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Adverse Effects of FK 506 Overdosage After Liver Transplantation

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FK 506 and cyclosporine (CyA) are not chemically related and have different cytosolic binding sites.[1,2] However, it was noted almost immediately after FK 506 was introduced clinically that its toxicity profile was similar to CyA.[3–5] The principal side effects of nephrotoxicity,[3–6] diabetogenicity,[7,8] and neurotoxicity[9,10] have been reported individually. However, we will present here the full range of these and other adverse reactions together in the first 370 consecutive liver recipients who were entered into the Pittsburgh FK 506 study during 1989 and 1990. This case accrual was during a learning curve in which the daily induction doses were two or three times greater than those presently recommended. Consequently, a unique and unintended opportunity existed for overdose toxicology studies.

METHODS

Case Material

The 370 consecutive adult patients received 417 liver transplants between August 1989 and December 1990. All patients were undergoing primary transplantation when they entered the study. Because older age was not a negative factor for candidacy, 76 (20.5%) of the 370 patients were 60 years or older, of whom many had been declined for treatment elsewhere. Mean age was 47.0 ± 12.7 years (range 15 to 75). The indications for liver transplantation are summarized in Table 1. Parenchymal liver disease, to which postnecrotic and alcoholic cirrhosis were the largest contributors, accounted for 64.6% of the cases. Cholestatic diseases, for which the liver replacement operation tends to be technically easier, accounted for only 19.2% of the total.

The urgency for transplantation for the majority of the candidates was high as defined by the United Network for Organ Sharing (UNOS) criteria that existed at the time (Table 1): status 1, at home, functioning without nursing care (4 patients); status 2, recurrently hospital-bound (126 patients); status 3 and 4, ICU-bound with 4 signifying ventilator dependence (228 patients); and UNOStat, patients with fulminant hepatic failure, need for retransplantation, or terminal condition (111 patients). Forty-one (11.1%) of these 370 patients required retransplantation; 35 had a second transplant, and 6 had 2 additional grafts. All of the detailed analyses were based on follow-ups until July 15, 1991. At this time, the median duration of follow-up was 12.2 months with a range of 6 to 23 months. Further, more limited analyses, including patient and graft survival plus ultimate renal function, were provided to July 1, 1992, with follow-ups of 18 to 35 months.

Immunosuppression

FK 506. The study was carried out in a developmental period when two or three times the dose of FK 506 was used for induction as is our current practice. An initial group of 196 patients (53% of the total) was treated with intravenous doses of FK 506 infused at a dose of 0.075 mg/kg over a 4-hour period and repeated every 12 hours. When the patients were able to eat, the intravenous FK 506 was continued for at least 1 day in an overlap period, while an oral dose of 0.15 mg/kg was begun every 12 hours.

Table 1. Characteristics of the Patient Population, Their Diseases, and the Severity of the Clinical Condition Before the Liver Transplant

Patient population	
No. patients	370
No. grafts	417
No. 1 re-OLTx	41
No. 2 re-OLTx	6
Age (y)	47 ± 12
Sex (M/F)	221/149
Disease categories [no. cases (%)]	
Nonalcoholic cirrhosis	146 (39.5%)
Alcoholic cirrhosis	93 (25.1%)
Cholestatic disease	71 (19.2%)
Tumor	27 (7.3%)
Fulminant failure	12 (3.2%)
Miscellaneous	21 (5.7%)
UNOS score [no. cases (%)]	
1	4 (1.1%)
2	27 (7.3%)
3	126 (34%)
4	102 (27.5%)
UNOSTAT	111 (30%)

The next group of 174 patients received the same starting daily dose of FK 506 (0.15 mg/kg), but as a continuous intravenous infusion rather than in 4-hour bolus every 12 hours. The conversion from intravenous to oral therapy was made without any overlap en route. The pharmacokinetic and other differences with the two different regimens have been reported by Abu-Elmagd et al.[11]

Plasma trough levels of FK 506 were determined with an enzyme-linked immunoassay technique developed by Tamura et al.[12] However, routine services and rapid turnaround for results were not available until the spring of 1990. Thus, the principal value of these results was to explain what already had transpired rather than to guide dosage. Toward the end of the trial, trough plasma FK 506 levels typically were determined twice weekly or, in complicated cases, more often. By this time, dose adjustments during both the intravenous or the oral administration of the drug were dictated by plasma trough FK 506 levels, the presence of an

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Supported by NIH Project Grant No DK 29961.

