Pharmacokinetics of Neoral in Stable Renal Transplant Recipients With Long-Term Diabetes Mellitus

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ABSTRACT

Therapeutic drug monitoring (TDM) of Neoral has been studied widely and C2 monitoring has been shown to be superior to C0 monitoring in predicting outcomes. However, data are scarce in diabetic renal transplant recipients who may have gastroparesis. We studied 0 to 8 hour pharmacokinetic profiles (AUC_{0-8h}) of Neoral on 3 consecutive days in 18 diabetic adults who had stable renal function for at least 6 months after transplantation and no overt symptoms of diabetic gastroparesis. All patients had diabetes mellitus (DM) for at least 5 years. Intrapatient variability of C2 levels was 28% (range, 6%–68%); it was ≤20% in 9 patients (50%) and >60% in 2 patients. Correlation coefficients between AUC_{0-8h} and AUC_{0-4h}, between C2 and AUC_{0-8h}, and between C0 and AUC_{0-8h} were 0.95, 0.86, and 0.77, respectively. Exposure phase (85% of AUC_{0-8h}) was longer than 4 hours in all completed (48/54; 89%) profiles; it was longer than 6 hours in 20 profiles. C4 levels had good correlation with AUC_{0-8h} (0.86) and low intrapatient variability (16% ± 11%; range, 2%–39%). Thirteen of 18 patients (72%) had intrapatient variability of C4 ≤ 20%. We conclude that the exposure phase of Neoral is prolonged more than 4 hours in adult renal transplant recipients with long-term diabetes, even in the absence of symptoms of gastroparesis. Because of very high intrapatient variability in this group of patients, C2 levels may not be reliable for TDM of Neoral despite high correlation with AUC_{0-8h}. C4 level may be a valid alternative for these patients.

CALCINEURIN INHIBITORS (cyclosporine and tacrolimus) continue to remain the mainstay of the maintenance immunosuppressive regimens for solid organ transplant recipients despite their toxicities. Therapeutic drug monitoring (TDM) of these agents continues to play a significant role in optimizing outcomes—minimizing rejections and nephrotoxicity. Recently, there has been a shift in the TDM of cyclosporine (CsA). Conventionally, C0 (12-hour trough level) has been used to guide dose adjustments of Neoral (microemulsion formulation of CsA). However, recent evidence suggests that C0 measurements correlate poorly with area under the time concentration curve over 12 hours (AUC_{0-12h}) and abbreviated area under the curve (AUC_{0-4h}), both of which have been shown to strongly parallel clinical outcomes in several studies.[1–4] Instead, C2 (CsA level 2 hours after the dose) has been shown to correlate closely with AUC_{0-4h} and clinical events.[4–6] In addition, pharmacodynamic effects of CsA (calcineurin inhibition and reduction of interleukin-2 [IL-2]-activated T cells) and nephrotoxicity have been found to be consistently maximal within the absorption phase correlating more with C2 than C0.[7–9] It has also been demonstrated that the overall safety profile of C2 monitoring over the short term is equivalent to C0 monitoring.[10,11] Recent recommendations were published for C2 monitoring emphasizing clear benefits over C0 monitoring.[12] However, no

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long-term controlled clinical studies have been performed comparing C2 with C0 monitoring. A recent study by Einecke et al[13] showed significant limitations of C2 monitoring in renal transplant patients and questioned the wisdom of widespread adoption of C2 monitoring without further studies. They showed that C2 monitoring did not have any discriminative power for rejection or toxicity and intrapatient variability was 20% or higher. Eleven of 41 of their patients (29%) had slow and/or poor absorption defined by C0 > 300 ng/mL and C2 < 800 ng/mL; 64% of these patients with absorption problems developed CsA toxicity and 18% of them had acute rejection. Intrapatient variability of C2 levels in renal transplant recipients in another study by Johnston et al[14] was 22%. Neither of these studies separated diabetics from nondiabetics.

In the United States, 22% of renal transplant recipients had end-stage renal disease (ESRD) due to diabetes mellitus (DM) in 2003.[15] There were also 867 kidney-pancreas combined and 159 pancreas transplants performed. However, pharmacokinetic studies of Neoral in renal transplant recipients with DM as a separate group are scarce. Gastroparesis, defined as delayed gastric emptying without mechanical obstruction,[16,17] affects 20% to 50% of the diabetic population.[18,19] We hypothesize that gastroparesis would slow or make absorption erratic, thus making C2 monitoring less useful than in nondiabetics. We studied our hypothesis in a study involving 18 stable renal transplant recipients with long-term diabetes (15 years or longer).

