MODELING AND SIMULATION GUIDED DESIGN OF A PEDIATRIC POPULATION PHARMACOKINETIC TRIAL

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INTRODUCTION

The pharmacokinetics (PK) and pharmacodynamics (PD) of oral hydromorphone (HM) have not been investigated in a pediatric (PED) population. A prospective population PK trial in PED patients with ages ranging from < 1 month to 16 years was planned. Decisions about the trial design and potential PED dosing rules, given prior information about HM efficacy, safety and PK in adults, were explored through modeling and simulation.

PURPOSE

The goal of this work was to evaluate potential design(s) for a PED population pharmacokinetic (PPK) trial of oral HM, through modeling and simulation. Goals of the planned study included the definition of a PED dosing rule for HM.

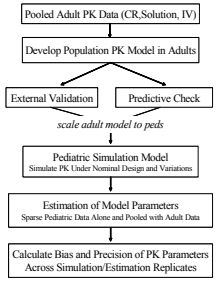
METHODS

Prior knowledge of HM PK in adults (AD), allometric scaling, and age-dependent development of clearance mechanisms were integrated into a PED PPK simulation model. Trial design factors included number of subjects, selection of age groups, number of samples per subject, duration of stay, use of rescue medication, and a PED dosing rule. S-PLUS and NONMEM were used to conduct 100 simulation-estimation replicates for each design scenario. Performance was measured as mean bias and precision of PPK parameter estimates.

Evaluation of Adult Model

In the current modeling and simulation analysis, the previously developed adult PK model (2 compartment disposition with separate IR, CR or solution inputs) was evaluated for goodness of fit and subjected to an internal predictive check, as well as an external prediction evaluation.

Figure 1: Flow Chart for Modeling and Simulation Plan



Predictive Check

Five hundred Monte Carlo simulation replicates of the original data set were generated using the final adult population PK model. Distributions of a characteristic of the simulated data were compared with the distribution of the same characteristic in the observed HMP data set, using exploratory graphics (quantile-quantile plots and histograms). The characteristic of interest was the average concentration across all data points within each individual (C_{avg}).

Nominal Trial Simulation Design

Trial design options were structured around a basic design, while variations due to number of subjects, number of samples per subject, duration of therapy, and use of rescue doses were explored (Table 1). The most realistic (Nominal) design was characterized by a multiple dosing, balanced design across five age groups:

I.) < 1 month, II.) 1 - 12 months, III.) >12 months - 4 years, IV.) > 4 - 12 years, V.) >12 - 16 years.

This Nominal design was framed within the context of expected in-patient hospital stays for PED patients requiring opioid analgesics. The proposed study size was 60 PED subjects, with 12 individuals in each age group. For the four youngest age groups, doses were assigned according to expected changes in clearance across the age/weight range (Equation 1), with the goal of achieving exposures that were approximately equivalent to the exposure resulting from HM doses of 12 mg/day in a 70 kg adult. Doses were administered every 6 hours as an IR oral solution. The oldest age group was dosed with a fixed 8 mg CR oral dose, once daily. Doses used in the trial simulations were based on a dosing rule defined in Equation 1. Rescue doses equal to half of the starting dose were allowed as an IR formulation every 2 hours, as needed.

Description	No. Subjects per Age Group	No. Samples per Subject	Duration of Study	Rescue Doses
Basic Design	12 (60 total)	6	72 hours	No rescue
Inreased Subjects	20 (100 total)	6	72 hours	No rescue
Random Duration	12 (60 total)	2-6	24, 48 or 72 hours (equal probability)	No rescue
Random Duration and Rescue Design	12 (60 total)	2-6	24, 48 or 72 hours (equal probability)	Dose titrated upward by 50% every 2 hrs if needed

Table 1. PED Population PK Trial Design Factors

$$Dose_{ped} = Dose_{adult} \cdot \left(\frac{WT_i}{WT_{ref}}\right)^{0.75} \cdot \left(\frac{AGE_i}{AGE_{ref}}\right)^{1.6} \quad \text{(Eq.1)}$$

where: the $Dose_{ped}$ (daily PED dose) was described as a function of the typical daily adult dose ($Dose_{adult}$ = 12 mg), individual body weight (WT_i), normalized by a reference weight (WT_{ref}), which was 70 kg. A fixed allometric power parameter (0.75) was assumed to scale dosing based on anticipated clearance changes across the range of weights. For PED subjects less than 1 year of age, an additional factor describing maturational changes in clearance was also assumed. The power of 1.6 is an approximation of the time-dependent maturational relationship previously reported for morphine glucuronidation (6) and is applied when AGE < 1 year. The age-effect power is 0 for AGE >= 1 year.