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0041-1345/93/$3.00/+0

adverse drug reaction with special emphasis on neurotoxicity and nephrotoxicity, and the function of the graft.

The crucial influence of hepatic graft function on FK 506 metabolism and the development of adverse drug reactions was quickly learned,[13,14] and by the end of the study, the recommended standard treatment was to maintain an optimal plasma trough level between 0.5 and 2.0 ng/mL. Higher doses (or plasma concentrations) of FK 506 were well tolerated if graft function was good, but when liver function was substandard, toxicity was anticipated even after major downward adjustments of the FK 506 dose had been made.

Other Immunosuppressive Drugs. One gram of solumedrol was administered intravenously in the operating room after graft reperfusion. A daily dose of 20 mg of prednisone was started and reduced in 1 or 2 weeks in the absence of rejection. Thereafter, prednisone was weaned and frequently discontinued. In addition, the first 58 patients were given a 5-day prednisone "burst" beginning at 200 mg/d for the first postoperative day, with reductions of 40 mg/d until 20 mg/d was reached on the sixth day.

When rejection supervened, it was treated with an increased maintenance dose of FK 506 if possible without toxicity, and a single 1-g bolus of either methylprednisolone or hydrocortisone. If the response to this form of treatment was unsatisfactory, a 3- to 5-day course of OKT3 (5 or usually 10 mg/d) was administered and followed if necessary by augmented steroid doses. In a few cases in which this therapy failed, azathioprine was added to the FK 506 plus prednisone regimen.

Definitions of Nephrotoxicity

Early Onset: A rise in the serum creatinine >3.0 mg/dL within the first 30 postoperative days after starting from a normal pretransplant level.

Late onset: A rise in the serum creatinine level >2.0 mg/dL occurring after 30 postoperative days (isolated late onset) when starting from a normal pretransplant level or after an episode of early onset nephrotoxicity as defined above followed by recovery to a normal baseline (early plus late onset).

Resistant: A serum creatinine level >2.0 mg/dL that failed to recover to the pretransplant level after either early or late onset nephrotoxicity and persisted until the time of death or the end date of the study.

Pretransplant renal dysfunction: A pretransplant serum creatinine >2.0 mg/dL and/or requirement for preoperative dialysis.

Other Toxicity Definitions

Hypertension: An arterial blood pressure elevation above 160 mm Hg systolic or 100 mm Hg diastolic for more than 2 months in a previously normotensive patient, or a need for antihypertensive drugs for any 60-day period to control hypertension regardless of the measured blood pressure.

Hyperkalemia: A serum potassium level >5.3 meq/L or the need for a potassium-reducing agent, such as sodium polystyrene sulfonate (Kay-exalate) or a synthetic mineral corticoid drug (Florinef).

Neurotoxicity: An acute severe neurological event (coma, delirium, dysarthria, and seizures) not related to any other well-defined cause.

Type I Diabetes Mellitus: A requirement for insulin therapy for more than 30 days to maintain a fasting blood sugar level in the normal range. The onset of insulin dependence was classified "early" within the first 30 days and "late" thereafter.

