

Optimal Design for a Population Pharmacokinetic Study of Oxycodone in Neonates



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Objectives

While the pharmacokinetics of oxycodone in children older than 6 months of age has been characterized, only one study is available for children aged 0-6 months¹. Therefore we designed a new, larger study about pharmacokinetics of oxycodone in children ranging from preterm neonates to two years of age. The final aim of our study is to give model-based oxycodone dosing recommendations for neonates and infants.

Methods

Data from two previous studies^{1,2} were gathered and fitted into a two-compartment model, scaling clearance by Equation 1. The sampling times and number of children in different age groups were optimized using PopED³. The maximum number of blood samples was restricted to 300, and the maximum number of pre-term infants was restricted to 20 in the design. The optimization results were verified by stochastic simulation and estimation (SSE).

$$CL_i = CL_{pop} \left(\frac{WT_i}{70} \right)^{0.75} * \frac{PMA_i^{Hill}}{PMA_i^{Hill} + PMA_{50}^{Hill}} \quad (1)$$

Where *Hill* is Hill coefficient, *PMA*₅₀ is the post-menstrual age at which clearance is 50% developed, and *WT*_{*i*} and *PMA*_{*i*} are the individual weight and post-menstrual age, respectively.

Results

The clearance was well predicted by the maturation function ($\omega_{CL}=45\%$), which was different from the ontogeny of CYP enzymes⁴ (Figure 1). The other pharmacokinetic parameters were similar to those observed for older children (Table 1). The SSE procedure predicted relative standard errors $\leq 20\%$ for all parameters. The optimal number of children in different age groups, and optimal sampling times for each group are presented in Figure 2.

Conclusions

- Differences were found between empirical clearance model and physiologically predicted clearance (Figure 1). The relative contribution of different CYP enzymes in oxycodone metabolism in infants is not known, and therefore a metabolite analysis will be included in the upcoming study.
- Predicted standard errors $\leq 20\%$ for the upcoming study

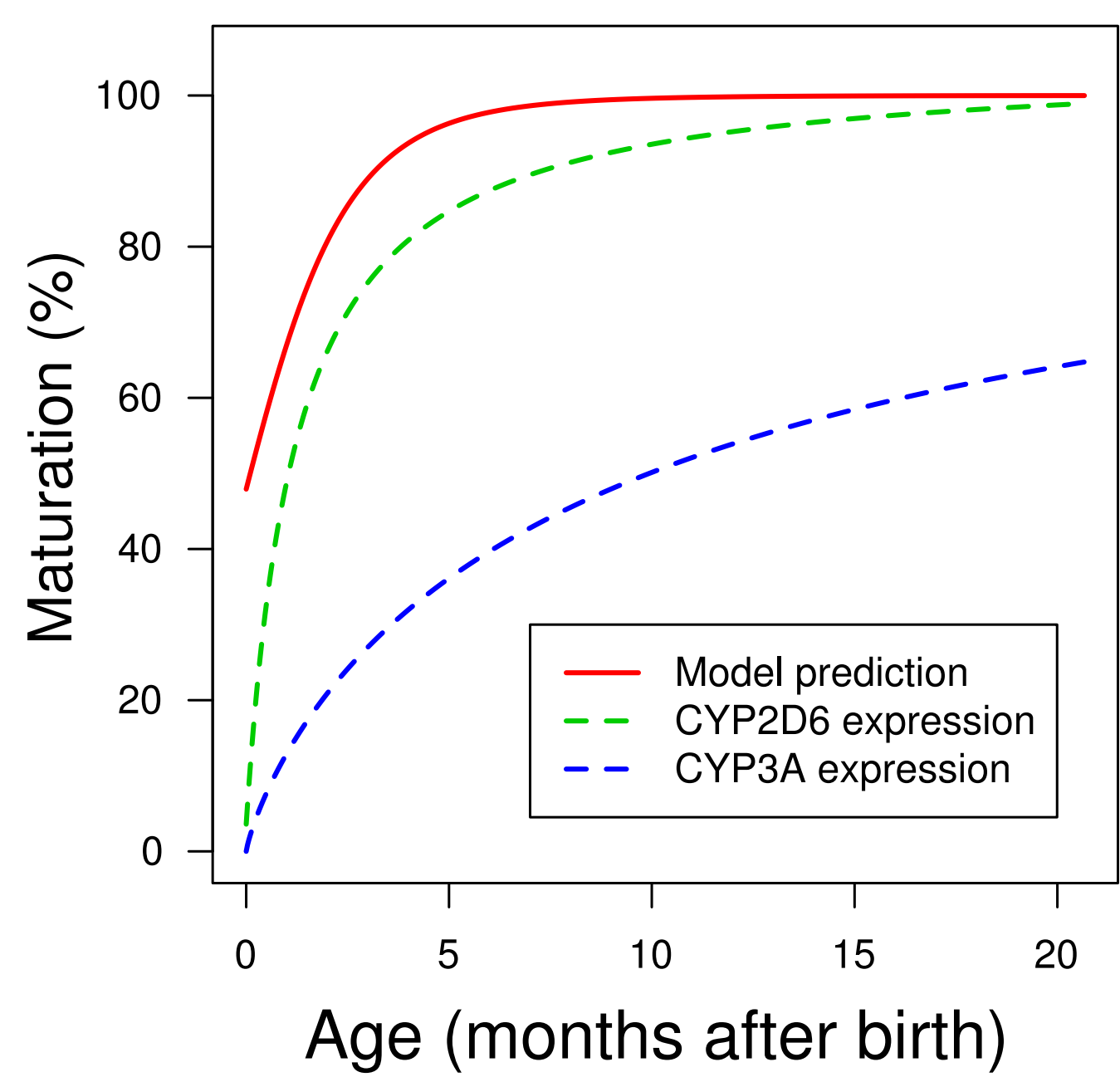


Figure 1. The model-predicted maturation curve for oxycodone clearance (red) and literature-based expression curves for CYP enzymes relevant to oxycodone metabolism (blue and green).

