

# Transplantation

## BRIEF COMMUNICATIONS

### FLUCONAZOLE THERAPY IN TRANSPLANT RECIPIENTS RECEIVING FK506<sup>1</sup>

Fungal infections remain an important cause of morbidity and mortality following solid organ and bone marrow transplantation (1-3). Use of amphotericin B, the antifungal agent of choice at present, is frequently associated with a high incidence of side effects. In organ transplant patients particularly, the nephrotoxicity of amphotericin may be amplified when combined with immunosuppressive agents such as cyclosporine or FK506.

Fluconazole, a new antifungal agent with low toxicity and excellent oral bioavailability has been shown to be effective in both the treatment and prophylaxis of fungal infections in immunocompromised patients (4, 5). However, fluconazole is known to inhibit the cytochrome P-450 enzyme system in humans and animals. Coadministration of fluconazole with cyclosporine, a drug that is primarily metabolized in the liver, results in increased cyclosporine blood concentrations in transplant patients (6). Since FK506 is also known to be primarily eliminated by hepatic metabolism, coadministration of fluconazole to patients on FK506 therapy is expected to increase FK506 concentrations in patients (7). In rats, fluconazole is known to increase FK506 blood concentrations (8). In this communication we report our observations on the interaction between FK506 and fluconazole in transplant patients.

Twenty organ transplant patients under FK506 immunosuppression were evaluated while receiving a course of fluconazole therapy. The patient population included 11 patients who received livers (OLT); 6 patients who received kidneys (KTX), 2 patients who received hearts (HTX) and one bone marrow patient. The immunosuppressive regimen included FK506 and low-dose steroids (20 mg/day). FK506 was given initially as a continuous i.v. infusion at 0.1 mg/kg/day, with conversion to the oral dose of 0.15 mg/kg every 12 hr with the return of normal bowel function. Subsequent dose adjustments were guided by the quality of the graft, the presence of any evidence of rejection, signs of toxicity, and trough FK506 plasma concentrations (normal range 0.5 to 2 ng/ml).

Sixteen of the patients studied had documented fungal infection (7 urinary tract infections, 4 esophagitis, 2 pyelonephritis, 2 tracheobronchitis, and 1 cholangitis). *Candida albicans* was the most common pathogen isolated (14 patients), whereas *Candida tropicalis* and *Cryptococcus neoformans* were isolated in one patient each. Four additional patients were considered high-risk patients and were treated with prophylactic fluconazole. The median time from transplantation to the initiation of fluconazole therapy was 60 days (range 2-1680 days). In patients with documented fungal

infection, fluconazole was given for a median of 14 days (range 7-100 days). Fourteen of the 16 patients were successfully treated and became culture-negative. Two failures were noted in two kidney transplant patients who required transplant nephrectomy for persistent fungal invasion of the graft. Four patients received prophylactic fluconazole for a median of 12 days (range 6-30 days), and all remained fungal culture negative. Fluconazole was used at a dose of 200 mg/day in 8 patients and 100 mg/day in 12 patients. FK506 plasma concentrations were measured by an ELISA (9). The intraday coefficient of variation for this assay ranged from 4.2 to 5.5% and the interday coefficient of variation ranged from 14.4 to 17% at concentrations measured in this study. Figure 1 shows the median plasma trough concentration of FK506 on days -1, 0, 1, 2, 3, 4, 5, and 7 after fluconazole therapy as a function of the fluconazole dose administered. On day 1, the median plasma trough concentration of FK506 increased 1.4-fold in patients receiving 100 mg/day of fluconazole and 3.1-fold in patients receiving 200 mg/day. Thereafter the FK506 plasma concentration decreased as the FK506 dose was reduced to prevent higher FK506 concentrations. Figure 2 shows the median dose of FK506 and the plasma concentration of FK506 on days -1, 0, 1, 2, 3, 4, 5, and 7 of fluconazole therapy. A median FK506 dose reduction of 56% (range 0% to 88%) was required in order to maintain the FK506 concentrations below 2 ng/ml. There was no change in the route of FK506 administration during the period studied. The initial

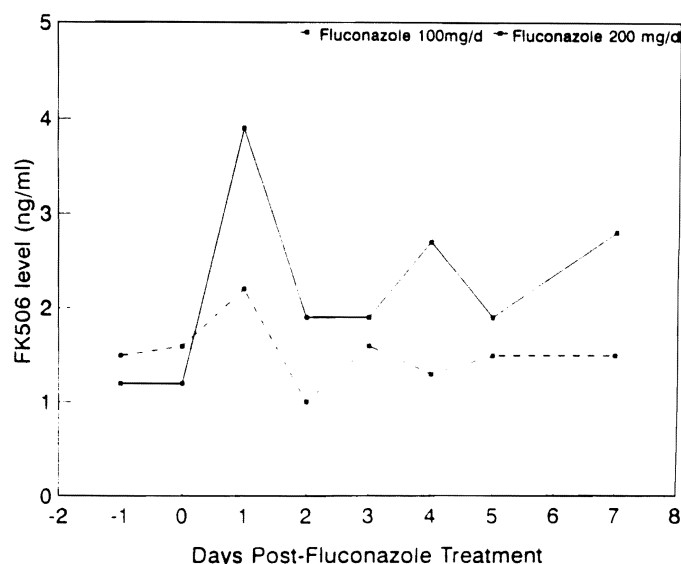


FIGURE 1. Median plasma trough concentration of FK506 in patients receiving 100 mg (continuous line) and 200 mg (interrupted line) of fluconazole.