In the nominal design, each subject could contribute up to 6 plasma samples for PK analysis over a three-day period. PK sampling times were defined by an initial random-block strategy, followed by trough samples, with the following time blocks (post first dose): 0.5-1.75, 2.25-3.75, 4.25-6, 9-14, 58-60, and 60.25-70 hours. Subjects in the oldest age group were assigned a slightly different sampling scheme: 1-3.75, 4.25-7.45, 8.25-11.3, 23.5-23.9, 47.5-47.9, and 50-60 hours. Duration of stay was randomly assigned to each subject with an equal probability of 24, 48, or 72 hours.

Simulations

The first step of the HM PED population PK trial simulation process was to perform stochastic simulations of PED trial design characteristics, such as demographics (weight and age), sampling times, visit duration, and rescue medication use. The result of this first step of the simulation served as a template data set for Monte Carlo simulation of PK data in NONMEM (3). The PED PPK simulation model was derived from the adult HMP PK model, by scaling parameters according to allometric principles. One hundred replicate trial simulations were conducted for each design scenario.

PED PPK Parameter Estimation and Evaluation of Trial Performance

Each of the PED trial simulation replicates was analyzed in a separate estimation step, given the scaled adult model. Two estimation conditions were explored. The first condition incorporated only the data from the 60 PED subjects, while a second estimation condition augmented the PED data set with full-profile PK data from 12 adult subjects.

Population parameter precision and bias were calculated based on the discrepancy between the resulting PPK parameter estimates and the "true" simulation parameters. Bias was calculated as the Mean Percent Prediction Error (MPPE), and precision was calculated as the Mean Percent Absolute Error (MPAE).

Modeling and Simulation Assumptions

Random interindividual variability in PK parameters was described with an exponential distribution and variance-covariance matrix estimated from the adult data. Random residual variability was described as a combination additive and proportional error model, as estimated from the adult data.

An attempt was made to incorporate known physiologic relationships into the covariate-parameter models. For example, the change in physiologic parameters as a function of body size is both theoretically and empirically described by an allometric model (Equation 2) (7-11).

$$TVP = \theta_{TYP} \cdot \left(\frac{WT_i}{WT_{ref}}\right)^{\theta_{allo}} \quad \text{(Eq.2)}$$

where: the typical value of a model parameter (TVP) was described as a function of individual body weight (WT_i), normalized by a reference weight (WT_{ref}), which was 70 kg. θ_{TYP} is an estimated parameter describing the typical PK parameter value for an individual with weight equal to the reference weight and θ_{allo} is a fixed allometric power parameter, which was assigned a value of 0.75 for physiologic processes, such as clearances, and a value of 1 for anatomical volumes.

For PED subjects less than 1 year of age, an age-dependent increase in the typical clearance ($TVCL$) was assumed, according to the time-dependent maturational relationship previously reported for morphine glucuronidation (6) (Equation 3). In this model, θ_{mat} is a power parameter to be used to simulate or estimate age-dependent effects on clearance in subjects less than 1 year of age, and AGE_{ref} is 1 year.

$$TVCL = \theta_{TVCL} \cdot \left(\frac{WT_i}{WT_{ref}}\right)^{\theta_{allo}} \cdot \left(\frac{AGE_i}{AGE_{ref}}\right)^{\theta_{mat}} \quad \text{(Eq. 3)}$$

RESULTS

Predictive performance of the adult model was good, as demonstrated by the predictive check results (Fig 2). The performances of the trial design and parameter estimation conditions are displayed in Table 2. When the PED data simulated under the Nominal design were analyzed, parameter bias was acceptable for CL/F and V/F, but bias was quite large for other model parameters. Precision was poor across the list of estimated parameters (Table 2, left). When the model was anchored with HM PK data from 12 adult subjects, estimation performance was dramatically improved (Table 2, right), and all fixed effect parameter estimates were within an acceptable range of bias and precision. Inclusion of the adult data did not bias the estimation of PED parameters and resulted in a good fit to the PED data (Fig 3).

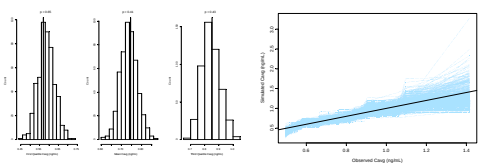


Figure 2: Predictive Check for Average HM Concentration
Left Panel (Left: population first quartile C_{avg}; **Middle** population mean C_{avg}; **Right**: population third quartile C_{avg}. The observed first quartile, mean and third quartile C_{avg} values are indicated by a solid black verticle line, with the predictive check p-value indicated above each histogram.); **Right Panel** (Q-Q plot of C_{avg} distributions, simulated vs. observed).

