

Psychiatric Morbidity in Liver Transplant Patients

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THE psychiatric care of patients with organ transplants is a rapidly growing area. Morbidity and mortality of transplantation are directly related to a number of factors including organ rejection and adverse complications of medications. FK 506, a promising new immunosuppressive drug, appears to significantly reduce the rate of rejection. During our center's several years of experience using FK 506, its side effect profile is being clarified. However, the psychiatric morbidity associated with FK 506 and the more traditionally used cyclosporine (CyA) has not been compared in any systematized fashion. Cognitive and psychiatric symptoms (eg, delirium, depression, insomnia, perceptual disturbances) may be important factors in the eventual outcome of these patients in that these symptoms may significantly impair their ability to comply with treatment regimens and interfere with their recovery.

METHODS

We participated in a randomized, nonblinded, controlled trial of FK 506 vs CyA in liver transplant patients. Exclusion criteria included previous/multiple transplants, hepatitis B or human immunovirus (HIV) carrier, cancer, renal failure, active infection, and coma. The outcomes of interest were cognitive function as assessed by the Mini-Mental State Exam (MMS) (Fig 1), Trail-making Tests (Trails) A and B, the Delirium Rating Scale (DRS), and a clinician-rated neuropsychiatric symptom checklist. Patients were initially assessed at 1 week postoperatively, a time when they had fully recovered from the effects of anesthesia, were mostly out of the intensive care unit, and had stabilized FK 506 or

CyA plasma levels. Pilot data for the first postoperative week are reported here ($n = 24$).

RESULTS

Demographic characteristics include age (mean = 40 ± 9 , range 22 to 57), gender (46% female), and education (29% college educated). The primary liver diagnosis was alcoholic cirrhosis in 42%, cryptogenic in 20%, primary biliary cirrhosis in 17%, and 20% other. There were no differences between the FK 506 group ($n = 14$) and CyA group ($n = 10$) regarding age, gender, education, and liver diagnosis. MMS, Trails A and B, and DRS scores revealed that approximately 35% of the total group was experiencing some cognitive impairment. The symptom checklist revealed that 51% had more than four psychiatric symptoms (Fig 2). There was no statistical difference between FK 506 and CyA with respect to numbers of psychiatric symptoms (FK 506 = 4 ± 3 , CyA = 5 ± 2) or DRS scores (FK 506 = 7 ± 6 , CyA = 5 ± 2). MMS scores also were not significantly different (FK 506 = 26 ± 5 , CyA = 28 ± 2), though more FK 506 patients had lower cognitive scores (21% less than 24 points) compared with none with CyA. The Trails tests are particularly sensitive to subtle disruptions of sustained attention, visual-motor coordination,

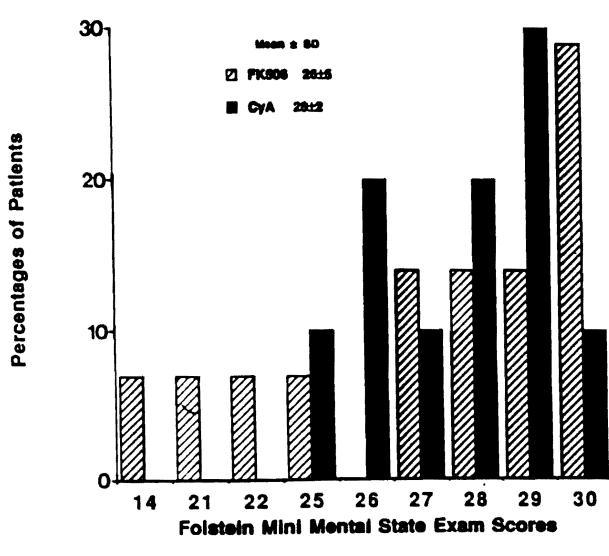


Fig 1. Cognitive status.

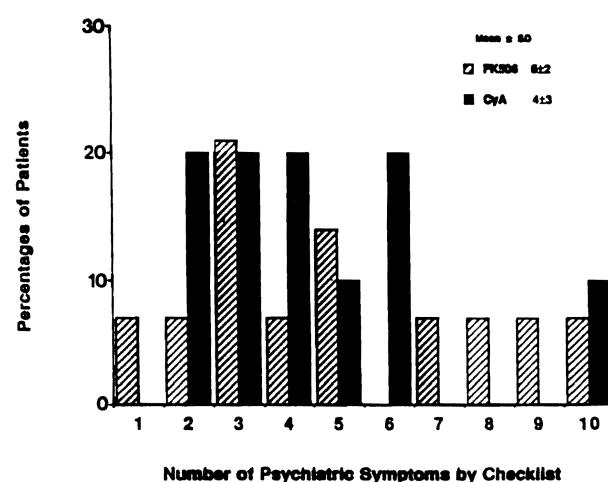


Fig 2. Psychiatric symptoms.

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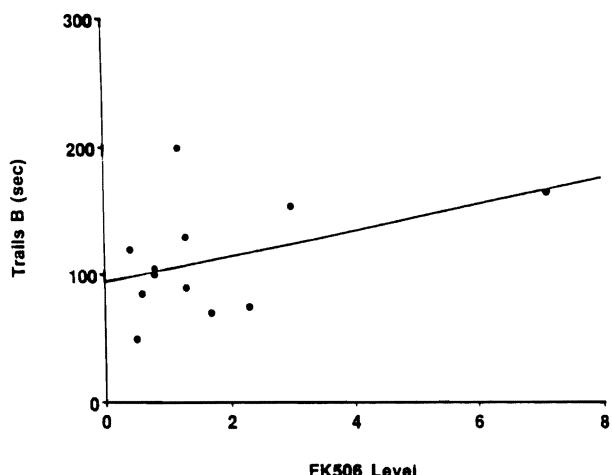


Fig 3. FK 506 serum level versus Trails B.

and symbol mediation. As we expected, plasma levels of both FK 506 and CyA were correlated with Trail B scores ($r = .60, P = .03$), suggesting that performances deteriorated with increasing drug levels (Fig 3).

DISCUSSION

Initial toxicologic studies in primates showed quietness, huddling postures, vomiting, anorexia, and weight loss at 3 to 36 mg/kg dose range of FK 506, with drowsiness and lethargy at the highest dosing range of 18 to 36 mg/kg.¹ In

humans, the most common symptoms previously reported include headache, nausea, vomiting, hyperesthesia, and flushing, which occurred with the greatest frequency during IV administration.² These previous findings and our data suggest that higher plasma levels of FK 506 result in cognitive impairment and the development of untoward side effects. Anecdotally, we have suspected FK 506 in the development of delirium especially when plasma levels are high (ie, >4 to 5 ng/dL).

CONCLUSIONS

Further clinical experience with FK 506 has shown that lower plasma levels than those initially felt to be effective can be maintained without organ rejection. Perhaps by working to achieve the lowest possible dose to provide immunosuppression without rejection we will see fewer of the cognitive and neuropsychiatric symptoms experienced at higher plasma levels. Though our numbers are small, the current data suggest no statistically significant differences between FK 506 and CyA with respect to gross cognitive functions and the development of neuropsychiatric symptoms.

REFERENCES

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