Whole-Body PBPK Modeling of Tacrolimus in Healthy Volunteers

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Kinesis
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Introduction

Tacrolimus (TAC or FK-506) is a potent immuno-suppressive agent, and is indicated for the prevention of allograft rejection in patients receiving liver, kidney, or heart transplant. It is a class II low-solubility high-permeability drug with a molecular mass of 804 g/mol and a solubility in water of around 4-12 µg/mL.
TAC binds to the intracellular protein FKBP-12 forming a complex which blocks the activity of calcineurin and interrupts an immune response, see Figure1. Due to the high variability in its PK and a low therapeutic index, prediction of individual dose requirements for patients is challenging and therapeutic drug monitoring should be standard practice.

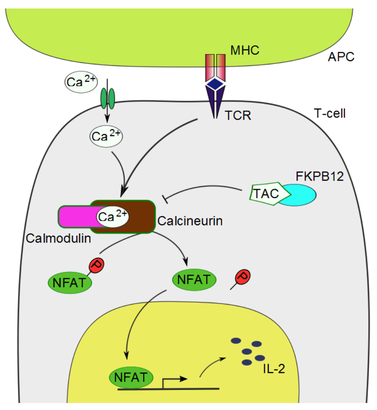


Figure 1: APC, antigen-representing cell; MHC, major histocompatibility complex; TCR, T-cell receptor; NFAT, nuclear factor of activated T-cells; IL, interleukin; FKBP, FK506-binding protein

Objectives

- To describe disposition of TAC in healthy volunteers by a whole-body PBPK model based on literature data.
- To determine blood-plasma partitioning in terms of logP and f_u by using plasma and whole blood concentrations simultaneously.
- To estimate the fraction of hepatic clearance and intestinal first pass effect.

Methods

- Physico-chemical and PK parameters of patients and HV were gathered in a literature search.
- Whole blood and plasma concentrations after IV and PO administration were taken from three studies in literature [1], [2], [3].
- The model was implemented in the PBPK platform PK-Sim® (v 5.2.3).
- Metabolism of TAC by CYP3A enzymes was implemented in the intestine and gut assuming linear kinetics (CL_{int}).
- Intestinal first pass effect also included the efflux pump Pgp; transport was implemented as Michaelis-Menten kinetics; distributions of CYP3A and Pgp were derived according to [4], Figure2.
- Cytosolic protein FKBP-12 was implemented as a protein binding partner.
- Physico-chemical and PK parameters were optimized using a simulated annealing algorithm implemented in PK-Sim®.
- Values for logP, f_u, CL_{int} of CYP3A, and kinetic binding parameters and concentrations of FKBP12 were optimized based on plasma and whole blood concentrations after IV administration described in [1].
- Values for intestinal concentration of CYP3A and Pgp, and kinetic parameters of Pgp are based on plasma and whole blood data after PO administration described in [1].
- Observed data from [2] and [3] were digitized using R [5].

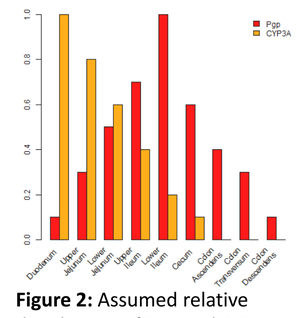


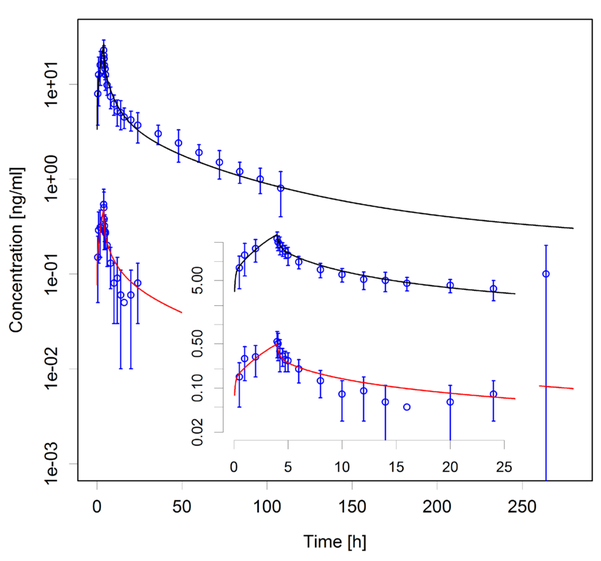
Figure 2: Assumed relative distribution of Pgp and CYP3A

