



# Optimisation and evaluation of a Physiologically based model for tacrolimus with mechanistic absorption to inform its use in Pregnant and Breastfeeding women

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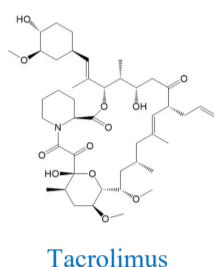
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## INTRODUCTION

Tacrolimus, a potent immunosuppressant, commonly used to prevent organ transplant rejection, presents challenges in dosing due to its narrow therapeutic index and significant high variability in drug exposure.

Ensuring appropriate blood concentrations through dose adjustments is particularly critical for special populations, such as pregnant and lactating women, where data on the safety and efficacy are limited.

The use of PBPK models to predict exposure in pregnant and breastfeeding women is of increasing interest and we have published on the investigation of the qualification of these models in pregnancy [1-2].



### Objectives:

- Improve the previously developed physiologically-based pharmacokinetic (PBPK) model of tacrolimus, optimising clearance, distribution, and absorption aspects.
- Evaluate the predictive performance of the drug model for its ability to inform the drug exposure in non-pregnant, pregnant and breast-feeding women.
- Explore the use of the model to inform dosing in these populations.

## MATERIALS AND METHODS

A previously developed PBPK model [3] was optimised incorporating a more mechanistic (ADAM) absorption model in SIMCYP describing the low solubility, and with consideration of super-saturation, precipitation and bile micelle partitioning [4].

Clearance pathways were optimised using Km and Vmax parameters for CYP3A4 and CYP3A5 enzyme pathways.

The extensive blood partitioning, blood/plasma= 15, was included in the model.

Refining of the drug distribution process was found to be required. A higher lipophilicity value for the molecule than that predicted by its measured LogD was required to adequately capture the distribution, this value is consistent with the calculated LogP value.

The predictive performance of the model was evaluated by graphical comparison against a population prediction with calculation and consideration of PK parameters: AUC and Cmax, and fold errors.

### Input parameters of the PBPK Model

Parameter	Value
<b>Physicochemical Properties</b>	
Molecular weight (g/mol)	804.02
Log P <sub>ow</sub>	4.8
Compound type	Neutral
Polar surface area (Å <sup>2</sup> )	178.4
<b>Blood Binding Properties</b>	
B/P	15
f <sub>up</sub>	0.021
<b>Absorption</b>	
Absorption model	ADAM model
UBL fluid volume	Open
f <sub>gut</sub>	1
P <sub>eff</sub> (x10 <sup>-4</sup> cm/s)	4.77
Solubility (mg/mL, pH 7.4)	0.02

Parameter	Value
<b>Distribution</b>	
Distribution model	Full PBPK
Kp Scalar	1
Vss (L/kg)	Predicted
Prediction method	Method 2
<b>Elimination</b>	
Pathway 1	
CYP3A4	
Vmax (pmol/min/pmol CYP)	7.8
Km,u (µM)	0.9
Pathway 2	
CYP3A5	
Vmax (pmol/min/pmol CYP)	10.8
Km,u (µM)	0.6
CYP3A4	
Vmax (pmol/min/pmol CYP)	0.3
Km,u (µM)	1.2
CYP3A5	
Vmax (pmol/min/pmol CYP)	0.8
Km,u (µM)	1.1
Renal clearance rate (L/h)	0.045

## RESULTS

Comparison between model-predicted total drug exposure parameters and clinical data for tacrolimus in healthy volunteers after oral single administration. Bekersky et al [5].

	3 mg		7 mg		10 mg	
	C <sub>max</sub> (ng/mL)	AUC (ng/mL.h)	C <sub>max</sub> (ng/mL)	AUC (ng/mL.h)	C <sub>max</sub> (ng/mL)	AUC (ng/mL.h)
Observed	14.5	131	31.2	303	45.1	420
Predicted	15.15	169.99	35.27	412.01	48.2	601
<b>Fold Error</b>	<b>1.04</b>	<b>1.30</b>	<b>1.13</b>	<b>1.36</b>	<b>1.07</b>	<b>1.43</b>

