

Whole-body physiology pharmacokinetic modeling of flip-flop behavior of oral oxycodone solution in pediatric patients 5-16 years old

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Objective

The semi-synthetic opioid analgesic oxycodone has in some trials exhibited flip-flop pharmacokinetics when administered as an immediate-release formulation [1]. We noticed the same phenomenon in an analysis of a trial of oral oxycodone solution (0.1 and 0.2 mg/kg) in patients 5-16 years old, and explored the underlying reasons using a whole-body physiological pharmacokinetic (PBPK) modeling approach.

Conclusion

Oxycodone oral solution (0.1 and 0.2 mg/kg, respectively) exhibited flip-flop pharmacokinetics in pediatric patients aged 5-16 years. This may be due to slowed gastrointestinal transit because of opioid effects and/or underlying medical or surgical conditions. This phenomenon can be modeled with a middle-out approach PBPK model when slowed oral absorption is accounted for with a Weibull function. Future studies of oral oxycodone should be wary of flip-flop behavior when defining sampling points.

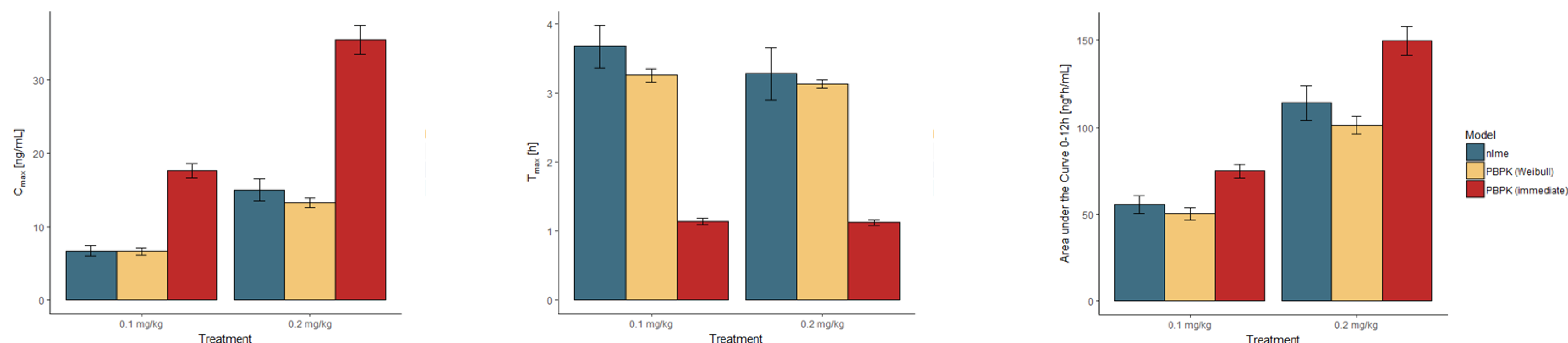


Figure 1 - Comparison of predicted secondary pharmacokinetic parameters (C_{max} , T_{max} , AUC 0-12h) from the population model ("nlme") and the whole-body physiological pharmacokinetic models with either delayed absorption ("PBPK (Weibull)") or immediate absorption ("PBPK (immediate)"). Values as mean +/- SEM.

Methods

Data are from a double-blind, randomized, dose-ranging study in patients 5 to 16 years old to evaluate pharmacokinetics, efficacy and safety of oxycodone 1 mg/mL solution (either 0.1 or 0.2 mg/kg) versus placebo. A total of 46 patients were enrolled in the active treatment group, with 1-8 samples taken per patient. PopPK analysis was carried out using NONMEM (version 7.4.1; <http://www.iconplc.com>). PK-Sim and MoBi (version 7.0; <http://www.systems-biology.com/products/pk-sim.html>) was used for PBPK modeling and simulation.

Results

The final population pharmacokinetic model is a one-compartment model with first-order absorption and elimination. We estimated the elimination rate constant (k_{el}) at 0.55 h⁻¹, and the absorption rate constant (k_a) at 0.14 h⁻¹. As $k_{el} > k_a$, we noted the presence of flip-flop pharmacokinetics, i.e. elimination is driven by absorption. Possible reasons for this may be opioid effects on gastrointestinal motility (either from oxycodone or concomitant morphine treatment), and underlying medical and surgical conditions.

To see whether drug- or disease-induced changes in oral absorption can be held accountable for this, we created a PBPK model of oxycodone in adult patients using a middle-out approach from a clinical trial of oral oxycodone solution (0.2 mg/kg) [2], and published data on the physico-chemical and absorption / distribution / metabolism / elimination properties of oxycodone. The model faithfully depicted the historical adult data. We then proceeded to scale the PBPK model to the population of this trial, and noted absorption was predicted to be much faster than observed. Particularly, maximum concentrations (C_{max}) and areas under the curve from 0-12h (AUC_{0-12h}) were over-predicted, and time to maximum concentration (T_{max}) was underpredicted.

