Predictive Performance of Caffeine Preterm PBPK Model and Effect of Time-Varying Physiology on Predictions

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Background

Neonatal apnea is a serious common disorder in premature infants with low birth weights. Incidence has been reported to be 25% in infants under 2500 g and increasing to 80% in those under 1000 g.[1] Caffeine has been extensively used in the treatment in apnea and in premature infants.[2] Caffeine disposition varies with postnatal age[3] and can differ markedly between premature and term neonates.

Methods

Preterm PBPK model was developed in Simcyp Simulator (V18R1) using default caffeine compound file with minimal PBPK distribution model (Vss = 0.85 L/kg)[4] and default elimination inputs were used to predict the pharmacokinetics of caffeine. Trial design was set as below to replicate the two clinical studies:

Single dose:[5]

No. of subjects: Total 120 (12x10 trials)
Gestational age: 28.5 weeks
Postnatal age: 3-30 days
Dosing regimen: 10.2 mg/kg i.v.
Duration: 5 days

Multiple dose:[1]

No. of subjects: 16 Individual simulations
Replicated the individual demographics for GW, Sex and weight(user defined weight function)
Gestational age: 28-33 weeks
                     (Mean 29 weeks)
Postnatal age: 3 days
Dosing regimen: Loading dose: 10 mg/kg i.v.
                     Maintenance dose: 2.5 mg/kg/day i.v. for 21 days
Duration: 22 days

Redefining subject over time features were selected to allow the growth of individual physiology alongside the simulation progress.

Caffeine Pharmacokinetic (PK) parameters were compared using single dose study and Effect of time-varying physiology on prediction of Caffeine PK was evaluated using multiple dose study by comparing the simulated (with and without redefined subjects) to the clinical PK profiles.
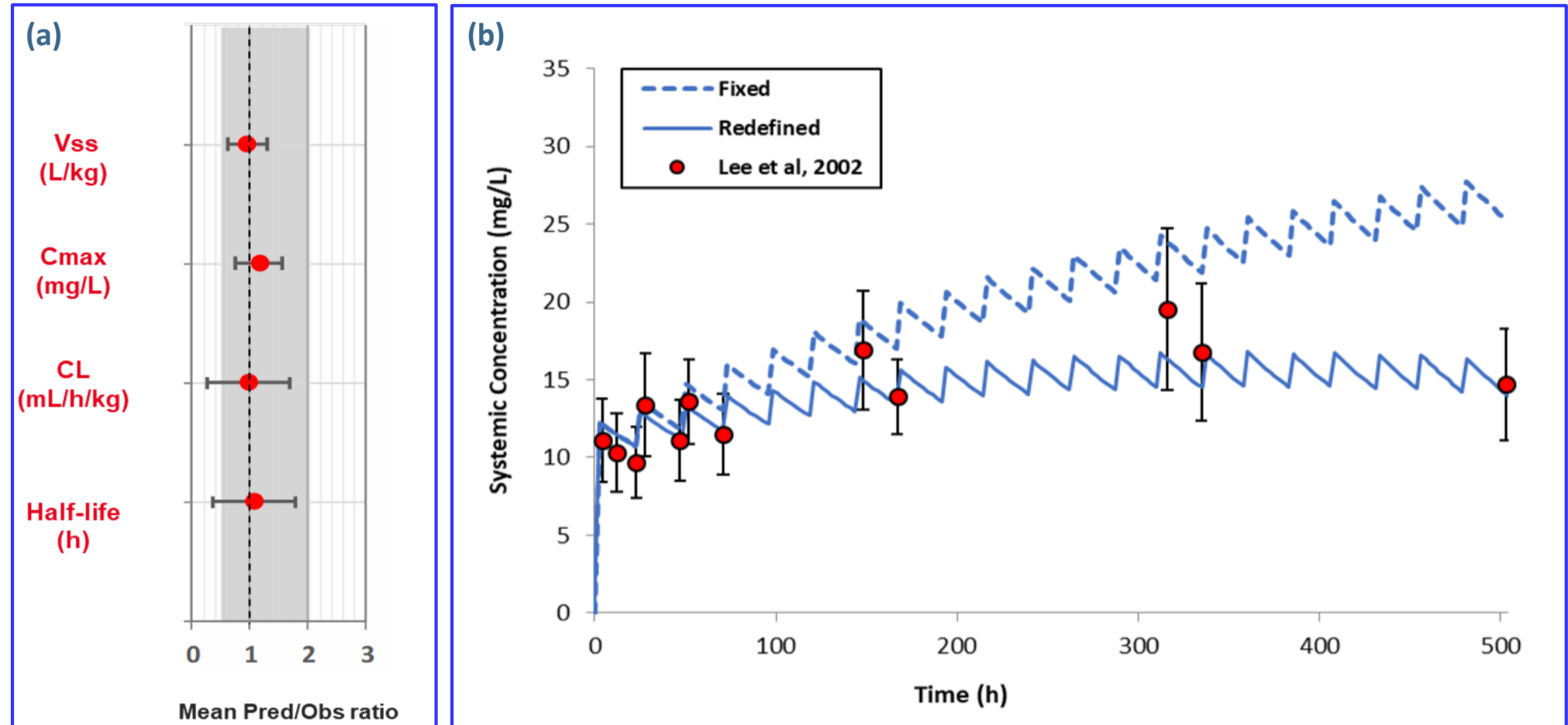

