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Case Report

Tacrolimus Induced Organ Failure: Reversal by Activation of the Cytochrome P450-3a System

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Abstract: Tacrolimus is the cornerstone component of all immunosuppressive regimens. Despite its long record of use, very little is known about its acute toxicity syndrome. We describe five patients with acute organ failure, involving both native and transplanted organs, which was reversed by inducing the cytochrome P450-3A system. In all patients, the causative drug was stopped and phenytoin was given intravenously to accelerate tacrolimus metabolism. Within 24 h, tacrolimus trough levels fell daily at a significant level ($p < 0.05$) and all failed organs recovered their normal function within 48–72 h. Therefore, phenytoin metabolic induction appears to be a safe therapeutic option for patients with acute tacrolimus toxicity.

Keywords: tacrolimus toxicity; organ failure; pharmacologic therapy; cytochrome P450-3A; phenytoin; metabolic enhancement

Citation: Nghiem, D.D. Tacrolimus Induced Organ Failure: Reversal by Activation of the Cytochrome P450-3a System. *Uro* **2021**, *1*, 222–227. https://doi.org/10.3390/uro1040024

Academic Editor: Tommaso Cai

Received: 7 October 2021
Accepted: 8 November 2021
Published: 11 November 2021

1. Introduction

Tacrolimus (TAC) is a macrolide antibiotic introduced in 1985 that has emerged as a cornerstone immunosuppressant over the last four decades. Despite this long record, its use is still hampered by difficulties in achieving optimal dosing, which has led to multiple chronic side effects such as nephrotoxicity, neurotoxicity, liver dysfunction and electrolyte imbalance. All these well-recognized complications responded to simple TAC dosage reduction.

Acute TAC toxicity, on the contrary, has rarely been recorded. Acute single ingestion of massive doses of TAC is usually well tolerated and, in the few instances reported, early oral administration of milk or inactivated charcoal suffices to mitigate organ dysfunction [1]. Few anecdotal reports describe the use of phenytoin to treat TAC-induced neurotoxicity and hepatotoxicity [2,3]. Drug interaction was reported in two heart transplant recipients who required a 2–3-fold increase in TAC dosing to achieve therapeutic levels when phenytoin was used concomitantly for seizure activity [4]. Encouraged by our earlier report on the successful treatment with phenytoin of a renal transplant patient receiving a single dose of 7500 mg of the calcineurin inhibitor cyclosporine, causing acute liver dysfunction and encephalopathy [5], we have elected to treat five patients with TAC-induced organ failure through parenteral administration of phenytoin. We recorded the concomitant accelerated clearance of TAC and the rapid reversal of organ failure. The institutional review board approval was waived because the study did not identify any patients.

2. Case Presentations

2.1. Patient 1

A 25-year-old patient underwent a successful living-related kidney re-transplant ten years following bladder drained, simultaneous pancreas–kidney transplants. The patient was discharged on day five, on TAC, mycophenolate mofetil and prednisone with serum creatinine of 1.2 mg/dL, fasting blood sugar (FBS) of 95 mg/dL and HbA1C of 5.8%. Ten days later, he was readmitted with a FBS of 450 mg/dL, serum creatinine 1.6 mL/dL, AST 65 IU/L and ALT 30 IU/L. The serum TAC trough level was 27 ng/mL (normally

within 5–15 mcg/L). A Technetium DTPA scan showed prompt renal and pancreas allograft blood flows. Serum amylase and lipase levels were normal. Random urine amylase was 60.000 U/L (baseline 50–75,000 U/L). No hematuria was noted. The pancreas was not enlarged on physical examination and on computed tomography. After work-up, he was treated with three daily doses of 250 mg methylprednisolone and intravenous phenytoin at a 10 mg dose every 8 h with a blood level of 15 mcg/ML (normally 10–20 mcg/L) the following day. TAC was also withheld concomitantly. Hyperglycemia was controlled with regular insulin. On the third day, normoglycemia was reestablished without exogenous insulin. TAC trough levels fell to 15 ng, 10 ng and 5 ng/mL, respectively, on days 2, 3 and 4. TAC was restarted at 0.08 mg/kg on day 5 upon discharge. Nine months later, he remained euglycemic with Hb A1C 5.0% and had normal renal function with serum creatinine of 1.0 mg/dL.

