CASE REPORTS

Severe Prolonged Tacrolimus Overdose with Minimal Consequences

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A 59-year-old man inadvertently received a 10-fold increase in his twice-daily oral dose of tacrolimus 1 mg that resulted in trough blood levels above 90 ng/ml for over a week. The patient had end-stage renal disease secondary to diabetes mellitus and had received a kidney transplant from his daughter 3 months earlier. Despite the numerous adverse effects commonly reported with tacrolimus, such as mild nephrotoxicity, nausea, tremors, and elevated liver enzyme levels, our patient's acute but prolonged overdose resulted in minimal signs and symptoms of toxicity. Nevertheless, education regarding the importance of accurate dosing, close monitoring, potential drug interactions, and the various capsule colors should be provided to all patients who receive tacrolimus, as well as their physicians, nurses, and pharmacists, in order to prevent as many errors as possible.
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Tacrolimus (FK 506, Prograf; Fujisawa Healthcare, Inc., Deerfield, IL) is an immunosuppressant agent commonly administered to prevent acute allograft rejection after solid organ transplantation. Long-term administration of tacrolimus has been associated with numerous adverse effects, such as nephrotoxicity, neurotoxicity, electrolyte abnormalities, and glucose intolerance.[1, 2] Case reports of acute overdoses of tacrolimus have not described the consequences of significantly elevated levels sustained for an extended period.[3-8] Our patient had supratherapeutic tacrolimus levels for over 9 days.

Case Report

A 59-year-old, 79-kg man with end-stage renal disease secondary to diabetes mellitus and hypertension received a living renal transplant from his daughter. Aside from tremors and mild confusion that were present before transplantation and continued subsequently, the patient had an uneventful recovery and was discharged 5 days after his operation; his serum creatinine level was 0.9 mg/dl. His immunosuppressant regimen at discharge consisted of oral prednisone 30 mg/day, oral tacrolimus 1 mg twice/day, and oral mycophenolate mofetil 1000 mg twice/day. His trough tacrolimus level at discharge was 12.6 ng/ml (normal 5–15 ng/ml).

Three months after transplantation, the patient was admitted to the hospital with symptoms of an upper respiratory infection, an elevated blood glucose level, changes in mental status, a 4-day history of combativeness and confusion, and a 2-day history of tremors. His tacrolimus level was 118.5 ng/ml. Because of a prescribing error, his twice-daily dose inadvertently had been increased from 0.5 to 5 mg 8 days before his hospital admission. Neither the patient nor his wife had questioned the different-color capsule that was dispensed. His trough tacrolimus level 4 days before his admission was 91.6 ng/ml. A mild elevation in his aspartate aminotransferase level (from 24 to 57 IU/L) and white blood cell count

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Table 1. Our Patient's Laboratory Test Results

Laboratory Test	On Hospital Admission	Day 2	Days 3–4	Normal Range
Sodium (mEq/L)	140	143	—	135–145
Potassium (mEq/L)	4.3	4.4	—	3.5–5.5
Chloride (mEq/L)	102	112	—	95–105
Bicarbonate (mEq/L)	18	19	—	22–27
Blood urea nitrogen (mg/dl)	21	13	—	5–20
Creatinine (mg/dl)	1.1	0.8	—	0.8–1.4
Glucose (mg/dl)	532	188	—	65–200
Calcium (mg/dl)	10.0	9.4	9.1	8.4–10.6
Phosphorus (mg/dl)	3.4	< 1.0	2.7	2.5–4.9
Magnesium (mg/dl)	—	—	0.7	1.6–2.9
Uric acid (mg/dl)	—	—	3.4	4–7
Creatine kinase (U/L)	—	—	61	50–180
Cholesterol (mg/dl)	—	—	152	120–200
Albumin (g/dl)	4.2	3.5	—	3.5–5.0
Alkaline phosphatase (U/L)	—	—	66	25–125
Aspartate aminotransferase (U/L)	—	—	29	25–45
White blood cell count (x $10^3/mm^3$)	17.7	18.8	—	4.5–11.5
Hematocrit (%)	50.4	48.2	—	14–18
Platelets (x $10^3/mm^3$)	200	218	—	150–450
International normalized ratio	1.1	—	—	0.9–1.1
Partial thromboplastin time (sec)	27.2	—	—	24.7–33.4
Tacrolimus level (ng/ml)	118.5	80.7	54.6 (day 3) 25.0 (day 4)	5–15

(from 12.0 to 16.1 x $10^3/mm^3$) were the only other biochemical abnormalities at that time.