Figure 1. (a) Ratios of predicted over observed Caffeine single dose PK parameters. *Mean with SD (bars), Dashed line: line of identity, Gray area: 0.5–2.0 ratio window.* (b) Simulated mean plasma concentration of multiple dose Caffeine with fixed and redefined subjects over time in Preterm-PBPK model
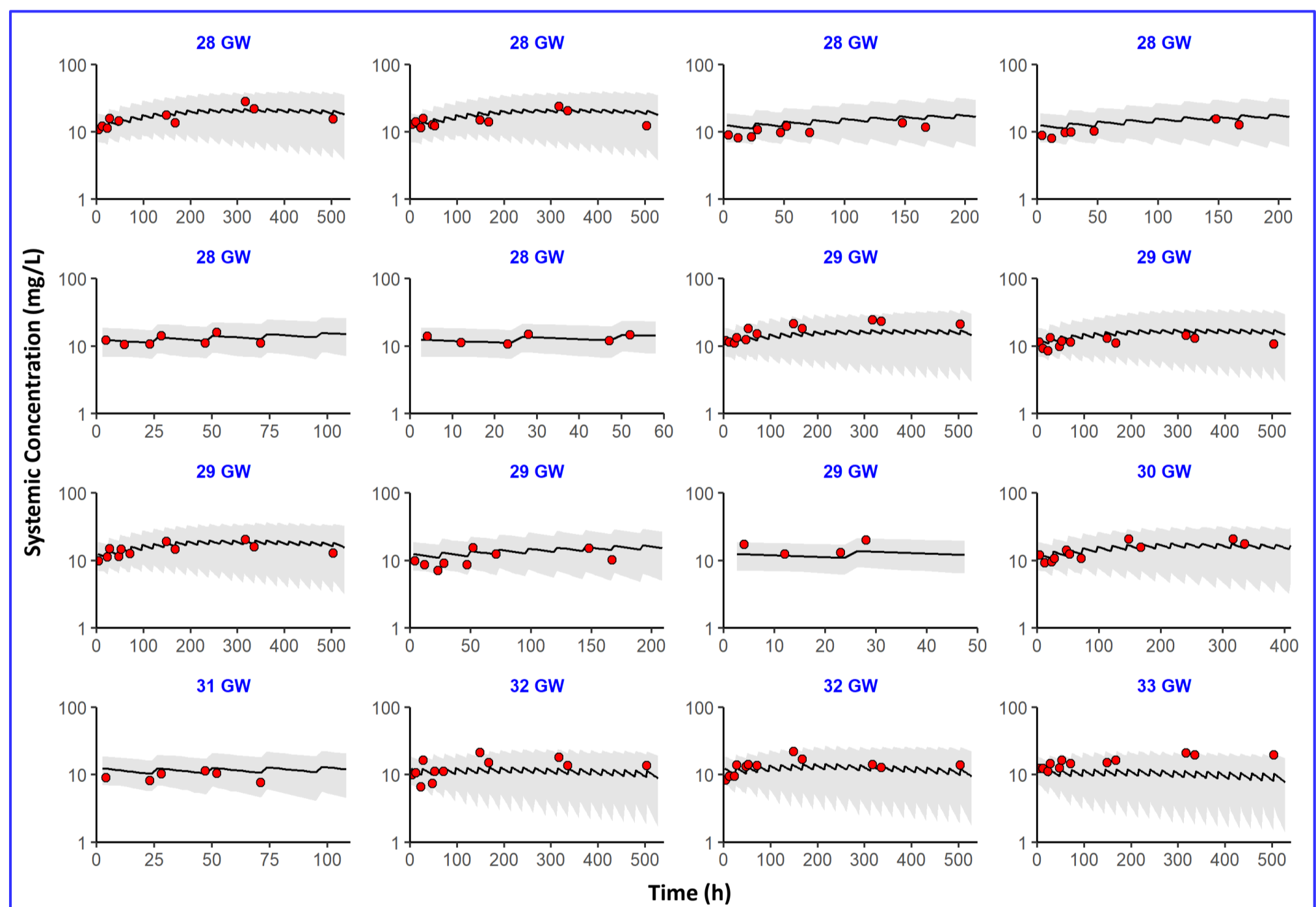

Figure 2. Predicted multiple dose Caffeine PK profiles for 16 preterm subjects. *Black line and Grey area: Simulated mean and 5th, 95th percentile respectively. Observations (Red circles): Lee et al, 2002.*

Results

PBPK model predictions for caffeine in preterm neonates were in good agreement with the clinical observations. For single dose administration, the ratios of predicted vs observed mean Volume of distribution (Vss), peak plasma concentration (Cmax), Clearance (CL) and Half-life were within 0.95-1.16 fold error (Figure 1a). For multiple dose study, simulated mean concentration-time profile for caffeine was much better predicted using the time-varying physiology-based model compared to the time-fixed model (Figure 1b). Individual observed concentration profile for multiple dose administration were replicated in the simulated individual data (Figure 2).

Conclusion

The predictive performance of preterm PBPK models for caffeine was found to be appropriate. A similar PBPK approach can be utilised for more realistic modelling of simulated subject for better Pharmacokinetic prediction and individualisation of dosage regimens in this vulnerable population. Accounting for time-varying physiology (aging) was shown to be critical for long simulations in the preterm population.

References

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