2.2. Patient 2

A 58-year-old male received a deceased donor renal transplant with serum creatinine of 1.8 mg/dL at discharge, on prednisone, TAC and MMF. The patient was readmitted 4 months later for an intractable, continuous, disabling hiccup resistant to chlorpromazine. No other neurologic findings were identified. The serum creatinine level was 4.4 mg/dL and TAC trough level was 34 ng/mL Liver function tests were normal. FBS was 435 mg/dL. The renal transplant ultrasound with Doppler study was unremarkable with a resistive index of 0.8. Computed tomograms of the head were normal. Intravenous phenytoin was given at the dose of 10 mg every 8 h to achieve therapeutic levels, while TAC was withheld simultaneously. TAC trough levels decreased to 8.3 ng/mL on day 2 and 4.5 ng/mL on day 3. Serum creatinine returned to 1.8 mg/dL on day 3 and FBS was 110 mg/dL. The disabling hiccup resolved 36 h after admission. The patient was discharged euglycemic after resumption of TAC at 0.08 mg/kg. At a 15-month follow-up, the patient was doing well.

2.3. Patient 3

A 38-year-old female was scheduled to have a living related donor kidney transplant. Because of panel reactive antibodies of 38%, the patient was pretreated with TAC 0.1 mg/kg/day. On the second day, the patient was admitted emergently for isolated cortical blindness. Other than the visual defect, the physical and neurological examinations were normal. Serum creatinine was 6.8 mg/dL, and liver function tests were normal. The TAC trough level was 20 ng/mL An MRI of the brain showed occipital microvascular vasoconstriction without bleeding or space occupying lesion. Phenytoin was administered parenterally upon admission and TAC was discontinued. During the following 3 days, TAC trough levels felt to 15 ng/mL, 7.5 ng/mL and 2 ng/mL, respectively. She regained normal vision 22 days later. She subsequently underwent a successful transplant using anti-thymocyte globulin, MMF and rapamycin.

2.4. Patient 4

A 65-year-old male discharged 5 days after a living related donor kidney transplant with serum creatinine of 0.8 mg/dL. The patient was on TAC, MMF and prednisone. The TAC trough level was 20 ng/mL upon discharge. The patient was readmitted on day 21 with a serum creatinine level of 8 mg/dL and TAC trough level of 25 ng/mL The renal allograft sonogram was normal. Liver function tests were abnormal with ALT 60 IU/L and AST 80 IU/L. The patient received three empirical methylprednisolone pulses. Simultaneously, TAC was withheld and parenteral phenytoin was started to achieve a blood level of 16 mcg/mL TAC trough levels decreased to 17 ng/mL, 10 ng/mL, and 5 ng/mL, respectively, on day 2,3 and 4. Serum creatinine returned to 0.9 mg/mL on day 3. Liver function tests were normalized. All medications were resumed afterwards. The patient was doing well at a 26-month follow-up.

2.5. Patient 5

A 45-year-old patient received a deceased donor kidney transplant with serum creatinine at 1.8 mg/dL and a TAC trough level of 14 ng/mL at discharge. The patient was maintained on TAC, MMF and prednisone. Thirteen days later, the patient was readmitted for minimal urine output, a serum creatinine of 14 mg/dL and BUN 92 mg/dL. The TAC trough level was 31 ng/mL. A technetium DTPA scan showed good renal transplant blood flow but very poor excretion. No radioactive material was retained in the renal pelvis. The allograft sonogram with Doppler study confirmed the excellent blood flow with a resistive index of 0.7 and the absence of hydronephrosis. He received methylprednisolone 250 mg daily for 3 days. TAC was withheld upon admission and simultaneously phenytoin was given parenterally with a serum level of 16 mcg/mL. TAC trough levels fell to 20 ng/mL, 17 ng/mL and 8 ng/mL over the following 3 days. Serum creatinine at discharge was 1.2 mg/dL. Low-dose TAC was resumed in conjunction with MMF. He was doing well at 32 months.

3. Discussion

Tacrolimus is a very potent immunosuppressant in transplantation. But despite 36 years of experience with the use of Tacrolimus, acute multiple organ dysfunction/failure due to TAC overdosing still occurs. It is rarely recognized and reported. Only 5 out of 1816 patients were identified in our transplant center during a 21 year period. Multiple reasons account for this lack of clinical acumen.