His drug regimen on admission consisted of prednisone, tacrolimus, mycophenolate mofetil, doxazosin, atorvastatin, nifedipine, nefazodone, sulfamethoxazole-trimethoprim, ranitidine, and insulin. Atorvastatin was the only drug added since his discharge after transplantation. Because of the well-known drug interaction with tacrolimus, the nefazodone dosage had not been changed since transplantation. Except for leukocytosis, hyperglycemia, and ketonemia, the patient's venous blood counts and laboratory values on admission were essentially normal (Table 1), as were his arterial blood gases (partial pressure of oxygen 81 mm Hg, partial pressure of carbon dioxide 35 mm Hg, pH 7.35). His average serum creatinine level before the tacrolimus overdose had been 0.9 mg/dl (range 0.7–1.0 mg/dl) since transplantation. Urinalysis was remarkable only for a glucose level greater than 1000 mg/dl and the presence of ketones. Because of the patient's worsened confusion, a lumbar puncture was performed and empiric antimicrobial therapy was started. Results of cerebral spinal fluid analysis revealed elevated glucose (151 mg/dl) and protein (108 mg/dl). When culture results were obtained, all antimicrobials were discontinued.

Throughout the patient's course of therapy, his serum creatinine level remained stable (Figure 1). His tacrolimus level was 9.8 ng/ml 6 days after admission, and tacrolimus therapy was restarted at 0.5 mg. Three days after therapy was restarted, serial tacrolimus levels were obtained to determine whether the patient's absorption or rate of elimination exhibited characteristics that would better help us manage his tacrolimus therapy (Figure 2). After 5 days, therapy was

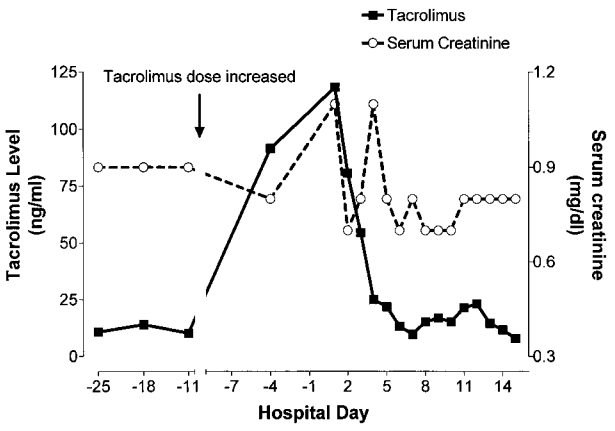

Figure 1. Tacrolimus (ng/ml) and serum creatinine (mg/dl) levels before and after the patient's hospital admission for tacrolimus overdose.

discontinued, and the patient was given prednisone and mycophenolate mofetil as immunosuppressive therapy to minimize the risks of neurotoxicity associated with either tacrolimus or cyclosporine. His confusion slowly improved throughout his hospital stay but did not resolve.

On hospital day 12, the patient's urine output decreased; a bladder scan revealed a dilated bladder with 700 dl residual urine. A urology consultant suggested restarting therapy with doxazosin (which had been held since admission) and scheduled intermittent urinary catheterizations due to benign prostatic hypertrophy with mild obstruction. Oral doxazosin 2 mg at bedtime given before admission was restarted at half the dose. The patient was discharged 2 days later to a rehabilitation facility. His drugs at discharge were prednisone, mycophenolate mofetil, sulfamethoxazole-trimethoprim, clotrimazole, atorvastatin, ranitidine, lisinopril, doxazosin, nefazodone, magnesium lactate, and insulin. He was readmitted 2 weeks later with urosepsis that was treated successfully with antibiotics. He underwent a transurethral resection of the prostate 1 month later, after which his mental status dramatically improved to a level that exceeded his pretransplant condition.

Discussion

Tacrolimus is a potent immunosuppressive agent associated with many adverse reactions, some of which are dose dependent.[1, 2] In several case reports of acute tacrolimus overdose,[3–8] patients remained asymptomatic or exhibited only mild, transient signs and symptoms. Main manifestations of toxicity were mild nephrotoxicity, nausea, tremors, and elevated liver enzyme levels.[3, 5, 8] Some patients were treated with anticonvulsant therapy to induce metabolism of tacrolimus.[4, 7, 8] A metabolism-inducing agent was not administered in this situation due to the presence of relatively mild toxicity and the possibility of confounding the ability to restart and manage tacrolimus levels. Our patient's case was unusual in that his tacrolimus levels remained at supratherapeutic levels for at least 9 days, with trough levels above 90 ng/ml for at least 4 days.