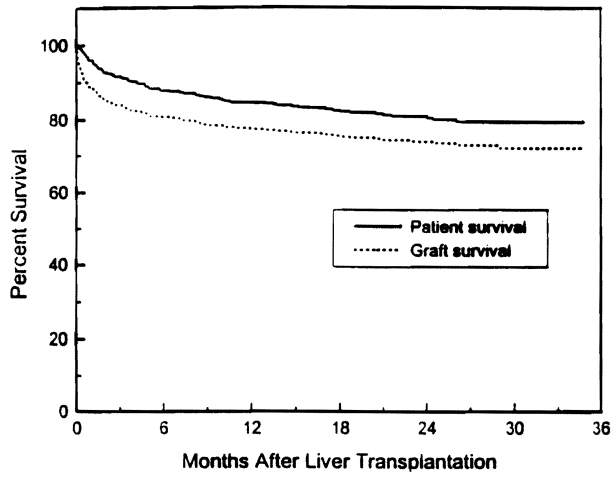

Fig 1. Patient and graft actuarial survival curve.

Statistical Analyses

Differences in means were assessed using the standard two-sample *t* test, while differences in proportions were assessed by the Pearson's chi-square test of association. The Wilcoxon Rank Sum test, a nonparametric equivalent to the standard two-sample *t* test, was used for highly skewed data. All tests were two-tailed. A *P*-value of less than .05 was considered statistically significant.

Patient survival was calculated from the date of orthotopic liver transplantation until death, and primary graft survival from the date of primary liver transplantation until retransplantation or patient death. Survival curves were generated using the Kaplan-Meier (product-limit) method.

RESULTS

Patient and Graft Survival

Although the toxicity study was completed on July 1, 1991, with a follow-up of 6 to 23 months, the actuarial patient and graft survival in all cases was obtained to July 1, 1992, for an 18- to 35-month follow-up. The actuarial 6-, 12-, and 18-month graft survival was 81%, 77%, and 75%, respectively. The patient survival at these times was 88%, 85%, and 82% (Fig 1).

Nephrotoxicity

Pretransplant Renal Dysfunction. Of the 370 patients, 31 had pretransplant renal dysfunction (Fig 2). In 23, this was severe enough to require preoperative dialysis. Six (26%) of these 23 recipients died postoperatively while on dialysis; 3 others never recovered kidney function and were being dialysed at the closing date of the study, whereas the remaining 14 patients became dialysis-independent after a median time of 34 days posttransplantation. In 10 of this last 14, renal function returned to normal.

Of the other 8 patients with pretransplant renal failure, 3 went on to postoperative dialysis which continued until the death of 1, but was of brief duration in the other 2. One of the remaining 5 recovered fully, but the other 4 still had renal function abnormalities at the close of the study.

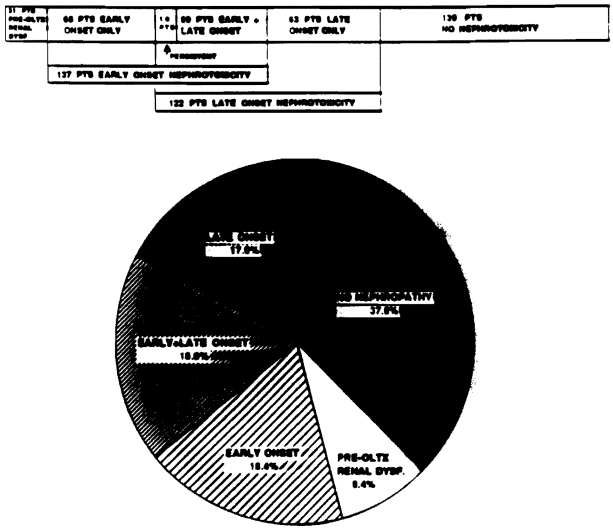

Fig 2. Summary of the incidence of nephropathy: a total of 54% of the patients developed nephropathy after the transplant. In 20% of cases, the nephropathy became chronic (see Fig 4).

