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ORIGINAL ARTICLE

Increased tacrolimus levels during diarrhea

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Abstract While it is well known that diarrhea results in decreased trough levels of cyclosporin A, experience with levels of tacrolimus (FK506) and diarrhea is limited. We have therefore measured the tacrolimus trough levels of four male and two female recipients of solid organs before, during, and after gastroenteritis. The average age of these six patients was 31 (1–60) years. Four patients had received a kidney transplant, one patient had undergone simultaneous kidney-pancreas transplantation, and another patient had received a liver transplant. Rotavirus was identified in the feces specimen of a 1-year-old child that had undergone liver transplantation. All patients showed an elevated tacrolimus trough level (peak 20–60 ng/ml) after onset of gastroenteritis. Under symptomatic therapy and adequate adjustment of tacrolimus dose, the gastroenteritis stopped and tacrolimus levels returned to the therapeutic range. We recommend that FK506 levels be carefully monitored during diarrhea in order to prevent intoxication.

Keywords Tacrolimus · Transplant · Diarrhea

Abbreviations *ATG* Antithymocyte globulin · *EEG* Electroencephalogram · *FK506* Tacrolimus · *FKBP* FK-binding protein · *IL* Interleukin · *MMF* Mycophenolate-mofetil · *TNF* Tumor-necrosis factor-alpha

Introduction

Tacrolimus (FK506) is a macrolide compound isolated from *Streptomyces tsukubaensis*, a soil fungus found in Northern Japan [14]. Since its discovery in 1984, tacrolimus has been increasingly used in transplantation. Compared to cyclosporin A, tacrolimus-based immunosuppression results in a reduced number of acute and steroid-resistant rejection episodes in kidney [12, 13] and liver transplantation [4, 15]. No differences have been observed regarding graft and patient survival in kidney and liver transplantation, although first reports appear to associate tacrolimus with improved graft- and patient survival following intestinal transplantation [1].

Tacrolimus has a higher affinity to the FK-binding protein (FKBP) in the cytoplasm than does cyclosporine to cyclophilin. FKBP-12 interacts with the calcium-dependent calcineurin/calmodulin complexes to impede calcium-dependent signal transduction subsequent to stimulation of calcium influx in lymphocytes. Tacrolimus inhibits the mixed lymphocyte reaction assay, the formation of IL-2 by T-lymphocytes, the formation of other soluble mediators, such as IL-3, IL-4, IL-5, TNF-, granulo-macrophage colony-stimulating factor, and the expression of IL-2 and IL-7 receptors.

Although tacrolimus does not differ from cyclosporin A in its capacity as a calcineurin-blocking agent, the pharmacokinetics of the two drugs are different. Following oral administration, tacrolimus is absorbed rapidly in the duodenum and jejunum and to a lesser extent also in the ileum and colon. The mean time of peak concentration is approximately 1.5 h. The extent of absorp-

tion varies considerably (range 5%–67%). Absorption is bile-independent and not influenced by oral food intake, although fatty meals were found to reduce the bioavailability of tacrolimus [7]. The drug is distributed extensively in the body, and normally most of the drug resides in tissue stores. Systemically available tacrolimus is metabolized mainly by the hepatic cytochrome P450 3A4 (CYP3A4) isoenzyme. Due to its hepatic elimination, the bioavailability of tacrolimus increases during hepatic dysfunction. Tacrolimus is a low-clearance drug with an extraction ratio of < 3% of hepatic blood flow.

Although it is well known that accelerated transit time in the intestine during diarrhea results in decreased trough levels of cyclosporin A [5], this does not seem to be true of tacrolimus. We here report on six patients, in whom elevated tacrolimus trough levels were measured during diarrhea.