First, drug poisoning is rarely reported in the transplant literature. Using the United States Renal Data System from July 1974 to June 1998 and ICD9 code, Abbott K.C. et al. were able to identify only 46 patients out of 42,096 (0.10%) who were hospitalized within 3 years of renal transplantation for poisoning by immunosuppressive agents. Most of the drug poisoning events occurred within 1–2 months after transplantation. The causal drugs were not identified in the report [6]. Ceshi A et al., from the Swiss Toxicological Information Center, recorded 8 cases of TAC poisoning out of 145,391 cases, for an incidence of 0.0055%. All cases were reported from 3 h to 10 days after the overdose event [7]. The FDA registry reported 13 cases out of 49,128 people taking TAC from 1998 to June 2015, for an incidence of 0.03% [8], whereas our report notes an incidence of 0.29%. This may imply that this clinical syndrome is rarely recognized or is under-reported since over 400,000 patients have taken the drug since its introduction.

Second, TAC has a peculiar pharmacodynamics profile. TAC absorption is extremely erratic and is influenced by food intake, which reduces the Area Under the Curve and Maximum Concentration by 37% and 73%, respectively. A high carbohydrate meal could decrease AUC and C Max by 28% and 65%, respectively. Less than 2% of the drug is eliminated in the urine. TAC has a high propensity for protein binding and sequestration in red blood cells, which renders hemodialysis and plasmapheresis ineffective in drug removal. TAC metabolism is carried out totally by the hepatic oxidase CYP450-3A/glycoprotein system and, as such, is influenced markedly by multiple drug interactions. Substances which inhibit the cytochrome oxidase decrease the catabolism and increase TAC levels. This is the case for diltiazem, fluconazole, ketoconazole, clarithromycin and erythromycin, which have been used in clinical settings to lower the drug dosing [9]. Conversely, substances that induce P450-3A/PGP activity such as phenytoin, phenobarbital, oxcarbazepine, antiretroviral agents and herbal supplements increase TAC catabolism and decrease TAC availability [8–12]. Taken all together, the ability to accurately assess the pharmacodynamic parameters and the drug half-life itself is limited in clinical settings, making daily serum TAC levels the only tool to monitor the drug clearance. In other words, improvements in renal, hepatic, neurologic and pancreatic function reflect the degree of TAC clearance.

Third, the symptoms of acute TAC toxicity are not well known. They vary widely from lack of symptoms to severe renal failure or neurotoxicity. Thus, most of the patients reported by the Swiss study presented with “minor” symptoms or signs such as vomiting, headache, somnolence, abdominal cramps and nonspecific ECG changes. Only two patients

had "severe" symptoms such as tremor, encephalopathy, extrapyramidal symptoms and worsening of renal function following large oral overdoses over 20.8 times the usual dose [7]. Conversely, our five patients had a total of nine organs or system failures affecting the transplant pancreas (n = 1), the native pancreas (n = 1), the brain (n = 2), the kidney (n = 3) and the native liver (n = 2), i.e., an average of 1.8 organ dysfunctions/failures per patient, and are still "asymptomatic" by the Swiss standard, with the exception of the two patients developing cortical blindness and intractable hiccups, respectively. This stark contrast strongly suggests that acute TAC toxicity should be considered when one or more organ dysfunctions/failures are noted in any patient taking TAC-based immunosuppression. For instance, the sudden onset of diabetes mellitus in a stable patient with a native or transplanted pancreas should evoke TAC toxicity since TAC has been known to cause islet cells degranulation in the rat [13]. Fortunately, this degranulation can be reversed with cessation of TAC therapy as well as phenytoin therapy without sequelae beginning as early as 3 days, as observed in our first pancreas transplant recipient and in our second patient with a native pancreas involvement. The occurrence of severe neurologic events of central origin should point at TAC toxicity and call for emergent treatment.