Results

- Parameters were finally optimized to both IV and PO data in a range of ±50% of the previously determined values. Final parameter estimates are listed in Table 1.
- Whole blood and plasma mean concentrations after IV and PO administration from [1] could simultaneously be described well, see Figure 3.
- Lipophilicity was close to a value reported in [6], [7]. Bioavailability with and without intestinal first pass effect were estimated to 30% and 61%, respectively.
- Predictions of mean whole blood concentrations reported in [2], [3], were within an acceptable range, Figure 4.
- Results from patient studies could not be reproduced without any adaptations of parameters. Predicted steady state trough concentrations were far above the therapeutic concentration range of 5-15 ng/ml, [8], Figure 5 (A).
- Possible factors which might explain lower whole-blood concentrations in patients are variability in expression of CYP3A5, reduced binding capacity of RBC, reduced free fraction f_u or lower hematocrit (Hct).
- In kidney and liver transplant patients, values of f_u and Hct were reported in a range of (0.15%-0.6%) and (25%-46%), respectively, [9]-[12].
- The impact of lower values in f_u and Hct was investigated with similar demographic data as in [13]. Simulated steady state concentrations using parameter values in Table 1 but with f_u=0.5% and Hct=35% were in range with reported 25, 50, and 75 percentiles (8.5,10.8,12.9 ng/ml) of renal transplant patients, [13], Figure 5 (B).

Table1 Optimized parameter values.

Parameter	Final	Range	Units
logP	5.82	[3-6.1]	
f_u	0.0129	[0.005-0.0195]	
CYP3A4/5			
CL_{int}	535	[6.95-750]	l/min
ref. conc. intestine	0.0397	[0.01-10]	µmol/l
FKBP12			
ref. conc.	0.633	[0.0043-4.3]	µmol/l
k_{off}	0.00824	[9.8e-4-0.098]	1/min
K_d	0.0398	[4e-4-0.4]	µmol/l
Pgp			
ref. conc.	14	[0.01-14.955]	µmol/l
V_{max}	5.55	[0.05-50]	µmol/l/min
K_m	5.63	[0.005-5.76]	µmol/l
Dissolution			
$t_{80\%}$	20.7	[2.85-40.8]	min



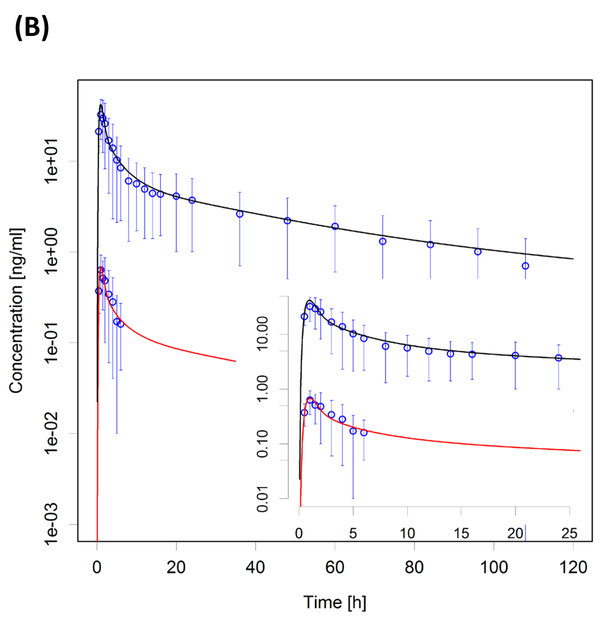


Figure 3: (A) IV data and (B) PO data from Möller et al. Black and red solid lines, predicted whole blood and plasma concentrations, resp. Blue circles and bars, observed data with standard error.