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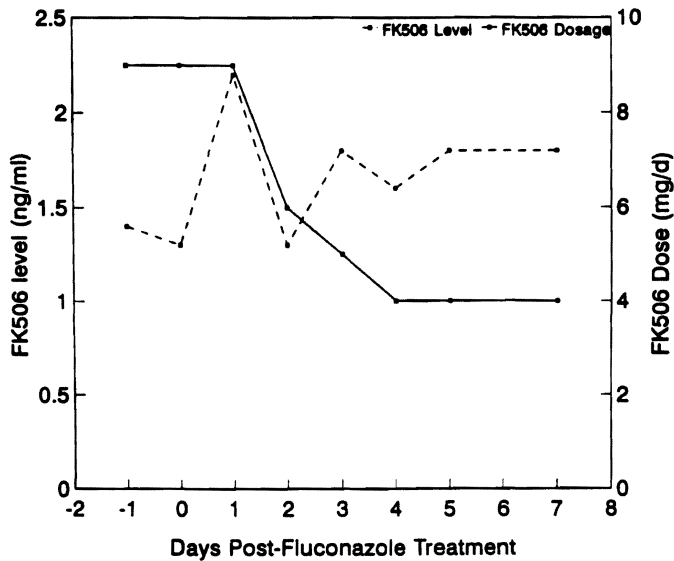


FIGURE 2. Median dose (mg/day) (continuous line) and plasma trough concentration (ng/ml) (interrupted line) of FK506 during fluconazole therapy.

increase in FK506 plasma concentration during fluconazole therapy was associated with acute renal dysfunction in 3 patients (hemodialysis required in one) and acute changes in the mental status in 2 patients.

The pharmacokinetics of FK506 was evaluated in one patient on two occasions, once while on fluconazole therapy (100 mg oral dose, 1 hr prior to FK506 dosing of 3 mg) and again eight days after stopping fluconazole therapy. Figure 3 shows FK506 the plasma concentration vs. time profile over a dosing interval in this patient with and without fluconazole therapy. Discontinuation of fluconazole therapy resulted in a significant decrease in the area under the plasma concentration-versus-time curve of FK506 (from 13 ng/ml/hr to 5.4 ng/ml/hr). The half-life maximum plasma concentration and the trough plasma concentration of FK506 also decreased during this period.

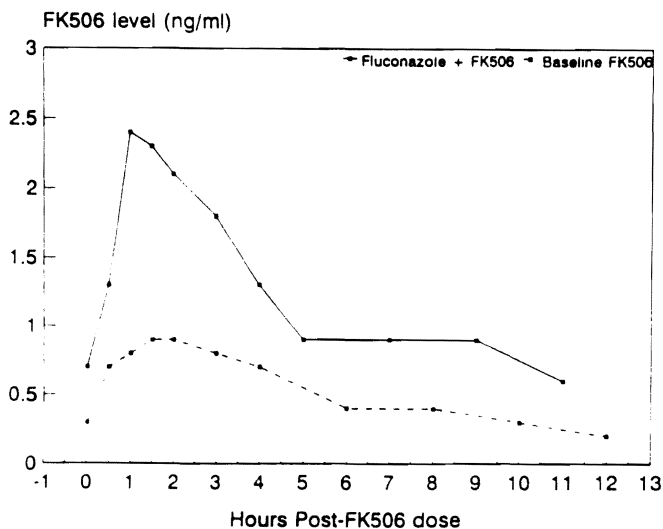


FIGURE 3. FK506 pharmacokinetic profile of one patient with (continuous line) and without (interrupted line) fluconazole therapy.

