

Neurologic Complications of FK 506

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FK 506 is used increasingly to prevent rejection in organ transplantation. Both experimental¹⁻³ and clinical^{4,5} studies suggest that FK 506 is a more potent immunosuppressive agent than cyclosporine (CyA), and there are indications that FK 506 may also be less toxic.⁶ The advent of any new agent such as FK 506 promises more effective immunosuppression, but also gives rise to the need for further study of potential toxic side effects. Indeed, a report by Reyes et al⁷ of two patients who developed speech dysfunction while on FK 506 suggests that this agent may under certain circumstances produce adverse effects on the nervous system. Thus, more information is needed about potential nervous system disturbances that may occur in association with the clinical use of FK 506 in transplant patients. We carried out this study to identify the spectrum and frequency of neurologic disturbances that may occur in transplant patients receiving FK 506.

PATIENTS AND METHODS

Data regarding the toxic effects of FK 506 on the nervous system were obtained from three major patient sources: group 1 consisted of those patients in the general transplant population who were seen routinely for neurologic events; group 2 comprised a prospective study of 294 consecutive adult recipients; and group 3 resulted from surveillance of outpatients for possible long-term complications of FK 506. The details of these patient groups are given below.

Group 1

The day-to-day monitoring of posttransplant patients is carried out by the transplant service, and neurologic consultations are obtained when disturbances in the nervous system function are suspected. Our data were obtained from a retrospective chart analysis of documented neurology consult findings. By this method, we identified 23 transplant recipients who developed neurologic complications from a total of approximately 800 reported transplant patients receiving FK 506 during the same time period. These 23 patients consisted of 20 liver transplantations, 1 heart, 1 kidney, and 1 combined liver/kidney transplant.

Group 2

The 294 adult patients in this group form part of a wider study comparing efficacy and side effects of FK 506 and CyA. The breakdown of types of organ transplant is as follows: 238 livers, 53 hearts, 2 double lungs, and 1 heart/lung. These patients were studied prospectively, and monitoring was again carried out by both the neurology and transplant services, although initial recognition of neurologic problems remained with the transplant service.

Group 3

This group consisted of 83 patients who were monitored in outpatient clinics and who were not primarily seen by a neurolo-

gist; however, if symptoms relating to neurologic function were elicited, neurologic follow-up was obtained. Among these patients, 62 received liver transplants and 21 heart transplants. The monitoring period ranged from a few weeks to 2 years.

Dosage of FK 506

In the initial phase of treatment, FK 506 was administered IV using an intermittent bolus of 0.075 mg/kg over 4 hours every 12 hours. This dosage was later modified to a continuous IV infusion of 0.15 mg/kg administered over 24 hours. While the number of days of IV treatment varied among patients, all were eventually switched to an oral dose of 0.15 mg/kg given at 12-hour intervals.

RESULTS

A number of neurologic abnormalities were evident in patients who received FK 506, ranging from a mild tremulousness, which was the most common finding, to major disturbances of neurologic function. Table 1 identifies the types of major and minor abnormalities that have been identified and shows their division into major and minor types. Major neurologic side effects were identified in 16 (5.4%) of the 294 prospectively studied patients, generally occurred within the first 30 days following transplantation (mean onset 12.8 ± 9 days), and were related in many instances to high plasma levels of FK 506 (Fig 1). Heart and lung transplant recipients were less vulnerable to complications of this nature, with only 3.6% developing nervous system dysfunction. In the liver recipients, there was no significant relationship between the development of this type of neurologic complication and the preexisting bilirubin level or type of liver disease. Patients with preexisting hepatic encephalopathy and prolonged graft dysfunction seemed to be more prone to neurologic complications.

Retrospective chart analysis of the patients in group 1 identified 19 patients with major neurologic side effects. There were four others who had minor disturbances, two with headache and two with severe tremors. Of the major disturbances, encephalopathy was the most common feature, occurring in 11 patients. Three subjects demonstrated focal abnormalities, and one exhibited signs of akinetic mutism. Myoclonic reactions were seen in one subject and