MATERIALS AND METHODS

In a single center, open-label study, we examined AUC_{0-8h} profiles in 18 diabetic adult renal transplant recipients who were on Neoral, prednisone, mycophenolate mofetil (MMF), or azathioprine for maintenance immunosuppression. We decided to study AUC_{0-8h} profiles on 3 consecutive days instead of AUC_{0-4h} profiles because of presumed gastroparesis and hence slow and/or erratic absorption in these patients. AUC_{0-12h} profiles were not performed to enhance convenience of the subjects and therefore recruitment. This study was approved by the local IRB. The subjects were selected from a large pool of posttransplantation renal patients (>1000) at Indiana University Medical Center by applying stringent inclusion and exclusion criteria as follows.

Inclusion Criteria

Inclusion criteria included age ≥ 18 years; kidney transplant at least 6 months before inclusion in the study; stable renal function for at least 3 months; duration of DM should be more than 5 years before transplantation; and signed and dated IRB-approved informed consent before screening and before any protocol specified tests.

Exclusion Criteria

Exclusion criteria included patients with kidney-pancreas or other multiorgan transplants; evidence of systemic infection; evidence of suspected malignancy (with the exception of adequately treated basal cell or squamous cell carcinoma of the skin); use of other investigational agent < 4 weeks; current use of terfinadine, cisapride, astemizole, pimozide, cimetidine, phenobarbitone, phenytoin, carbamazepine, verapramil, diltiazem, rifampin, ketoconazole, or fluconazole.

Study Procedure

After the informed consent, patients were advised to take their usual dose of Neoral at 9 AM and 9 PM daily and maintain the same doses of MMF/azathioprine and prednisone. They were also advised to avoid all medications mentioned in the exclusion criteria and to report any medications (prescribed, over-the-counter, or herbal) taken during or within a week of their visit or admission to the General Clinical Research Center (GCRC). Nine hourly samples of blood (5 mL) were collected between 9 AM and 5 PM daily for 3 consecutive days to study AUC_{0-8h} profiles of CsA. No adjustments in immunosuppressive regimens were allowed during these 3 days and all medications mentioned in the exclusion criteria were avoided. Any undesired, untoward, or unplanned clinical events were recorded regardless of causal relationship. Whole blood CsA levels were measured by Indiana University Hospital Laboratory using a previously approved and validated Abbott FLX Polarization.

Analysis

AUC_{0-8h} was calculated by the linear trapezoidal method. Intrapatient and interpatient variabilities were calculated for AUC_{0-8h} profiles and for CsA levels at various time points (C0, C1, C2, etc). All levels and profiles were corrected for CsA dose. Cmax (maximum CsA level) and Tmax (time of maximum CsA level) were also studied for all profiles. Correlation coefficients between AUC_{0-8h}, profiles, AUC_{0-4h} profiles, and CsA levels at various time points were also analyzed.

RESULTS

Patient Characteristics

Median age of patients was 56.5 years (Table 1). Of 18 patients, 14 (78%) were male. Ethnic distribution was as follows: Caucasian 15 (83%); African-American 2 (11%); and Hispanic 1 (6%). Median weight was 84.5 kg. Etiology

Table 1. Patient Characteristics

Characteristic	N = 18
Age in years (mean ± SD)	54.6 ± 9.5 (range, 32–65)
Gender, male (%)	14 (78)
Race, Caucasian (%)	15 (83)
Weight in kg (mean ± SD)	86.5 ± 20.3 (range, 55.6–130.3)
Duration of DM in years (mean ± SD)	24.7 ± 7.2 (range, 15–40)
Posttransplantation duration in months (mean ± SD)	63.5 ± 48.2 (range, 7–173)
H/O neuropathy, n (%)	14 (78)
H/O gastroparesis, n (%)	5 (28)
Neoral dose, mg/d (mean ± SD)	232 ± 88 (range, 100–450)
Neoral dose, mg/kg/d (mean ± SD)	2.8 ± 1.2 (range, 0.8–5.3)