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Short communication

Use of low-dose tacrolimus and associated hypomagnesemia in the prevention of erectile dysfunction following prostatectomy for prostate cancer

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ABSTRACT

Background: Hypomagnesemia with urinary magnesium wasting is a well described adverse event with calcineurin inhibitor therapy. Prostate cancer is the most prevalent cancer in men in the United States. Injury to the cavernous nerves during radical prostatectomy frequently results in erectile dysfunction. Tacrolimus has been shown to be neuroprotective in the rat cavernous nerve injury model, an animal model representative of the neural injury that occurs in humans at the time of radical prostatectomy.
Methods: In a randomized, double-blind, placebo-controlled trial, the utility of tacrolimus was assessed for prevention of erectile dysfunction following bilateral nerve-sparing radical prostatectomy.
Results: Low dose tacrolimus, associated with low trough levels, resulted in mild hypomagnesemia, which was an early and persistent finding. As early as one week after institution of therapy, mean and median serum magnesium levels were significantly lower in the tacrolimus arm as compared to the placebo arm ($p < 0.001$ for both). While the mean and median levels were within the normal range at Week 1, 10.9% of tacrolimus-treated patients had levels <1.8 mg/dL, compared to none in the placebo arm ($p = 0.017$). Median and mean levels remained significantly different at Week 5, Month 3 and Month 6. No clinical manifestations of hypomagnesemia were noted and no subject required treatment with magnesium. Changes in serum magnesium occurred earlier than other potential metabolic adverse events described with tacrolimus (changes in serum glucose, creatinine or potassium).
Conclusions: These data indicate that mild hypomagnesemia is an early and sensitive biomarker for the effect of tacrolimus on the kidney.

Introduction

Hypomagnesemia with urinary magnesium wasting is an acknowledged side effect of calcineurin inhibitor (CNI) therapy having been described with both cyclosporine [1] and tacrolimus [2]. These drugs down-regulate transient receptor potential melastatin 6 (TRPM6)-mediated magnesium influx [3,4]. In tacrolimus-treated renal transplant recipients, fractional excretion of magnesium (FE_{Mg}) was 7.42% and magnesium excretion 112.4 mg/dL, compared to 1.88% and 6.7 mg/dL, respectively, in healthy controls [2]. Tacrolimus (FK-506) inhibits calcineurin by binding to FK binding-protein12 (FKBP12). In T-cells this results in immunosuppression. In an inducible kidney tubule-specific FKBP12 knockout mouse model, the kidney is protected from tacrolimus effects on renal magnesium and calcium transport [5]. Symptoms of hypomagnesemia include neuromuscular manifestations, cardiovascular abnormalities, disorders in calcium metabolism, and hypokalemia.

Approximately 99% of total body magnesium is located in bone, muscles and non-muscular soft tissue [6]. The majority of magnesium is absorbed in the small intestine by passive diffusion driven by electrochemical gradient and solvent drag [7]. TRMP6 and TRPM7 are channel kinases involved in the active transcellular magnesium transport in intestine and kidney [8]. 24–76% of dietary magnesium is absorbed in the gut and the rest is eliminated in the feces. Intestinal absorption is largely dependent on magnesium status. Serum magnesium homeostasis is primarily controlled by its excretion in urine [9]. Approximately 80% of the total plasma magnesium is filtered at the glomerulus; 15–25% is reabsorbed passively in the proximal tubule down concentration

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gradients and 5–10% in the distal tubule. The major site of magnesium transport is the thick ascending limb of the loop of Henle where 60–70% of the magnesium is reabsorbed. Only 3–5% of the filtered load is excreted in the urine. The kidneys have the ability to lower or increase magnesium excretion and reabsorption within a sizeable range; FE_{Mg} may vary from 0.5 to 70%; reabsorption depends predominantly on magnesium levels in plasma [9,10]. The serum magnesium level in healthy individuals is 1.8–3.0 mg/dL [11].

Prostate cancer is the most prevalent cancer in men in the United States and the second leading cause of cancer death [12]. The surgical procedure, radical prostatectomy (RP) is performed in >50,000 men each year in the United States alone. Erectile dysfunction (ED) is a frequent complication of RP resulting from injury to the cavernous nerves during the surgical procedure. Nerve sparing surgical techniques have reduced ED rates after RP; however, the prevalence of post-operative ED has been reported as 20–60% [13]. Adequate erectile function is more common after bilateral than unilateral nerve sparing, and in men <70 years [14]. Novel strategies have been explored to further minimize post-surgical ED, including the use of neuromodulatory interventions to promote neuroregeneration and preserve erectile tissue integrity. Tacrolimus (Prograf®, Astellas Pharma Inc. Tokyo, Japan) is a macrolide immunophilin ligand which is FDA-approved for the prevention of allograft rejection in liver, kidney and heart transplantation. Tacrolimus has been shown to have neuro-protective and neuroregenerative properties in various animal models, including the rat cavernous nerve injury model, an animal model representative of the neural injury that occurs in humans at the time of RP [15]. In these model, it can prevent axonal degeneration and preserve electrically induced penile erections [16–18].