FK506 is a new immunosuppressive drug with a proven beneficial effect over currently available agents (10-12). Its elimination through hepatic metabolism by cytochrome P-450 enzyme makes it susceptible to possible interactions with other drugs as that are known to induce or inhibit these enzymes, such as phenobarbital, phenytoin, rifampin, clotrimazole, ketoconazole, itraconazole, fluconazole, cimetidine, and erythromycin (7). In rats, FK506 blood concentrations are reported to increase in the presence of fluconazole, erythromycin, ketoconazole, and diltiazam (8). Erythromycin and methylprednisolone have been reported to increase FK506 plasma concentrations (7). Clotrimazole treatment also increases FK506 plasma concentrations in liver transplant patients (13). The data reported here show an increase in trough and maximal plasma concentration of FK506, along with an increase in the half-life of FK506 in the presence of fluconazole. This suggests that fluconazole inhibits FK506 metabolism. It is not possible to predict whether fluconazole decreases FK506 metabolism in the gut and therefore increases the extent of absorption or whether it affects only the hepatic metabolism of FK506. Additional studies are required to understand the extent to which this interaction takes place in the small bowel and/or the liver. The increases in the plasma concentration of FK506 were higher at a 200 mg/day fluconazole dose than at a 100 mg/day dose. This dose-related effect, also reported with CsA (6), may have important implications when fluconazole is used in the treatment of severe fungal infections. Recently, a new fluconazole dosing regimen (200-400 mg/day) has been suggested for the treatment of invasive candidiasis (14). FK506 concentrations should be carefully monitored when using these dosing regimens. Despite the similarities between fluconazole's interaction with CsA and FK506, some differences were observed. In renal transplant recipients, fluconazole slowly increased cyclosporine trough concentrations over a two-week period, reaching a maximum of twice the baseline level (6). In our patients the highest concentration of FK506 was seen within three days after the introduction of fluconazole therapy.

In summary, fluconazole therapy in patients under FK506 immunosuppression appears to be beneficial for both prophylaxis and treatment of fungal infections. Fluconazole doses of up to 200 mg/day can be safely and effectively administered to transplant patients on FK506 therapy provided that the FK506 dose is reduced by half. Use of higher doses of fluconazole would require careful monitoring of trough FK506 plasma concentrations and corresponding reduction in FK506 doses to avoid nephrotoxicity.

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#### POSTTRANSPLANT BLADDER RECOVERY—A PROSPECTIVE RANDOMIZED TRIAL OF TWO TECHNIQUES OF URETERIC ANASTOMOSIS

There is good evidence that vesical function deteriorates significantly while patients with end-stage renal failure are on dialysis (1-3) but the extent of its recovery posttransplantation is not clear. Prat et al. (4) reported on bladder evacuating capacity after renal transplantation and found it to be impaired, especially in the presence of a urinary tract infection. The impairment could not be related to age, the volume of urine passed prior to transplantation, or the length of the postoperative period. They attributed the disturbed bladder evacuating ability to the degree of bladder wall injury sustained on ureteral implantation, with subsequent predisposition to recurrent urinary tract infection. This study investigates the extent of recovery of the bladder function posttransplantation and whether the less-traumatic technique of extravesical ureteroneocystostomy allows greater improvement than the intravesical tunneled ureteric implantation.

This prospective randomized study allocated 48 patients to either intravesical (Int) or extravesical (Ext)\* ureteroneocystostomy (UNC) following an initial preoperative urodynamic study and clinical examination (5). Patients with a previous history of a surgical operation on the urinary bladder and those with a vesical capacity of less than 150 ml were excluded. Randomization was carried out by using a statistical package (Epistat, Round Rock, TX) to produce a numerical sequence for allocation of patients to either arm of the study, using sealed blank envelopes opened following revascularization of the kidney.

Immediately prior to surgery all patients completed two

detailed urological questionnaires at the time of the initial study (one surveying the pre-renal failure stage and the other the pretransplant period) that provided information on vesical function (such as frequency of micturition, nocturia, quality of flow, and hesitancy).

The internal ureteroneocystostomy (int. UNC) involved reflecting the peritoneum off the posterolateral aspect of the bladder, after which a 4-5-cm midline cystotomy was made. A 1-2-cm submucosal tunnel was then created, and, after marking the superior aspect of the ureter with a suture, it was pulled through into the tunnel. The ureter was anastomosed to the vesical mucosa, using interrupted 3/0 plain catgut in such a way as to produce a nipple at the junction. The cystotomy was closed in two layers using 2/0 catgut and Surgilon (braided nylon).

The external ureteroneocystostomy (ext. UNC) comprised the creation of a small 1-cm cystotomy and direct anastomosis of the ureter to the edge of the bladder mucosa using interrupted 3/0 plain catgut sutures. A short (1-cm) extravesical tunnel was then created by suturing the perivesical tissue over the distal ureter and the anastomosis.

At 3 months posttransplant the patients completed a further questionnaire and also underwent a repeat urodynamic study of the bladder. Follow-up data on graft function has been obtained for up to 2 years.

Only patients with full data are included in the final evaluation. The Mann-Whitney *U* test was used for statistical analysis of the data.

A total of 39 completed studies (19 ext. UNC; 20 int. UNC) are available for full analysis because the randomized procedure was not carried out in one patient, one recipient withdrew immediately after the pretransplant study and random-

\* Abbreviations: Ext, extravesical; Int, intravesical; UNC, ureteroneocystostomy.