

Tacrolimus Levels in Adult Patients With Renal Transplant

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Abstract

Tacrolimus, a macrolide immunosuppressant agent, is indicated for the prophylaxis of organ rejection in patients receiving allogenic liver or kidney transplantation. Successful therapy is complicated by both intra- and inter-patient variability in drug absorption, coupled with the drug's narrow therapeutic index. Moreover, clearance, is significantly affected by co-administration with food and with additional factors such as length of post-transplantation time. At the National Institute of Cardiology, Mexico, the measure of tacrolimus levels is carried out as a common analysis on patients who have been transplanted as a measure to make empiric dosage adjustments. The purpose of this study was to investigate whether tacrolimus levels exceed the desired therapeutic range in adult patients being initiated on a dosage regimen and to establish the use of pharmacokinetic concepts to avoid organ rejection and other complications related to tacrolimus over-exposure. The patients were followed from 1 week to 6 months after transplantation and a mean of 12 samples were collected (11.92 ± 2.59 ng/mL) from each patient. Modeling was used to establish the correlation between the doses administered per kilogram of body weight, the tacrolimus level measured and the post-transplantation time. Of 155 tacrolimus measurements, only 48.4% were found within the therapeutic range (5-10 ng/mL); 7.1% below and 44.5% with elevated levels. Tacrolimus has proven its usefulness in solid organ transplants, but this study demonstrates that it is essential to carry out close monitoring through the application of pharmacokinetic concepts to optimize therapy.

Introduction

Tacrolimus is a macrolide immunosuppressant that has been shown to be safe and effective for the prevention of rejection after liver and kidney transplantation [1]. It has been used in thousands of allograft recipients and has become the standard immunosuppressive drug of choice in numerous transplant centers. Because of its variable pharmacokinetics and narrow therapeutic index, monitoring drug concentrations is essential to avoid the risks of over- and under-immunosuppression. Therapy is complicated by both intra- and inter-patient variability in drug absorption (absolute bioavailability ~15%-25%), coupled with the drug's narrow therapeutic index. Clearance is significantly affected by co-administration with food and with additional factors such as length of post-transplantation time [2,3]. In the National Institute of Cardiology, Mexico, the measure of tacrolimus levels is carried out as a common practice in patients who have been transplanted, but it is used to make an empiric dose adjustment.

Material and Methods

The study was comprised of 13 patients (10 men and 3 women) with a mean age 30 yr (range 18-46; mean \pm SD (30.08 \pm 8.41), who participated in the study from the day following transplantation until 6.5 months later. Levels were measured in the Laboratory of Clinical Chemistry at the hospital with the routine method MEIA (Abbott Diagnostics AXSYM). The inter and intra-assay variability was less than

10%. Statistical analysis was performed by one way ANOVA for non paired samples. Significance was set at $p < 0.05$. All blood samples were collected before the next dose in the morning. The patients were followed from 1 week to 6 months after transplantation. Pharmacokinetic models were built to establish the correlation between dose administered per kilogram of body weight and the tacrolimus level versus the post-transplantation time. Graphs were constructed to establish the correlation between dose per kilogram of body weight and the level and concentration of tacrolimus with respect to post-transplant time (0 to 6.5 months).

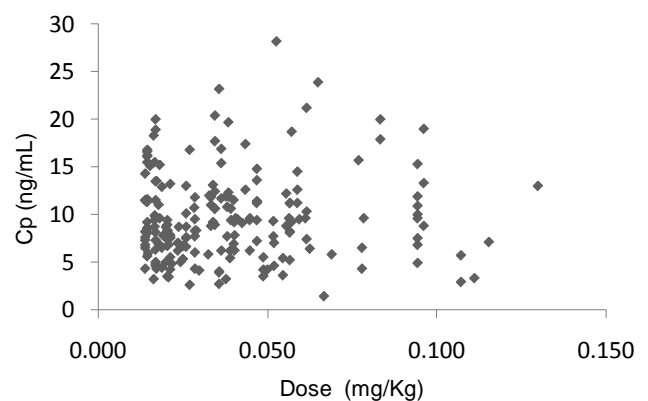


Figure 1. Relationship between steady-state blood tacrolimus concentration and the weight-normalized daily dosage of the drug in 13 patients.

Results and Discussion

The analysis showed that an average of 12 determinations were made per patient (mean \pm S D, 11.92 ± 2.59 ng/mL). Of the total of 155 determinations of tacrolimus, only 48.4% were within the therapeutic range of reference for the hospital (4-14 ng/mL), 7.1% below it and a 44.5% with high levels of tacrolimus (Figure 1). This is of particular interest, since we found high levels of the drug in a large number of patients, resulting in a greater likelihood of adverse reactions that may involve endocrine and metabolic changes, hematologic, hepatic, CNS, renal or respiratory system side effects.

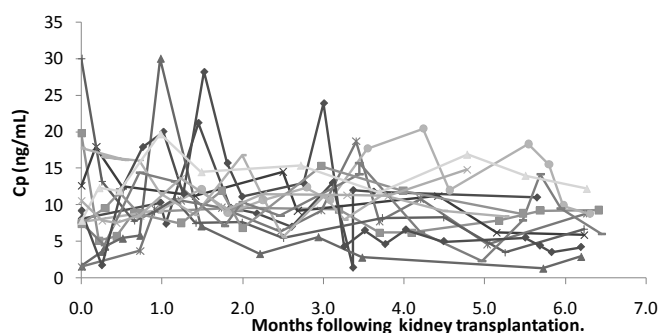


Figure 2. Whole-blood trough tacrolimus concentrations during the first six and a half months post-renal transplantation

Figure 2 shows the steady state plasma levels of tacrolimus (as suggested by trough determinations) for patients in our study; a great inter-individual variability was found. When the drug levels were correlated with the tacrolimus dose administered per patient body

weight, no linear correlation was found ($r=0.06$). These data demonstrate a significant possibility of toxicity developing in patients since the same dose can result in markedly different blood levels. The therapeutic range for tacrolimus, based on trough whole blood concentration, is considered by some authors, to be 10 to 20 ng/mL during the early post-transplant period. Exposure to concentrations <10 ng/mL is associated with an increased risk of acute rejection, whereas extended exposure to concentrations >20 ng/mL increases the risk of developing adverse events [4].

By the pharmacokinetic profile of tacrolimus concentrations and post-transplant time, we observed a large fluctuation in tacrolimus concentrations, so it is not possible to establish whether there is a need to decrease the dose as time passes. Tacrolimus has proven its usefulness in solid organ transplants, but this work showed that it is essential to carry out close monitoring through the application of pharmacokinetic concepts to optimizing individual drug therapy.

References

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