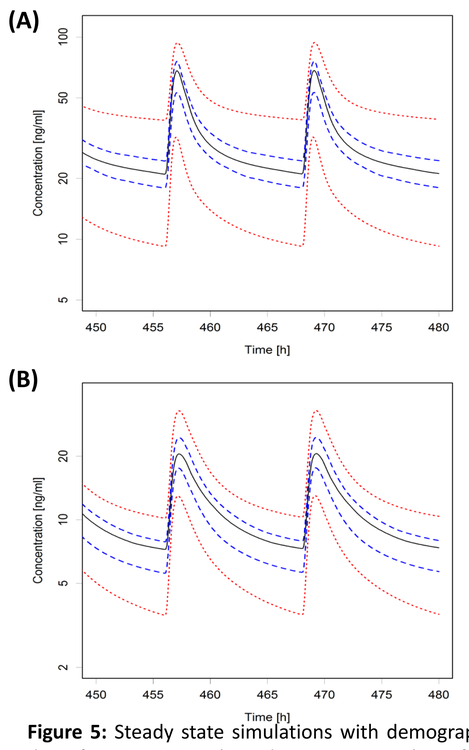


Figure 5: Steady state simulations with demographic data from Mai et al. and parameter values from Table1. (A) with Hct=47%; (B) with f_u=0.5% and Hct=35% (B).

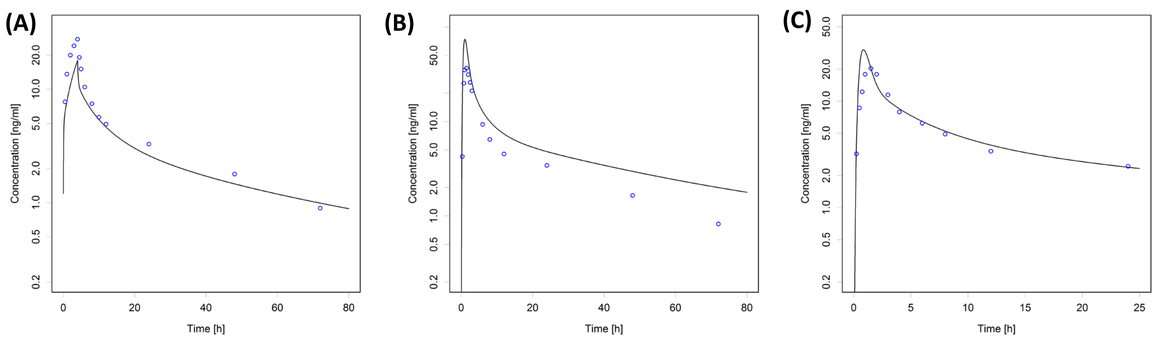


Figure 4: Predictions of TAC concentrations (solid lines) using parameter values from Table1. (A) Demographic and IV data from Mancinelli et al. (B) Demographic data and PO data from Mancinelli et al. (C) Demographic data and PO data from Xin et al.

Conclusion

Observed TAC plasma and whole blood concentration data after IV and PO administration from Möller et al., could simultaneously be described well by a whole-body PBPK model. Despite the reported high variability of PK parameters, whole blood concentrations in white Americans and Asian population could be predicted in an acceptable manner in a dose range from 2–5 mg without further adaptations. Using whole blood and plasma concentrations simultaneously the estimated value of logP was at the high end of reported parameter range in literature. Based on model prediction, intestinal first pass effect reduces bioavailability by 50% compared to hepatic metabolism alone. Prediction of patient data needs further investigation since trough concentrations were overpredicted by the model. Possible causes which might explain lower whole blood concentrations in patients are reduced free fraction in plasma and lower hematocrit values.

References:
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