Early Onset Nephrotoxicity. Of the remaining 339 patients, 137 (40.4%) experienced early onset nephrotoxicity (Fig 2). In 74 (21.8%), the onset of the nephrotoxicity seemed related solely to the use of FK 506 and was correlated with significantly higher levels of plasma FK 506 than in the nontoxic cohort (Fig 3). In the remaining 63 (18.6%), other potentially nephrotoxic factors played a potentially important role: (1) nephrotoxic drugs (principally aminoglycoside antibiotics); (2) prolonged and difficult surgical procedure; (3) the need for retransplantation; (4) one or more episodes of severe hypotension or cardiac arrest; and (5) severe hepatic dysfunction. An elevated FK 506 level usually was found when one or more of these five cofactors were present (Fig 3).

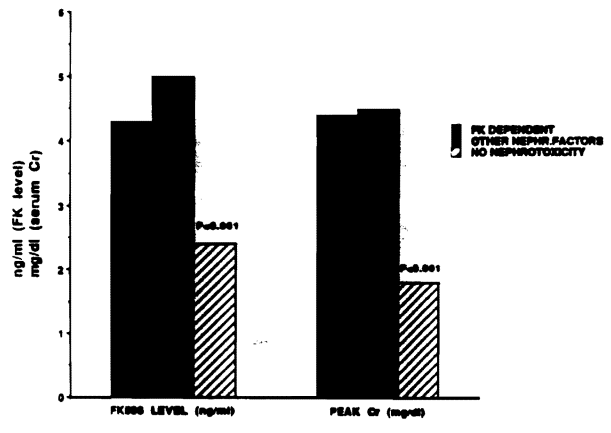

Fig 3. FK 506 trough plasma levels at peak SCr during the first 30 days post-OLTx: patients with early onset nephropathy (FK-dependent or with other concomitant nephrotoxic factors) vs patients without nephropathy. The difference is statistically significant.

The characteristics of the patients with and without concomitant nephrotoxic factors are shown in Table 2 and Fig 3. Those exposed to nephrotoxic factors other than FK 506 had a significantly greater need for dialysis ($P < .001$), a higher death rate during the period of early onset renal dysfunction ($P < .0001$), longer duration of early onset kidney failure, and poorer rate of renal recovery. However, the subsequent incidence of late onset nephrotoxicity was greater in patients with pure FK 506 toxicity. Sixty-eight of the 137 patients with early onset nephrotoxicity had complete recovery.

Persistent Nephrotoxicity. Amongst the 137 liver recipients who developed early onset nephrotoxicity, there were 10 (6 in the FK-dependent group, 4 in the group with other concomitant factors) whose renal dysfunction was remarkably longer (more than 180 days) than in the other 127 patients (Fig 2). This was defined as "persistent." One of these 10 patients died while still nephrotoxic. In 7, the nephrotoxicity became resistant (see below) and only 2 patients recovered completely. Three of these 7 patients became dialysis-dependent.

Late Onset Nephrotoxicity. After an initial period of seemingly complete recovery, 59 of the 137 patients with early onset nephrotoxicity had another episode of nephropathy sometime after 30 days. Added to the 10 patients with persistent nephropathy, and to these 59, were an additional 63 patients who developed de novo late onset nephrotoxicity (Fig 2). Although no statistical differences between the recurrent (n = 59) and late onset groups (n = 63) were found (Table 3), the trend was for patients with early onset nephrotoxicity to develop late nephropathy earlier and at a lower FK 506 level. Sixty-seven of the 122 patients with de novo or recurrent late onset nephropathy never recovered to their baseline level of kidney function and were defined as having resistant nephrotoxicity.

Late Nephropathic Liability

In-Study Period. When the study was concluded in July 1991, 200 patients from the total of 339 experienced a nephrotoxic episode (137 early onset, 63 de novo late onset); 166 were still alive (83%). Seventy-four (22% of the original 339) developed resistant nephrotoxicity, 7 after an early onset episode that was persistent, and 67 after a late onset. Complete recovery was seen in the other 92 within the time frame of the study.