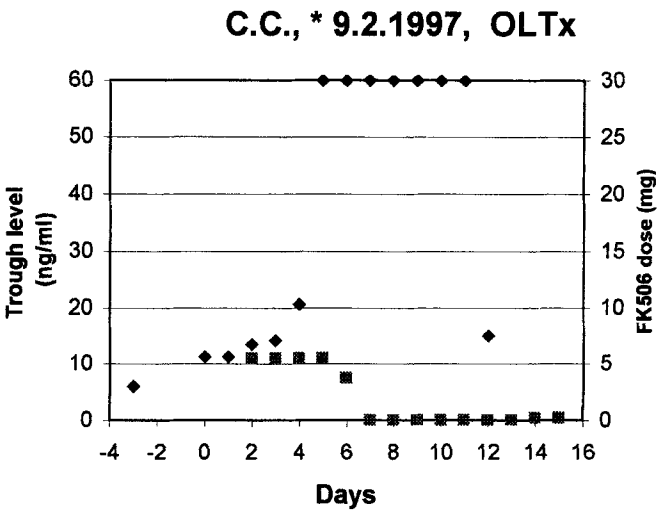

Fig. 1 Tacrolimus trough levels nd daily dose of patient C. C. *Day 0* Onset of gastroenteritis, *OLTx* orthotopic liver transplantation, ◆ FK506 through level, ■ FK506 dose

Materials and methods

Tacrolimus was administered orally in two doses with target whole blood trough levels from 5–15 ng/ml. Whole blood trough levels were measured using a microparticle enzyme immunoassay (IMx Analyzer, Abbott) [6, 8]. Tacrolimus trough levels of four male and two female recipients of solid organs were measured before, during and after gastroenteritis. The mean age of these six patients was 31 (range 1–60) years.

Four patients had received a kidney transplant, one patient underwent simultaneous kidney-pancreas transplantation, and another pediatric patient was the recipient of a segmental liver transplant. Gastroenteritis was defined as the occurrence of vomiting and diarrhea after exclusion of intoxication. Rotavirus was cultured from the feces of the pediatric liver recipient. The other patients remained negative for abnormal pathogens in their feces. Drug interactions with tacrolimus, a possible cause of increased trough levels, were excluded in all cases.

Results

In patient 1 (C. C.), female, suffering from intra- and extrahepatic biliary atresia, a Kasai's procedure was performed with limited success at the age of 3 months. She therefore underwent living-related segmental (segments 2 and 3) – orthotopic liver transplantation 5 months later. Prophylactic immunosuppression was achieved with tacrolimus, corticosteroids and azathioprine. One year after an uneventful peri- and postoperative course, the child was hospitalized for rotavirus-positive gastroenteritis. Figure 1 shows tacrolimus trough concentrations and daily tacrolimus doses during that episode. At FK506 trough levels higher than 60 ng/ml the child developed pneumonia, requiring ventilation for two months, as well as renal failure, necessitating peritoneal dialysis and neurotoxicity with coma and abnormal EEG findings. Pneumocystis carinii was cultured from sputum samples, and staphylococci were identified in blood cultures. FK506 was discontinued until blood levels below 5 ng/ml were reached and then replaced by low-dose cyclosporin A. The infant recovered from pneumonia and regained normal renal function. Eighteen months later, however, the child is still suffering from significant developmental retardation.

Patient A.H.: Five months after a simultaneous cadaveric pancreas-kidney transplantation, which was complicated by transplant pancreatitis, the 28-year-old, male was readmitted for gastroenteritis. The patient initially underwent induction therapy with a single dose of ATG, tacrolimus, mycophenolate-mofetil (MMF) and corticosteroids for prophylactic immunosuppression. Figure 2 depicts the excessively high tacrolimus trough level (> 30 ng/ml), measured one day after the onset of diarrhea. The patient remained normoglycaemic, and renal function was not compromised. After temporary reduction of the FK506 dosages and symptomatic therapy for diarrhea, the patient recovered rapidly.