Finally, because of its extremely rare occurrence, the therapy for TAC poisoning has been anecdotal. Two adult liver transplant recipients receiving phenytoin, which improved both liver functions and TAC levels to such an extent that phenytoin was hinted at as the treatment option for acute TAC overdose after liver transplantation [2]. Two heart transplant recipients, taking phenytoin for seizure activity, required a 2–3-fold dosage of TAC to maintain therapeutic TAC blood levels. In these last patients, P450-3A induction even persisted up to 10–21 days after discontinuation of phenytoin [3]. A recent patient who received a 25-fold TAC overdose was treated successfully with pharmacologic enhancement of TAC catabolism with phenobarbital. The pharmaco–dynamic studies performed in this single patient showed that the TAC half-life was reduced to 14.1 h, in contrast to 27.5 h determined in a similar but untreated patient [7]. Classically, discontinuation of the offending drug is a very reasonable first step to take, although there was a 24-h delay in clearing the drug in the four patients who had TAC withheld upon admission [14]. Withholding TAC alone does not allow the drug to clear pharmacodynamically as fast as our levels would show clinically, as in TAC chronic toxicity. As shown in Table 1, under the effects of parenteral phenytoin, TAC trough levels decreased daily between day 1 and subsequent days ($p < 0.05$) as well as between each subsequent day.

Table 1. Daily TAC levels (ng/mL). Comparison using *t*-test.

	Day 1	**Day 2**	**Day 3**	**Day 4**
Patient 1	27	15	10	5
Patient 2	34	8.3	4.5	NA
Patient 3	20	15	7.5	2
Patient 4	25	17	10	5
Patient 5	31	20	17	8
Mean	27.4	15.1	9.8	5.0
Mean ± SD	27.4 ± 4.8 [a, b]	15.1 ± 3.8 [a, b]	9.8 ± 4.1 [a, b]	5.0 ± 2.1 [a, b]

[a] $p < 0.05$ between day 1 vs. day 2, day 3 and day 4; [b] $p < 0.05$ between day 1 vs. day 2, day 2 vs. day 3 and day 3 vs. day 4.

The rapid effects of phenytoin on TAC favor the induction of CYP 450-3A on the central-lobular hepatocytes as opposed to the peripheral hepatocytes which can take up to 14 days [14]. The rapid clearance of TAC levels leads to the rapid reversal, within a few days, of the multiple organ dysfunction/failure observed in our patients. Taken all together, in this emergent situation of acute TAC toxicity, the clinician does not have any choice except to classically discontinue the offending drug and then enhance its elimination as practiced in this series. The use of small doses of methylprednisolone—albeit a weak CYP-3A enhancer—as a first step to increase TAC elimination and to treat a presumed rejection episode, with minimal infectious risks, would still be clinically acceptable although

frowned upon by some clinicians, since a decrease in function in a transplant would most likely suggest clinical rejection and warrant early therapy. Phenytoin comes next in line because of its effectiveness in accelerating the catabolism of TAC, besides preventing and treating convulsions and seizures that may be caused by TAC toxicity. The rapid onset of action and the ease of monitoring make it the drug of choice. Parenteral phenytoin can provide a faster way to achieve optimal levels as compared to the oral route used previously, which causes gastrointestinal side effects related to a 300–400 mg/day dose [13]. Our case series demonstrate the effectiveness of a novel pharmacokinetic approach to accelerate TAC catabolism in the treatment of acute TAC toxicity on native as well as transplanted organs. In the 32-month follow-ups we have not seen any side effects of the short course of phenytoin administration.

As in all retrospective clinical studies, this report has limitations including the very small sample size and the lack of a control arm subjected to discontinuation of TAC alone. It is intended to, first, call the attention of all clinicians taking care of transplant patients to the identification of the syndrome, then to stimulate the development of a multicenter prospective trial comparing discontinuation of TAC with/without pharmacologic enhancement of TAC elimination with phenytoin, to establish the best therapy for TAC-induced organ failure.

4. Conclusions

The syndrome described herein, although very rare, has been recorded only 3 decades after the introduction of TAC and should be suspected based on the combination of high TAC trough levels and native or transplanted organ dysfunction/failure. Phenytoin, a very well-known anticonvulsant and potent enzyme inducer of P450-3A with its rapid onset of action and ease of monitoring, should be started intravenously immediately in conjunction with the immediate discontinuation of TAC.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

TAC: tacrolimus, HbA1c: Glycated Hemoglobin, AST: Aspartate Amine Transferase, ALT: Alanine Amino Transferase, FBS: Fasting Blood Sugar, AUC: Area under the curve, DTPA: Diethylene-triamine Technetium Penta-Acetic acid.

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