At 6 months follow-up, 302 (89.1%) of the 339 patients entered were alive. Of these 302 patients, 76 were nephrotoxic, of whom 23 recovered to achieve a normal baseline creatinine; 6 died while still in renal failure; and 47 still have some evidence of nephrotoxicity.

At 12 months follow-up, 293 (86.6%) survived and 71 (24.2%) were nephrotoxic as defined by serum creatinine (SCr) >2 mg/dL (2.93 ± 1.9 (SD) mg/dL). Throughout the

Table 2. Incidence, FK 506 Trough Plasma Levels, General Characteristics, and Outcome of the Early Onset Nephropathy

	FK-Dependent	Other Factors	*P* Value
No. patients (%)	74 (21.8%)	63 (18.6%)	NS
FK 506 levels (ng/mL)			
At start onset	5.8 ± 5.0	5.7 ± 5.1	NS
At peak SCr	4.3 ± 3.7	5.0 ± 5.2	NS
At end onset	1.6 ± 1.6	2.4 ± 2.7	NS
Peak SCr during onset (mg/dL)	4.4 ± 1.5	4.5 ± 1.4	NS
Median time of occurrence (d after OLTx)	5.5	5	NS
Median duration of onset (d)	10	14	NS
No. patients requiring dialysis	20 (27%)	37 (59%)	$P < .001$
Outcome [no. patients (%)]			
Deaths during onset	2 (2.7%)	18 (28.6%)	$P < .001$
Late onset without recovery	6 (8.1%)	4 (6.3%)	NS
Late onset after recovery	36 (48.6%)	23 (36.5%)	NS
Complete recovery	30 (40.6%)	18 (28.6%)	NS

first 6 months, the percentage of nephrotoxic patients increased, but after it declined steadily (Fig 4).

Late Follow-up. By July 1992, with follow-up of 18 to 35 months, 273 (80.5%) survived and 56 (20.5%) were nephrotoxic. Their mean SCr was 2.62 ± 1.22. The mean plasma levels of FK 506 in these patients was 0.77 ± 0.64, which is in the putative nontoxic range.

Dialysis Requirements

Seventy-five (22.1%) of the 339 patients required dialysis (Table 4), 57 within 30 days. Recovery usually was associated with a reduction in the FK 506 level. In cases with nephrotoxic cofactors other than FK 506, recovery occurred even when the FK level remained above the acceptable therapeutic range (2.3 ng/mL), but in this high-risk group, the duration of the required dialysis was greater.

Table 3. Incidence, FK 506 Trough Plasma Levels, General Characteristics, and Outcome of the Late Onset Nephropathy

	Prior Early Onset	No Prior Nephropathy
No. patients (%)	59 (17.4%)	63 (18.6%)
FK 506 levels (ng/mL)		
At start onset	1.4 ± 1.1	1.6 ± 1.1
At end onset	0.8 ± 0.7	0.9 ± 0.7
Median time of occurrence (d after OLTx)	98	130
Median duration of onset (d)	168	159
No. patients requiring dialysis	5 (8.5%)	10 (15.9%)
Outcome [no. patients (%)]		
Deaths during the onset	6 (10.2%)	8 (12.7%)
Ongoing nephropathy	32 (54.2%)	35 (55.5%)
Complete recovery	21 (35.6%)	20 (31.8%)

The 10 patients that developed a long-lasting nephropathy progressing from early onset without recovery (persistent nephrotoxicity) are not included (see text).

Eighteen patients required dialysis at some time after the first month, in 5 instances after initial recovery from an early onset nephropathy, and in the other 13 during a long-lasting nephropathy progressing from an early onset without recovery (persistent nephrotoxicity). The need for dialysis was associated with toxic FK 506 levels, and recovery from the episode appeared to be dose-dependent (Table 4).