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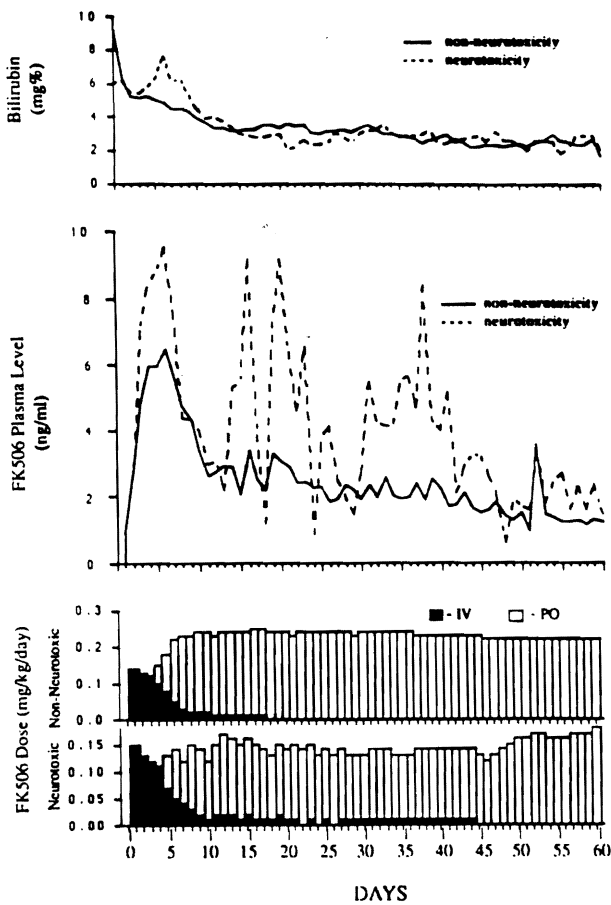


Fig 1. Average daily bilirubin levels in the two patient groups during the first 60 days posttransplantation, trough plasma FK 506 levels in the same patients, and daily doses of FK 506 are shown. A total of 215 patients with no neurotoxicity and 14 patients with signs of neurotoxicity are shown, which do not represent all of the prospective patients.

seizures in three others. In this group, high plasma FK 506 levels were a common, but not invariable association.

Neurotoxicity usually develops during the IV phase of drug administration. The dose of FK 506 was no higher in patients with observed neurotoxicity than in those who remained symptom-free. However, in more than 50% of those with neurotoxicity, FK 506 trough plasma levels were greater than 3 ng/mL (mean value 3.4 ± 3 ng/mL), with normal upper therapeutic levels being 2.5 ng/mL (Fig 1). Neurologic function improved after FK 506 levels declined, but often with a delay of several days between recovery of function and normalization of plasma FK 506 concentration. Figure 2 shows a representative example of one patient's course of FK 506 levels.

Akinetic mutism was the most common of the major neurologic side effects noted in the prospectively studied patients. This condition is characterized by an apparent state of wakefulness in which the patient may follow the examiner with the eyes, but shows no other evidence of

voluntary muscle activity. Motor responses to noxious stimuli are very much reduced and often absent. The patient is unable to talk and shows no other ability to communicate. This clinical presentation was seen several days after transplantation and was associated with either high plasma FK 506 levels, severe pretransplant hepatic dysfunction, or preexisting disease of the nervous system. Temporary withdrawal or reduction in the dose of FK 506 resulted in improvement in neurologic function, and reintroduction of FK 506 was not associated with a recurrence of akinetic mutism.

The encephalopathy was characterized by an initial disturbance of consciousness, but, in some cases, agitation heralded its onset. Impairment in consciousness ranged from a mild lethargy to a severe state of coma, with only minimal reaction to painful stimuli. Seizure activity complicated the encephalopathy in two patients. This condition was generally related to high plasma FK 506 levels with improvement occurring after adjustments in drug dosage. Return of consciousness lagged behind the falling FK 506 levels by several days (Fig 2). Computerized tomography studies of the brain carried out in four patients demonstrated nonspecific changes in the form of volume loss. Recovery of function was the rule following changes in FK 506 dosage.

Seizures developed either as an isolated complication or as a component of the encephalopathy and ranged from partial motor attacks (focal seizures) to generalized tonic-clonic seizures. Partial complex status epilepsy also developed in one patient as a feature of the encephalopathy.

Focal neurologic abnormalities occurred in four patients, including dysarthria and aphasia in two as previously described,⁷ hemiplegia in one, and cortical blindness in the other one. Magnetic resonance imaging (MRI) studies obtained in these patients revealed focal changes in the white matter. The clinical and MRI findings improved over time.