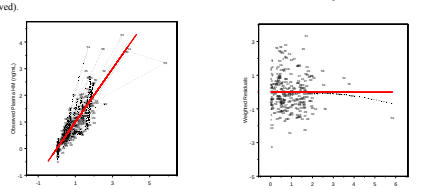


Figure 3: Goodness of Fit Plots
Goodness of fit diagnostic plots are shown for the PED patients from a randomly selected trial replicate. Estimation was performed under conditions with included all sparse PED data plus full profile data from 12 adults.

Table 2. Parameter Estimation Precision and Bias for Nominal PED Trial Design: PED Data Alone or in with Data from 12 Adult Subjects

Parameter	Sparse Pediatric Data Alone (N=60) % Precision	% Bias	Sparse Pediatric Data Plus Adult Data (N=72) % Precision	% Bias
CL/F	64.4	10.1	7.7	-0.6
V/F central	85.1	-7.8	17.3	-0.6
Ka (CR fast)	37.8	-24.5	15.2	6.9
Ka (CR slow)	116.0	79.3	12.1	1.8
Ka (solution)	56.1	-44.6	12.9	2.8
Alag1 (fast)	35.4	30.9	NA	NA
Alag2 (slow)	68.3	42.8	2.9	-0.7
Alag3 (solution)	55.0	12.3	NA	NA
Fraction CR fast	98.0	-35.6	7.4	-1.6
Abs Bio for CR	69.4	-19.6	12.1	2.5
Q/F	66.2	15.1	9.0	4.1
V/F peripheral	11.4	-6.6	7.6	3.8
Abs. Bio. For Solution	56.2	-22.2	8.6	2.2
Age effect on Glucoronidation	47.9	-26.0	7.8	-6.0
Ω 1,1 (CL/F)	68.5	-5	58.5	-0.6
Ω 2,1 (corr of CL/F, V/F)	174.6	-34.3	160.6	-23.3
Ω 2,2 (V/F)	495.3	411.0	83.6	3.2
Ω 3,3 (Ka SR fast)	229.8	113.1	89.3	-17.3
Ω 4,4 (Ka SR slow)	2426.2	2302.0	156.6	35.7
Ω 5,5 (Ka solution)	78.6	-50.7	67.0	1.6
Ω 6,6 (Abs Bio for CR)	98.3	-58.4	70.9	3.5
Ω 7,7 (Abs. Bio. For Solution)	60.7	-35.0	38.0	-3.3
Σ 1,1 (CR Prop Error)	36.7	-16.8	18.1	2.3
Σ 2,2 (CR Add. Error)	76.2	-30.5	30.9	-2.5
Σ 3,3 (Solution Prop. Error)	23.0	11.6	18.3	3.7
Σ 4,4 (Solution Add. Error)	29.2	-28.1	10.8	-1.7

Expected HM PK in PED Patients

The population model with allometric scaling was used to project the plasma concentration-time profile for one-month-old children given a certain dosing regimen (0.09 mg q 6 hr). As illustrated in Figure 4, the predicted range of concentrations is consistent with safe and effective exposure ranges in adults. If the assumption is made that clearance of HM is affected by maturation of UGT enzymes, higher exposures would be expected (Figure 4, right).

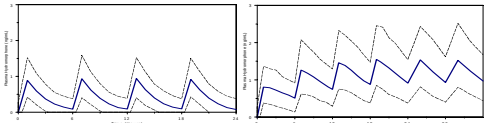


Figure 4: HM Plasma Concentration-Time Profile
Left: HM plasma concentration profile (Median = solid line, 5th quantile = lower dashed line, 95th quantile = upper dashed line, population prediction intervals for 1000 PED subjects at an age of one-month) after administration of 0.09 mg hydromorphone solution . **Right**: HM plasma concentration profile (Median = solid line, 5th quantile = lower dashed line, 95th quantile = upper dashed line, population prediction intervals for 1000 children at an age of one-month) after administration of 0.09 mg HM solution, assuming the additional effect of age on UGT maturation.

DISCUSSION & CONCLUSIONS

- Results for simulated trial design scenarios indicated acceptable estimation performance when the PED data set was augmented with minimal adult data. Bias was within +/- 6% and precision was less than 20% for all fixed effect parameters.
- In particular, the parameters describing typical clearance and age-dependent maturation in children less than 1 year old, were very well estimated.
- Given these results, the proposed Nominal design is likely to provide sufficient information for the estimation of PPK parameters in PED patients and should lead to the definition of a robust dosing rule.
- The trial simulation results also indicated that given the proposed doses, the PK profile and projected variability are consistent with safe and effective exposure ranges in adults.

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