Of the 75 patients who required dialysis support, 51 (69%) recovered and did not require long-term dialysis, 5 were still on dialysis when the study was concluded in July 1991, and 19 died.

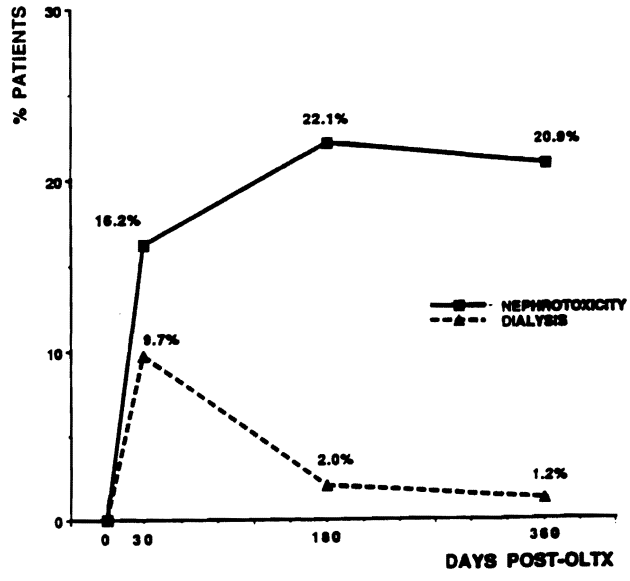

Fig 4. Incidence of nephropathy and of dialysis requirement at 30, 180, and 360 days post-OLTx. At the latest follow-up (540 days), 20.5% of the alive patients are still nephropathic.

Table 4. Incidence of Requirement for Dialysis, FK 506 Trough Plasma Levels, General Characteristics, and Outcome

	Early Onset		
	FK 506	Other	Late Onset
No. patients	20 (5.9%)	37 (10.9%)	18 (5.3%)
FK 506 levels (ng/mL)			
At start of dialysis	6.4 ± 4.9	6.9 ± 6.9	4.1 ± 4.1
At end of dialysis	1.5 ± 1.2	2.3 ± 2.5	1.3 ± 1.2
Median time of occurrence (days after OLTx)	8	9	131
Median duration (d)	20	27	29
Outcome [no. patients (%)]			
Deaths on dialysis	1 (5%)	14 (37.8%)	4 (22.2%)
Still on dialysis	1 (5%)	1 (2.7%)	3 (16.7%)
Complete recovery	18 (90%)	22 (59.5%)	11 (61.1%)

Hypertension

Fourteen of the 370 patients were hypertensive before transplantation and were excluded from this analysis. A total of 122 patients, or 32.9% of the culled study population, developed new onset hypertension after transplantation (Table 5). The hypertension occurred at a median time of 52 days posttransplant and was transient in only 10.7%; 84.5% started on therapy still require some form of antihypertensive medication, while the remaining 4.9% died while hypertensive. Most of the hypertensive patients (63.2%) were treated with only one antihypertensive drug.

In more than half of the cases, a clear association between a toxic FK 506 level and the hypertension could not be demonstrated; the mean FK 506 level at the diagnosis of hypertension was 1.78 ± 1.98 ng/mL. However, recovery, when it occurred, was associated with a reduction in the FK 506 dose.

A comparison between the hypertensive and the nonhypertensive patients failed to show a significant difference in their steroid requirement at day 30 posttransplant, but a tendency for a higher steroid dosage at day 180 appeared to be present, suggesting a role for steroids in the pathogenesis of the hypertension.

Hyperkalemia

Hyperkalemia, which occurred in 239 patients (64.6%) (Table 5), was not associated with elevated plasma FK 506 levels. Nevertheless, spontaneous recovery, which occurred in 27% of the cases, was associated with a reduction in the FK 506 dose. The hyperkalemia generally was controlled easily. For patients who did not experience a spontaneous decline of the elevated potassium, a synthetic mineralocorticoid drug was prescribed. Such treatment was required in 46% of the affected population.