The minor neurologic side effects were generally more common, occurring in about 20% of the patients. Sleep disturbances and tremulousness of the hands were the most common findings and tended to be most prominent shortly after transplantation. These diminished with time and were not associated with high FK 506 plasma levels.

Table 1. Neurologic Side Effects of FK 506

Major	Minor
Akinetic mutism	Tremors
Seizures	Headache
Psychosis	Sleep disturbances
Encephalopathy	Nightmares
Focal deficits	Vertigo
Movement disorder	Dysesthesia
	Mood changes
	Photophobia

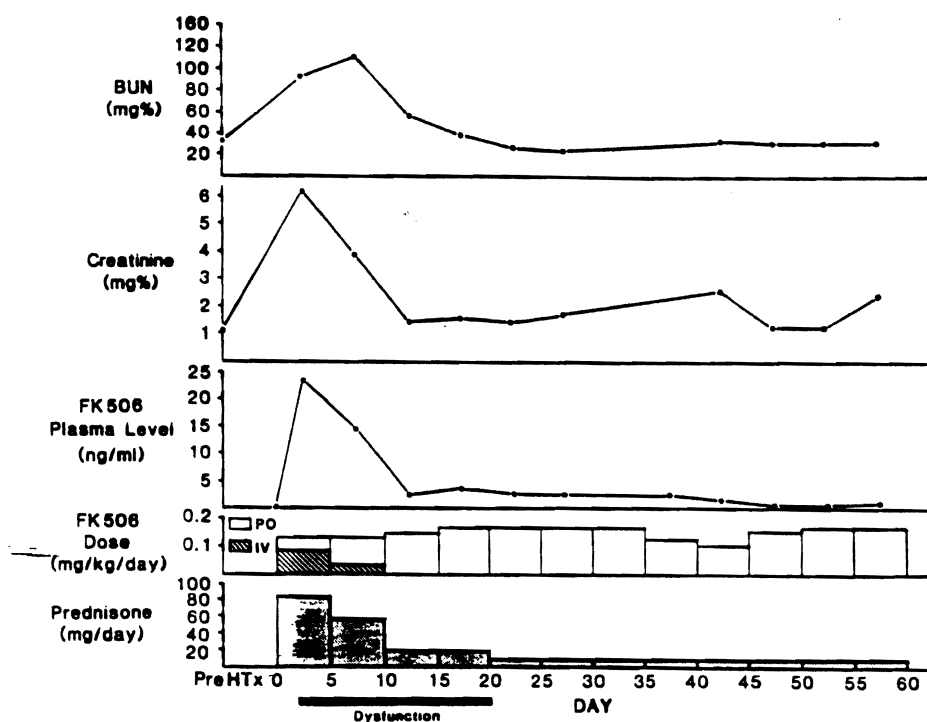


Fig 2. Posttransplant course of a 48-year-old cardiac transplant recipient. Elevated blood urea nitrogen and creatinine during the first 2 weeks was related to perioperative hypotension with secondary renal failure. Neurologic dysfunction was characterized by an encephalopathy with concomitant rising plasma FK 506 level.

DISCUSSION

Our findings indicate that a wide variety of neurologic side effects may occur with the use of FK 506, which are similar to those associated with CyA.⁸⁻¹² These effects have been classified into major and minor, based on the nature of the clinical impact rather than on eventual outcome. The major side effects include akinetic mutism, encephalopathy, seizures, and focal neurologic disturbances while the minor ones relate to insomnia, visual symptoms, headache, tremors, dysesthesia, and mood changes.

In evaluating the neurologic impact of FK 506, it is important to consider the background medical status of the patient. Similar neurologic manifestations are seen in non-immunosuppressed patients with end-stage liver disease,¹³ suggesting that a predisposition could be present. In addition, posttransplant liver recipients are likely to develop a variety of metabolic and circulatory disturbances and are also prone to acute graft rejection. They are often given pharmacologic agents that may adversely affect the nervous system. Thus, the clinical picture is compounded by a variety of interacting factors that may either individually or collectively produce disturbances in neurologic function, making it difficult to differentiate the specific factors operating to produce the neurologic disturbance. The medical picture was indeed complex in all our patients; however, FK 506 was determined to be contributory, if not the cause of the neurologic dysfunction, by a process of exclusion of other potential causes of the clinical presentation. It is still possible that additional background disturbances contributed in some measure to the neurologic syndrome, which could have influenced our early estima-

tion of the neurotoxic effects of FK 506. Moreover, the same predisposition of liver recipients to CyA toxicity has been noted.