Patient S. B.: This 37-year-old female underwent kidney retransplantation after having lost her first graft due to chronic rejection. Prophylactic immunosuppression was achieved with a triple-drug regimen (cyclosporin A, azathioprine and corticosteroids). Three weeks later, the patient was switched to FK506 for corticosteroid-resistant rejection. Eighteen months after retransplantation, the patient was readmitted for massive dehydration due to severe diarrhea. Graft function deteriorated, with a rise in serum creatinine levels from 1.3 mg/dl before the onset of diarrhea to above 3.3 mg/dl. FK506 doses and blood levels are summarized in Fig. 3. The diarrhea stopped, and creatinine levels returned to normal after adjustment of the tacrolimus dose. Rehydration and antibiotic treatment of a simultaneous urinary

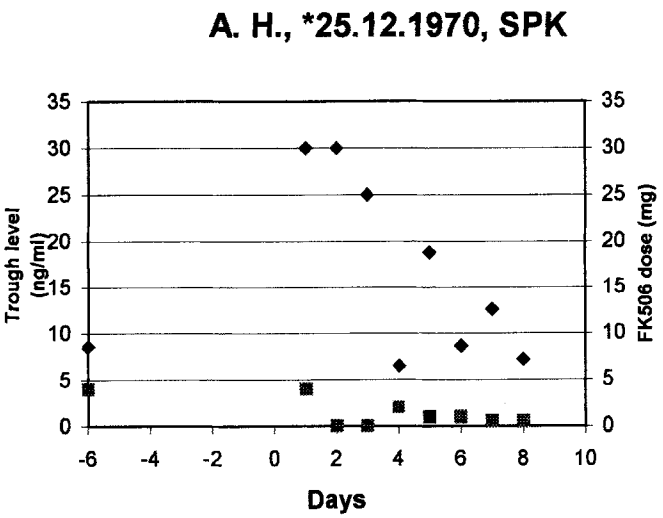

Fig. 2 Tacrolimus trough levels and daily dose of patient A.H. *Day 0* Onset of gastroenteritis, *SPK* simultaneous kidney and pancreas transplantation, ◆ FK506 through level, ■ FK506 dose

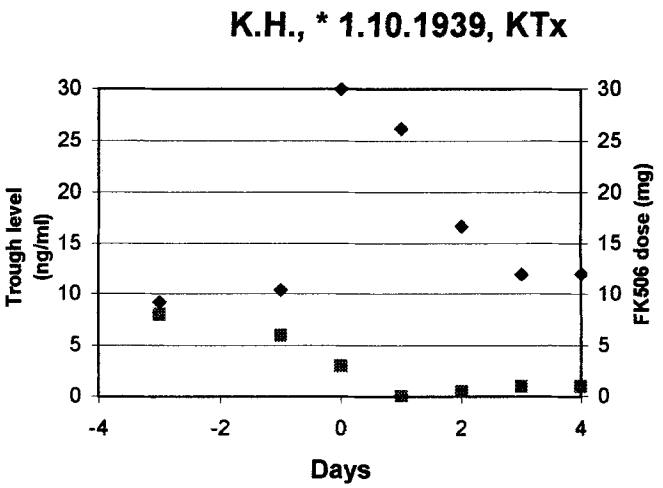

Fig. 4 Tacrolimus trough levels and daily dose of patient K.H. *Day 0* Onset of gastroenteritis, *KTx* kidney transplantation, ◆ FK506 through level, ■ FK506 dose

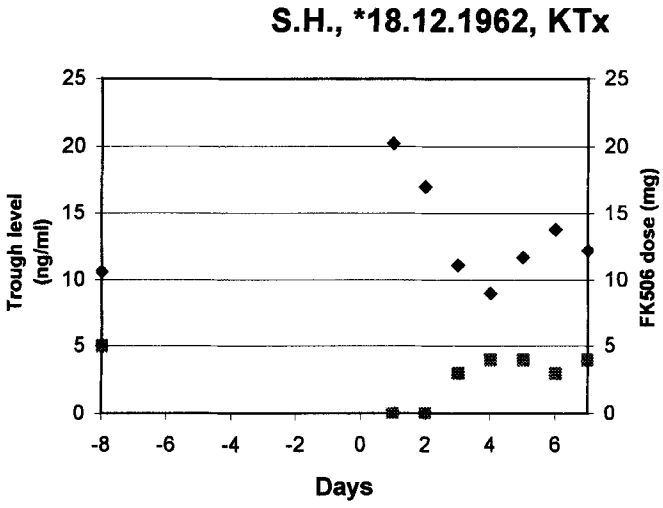

Fig. 3 Tacrolimus trough levels and daily dose of patient S.B. *Day 0* Onset of gastroenteritis, *KTx* kidney transplantation, ◆ FK506 through level, ■ FK506 dose

tract infection with ciprofloxacin (antibiotic treatment was begun after detection of the increased FK506 level).