A randomized, double-blind, placebo-controlled trial to assess the utility of tacrolimus for prevention of ED following bilateral nerve sparing RP was performed [19]. Tacrolimus levels and potential adverse events were closely monitored. Post-study analysis revealed the unanticipated finding that as early as one week after institution of tacrolimus therapy, mean and median serum magnesium levels were significantly lower in the tacrolimus arm as compared to the placebo arm. The results of the metabolic assessments from this study form the basis for this report. It is important to note that no a priori hypothesis about the effect of low tacrolimus exposure on the selected metabolic parameter. The metabolic changes described in the manuscript were only discovered when we did the post-study analysis.

Materials and methods

Study population

The subjects were males undergoing bilateral nerve sparing RP for the treatment of prostate cancer at six centers in the US. Subjects were ≤65 years of age, with a pre-operative serum creatinine level ≤1.4 mg/dL. Baseline demographics and co-morbidity data were collected. Informed consent was obtained prior to enrollment. The study was approved by the Institutional Review Board (IRB) at each participating center, and was conducted in accord with the Helsinki Declaration of 1975.

Study design

This was a randomized, multicenter, double-blind, placebo-controlled study comparing tacrolimus (Prograf®) therapy to placebo. Patients were randomized 1:1 prior to RP. Patients received study drug for of 6 months and were followed for 2 years post-RP. Patients were seen at weeks 1, 3, 5, 9 and months 3, 5, 6, 12, 18 and 24 after RP.

The primary endpoint in this study was a comparison of the International Index of Erectile Function (IIEF) [20] 24-months after prostatectomy in the tacrolimus and placebo arms.

Laboratory assessments (including serum glucose, potassium, magnesium and creatinine levels) were conducted at every postoperative visit up to month 6, and were repeated at month 7 in subjects with abnormal values at month 6. After cessation of tacrolimus therapy, only urological assessments were made. Therefore, we do not have any information on the metabolic parameters beyond the 6-month time point.

Dosing and dose adjustments

Patients received 2 mg of study medication (tacrolimus or placebo) daily beginning 7 days prior to surgery. Study drug was taken the morning of surgery, and was re-initiated 24–36 h after the operation. On discharge from hospital, the dose was increased to 3 mg/day; this dose was maintained until study drug was discontinued at 6 months. The scientific rationale for the dose selection in this study was based on the fact that oral tacrolimus at a dose of 1.5–3 mg/day has been approved in Japan and Canada for the treatment of rheumatoid arthritis in patients who respond insufficiently to other therapies [21].

Dose adjustments were made if a patient demonstrated clinical evidence of toxicity (tremor, insomnia, nausea/vomiting, glucose intolerance, hyperkalemia, hypomagnesemia) or an increase in serum creatinine of 30% compared to baseline. Study drug was reduced to 2 mg daily until symptoms of toxicity improved or patient's serum creatinine returned to baseline. If symptoms did not improve after two weeks, the dose was reduced to 1 mg daily for an additional two weeks. At this time, if symptoms had not improved, the patient was discontinued from study drug.

Statistical analysis

An ANOVA was performed comparing treatment groups for all visits, but the residuals were not normally distributed, which violates the assumptions of this test. Therefore, a Wilcoxon-rank sum test was performed at each time point because it is a non-parametric test that does not assume a normal distribution. Continuous data were analyzed using parametric (*t*-test) or non-parametric (Wilcoxon-rank sum test) test methodologies as warranted by the data distribution. Categorical data were analyzed using Fisher's exact test to compare proportions between treatment groups.

Results

Demographics

124 subjects (59, tacrolimus arm; 65, placebo arm) were randomized into the study, took study drug, and had a RP. There were no differences between the two arms with regards to age (mean ± SD 54.6 ± 6.2 years), race (95.2% White), weight (89.5 ± 13.6 kg), height (178.2 ± 7.4 cm), nor BMI (28.2 ± 3.9 kg/cm^2).

Patient characteristics

There were no differences in the comorbidities between the two study groups at baseline. Patients were excluded from the study if they were on any concomitant medications that are known to influence tacrolimus metabolism.