a delayed film of a normal small bowel homograft. The arrow in the left upper quadrant is the residual outpouching from a jejunal chimney that was brought to the skin and closed after 2 postoperative months (see Fig 1).

Table 3. Nonimmunologic Profile (4+ Worst) (All Dose Related)

	FK 506	CyA
Nephrotoxicity	+*	++
Neurotoxicity	+	+
Diabetogenicity	+	+
Growth Effects		
Hirsutism	0	+++
Gingival hyperplasia	0	++
Facial brutalization	0	+
Hepatotrophic	++++	+++
Gynecomastia	0	+
Other metabolic effects (in blood)		
Cholesterol increase	0†	++
Uric acid increase	+?	++

*Minor if any hypertension.
†However, in rats Van Thiel has shown an increase in cholesterol synthesis and serum concentration (unpublished).

TOXIC AND METABOLIC PROFILE

The full extent of these applications in and out of transplantation will depend on the toxicity profile of FK 506 (Table 3). The metabolic effects of this drug are wide ranging, and resemble qualitatively those of CyA.[14] However, much evidence gathered from animals and humans suggests that its therapeutic index is better. Both drugs are moderately diabetogenic by inhibiting the release of insulin from islets, and possibly by increasing peripheral insulin resistance.[15] Both are neurotoxic. FK 506 causes little if any hypertension. Other questions of nephrotoxicity will be considered further on. Lipid and uric acid metabolism are not seriously perturbed with FK 506. We have not seen gingival hyperplasia, hirsutism, or coarsening of the facial features in FK 506-treated patients. These various qualities are dose related. Such drug comparisons are flawed by the confounding factor of steroid need that appears to be less with FK 506.

HEPATIC GROWTH CONTROL

However, we are not discussing a competition between drugs, but rather an understanding of their uses and actions. A growth control effect of FK 506 is augmentation of the regeneration that occurs after partial hepatectomy.[16] This normal regeneration response to 70% hepatectomy is also increased in rats treated with CyA.[16-19]

FK 506 is profoundly hepatotrophic in other ways as can be shown with a simple experiment with Eck fistula in which the drug is infused into one of the tied off portal veins above the completely diverting portacaval shunt (Fig 3). Each experiment is its own control since the structure of the infused liver lobes can be compared with those not directly exposed to the drug. In the lobes directly exposed to FK 506 infusion (Fig 4) the hepatocytes are spared the atrophy, fat accumulation, and disruption and distortion of the organelles that occur on the unprotected (noninfused) side.[20] Such experiments have shown that FK 506 can prevent liver injury and promote liver healing. This may explain in part the remarkable effectiveness of this drug for liver transplantation. It is noteworthy that CyA is also hepatotrophic.[21]

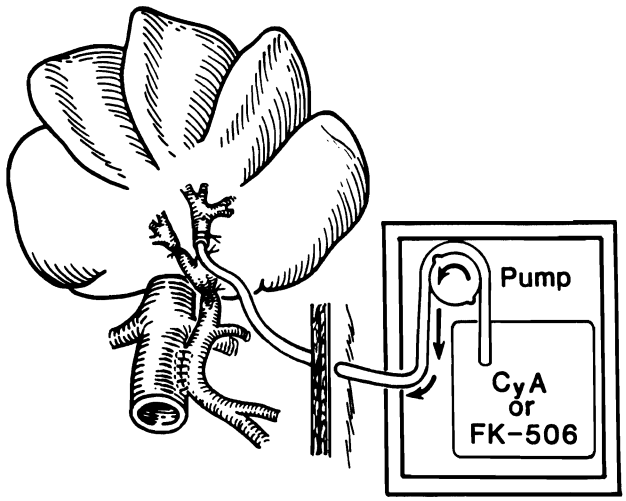

Fig 3. Experiment to test the hepatotrophic effect of FK 506. A completely diverting portacaval shunt is constructed, and the drug being tested is infused over 4 days into the tied off left portal vein. The morphologic changes in the infused left lobes can be compared with those in the right lobes (see Fig 4).