Patient K.H.: This 60-year-old male with a polycystic kidney disease lost his first kidney graft after 10 years due to chronic rejection. Following retransplantation, immunosuppression was achieved with tacrolimus, 2 g MMF and corticosteroids. The second graft was initially non-functioning due to acute tubular necrosis. During the anuric phase, an acute vascular rejection was diagnosed by Doppler ultrasound and confirmed by histology; it was treated with bolused corticosteroids and extensive plasmapheresis. Two weeks after transplantation, the kidney began to function. Four weeks later, the patient developed severe diarrhea, which was ascribed to MMF, and an otherwise unexplained increase in FK506 levels. After reduction of MMF, diarrhea stopped, and FK506 levels normalized.

Two further patients being treated on an outpatient basis also experienced elevated tacrolimus trough levels after an episode of gastroenteritis, however to a lesser extent, and diarrhea seemed to have already stopped at the time of presentation. Table 1 summarizes their clinical data.

Discussion

In 1996 two infants with increased trough levels of tacrolimus caused by acute infantile diarrhea after liver transplantation for biliary atresia were reported [11]. We observed the same symptoms in adults and recipients of other solid organs, suggesting that this phenomenon is not specific for pediatric recipients of liver allografts.

In another very recent report on the case of a pediatric renal transplant patient with a three-fold increase in serum tacrolimus concentrations during an episode of gastroenteritis, the authors speculate that the bioavailability of tacrolimus may be influenced by changes in gastrointestinal transit time [3].

Bousaros et al. [2] treated pediatric autoimmune enteropathy with tacrolimus. Autoimmune enteropathy is characterized by chronic secretory diarrhea, villous atrophy and associated autoantibodies, and partially responds to immunosuppressive therapy. Despite poor absorption of oral cyclosporine, therapeutic tacrolimus levels were easily achieved in the three studied patients with

Table 1 Summarizes data of two further patients who also experienced increased tacrolimus trough levels during an episode of gastroenteritis

	Patient F. G.	Patient M. G.
Age (years)	57	59
Gender	Male	Male
Transplanted organ	Kidney	Kidney
Primary disease	Polycystic nephropathy	Membranoproliferative glomerulonephritis
Lag phase between transplantation and diarrhea episode	4 Months	58 Months
Peak tacrolimus trough level during diarrhea episode (ng/ml)	21.0 ng/ml	20.3 ng/ml

autoimmune enteropathy. All patients showed clinical improvement as documented by decreased stool output and the ability to be weaned off parenteral nutrition.

One possible explanation for the observed effect might be two competitive reactions taking place in small bowel mucosa. These are 1) absorption and 2) enzymatic, presystemic metabolism of the drug by gastrointestinal CYP3A4. This enzyme is considered to influence the oral bioavailability of tacrolimus considerably, reducing it to approximately 20% [9, 10]. Absorption is speculated to be a relatively fast process compared to drug metabolism. Under normal conditions, up to 80% of the drug undergoes slow metabolic degradation within the intestinal mucosa, and only about 20% is absorbed. In the case of diarrhea with a short transit time, more of the drug is absorbed and less metabolized, which may result in increased tacrolimus trough levels.

Because of its poor aqueous solubility and extensive erythrocyte- and plasma protein binding, tacrolimus is not dialysable. Therefore no specific treatment for tacrolimus intoxication is available, and all therapeutic measures are purely symptomatic. Side-effects of tacrolimus intoxication observed in our series were fully reversible in all patients. Retardation in the pediatric liver recipient may be due to long-term intensive care, which was temporarily also complicated by poor oxygenation as well as by severe electrolyte imbalances. In conclusion, we recommend that FK506 levels be carefully monitored during diarrhea in order to prevent intoxication.

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