Therapeutic Drug Monitoring of Mycophenolic Acid in Kidney Transplant Patients: A Abbreviated Sampling Strategy


ABSTRACT

Mycophenolic acid (MPA) levels have demonstrated a good correlation with clinical outcomes, but with great pharmacokinetic variability between patients. Therapeutic drug monitoring (TDM) is recommended to include a 12-hour area under the concentration–time curve (AUC). Since full AUC estimates are not practical for routine monitoring, limited sampling strategies have been suggested. We evaluated MPA pharmacokinetics in 18 stable renal transplant patients receiving mycophenolate mofetil (MMF) as part of their immunosuppressive therapy. The correlation between measured and estimated AUC was assessed using 4 different sparse sampling algorithms. The mean values for C₀ and AUC₀₋₄h were 1.8 ± 1.2 mg/L and 31.1 ± 14.8 mg•h/L, respectively. The dose-corrected AUC₀₋₄h was 35.4 ± 17.9 mg•h/L. Regarding the single time points, C₀ showed a low correlation with AUC₀₋₄h ($r^2 = .34$); C₁₅, the best correlation ($r^2 = .72$); and C₅, the worst ($r^2 = .07$). Sparse sample algorithms used to estimate 12-hour AUC including C₀, C₁, C₂, C₃, C₄, and/or C₆ showed a good correlation with the calculated AUC₀₋₄h ($r^2 = .81–.96$). The algorithm that used C₀, C₁, C₃, and C₄ showed the best correlation, while we also found a good correlation ($r^2 = .91$) with C₀, C₁, and C₂. Based on these results, we have suggested using the 3-point algorithm (C₀, C₁, and C₂) for MPA TDM in stable renal transplant patients due to the good correlation with drug exposure and better functionality than an algorithm using a 4-hour postdose measurement.

Mycophenolate Mofetil (MMF) is an ester prodrug of the active immunosuppressant mycophenolic acid (MPA), a noncompetitive, selective, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), thus blocking “de novo” purine nucleotide synthesis in T and B lymphocytes. It is a powerful and selective immunosuppressant that is significantly more potent and efficacious in reducing rejection episodes and prolonging renal allograft survival than azathioprine. It reverses refractory allograft rejection episodes, allows steroid sparing and steroid withdrawal, and reduces anticalcineurin inhibitors in chronic allograft dysfunction.

MPA therapeutic drug monitoring (TDM) is recommended due to its great intra- and interpatient pharmacokinetic variability. The 12-hour area under the curve concentration versus time (AUC), but not the predose, trough level (C₀), has shown a good correlation with clinical outcomes and the likelihood of acute rejection. For this reason, it is recommended to perform MPA TDM with a 12-hour AUC (AUC₀₋₁₂h). Since AUC₀₋₁₂h is not practical and unacceptable expensive for routine monitoring, it has been suggested to use limited sampling strategies. To determine an adequate surrogate marker for MPA exposure, we evaluated MPA pharmacokinetics in stable renal transplant patients treated with MMF and cyclosporine (CSA). We assessed the correlation between measured and estimated AUC from 4 sparse sample algorithms used clinically to estimate MPA AUC in patients.

MATERIALS AND METHODS

Patients

We enrolled 18 stable renal transplant patients (9 men and 9 women; 35 ± 13 years old). Time posttransplantation was 33 ± 28 months (median, 23.5 months; range, 2–71 months). The primary disease was chronic glomerulonephritis in 4 patients, unknown in 7

From the Transplant Unit, Hilgueras Hospital, Talcahuano, Chile (H.M., J.T., R.O., J.M., C.P.); Department of Internal Medicine, Faculty of Medicine, Universidad Catolica Santisima Concepcion, Concepcion, Chile (H.M., C.Z.); and Academic Unit, Faculty of Medicine, Pontificia Universidad Catolica de Chile, Santiago, Chile (S.S., I.G.).