FK 506 AND CyA CONVERGENCE THROUGH PPIase

Because FK 506 and CyA are unrelated, the similarity of their desired as well as other effects was puzzling. The mystery was partly lifted 9 months ago by Siekierka et al[22] and Harding et al[23] who showed that FK 506 and CyA have different cytosolic binding sites but that these binding sites had in common a recently discovered enzyme called peptidyl-prolyl isomerase (PPIase) that facilitates protein folding.[24] We have suggested that CyA, FK 506, and also a third drug, Rapamycin (which has recently surfaced) act in some way by PPIase inhibition.[14,20] If so, we could better understand, and eventually even predict, the wide range of physiologic effects of such drugs. Mark Lorber of Yale has shown that cyclophilin, the binding site of CyA, is in the cytoplasm of essentially all mammalian tissues and even in the nuclei of some cells (unpublished observations, August 3, 1990). Lorber's work had, at least by implication, defined the extent of the PPIase network and made it clear why there were so many consequences of its use that were not limited to the immune system. Little imagination is required to associate the dense concentration of cyclo-

Table 4. Recovery After Liver Transplantation

Class	Bilirubin · 2 mg/dL	ICU-Bound
I	<10 d	<4 d
II	10-20 d	>4 d
III	up to 1.5 mo	Chronic
IV	>1 mo or never	Chronic

Abbreviation: ICU, intensive care unit.

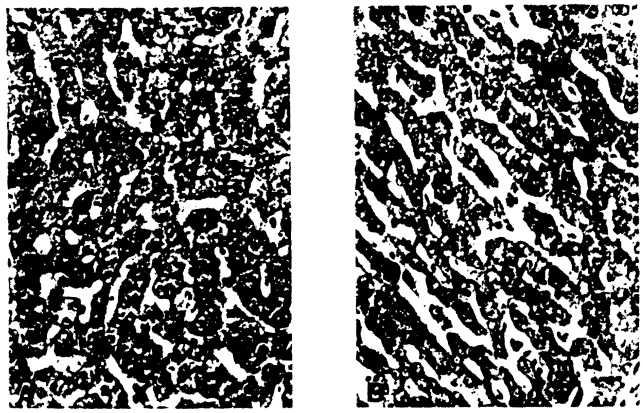

Fig 4. Dog liver 4 days after Eck Fistula, and selective continuous infusion of FK 506 into the left portal vein. **(A)** Biopsy from a left lobe which had been directly infused with FK 506. **(B)** Biopsy noninfused infusion right lobe. The design of the experiment is shown in Fig 3. H&E ×120.

philin in nervous, renal, and pancreatic tissues with neurotoxicity, nephrotoxicity, and diabetogenicity.

LIVER FUNCTION AND FK 506 METABOLISM

The optimal use of FK 506 has not yet been standardized because questions remain concerning the influence of hepatic dysfunction on FK 506 dose requirements, plasma FK 506 levels, and toxicity in patients. We have examined these issues in 49 patients who underwent liver replacement under FK 506 and low doses of prednisone. Although 47 (96%) of these recipients have survived, they could be stratified (Table 4) according to the quality of initial graft function: class 1 patients being those with superior graft function, class 4 patients being those with catastrophic graft injury, and the other classes being in between. All of the class 3 and 4 patients had prolonged stays in the intensive care unit with ventilator dependence, a high rate of tracheostomy, and a protracted need for IV drug dosing, especially in the class 4 recipients.

The plasma FK 506 trough levels postoperatively reflected the stratification. Patients with the best grafts had the lowest perioperative plasma trough levels while those with severely dysfunctional grafts (class 4) had astronomical rises in plasma FK 506 in spite of curtailment of doses (Fig 5). Patients with moderate (class 2) or severe (class 3) but reversible liver damage appeared to "auto regulate" the plasma trough levels which decreased at the same time as hepatic function returned and with little dose adjustment (Fig 5).