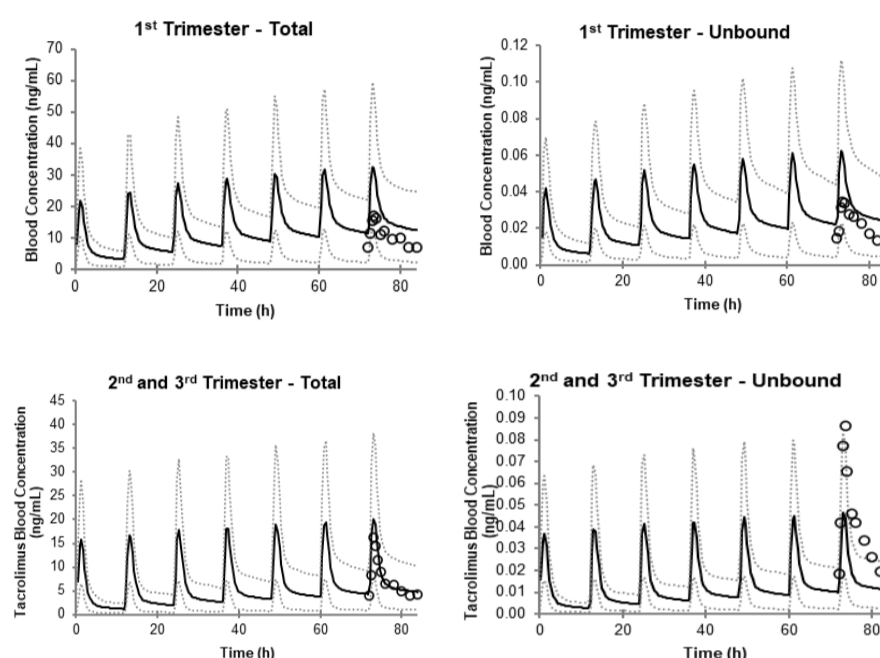
The simulations showed an improved fit to clinical blood concentration data for total and free drug for both non-pregnant and pregnant populations and at a range of doses.

## REFERENCES

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## RESULTS (continued)

Tacrolimus exposure in pregnant population after oral administration. Comparison of simulations using the full PBPK model to clinical studies. Zheng et al [6].

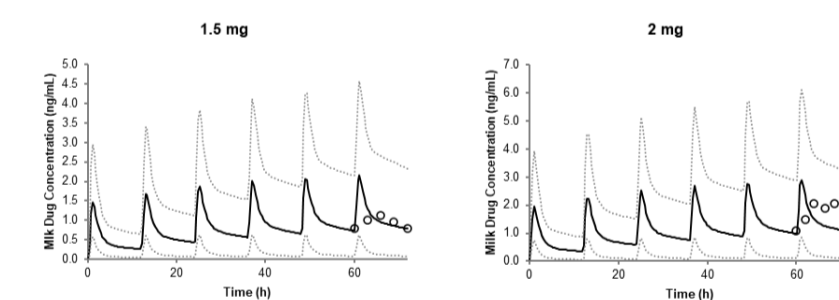


Compared to clinical data collected in the second and third trimester of pregnancy [6] AUC and Cmax values were 1.23 and 1.1 fold for Cmax and AUC respectively.

Calculated free/ unbound concentrations in late pregnancy were somewhat unpredicted by ~2 fold, 0.54 and 0.46 for Cmax and AUC, respectively.

The modelling supports the clinical finding of a decrease in exposure to total in blood during pregnancy compared to post-partum (64% of exposure) but a reduced effect on free (89% of exposure) [3].

Tacrolimus exposure in breast milk after oral administration. Comparison of the final PBPK model simulations to clinical studies. (1.5 mg and 2 mg). Zheng et al [7]



Simulations for drug in breast milk used the observed milk/plasma ratio of 2.89. Predicted milk plasma ratio using the Atkinson and Begg model in the software was 2.0, which was lower than the observed value.

Comparison with clinical data following a 2 mg dose given to breastfeeding women showed a reasonable predicted Cmax and AUC value in milk of 1.43 and 0.82 fold of the observed data [7].

Clinical data is limited with only 3 case studies, however the profile shape appeared different possibly due to the involvement of transporters, not captured in the model..

The predicted infant daily dose is 400ng/kg/day, much lower, less than 1% of the weight adjusted maternal dose.

## CONCLUSIONS

- PBPK modelling can be used to support the safer and more effective use of tacrolimus in pregnant and breastfeeding women.
- The mechanistic absorption model improves the prediction of exposure in women and can be used with more confidence to support exposure profiles in pregnant women.
- Some misprediction is still evident which may be due to the exclusion of additional enzymes and transporters involved in the disposition and elimination.
- Data suggests that dose adjustment does not appear to be necessary in the pregnant population.

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