Address reprint requests to Hans Muller, MD, Department of Internal Medicine, Faculty of Medicine, Universidad Catolica Santisima Concepcion, Concepcion, Chile. E-mail: hkmol@cidial.cl

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Table 1. Equations and Concomitant Immunosuppression (ISD) of the Different Algorithms

<table>
<thead>
<tr>
<th>Time Points</th>
<th>Equation for the Estimation of AUC</th>
<th>Concomitant ISD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 1 h, 2 h</td>
<td>15.19 + 6.92xC0 + 1.08xC1 + 0.72xC2</td>
<td>CsA</td>
<td>Yeung et al.¹¹</td>
</tr>
<tr>
<td>1 h, 2 h, 6 h</td>
<td>10.75 + 0.98xC0 + 2.39xC1 + 4.86xC2</td>
<td>CsA/tacrolimus</td>
<td>Filler and Mal¹²</td>
</tr>
<tr>
<td>0, 1 h, 2 h, 4 h</td>
<td>8.22 + 3.16xC0 + 0.99xC1 + 1.33xC2 + 4.18xC4</td>
<td>CsA/tacrolimus</td>
<td>Filler et al.¹³</td>
</tr>
<tr>
<td>0, 1 h, 3 h, 6 h</td>
<td>9.02 + 3.77xC0 + 1.33xC1 + 1.68xC3 + 2.96xC6</td>
<td>CsA</td>
<td>Johnson et al.¹⁴</td>
</tr>
</tbody>
</table>

patients, and other diseases in 7 patients. All kidney transplant recipients on a CsA-based immunosuppressive regimen were receiving MMF dosed empirically at 1 g (n = 15) or 0.5 g (n = 3) twice daily. All patients had their CsA dose adjusted using C2 according to our standard practice with a target range of 600 to 800 μg/L. Patients with active bacterial or viral infections or with rejection episodes within the prior 4 weeks were excluded from this study. None of the patients were enrolled in another clinical trial. Before enrollment, all patients gave written informed consent.

Immunosuppression

All patients received immunosuppression with CsA, MMF, and prednisone without lymphohydrotic induction therapy. Patients received the CsA microemulsion formulation (Neoral; Novartis Pharma AG, Basel, Switzerland) and MMF (Linfexon; Recalpine Pharmaceutical Corp, Santiago, Chile) at 12-hour intervals. Prednisone was given at a maintenance dose of 0.15 mg/kg/d.

MPA Determinations

MPA concentration was measured using a validated high performance liquid chromatography method with ultraviolet detection (HPLC-UV; Chromsystems Instruments & Chemicals GmbH, Germany) on plasma samples collected in EDTA Vacutainer tubes at the time of the scheduled routine clinical visits. Plasma samples were stored at −20°C until analysis. Recovery for the method is 95% over a concentration range from 1 to 25 mg/L; within-day variability (n = 9) of 2.6% and 1.3% in whole blood commercial controls (Chromsystems) containing MPA at concentrations of 1.7 mg/L and 4.7 mg/L, respectively. The between-day variability (n = 24) was 5.6% and 7% for the same blood controls.

Plasma samples (EDTA) were collected at the following times after an overnight fast: predose (fasting sample within 1 hour before the morning dose) and 0.5, 1, 1.5, 2, 3, 4, and 6 hours after the morning dose of MMF. AUC0−6h was calculated using the linear trapezoidal method with GraphPad Prism Statistical Software (USA). Total AUC0−12h was estimated using 4 sparse sample algorithms from the literature¹⁵⁻¹⁸ using different time points. All the algorithms developed herein were taken from kidney transplant patient studies. Table 1 describes concomitant immunosuppression and the equations of the various algorithms.

RESULTS

MPA determinations performed in 18 patients showed a mean value ± standard deviation (SD) for MPA dose of 1.83 ± 0.4 (1–2) g/d. The mean values ± SD (median and range) for C0, calculated AUC0−6h, and dose-corrected AUC0−6h were 1.8 ± 1.2 (1.5, 0.3–5.1) mg/L, 31.1 ± 14.8 (30.3, 12.6–63.2) mg·h/L, and 35.4 ± 17.9 (32.6, 12.6–71.4) mg·h/L, respectively.

There was great pharmacokinetic variability between patients as shown by the AUC0−6h, which was also seen in the dose-corrected AUC0−6h (Fig 1). None of the single time points showed a good relationship with the AUC0−6h (r² = .07–.72). C1.5 showed the best correlation and C3 the worst. C0 showed a low correlation with the AUC0−6h (r² = .34; Fig 2). The results for the estimated AUC0−12h from the 4 sparse sample algorithms gave similar values between the different equations, although they used various single time points. All of them showed a good correlation with the

Fig 1. (A) Concentration versus time graph for 18 renal transplant patients. (B) Dose-corrected MPA AUC0−6h graph shows the great dispersion of the values in the 18 transplant patients.