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

Reinier van Hest[1], Teun van Gelder[1,2], Arnold Vulto[1], Leslie Shaw[3], Ron Mathot[1]

[1]Department of Hospital Pharmacy and [2]Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands, [3]Department 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).
- First, a basic model for total (C_t) and unbound (C_u) MPA was developed, where after the covariate effects of renal function and Albm were studied.

Results:

- 774 MPA C_t, 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 MPAG with a link between the central compartments (figure 1).
- Total MPA concentrations were modeled using equation 1:

$$\text{MPA } C_t = \text{MPA } C_u + \text{MPA } C_u * \theta_{\text{protein binding}} \qquad \text{(Eq 1.)}$$

where MPA $C_u * \theta_{\text{protein binding}}$ is the bound MPA concentration.

- f_u follows from equation 1 (equation 2):

$$f_u = \frac{\text{MPA } C_u}{\text{MPA } C_t} = \frac{\text{MPA } C_u}{\text{MPA } C_u + \text{MPA } C_u * \theta_{\text{protein binding}}} = \frac{1}{1 + \theta_{\text{protein binding}}} \qquad \text{(Eq. 2)}$$

- Albm, creatinine clearance (CrCl, as measure for renal function) and total MPAG concentrations were significantly correlated with $\theta_{\text{protein binding}}$ in the final model ($p<0.001$, equation 3, figure 2), whereas no significant correlations were found between these covariates and MPA_u CL.

$$f_u = \frac{1}{1 + (64 * \text{Albm} * (\text{CrCl}/47)^{0.29} * (1 - 1.28 * (\text{MPAG } C_t - 0.13)))} \qquad \text{(Eq. 3)}$$

- Parameter estimates of the basic and final model are presented in table 1; goodness-of-fit is shown in figure 3.

Conclusion:

1. The final model supports the hypothesis that impaired renal function and low Albm increase total MPA CL by affecting MPA binding to albumin.
2. The relationship between f_u and MPAG provides evidence that MPAG displaces MPA from its albumin binding sites.

References:

- Van Hest RM et al. Clin Pharmacokinet 2005;44:1083-96.

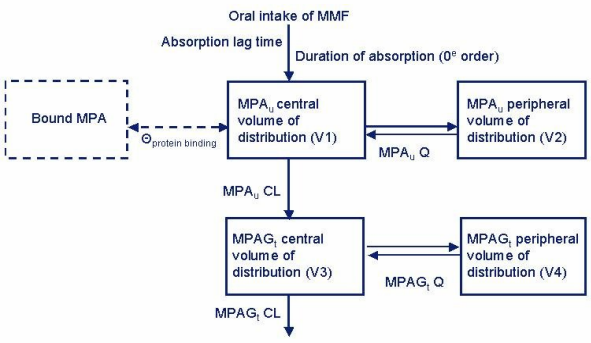

Figure 1: Representation of the final 4 compartment model. MPA_u = unbound MPA, $MPAG_t$ = total MPAG

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

Parameter	Basic model	Final model
Objective function	-82	-1109
PK parameter:		
T_{lag} (h)	0.09 (62)	0.10 (41)
Absorption duration (h)	0.66 (22)	0.88 (7)
MPA_u V1 (L)	3700 (17)	2990 (27)
MPA_u V2 (L)	36700 (22)	6240 (26)
MPA_u CL (L/h)	877 (8)	1070 (6)
MPA_u Q (L/h)	1030 (13)	1210 (13)
$MPAG_t$ V3 (L)	-	6.5 (23)
$MPAG_t$ V4 (L)	-	9.1 (17)
$MPAG_t$ CL (L/h)	-	1.7 (3)
$MPAG_t$ Q (L/h)	-	11 (44)
$\theta_{\text{protein binding}}$	31 (4)	64 (3)
Between-patient variability:		
Absorption duration (%)	100 (29)	84 (39)
MPA_u V1 (%)	86 (49)	91 (30)
MPA_u CL (%)	36 (38)	25 (32)
$MPAG_t$ CL (%)	-	27 (22)
$\theta_{\text{protein binding}}$	22 (60)	12 (88)
Within-patient variability:		
MPA_u CL (%)	27 (33)	20 (33)

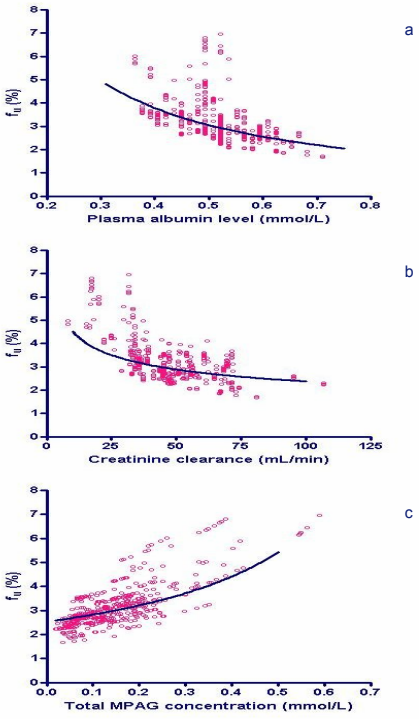

Figure 2a to c: Relationships between unbound fraction (f_u) and a: plasma albumin level, b: creatinine clearance, and c: total MPAG concentration

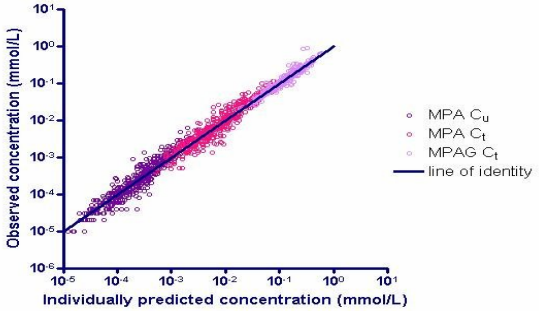

Figure 3: Individually prediced concentration versus observed concentration