By changing the release model of oxycodone to conform to a Weibull function parameterized from visual inspection, we were able to create a modified PBPK model that matches all three relevant secondary pharmacokinetic parameters. The Weibull function has been previously established as an alternative for time-dependent first-order release [3-5]. A similar approach was taken by Li et al. who used semi-mechanistical modeling using a Weibull function for oral absorption of oxycodone [1].

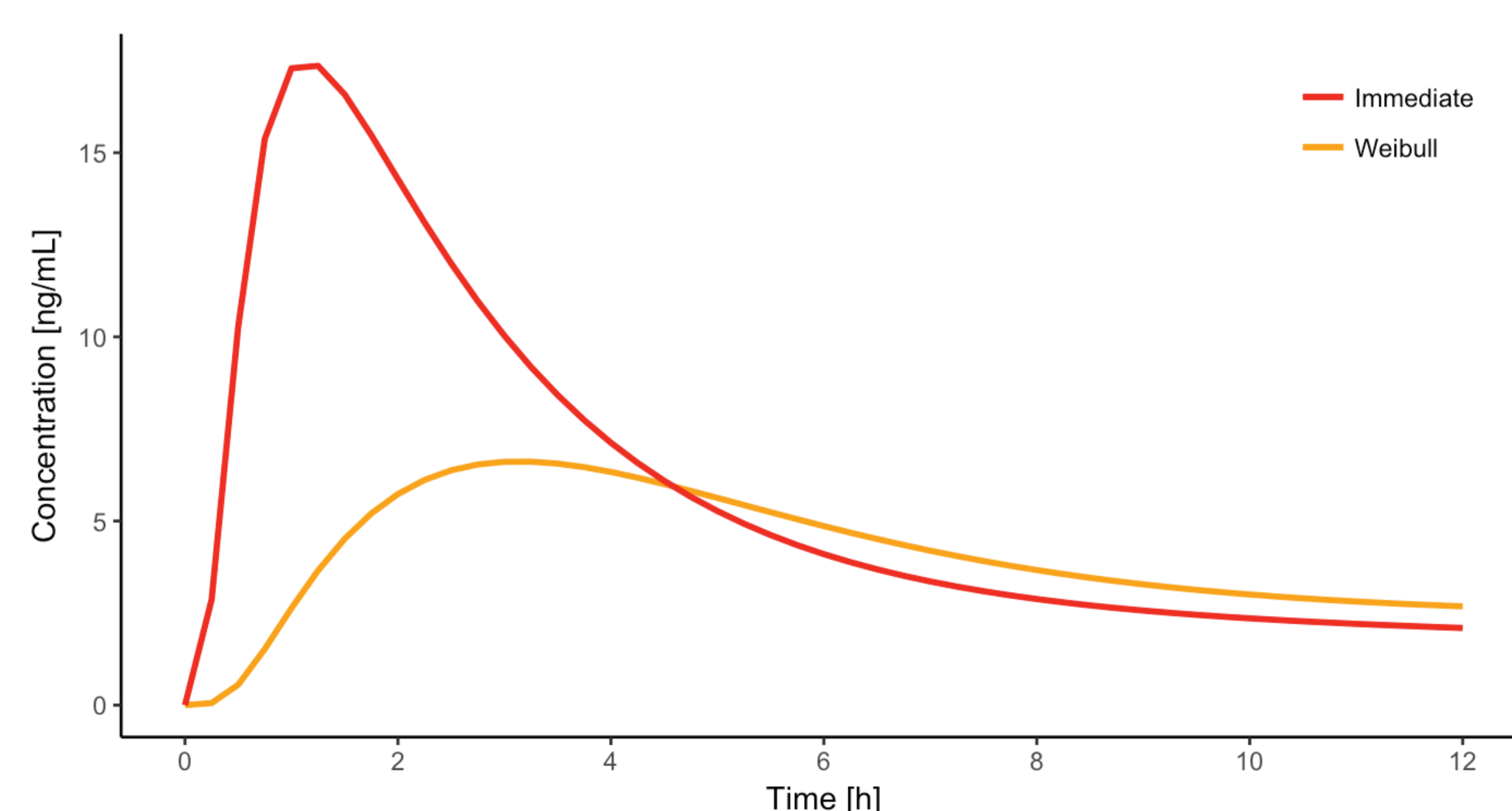


Figure 2 - Simulated (PBPK) mean plasma concentration curves for a single dose of 0.1 mg/kg in 5-16 year old patients using the two different absorption models