Renal function was severely impaired requiring dialysis in more than 25% of class 3 patients in almost all of the class 4 patients. This was obviously multifactorial including sepsis, hypotension, and the use of nephrotoxic antibiotics. However, renal failure and high plasma blood levels in patients with hepatic dysfunction seemed to be associated (Fig 6). The renal injury was reversible. By the end of this 60-day study period, five patients were still on dialysis but three have subsequently recovered from renal failure leaving only two who are currently being weaned from dialysis.

The take home message is clear, that downward dose adjustments guided by careful monitoring must be considered if there is abnormal liver function. Furthermore, liver

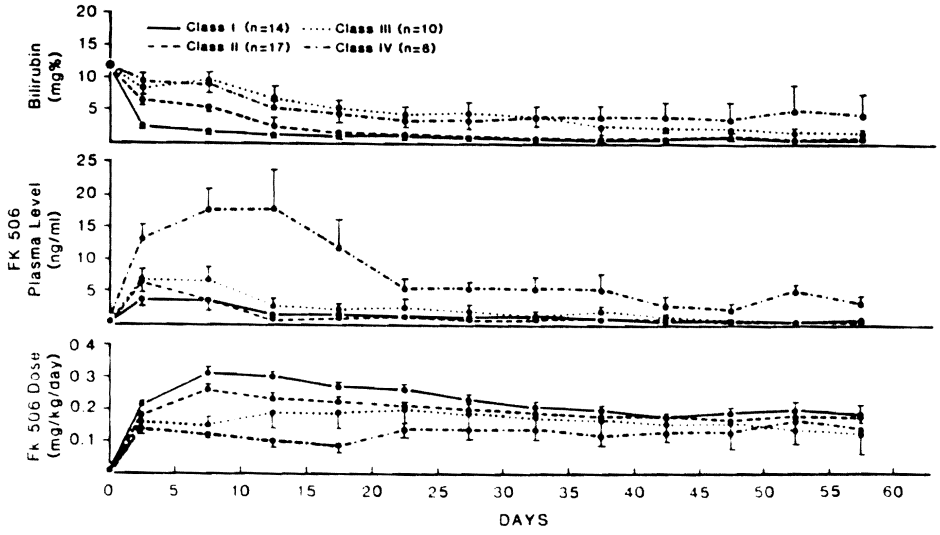

Fig 5. The effect of liver graft function on FK 506 doses and plasma levels. Note that the lowest doses and highest plasma levels were in the patients with unsatisfactory early hepatic function.

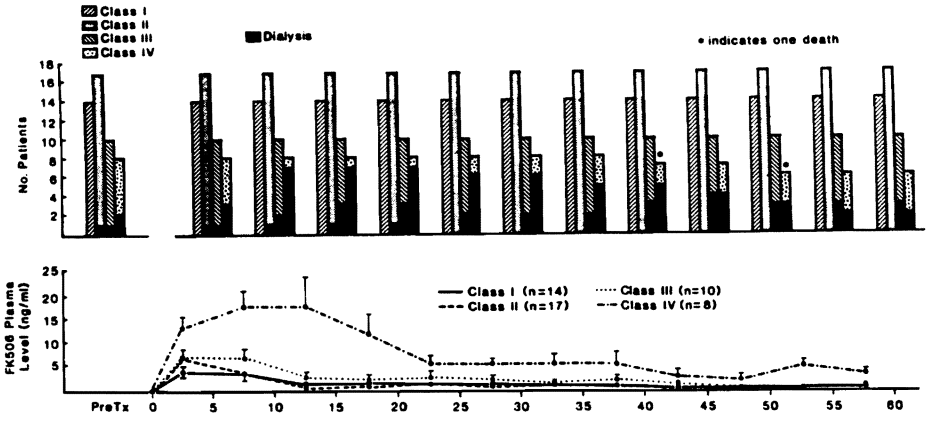

Fig 6. FK 506 plasma levels and renal failure in liver recipients. Some of class 3 and most of class 4 patients with early graft dysfunction and persistent high FK 506 plasma levels required postoperative dialysis for some time.

function tests should be part of the baseline information before starting FK 506 for any reason.

