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Mechanism-based PK modeling of protein binding of MPA and its glucuronide metabolite

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INTRODUCTION

Mycophenolic acid (MPA), the active compound of mycophenolate mofetil (MMF), is used to prevent rejection in renal transplant recipients. MPA is mainly glucuronidated to the metabolite MPAG, which exhibits enterohepatic recirculation (EHC). Both compounds are highly protein bounded, MPA for 97% and MPAG for 82%. Low plasma albumin levels, impaired renal function and coadministration of cyclosporine (CsA) are associated with increased clearance of total MPA (tMPA). Decreased tMPA exposure is correlated with a higher risk for acute rejection, whereas increased unbound MPA (fMPA) exposure may produce side effects.

AIM

Develop a mechanism-based population PK model to describe the relationship between dose and tMPA, fMPA, tMPAG, and fMPAG and the correlation with renal function, plasma albumin levels and cotreatment with CsA.

METHODS

Time profiles of logarithmically transformed concentrations of tMPA, fMPA, tMPAG, and fMPAG of renal transplant recipients receiving MMF cotreated with CsA (n=48) or tacrolimus (n=45) were analysed retrospectively using NONMEM (ADVAN9, FO). Patients received median 1000 (range 400-2200) mg MMF twice daily and were median 11 (range 4-155) days after transplantation. The model described the competitive protein binding of MPA and MPAG. tMPA(G) was described as the sum of the bound and unbound fraction.

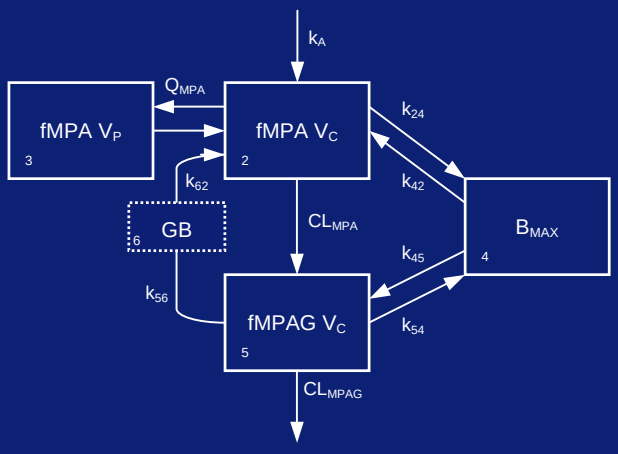

Figure 1: Graphical representation of the final model

	Cyclosporine		Tacrolimus	
	tMPA AUC	fMPA AUC	tMPA AUC	fMPA AUC
Alb=0.4	17.7	0.96	20.4	0.93
Alb=0.5	24.2	0.95	25.6	0.92
Alb=0.6	30.1	0.82	31.1	0.84
CrCL=10	21.5	0.95	31.6	1.12
CrCL=30	23.7	0.95	26.8	0.97
CrCL=50	23.9	0.84	25.1	0.95

*Table I: Effect of albumin level and renal function on tMPA and fMPA AUC (mg*h/L), presented as median from 50 simulated patients receiving 1 gram MMF twice daily.*

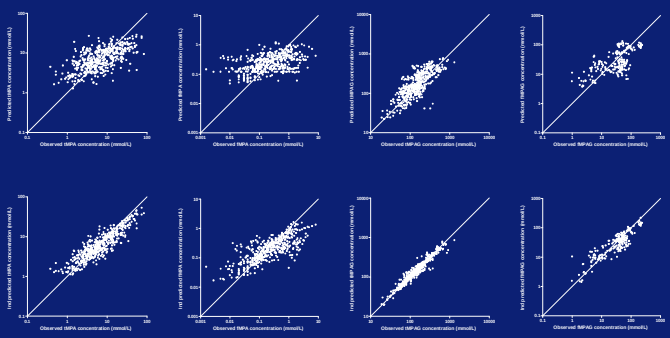

Figure 2: Goodness-of-fit plots of the final model for tMPA, fMPA, tMPAG and fMPAG

RESULTS

In the final model (fig.1) albumin level was correlated with the number of binding sites (B_{MAX}), clearance of fMPAG decreased when creatinine clearance was reduced and CsA inhibited EHC ($p<0.001$). The goodness-of-fit plots (fig.2) and visual predictive check showed no structural bias. The effect of changes in albumin level and renal function on the PK profile (fig.3+4) and AUC (table I) were simulated.

CONCLUSION

Simulations with the final model showed that a decrease in albumin level resulted in a decrease in tMPA AUC. However, fMPA AUC increased a little. Impaired renal function resulted in elevated MPAG levels, which displaced MPA from the binding sites, resulting in a small decrease in tMPA AUC in patients cotreated with CsA. However, in patients cotreated with tacrolimus MPAG could be converted to MPA by EHC, resulting in increased tMPA AUC. The effect on fMPA AUC was less than on tMPA AUC. Changes in protein binding cause differences in tMPA AUC. However, the effect on fMPA, which is thought to be the active fraction, is small and will therefore have little clinical relevance.

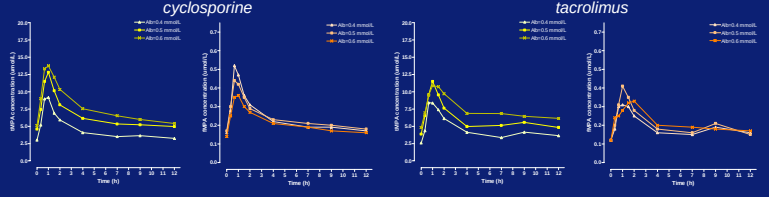

Figure 3: Effect of changes in albumin level on the PK profile of tMPA and fMPA

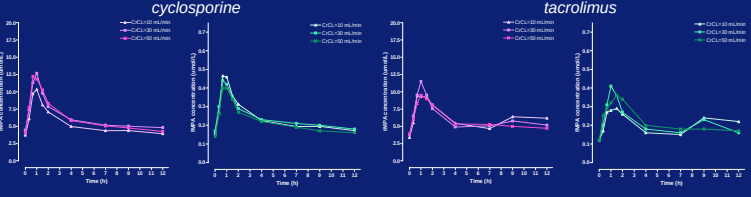

Figure 4: Effect of changes in renal function on the PK profile of tMPA and fMPA

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