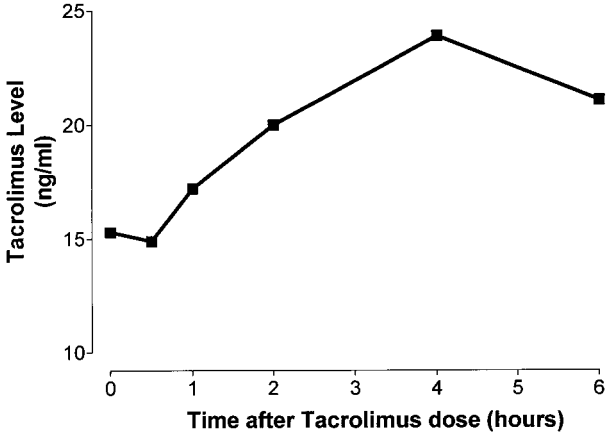

Figure 2. Serum tacrolimus levels over time immediately before and for several hours after he received a 0.5-mg dose to measure tacrolimus absorption.

Manifestations of tacrolimus toxicity in our patient were fairly mild. Potassium levels were higher than his previous posttransplantation levels both on admission and during the period of supratherapeutic tacrolimus levels; however, none of the potassium levels were outside the normal range. Phosphorus and magnesium levels were extremely low during the first few days after hospital admission. Blood pressure was variable but not constantly elevated. Hepatic dysfunction was mild, demonstrated by a transient increase in aspartate aminotransferase. The patient's mental status was relatively worse according to his wife, but examination revealed no new or focal neurologic deficits. Onset of the signs of tacrolimus toxicity may have been masked due to the patient's tremors and mild confusion, which were present even before transplantation.

Although these abnormalities have been reported with tacrolimus, each one may reflect complications of our patient's poor glucose control. Indeed, the main consequence of tacrolimus therapy and overdose appears to have been impaired diabetes therapy. Our patient's condition had been stable and well controlled by administration of oral hypoglycemic agents before transplantation, but he required insulin afterward. His fasting blood glucose level, measured in the hospital 1–2 times/week after transplantation, was 65–326 mg/dl; most values were above 150 mg/dl during the 2 months before his hospital admission for tacrolimus overdose. Home monitoring, performed several times/day with a portable dextrose-monitoring device, indicated that his blood glucose level was usually 100–200 mg/dl, with infrequent escalations above 500 mg/dl. His blood glucose control worsened during the period of tacrolimus overdose, including the initial blood glucose level

of 532 mg/dl at his hospital admission. The patient was managing his diabetes through dietary modification alone since his tacrolimus therapy was discontinued.

The role of the patient's urologic problems is difficult to discern. Worsening confusion was the chief clinical finding at the time of tacrolimus overdose, but his confused state lasted for approximately 1 month after tacrolimus levels were undetectable and improved significantly only after resolution of his urologic problems. Whether a direct correlation, or any correlation, exists between the patient's urologic problems and his confusion is unclear. Some confusion may have been uremic in origin and may not have resolved until several months after transplantation. Another, not mutually exclusive, possibility is that he experienced continuing low-grade urinary tract infection that augmented his pretransplantation confusion, and that this infection resolved with resolution of his benign prostatic hypertrophy. The specific etiology regarding his chief symptom of confusion is unclear and almost certainly multifactorial.

Conclusion

Tacrolimus is a widely prescribed immunosuppressant administered for prevention of graft rejection in organ transplant recipients. Long-term administration of tacrolimus is associated with numerous adverse effects. Acute overdose of the drug, however, may exhibit minimal signs and symptoms of toxicity. This absence of early clinical manifestations of toxicity supports the need for routine measurement of drug levels even in patients whose conditions are stable. Careful monitoring of tacrolimus levels is extremely important given the drug's narrow therapeutic window, the risks of chronic toxicity, and the multitude of drug interactions that may occur anytime after transplantation. Management of our patient's acute overdose consisted solely of monitoring for signs of toxicity and providing supportive care. Education concerning the importance of accurate dosing, close monitoring, potential drug interactions, and the various capsule colors should be provided to all patients who receive the drug, as well as their physicians, nurses, and pharmacists, in order to prevent as many errors as possible.

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