OVERDOSAGE WITH IV FK 506

Another practical warning from these studies was that dangerous IV dosing can occur. In the 49 patients, 0.075 mg/kg FK 506 were given IV over 4 hours every 12 hours. Even in the class 1 and 2 liver recipients, there was a transient increase in plasma FK 506 to potentially toxic levels and temporary renal dysfunction; the same thing was noted in heart recipients (Fig 7). These increases receded with conversion to oral doses of 0.15 mg/kg every 12 hours. Because the oral absorption of FK 506 usually is only 20% to 30%, we believe that our IV dosing was systematically too high. The total daily quantity of IV FK 506 probably should be one fourth to one third of the oral dose instead of the one half which we were using.

It may be that continuous FK 506 infusion instead of the 4-hour infusion method is preferable, but preliminary comparisons in these liver recipients (8 and 14 in the respective groups) have not shown a difference between the pulse vs continuous infusions either in the trough levels or the perioperative renal function (Fig 8).

SUMMARY

FK 506 is a superior immunosuppressive agent that should improve the grafting of organs that already are part of our every day transplant practices, as well as those which are presently impractical. Immune intervention for serious autoimmune diseases also should be a more attractive option with this drug. Lessons are still being learned about dosage and what determines safe dose schedules. At a basic level, the study of FK 506 and its comparison to CyA

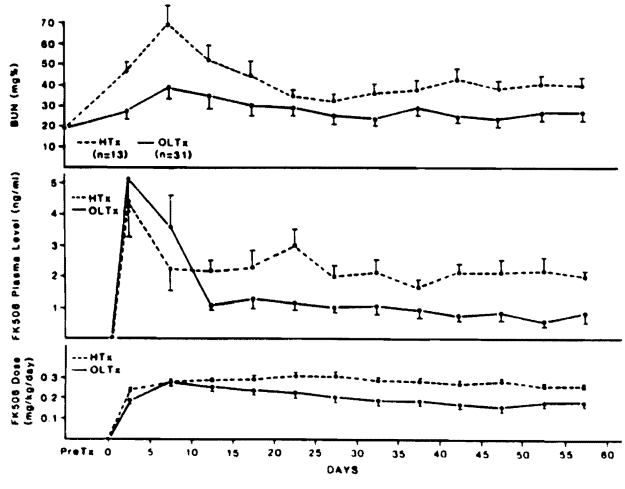

Fig 7. FK 506 doses, plasma levels, and kidney function in liver (classes 1 and 2) and heart transplant recipients. In both groups, IV administrations of FK 506 within the first 5 postoperative days were associated with the highest plasma levels and maximal increase in blood urea nitrogen.

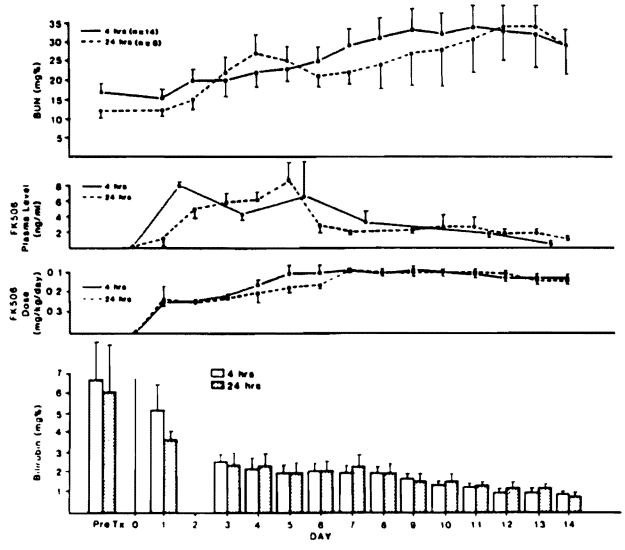

Fig 8. The effect of 4-hour (every 12 hours) and continuous IV infusion of FK 506 within the first 5 postoperative days on FK 506 plasma levels and renal function in liver recipients with good hepatic function.

may have shed light on mechanisms and characteristics of the whole class of so-called macrolide immunosuppressants and their cytosolic binding sites.

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