Pharmacokinetic modeling of the plasma protein binding of mycophenolic acid in renal transplant recipients

Reinier van Hest, Teun van Gelder, Arnold Vulto, Leslie Shaw, Ron Mathot

1Department of Hospital Pharmacy and 2Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands; 3Department of Pathology & Laboratory Medicine, University of Pennsylvania, Philadelphia, USA

Background:
- Mycophenolic acid (MPA) is the immunosuppressive active moiety of the prodrug mycophenolate mofetil (MMF), and is used to prevent acute rejection after organ transplantation.
- A previous population pharmacokinetic analysis showed that impaired renal function and low plasma albumin level (Albm) were associated with an increased apparent oral clearance (CL) of total MPA.
- Hypothesis: low Albm and accumulation of the glucuronid metabolite of MPA (MPAG) decreases MPA protein binding; CL is increased due to a higher unbound fraction ($f_u$).

Aim:
- Elucidate the mechanism of the effect of impaired renal function and low Albm on the pharmacokinetics of MMF by developing a population pharmacokinetic model for total and unbound MPA, as well as for total MPAG plasma concentrations.

Methods:
- Retrospective pharmacokinetic data of unbound and total MPA, and total MPAG were obtained from 88 renal transplant recipients on day 11 and 140 after transplantation.
- Data were analyzed using nonlinear mixed effects modeling (NONMEM).

Results:
- 774 MPA $C_0$, 479 MPA $C_u$, and 772 total MPAG data were best described by a 4 compartment model: central and peripheral compartments both for $C_u$ and total MPA with a link between the central compartments (figure 1).
- Total MPA concentrations were modeled using equation 1:
  \[
  MPA\; C_u = MPA\; C_{u0} + \theta_{protein\; binding}\; MPAG\; C_u \quad \text{(Eq. 1)}
  \]
  where $MPA\; C_{u0}$ is the bound MPA concentration.
- $f_u$ follows from equation 1 (equation 2):
  \[
  f_u = \frac{MPA\; C_{u0}}{MPA\; C_u} = \frac{MPA\; C_{u0}}{MPA\; C_u + \theta_{protein\; binding} \cdot MPAG\; C_u} + 1 + \theta_{protein\; binding} \quad \text{(Eq. 2)}
  \]
- Albm, creatinine clearance (CrCl, as measure for renal function) and total MPAG were obtained from 88 renal transplant recipients on day 11 and 140 after transplantation.
- Between-patient variability:
  - Absorption duration (%): 100 (29), 84 (39)
  - Between-patient variability:
    - Absorption duration (h): 0.66 (22), 0.88 (7)
    - $MPA\; CL$ (L/h): 877 (8), 1070 (6)
    - $V_1$ (L): 36700 (22), 6240 (26)
  - Within-patient variability:
    - Absorption duration (h): 0.91 (62), 0.10 (41)
    - $MPA\; CL$ (L/h): 1030 (13), 1210 (13)
    - $f_u$ = 0.09 (62), 0.10 (41)

Conclusion:
- The final model supports the hypothesis that impaired renal function and low Albm increase total MPA CL by affecting MPA binding to albumin.

References:

Table 1: Parameter estimates (with %coefficients of variation)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basic model</th>
<th>Final model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective function</td>
<td>-82</td>
<td>-1109</td>
</tr>
<tr>
<td>PK parameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_{lag}$ (h)</td>
<td>0.09 (62)</td>
<td>0.10 (41)</td>
</tr>
<tr>
<td>Absorption duration (h)</td>
<td>0.66 (22)</td>
<td>0.88 (7)</td>
</tr>
<tr>
<td>MPA, V1 (L)</td>
<td>3700 (17)</td>
<td>2990 (27)</td>
</tr>
<tr>
<td>MPA, V2 (L)</td>
<td>36700 (22)</td>
<td>6240 (26)</td>
</tr>
<tr>
<td>MPA, CL (L/h)</td>
<td>877 (8)</td>
<td>1070 (6)</td>
</tr>
<tr>
<td>MPA, Q (L/h)</td>
<td>1030 (13)</td>
<td>1210 (13)</td>
</tr>
<tr>
<td>MPAG, V3 (L)</td>
<td>-</td>
<td>6.5 (23)</td>
</tr>
<tr>
<td>MPAG, V4 (L)</td>
<td>-</td>
<td>9.1 (17)</td>
</tr>
<tr>
<td>MPAG, CL (L/h)</td>
<td>-</td>
<td>1.7 (3)</td>
</tr>
<tr>
<td>MPAG, Q (L/h)</td>
<td>-</td>
<td>11 (44)</td>
</tr>
<tr>
<td>$\theta_{protein; binding}$</td>
<td>31 (4)</td>
<td>64 (3)</td>
</tr>
</tbody>
</table>

Figure 1: Representation of the final 4 compartment model. MPA$_u$ = unbound MPA, MPAG = total MPAG

Figure 2a to c: Relationships between unbound fraction ($f_u$) and a: plasma albumin level, b: creatinine clearance, and c: total MPAG concentration

Figure 3: Individually predicted concentration versus observed concentration