Glucose Intolerance

Of the 370 patients studied, 25 who were diabetic before their transplantation were excluded from the analysis. Glucose intolerance requiring insulin within 30 days was seen in 61 patients (17.7%) at a median time of 1 day. However, all were receiving TPN. Twenty-three of these patients recovered, 23 more (37.7%) developed permanent diabetes mellitus, and 15 died while receiving insulin therapy (Table 5).

Late onset diabetes occurred at a median of 152 days in 18 (5.2%) of the 345 patients studied. The mean FK 506 level at the onset of the late diabetes mellitus was 2.67 ± 2.82 ng/mL (Table 5). With an appropriate reduction in the FK 506 dose, the requirement for insulin therapy was reduced. Three of the 18 patients required insulin treatment temporarily. Of the remaining 15 patients, 4 died on insulin therapy, and 11 more are still insulin-dependent.

Neurotoxicity

Thirty-one (8.4%) (Table 5) of the patients had major neurological complications related to the use of FK 506: seizures (12 cases), delirium (11), dysarthria (5), and coma (4). These events tended to occur in the early posttransplantation period after a median time of 10 days. The episodes were associated with toxic FK 506 levels, and

Table 5. Incidence, FK 506 Trough Plasma Levels, and Outcome of Neurotoxicity, Hyperkalemia, Hypertension, and Glucose Intolerance

				Glucose Intolerance	
	Neurotoxicity	Hyperkalemia	Hypertension	Early	Late
No. patients	31 (8.4%)	239 (64.6%)	122 (32.9%)	61 (17.7%)	18 (5.2%)
FK 506 levels (ng/mL)					
At start	3.3 ± 3.4	1.6 ± 1.4	1.8 ± 1.9	4.5 ± 4.1	2.7 ± 2.8
At end	1.9 ± 3.1	0.7 ± 0.5	0.9 ± 0.7	1.9 ± 3.1	1.6 ± 2.5
Median time of occurrence (d)	10	23	52	1	152
Outcome [no. patients (%)]					
Death during episode	1 (3.2%)	6 (2.5%)	6 (4.9%)	15 (24.6%)	4 (22.2%)
Still present	1 (3.2%)	169 (70.7%)	103 (84.4%)	23 (37.7%)	11 (61.1%)
Complete recovery	29 (93.6%)	64 (26.8%)	13 (10.7%)	23 (37.7%)	3 (16.7%)

responded to dose reduction in all but one case (Table 5). The exceptional patient, a previously reported 38-year-old woman[4] developed expressive dysphasia at the same time that magnetic resonance (MR) imaging demonstrated areas of demyelinization in her pons. She had a slow improvement in her speech over a 90-day period, but subsequently, she developed a severe depression with recurrence of dysphasia and ataxia. The clinical evaluation of her neurological symptoms was complicated by the pre-existing presence of both alcohol and drug abuse. A recent MR scan of her head has demonstrated diffuse cortical atrophy which was the same as at the first examination.

DISCUSSION

Within a few weeks after beginning the first clinical trials with FK 506, the similarity of its side effects to those of CyA was identified.[1-9] The principal undesirable effects of both drugs were nephrotoxicity, diabetogenicity, and neurotoxicity. Although both agents promoted liver growth (the regeneration after partial hepatectomy[15,16]) and prevented the hepatic atrophy of Eck fistula,[17,18] FK 506 has not caused the somatic growth complications of gingival hyperplasia, hirsutism, and coursening of facial features that have been seen with CyA. FK 506 also had a smaller hypercholesterolemia effect than CyA and appeared to have a lesser tendency for the development of hypertension.[4,19,20]

