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Metabolic Effects of FK 506 in Patients With Severe Psoriasis: Short-Term Follow-Up of Seven Cases

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CYCLOSPORINE (CyA) has been shown to be effective in a variety of human autoimmune diseases, including psoriasis, nephrotic syndrome, type 1 diabetes, and sight-threatening uveitis.[1] Its potential side effects include nephrotoxicity, diabetogenicity, and neurotoxicity. Several studies (see elsewhere in this symposium) have shown that FK 506 prevents or suppresses autoimmune disorders in experimental animals and that it induces rapid remission in severe, recalcitrant, chronic plaque-forming psoriasis.[2,3] In this paper, the metabolic effects of FK 506 are reported in seven patients with severe recalcitrant chronic plaque-forming psoriasis treated at the University of Pittsburgh Medical Center with a median study follow-up time of 6 months.

PATIENTS AND MATERIALS

Seven patients (2M:5F; mean age 37 years; range 30 to 49 years) with severe, chronic plaque-forming psoriasis unresponsive to conventional therapy were studied. Four patients had psoriatic arthritis and two of these, plus one other, had methotrexate-induced cirrhosis. The median follow-up period for analysis was 6 months (range 4 months–1 year). Patients received a starting dose of 0.3 mg/kg/d FK 506 in oral capsule form. The dose was adjusted according to the FK 506 plasma levels during the study period. No other treatment for psoriasis was administered. One patient with methotrexate-induced cirrhosis required furosemide diuretic therapy (40 mg/d) from week 5 to week 9.

Physical findings, including blood pressure and biochemical indices of renal and hepatic function and other variables, including glucose and cholesterol, were monitored at each clinic visit. Trough plasma FK 506 levels were estimated by ELISA.[4]

Friedman's test was used to determine whether biochemical parameters changed significantly over time. The Spearman correlation coefficient was calculated to investigate the association between FK 506 plasma levels and biochemical parameters. FK 506 plasma levels and biochemical parameters were correlated with time of treatment using Spearman's correlation coefficient. A 95% confidence interval was generated for the correlation between FK 506 plasma levels and time of treatment to compare biochemical parameters and FK 506 plasma levels over time.

RESULTS

Psoriasis

There was complete remission of the psoriasis in all seven cases, as reported elsewhere.[2,3]

Renal Function

All patients showed a rise in serum creatinine compared to pretreatment values during the course of the study. The median values are shown in Fig 1. The maximal median levels of plasma creatinine and BUN (Fig 2) were recorded at 8 weeks, after which BUN levels returned to normal. Elevations in creatinine levels above the normal range were reversible and responded to dose reduction.

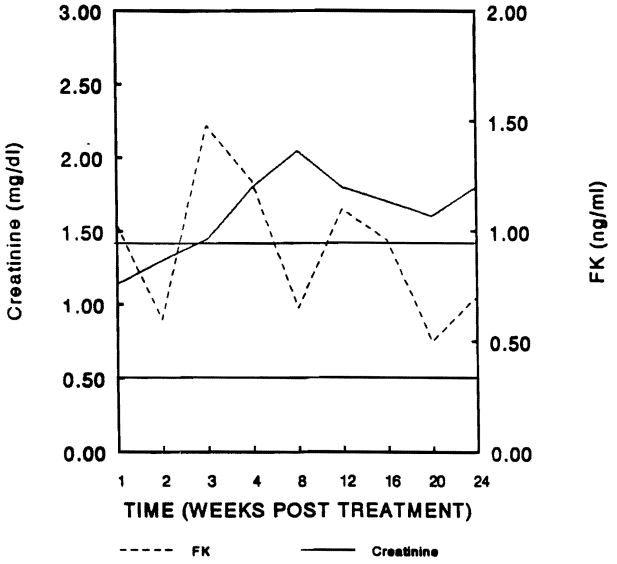

Fig 1. Median serum creatinine and FK 506 plasma levels in seven psoriasis patients treated with systemic FK 506. Horizontal bars denote normal range for serum creatinine.

Uric acid levels showed an early, transient, and minor increase above normal levels. There were no alterations in the serum K^+ or Mg^{++} levels throughout the study period (data not shown).

Glucose Homeostasis

An elevation in plasma glucose level was evident after 4 weeks of treatment. The median level remained near the upper limit of normal from week 4 to 6 months of treatment (Fig 3). No patients required insulin therapy.

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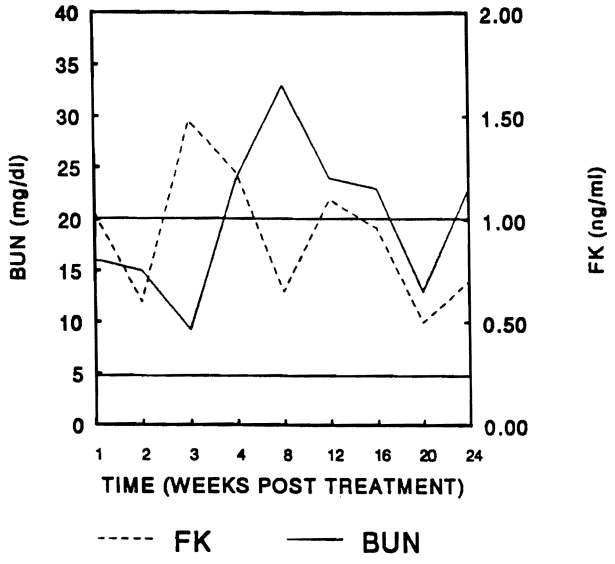

Fig 2. Median serum BUN and FK 506 plasma levels in seven psoriasis patients treated with systemic FK 506. Horizontal bars denote normal range for serum BUN.