Although the major complications of FK 506 neurotoxicity are much more common in liver transplant recipients, heart and lung patients may also develop these neurologic side effects. In the two heart recipients who presented with posttransplant encephalopathy, there were underlying predisposing conditions. One subject had chronic, progressive multiple sclerosis (MS), and the other had been in severe cardiac failure, with a prolonged episode of profound hypotension perioperatively. Disturbances in the blood-brain barrier are known to occur in MS,¹⁴ and cerebral blood flow is known to be abnormal in severe end-stage cardiac failure.¹⁵ These conditions may adversely affect the blood-brain barrier, thereby producing a relatively higher central nervous system (CNS) FK 506 concentration with resultant clinical effects. Four of the liver recipients with postoperative neurologic dysfunction also exhibited signs of severe hepatic encephalopathy prior to transplantation, and an additional four were subject to prolonged posttransplant graft dysfunction.

High plasma levels of FK 506 probably are associated with the development of neurotoxicity, and peak plasma concentrations are generally higher in patients who exhibit signs of nervous system involvement. In our patients, neurologic complications were most common when the drug was administered IV in bolus form. However, the profound neurologic effects were of a temporary nature, and all patients improved when the dose of FK 506 was reduced or when the agent was temporarily withdrawn.

The patient with MS developed akinetic mutism 3 days after cardiac transplantation. Although serum FK 506 levels were not elevated, the drug was nonetheless withheld and his condition improved. There was no recurrence of this acute neurologic dysfunction after subsequent reintroduction of FK 506. It is noteworthy that his condition at 6 months posttransplantation with respect to the MS was much better than prior to the procedure. We speculate that this improvement could be attributed to the beneficial effect of FK 506 on the disease process (MS) itself.

Other immunosuppressive drugs were administered, and prednisone in doses ranging from 20 to 40 mg/d was used as adjunctive therapy in patients. Azathioprine was added to the therapeutic regimen in 25% of the patients. None of these agents was expected to play a major contributing role in the development of the particular neurologic syndromes that were recorded, although all were described in the early days of liver transplantation under azathioprine-prednisone therapy.¹⁶

Various laboratory assays were carried out, including measurements of serum cholesterol, magnesium, bilirubin, and hemoglobin. There was a tendency for the magnesium to be on the low side of the normal range, but hypomagnesemia was not consistently evident, and there was no clear relationship between low magnesium levels and FK 506 neurotoxicity as with CyA.¹⁷

Minor neurologic side effects were most obvious at an early stage following transplantation, and there was a tendency for these to become less apparent over time. This tendency may relate in part to higher serum FK 506 levels during the early posttransplantation phase when individual patient dosages were titrated. In some patients, however, the abatement of symptoms did not relate to lower FK 506 levels, suggesting that other mechanisms may have been operative in producing an increased tolerance to the drug.

When comparing FK 506 neurotoxicity with CyA, many similarities are apparent. CyA induces encephalopathy,¹⁰ akinetic mutism,¹² seizures,⁹ and focal neurologic signs.¹¹ Abnormalities have been detected on MRI imaging in patients receiving FK 506,¹⁸ and similar changes have also been evident in this study. However, the abnormalities are smaller and localized, unlike those described in patients on CyA. CyA-induced neurotoxicity has been reported to occur in 25% of patients on this agent,¹⁸ but our experience with FK 506 suggests that neurotoxicity is less frequent with this drug, occurring in only 6% of the prospectively studied subjects. Also, in contrast to FK 506, CyA-induced side effects have not been reported to show such a distinct relationship to high levels of this immunosuppressive agent.

Hypocholesteremia has been implicated as a possible

factor related to the development of CyA nervous system toxicity.¹⁸ While there is a tendency for FK 506 to lower serum cholesterol, there was no clear relationship between hypocholesteremia and neurotoxicity in this series of patients.

CONCLUSIONS

The drug FK 506 has the potential to adversely affect the nervous system, provoking both major and minor complications with its use. However, these side effects are reversible and usually occur either as a result of high plasma FK 506 levels or in association with an underlying predisposing condition. A better understanding of the clinical pharmacodynamics of FK 506 should result in better control of plasma FK 506 levels, which, in turn, should reduce the incidence of major neurotoxicity.

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