Because FK 506 and CyA are chemically unrelated, and have different cytosolic binding sites, the similarities in their actions and side reactions were puzzling at first. When it was discovered that both binding sites were rich in the enzyme, peptidyl-prolyl isomerase (PPIase), which facilitates protein folding,[1,2] an inhibitory action on these drugs on PPIase was suggested at first to rationalize the commonality of their action.[3,4,13] However, the explanation for the shared pleiotropic effects of these drugs has been more complex. It is realized now that both FK 506 and CyA are "pro-drugs" that are pharmacologically inert until they complex with their binding sites. Apparently, modulation by the drug–immunophilin complex occurs at a common target, the protein phosphatase calcineurin.[21]

These developments and the results from sophisticated drug-modeling experiments have raised the possibility that the principal toxicities of these two drugs may be immutably linked to their desired immunosuppression. With either drug, the severity of the side effects is dose related. Because the quantities of FK 506 given to the patients in this study were two or three times the currently prescribed doses, it was not surprising that there was a high incidence of adverse reaction. In spite of this, and the acquisition of experience during a learning curve, the results in this consecutive series of 370 patients, with a large representation of high-risk candidates, was better than in our historical experience with CyA.[22] This superiority also was noted in a subsequent randomized trial[23] in which the usefulness of FK 506 was retained with the lower induction doses.

Nevertheless, nephrotoxicity is the principal dose-limiting factor in the use of FK 506 as it was with its predecessor, CyA. Prior to the utilization of pharmacologic monitoring techniques for both CyA and FK 506, renal dysfunction often was used as a guideline to effective dosing. The use of trough drug levels has allowed an easier and safer use of these drugs, but there still is a variability factor in that some patients manifest toxicity at "therapeutic" levels in the range of 1 ng/mL while others do not show side effects at "excessive" levels far above this.

The problem would be less sinister if simple dose adjustments could eliminate the nephropathic liability. CyA-related acute nephrotoxicity after liver transplantation has been reported in up to 40% of cases[24-26] and, in long-term follow-up studies, there is evidence that CyA can result in chronic renal failure in more than 70% of patients.[27,28] It would not be hard to extrapolate these findings to those reported herein with FK 506 unless appropriate dose adjustments are made for subsequent cases.

The mechanism of CyA nephrotoxicity has not been completely clarified, but a reduction of blood flow due to vasoconstriction, and then a consequent reduction of the glomerular filtration rate (GFR), has been demonstrated.[24] When chronic nephrotoxicity supervenes in CyA-treated patients, the vascular endothelial changes and chronic structural interstitial alterations do not respond to dose reductions or even complete withdrawal.[29] It is unrealistic to believe that these same lessons do not pertain to FK 506. Therefore, prophylaxis must be a foremost concern in treatment strategies with FK 506 including an effort to use lower doses, avoid high trough levels, and incorporate other nonnephrotoxic agents into drug cocktails that will reduce the need for high-dose FK 506 to achieve the desired immunosuppression.

As these strategies are evolved, it must be borne in mind that there are pharmacokinetic differences between FK 506 and CyA. Both agents are virtually completely metabolized in the liver, but it has happened that the risk from astronomical blood levels and clinical toxicity is greater under FK 506 than CyA in patients who do not achieve good hepatic function postliver transplantation. Such errors can be avoided by close monitoring of serum plasma or blood FK 506 levels.

Other differences between the two drugs also should be recognized. The oral absorption of FK 506, unlike CyA, is not dependent upon bile and is also much better maintained in the face of diarrhea and certain malabsorption disorders.[30] These characteristics make it particularly advantageous for transplantation of all of the gastrointestinal organs.

We have reported elsewhere the incidence of nervous system complications,[9,10,31] and of diabetes mellitus.[4,5,7,8] The incidence of these complications was less than nephrotoxicity, but was similarly related to elevations in the

monitored plasma FK 506 level. The only parameters studied that were not seemingly correlated with the FK 506 trough levels were hyperkalemia and hypertension, but even these complications were responsive to dose reduction and easily controlled with specific medications.

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