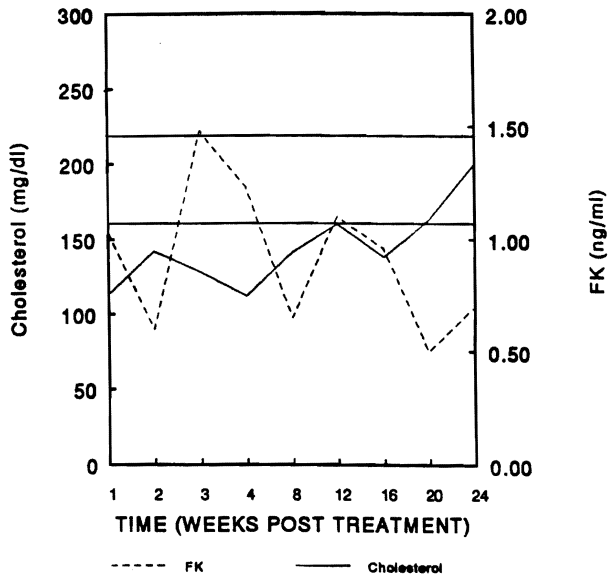

Fig 4. Median serum cholesterol and FK 506 plasma levels in seven psoriasis patients treated with systemic FK 506. Horizontal bars denote normal range for serum cholesterol.

Liver Function

The median total bilirubin and liver enzyme (SGOT and SGPT) levels remained within the normal range. In two patients with abnormal liver-function tests at the start of treatment, total bilirubin and SGOT remained elevated during the course of the study.

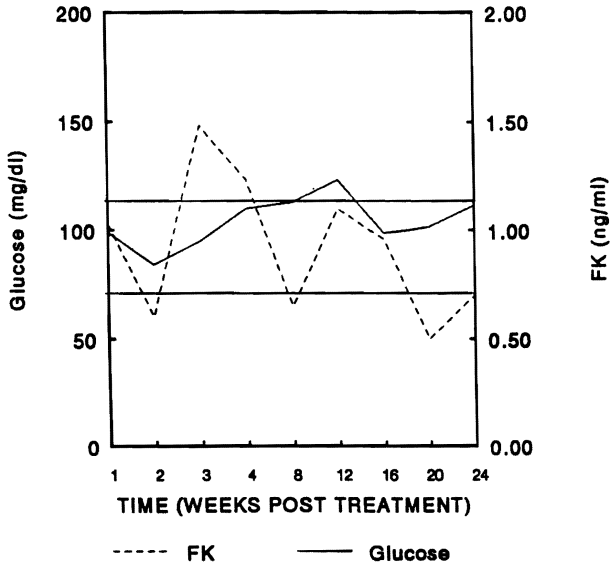

Fig 3. Median plasma glucose and FK 506 plasma levels in seven psoriasis patients treated with systemic FK 506. Horizontal bars denote normal range for plasma glucose.

Cholesterol

Cholesterol levels tended to be low throughout the study (Fig 4) although one patient persistently showed a minor elevation above the normal range.

Blood Pressure

Blood pressure determinations remained within the normal range except for one patient, whose blood pressure was at the upper limit of normal before treatment and who exhibited minor hypertension between weeks 8 and 24 of treatment.

FK 506 Plasma Levels

The median FK 506 plasma level (shown in Figs 1 through 4) ranged from 0.5–1.4 ng/mL during the study period. This range of FK 506 plasma levels was effective in inducing and maintaining complete remission in patients unresponsive to conventional therapy.

Statistical Analyses

No significant change with time in any of the biochemical parameters was found using Friedman's test. There was a positive but not significant correlation between FK 506 plasma level and serum creatinine ($r = 0.071$), BUN ($r = 0.084$), uric acid ($r = 0.193$), glucose ($r = 0.033$) blood pressure (systolic $r = 0.778$, diastolic $r = 0.569$), while a negative correlation ($r = -0.6333$; NS) was found with cholesterol levels.

DISCUSSION

FK 506 shares with CyA the potential for impairment of renal function and carbohydrate metabolism.[5] In this study

of a small number of nontransplant patients, plasma levels of FK 506, about 1 ng/mL and similar to those compatible with organ allograft survival, were highly effective in clearing psoriatic skin lesions within 1 month of the start of therapy.

Associated with this rapid clinical response, however, was evidence of mild renal dysfunction and minor, transient disturbance of carbohydrate metabolism expressed as a mild elevation in the blood glucose level. Although hyperlipidemia is seen in both transplant and nontransplant patients treated with low-dose CyA, this investigation has shown low cholesterol levels in FK 506-treated patients compared with values for normal subjects. Similar observations concerning lipid metabolism have been made in FK 506-treated transplant patients.

There was no evidence of drug-induced hypertension in the present study. Hypertension may occur in as many as 50% of patients given CyA for autoimmune disease.[6] Liver function was normal in this study; even with low-dose CyA (3 mg/kg/d), disturbances in liver function, particularly in bilirubin levels, have been reported in psoriasis patients within 4 months of the start of treatment.[7]

These preliminary observations on a small number of nontransplant patients with psoriasis show that effective doses of FK 506 are associated with only minor metabolic side effects. Further studies must now include plasma drug level range and long-term evaluation of FK 506 therapy in psoriasis.

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