Acute Overdoses of Tacrolimus (FK 506)

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Tacrolimus (FK 506) is a new molecular entity discovered in 1984 and produced as a fermentation product of Streptomyces tsukubaensis. The compound is a macrolide lactone that has potent immunosuppressive activity both in vitro and in vivo (1). In clinical studies, tacrolimus has been demonstrated to effectively prevent allograft rejection and to rescue patients with refractory rejection after human liver, kidney, or heart transplantation (2). Chronic use of tacrolimus is associated with a number of adverse effects, but little is known about the acute overdosing of tacrolimus. Up to now, only 17 cases of acute overdosing of tacrolimus have been reported in the English literature. We encountered a case of acute overdosing of tacrolimus due to an error in tacrolimus administration. Although no severe side effect occurred, this case is being reported to better characterize the effects of acute Tacrolimus overdosing.

CASE REPORT

A 36-year-old 60-kg male Wilson's disease patient, diagnosed when he was 31 years old, had neurological manifestations including involuntary movement, slurred speech, dysarthria, rigidity, and dystonia. His two brothers died of Wilson's disease. He had been admitted to our hospital four times previously for complications of decompensated liver cirrhosis and sequelae of central nervous system involvement induced by Wilson's disease between July 1994 and April 1997. Liver transplantation was indicated due to failure of medical treatment to improve the deteriorating liver and neurological function.

Orthotopic liver transplantation with piggy-back side-to-side anastomosis of IVC was performed in July 1997. The primary immunosuppressive therapy after liver transplantation consisted of tacrolimus and steroids. The initial dosage of tacrolimus was 0.2 mg/kg orally in two divided doses. Inadvertently, a single oral dose of 60 mg (1 mg/kg) tacrolimus was administered due to a medication error on day 17th after liver transplantation. The accident was disclosed 5 hr after administration. The following procedures were then applied in the management of this patient: (1) discontinuation of tacrolimus for three days with aggressive measurement of whole blood level of tacrolimus every 2 hr for one day; (2) phenytoin 100 mg for seizure prophylaxis and enhancement of tacrolimus metabolism through stimulation of cytochrome P-450 IIIa; and (3) close observation for signs and symptoms of tacrolimus toxicity. Gastric lavage, activated charcoal, hemodialysis, and charcoal hemoperfusion were not given. The patient did not manifest any symptoms and signs of tacrolimus overdose. Serum levels of blood urea nitrogen (13–18 mg/dl), creatinine (1.1–1.2 mg/dl), AST (98–144 IU/liter), and ALT (671–767 IU) were not changed as compared to those before overdosage (Figure 1). There was no evidence of exacerbation of neurotoxicity (hand tremors, headache) or gastrointestinal adverse effects (nausea, vomiting, and diarrhea) during the observation period.

DISCUSSION

Tacrolimus is a macrolide lactone produced by Streptomyces tsukubensis. It is a potent immunosuppressant, as demonstrated by in vivo and in vitro studies (1, 2). Tacrolimus is poorly and highly variably absorbed after oral administration. A mean bioavailability of 21% has been measured in liver or renal transplant recipients (3). After a single oral dose of 0.15 mg/kg, peak plasma concentration of 0.4–5.6 ng/ml occurred over a time period ranging from 0.5 to 8 hr (4). Tacrolimus is highly lipophilic and undergoes extensive tissue distribution, as evidenced by a large volume of distribution (V = 1300) estimated from plasma data (5).

Tacrolimus undergoes extensive hepatic metabolism, with less than 1% of the parent compound being excreted unaltered in the bile, urine, or feces (5). Cytochrome P-450 subtypes Ia and IIIa appear to have a major regulatory role in the metabolism of

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tacrolimus, which is affected by some drugs competing at the cytochrome P-450 IIIa receptor.

The principal adverse effects of tacrolimus are nephrotoxicity, infectious and malignant complications, neurotoxicity, and diabetogenic effects. Patients treated with tacrolimus do not develop gingival hyperplasia and hirsutism (6).

Although a number of adverse effects associated with chronic use of tacrolimus have been reported, there are only a few reports discussing management, side effects, and outcome of acute overdosing of tacrolimus. Curran et al. reported 12 cases of acute tacrolimus overdose (7). Eleven cases occurred with a single dose. In the twelfth case, accidental overdoses were taken on three occasions over two consecutive days. Four cases were suicidal attempts, and eight were the result of medication error. In 10 patients (age range 1–44 years), dosage was up to 30 times the intended dose. The following procedures have been used in the management of these 12 patients: gastric lavage, orally activated charcoal, phenytoin administration (for seizure prophylaxis and the enhancement of tacrolimus metabolism through stimulation of cytochrome P-450), and close observation for signs and symptoms of tacrolimus toxicity. These measures are based on the pharmacokinetics of tacrolimus. It has also been pointed out that hemodialysis would be futile due to the lipophilicity and relatively large molecular weight of tacrolimus (822 Da), and its extensive tissue distribution. It was concluded that acute overdosing did not result in any long-lasting adverse effects. Marvos et al. reported five cases of tacrolimus overdose (8). Overdose ranges from 0.25 to 7 mg/kg. Only two patients were treated with activated charcoal and the remaining patients were treated with conservative management. No acute physiologic injury was produced by tacrolimus overdose. They concluded that acute overdosing with tacrolimus could be managed with conservative treatment without significant outcome (Table 1).

In our case, neither gastric lavage nor activated charcoal was administered because the accident was disclosed 5 hr after medication error. If gastric lavage and activated charcoal are considered for treatment of acute overdosing of tacrolimus, they should be performed within 1 hr following ingestion in order to maximize their effectiveness (9). Phenytoin administration was applied for seizure prophylaxis and enhancement of metabolism of tacrolimus by increasing cytochrome P-450 IIIa activity. We also discontinued tacrolimus temporarily and the whole blood level returned to the recommended therapeutic level within three days. Hemodialysis is ineffective for acute overdose of tacrolimus due to the lipophilicity of tacrolimus. No obvious symptoms or signs of tacrolimus overdose were found in our patient after conservative treatment with phenytoin administration.

Fig 1. Liver function markers, renal function marker, tacrolimus dosage, and tacrolimus whole blood level in the patient reported (30 days after transplantation); dark arrow indicates the date of overdose.

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