Table 1. The preliminary modeling results and predicted improvement in parameter precision (right column). Clearance and volumes of distribution are scaled to 70kg.

Parameter	Estimate	CV% (orig)	CV% (pred)
CL_{pop}	48.4 L/h	9.2	6
Q	236 L/h	12	9.5
V _c	88.9 L	9.5	6.6
V _p	142 L	9	5.7
Hill	7.8	25	9.4
PMA_{50}	283 days	4	1.9
ω_{CL}	45.00%	33	19
ω_{V_c}	37.00%	29	20

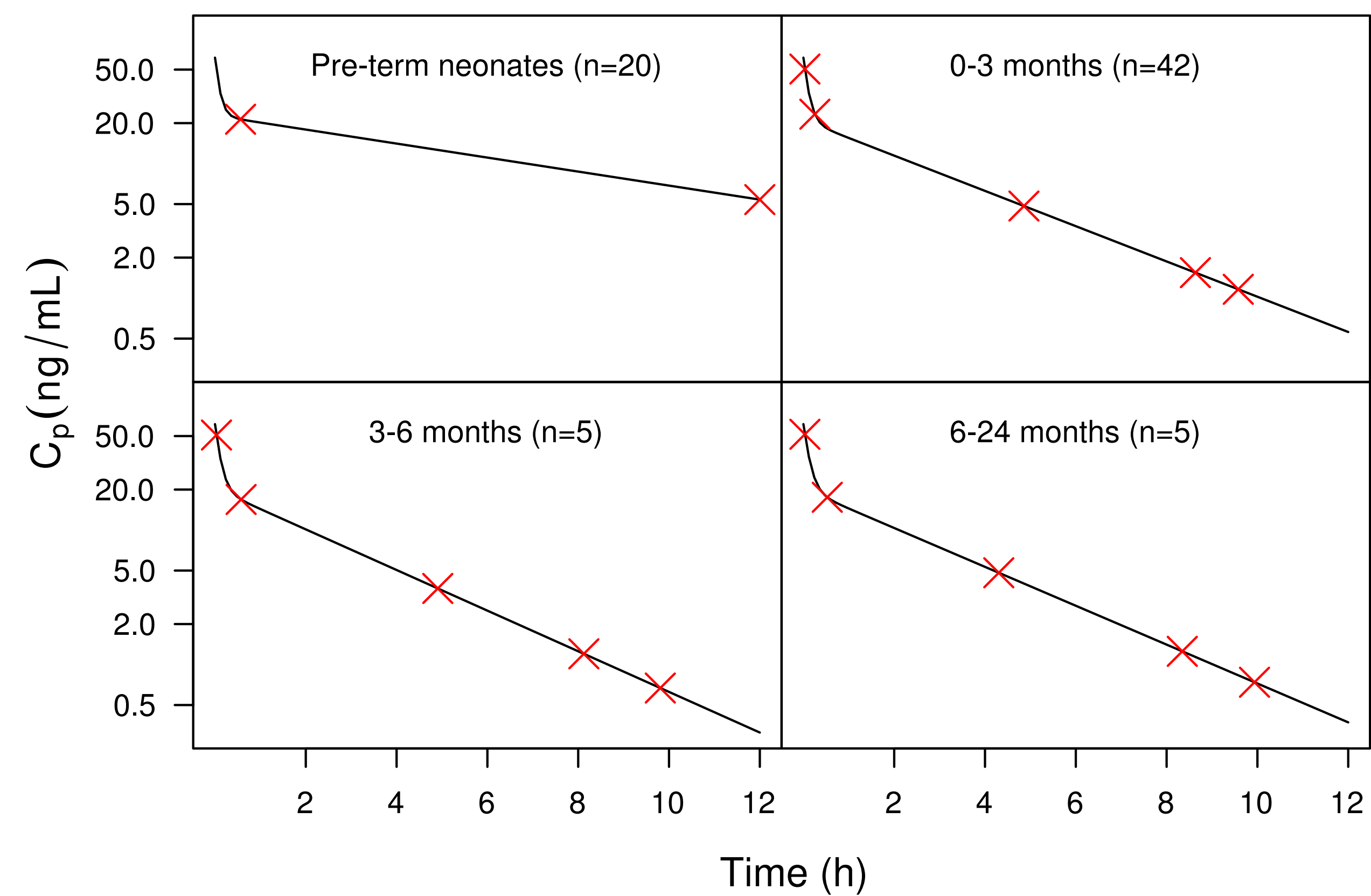


Figure 2. The number of children in different age groups, and the optimal sampling times for children of different ages.

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References

1. Pokela et al. Paediatr Anaesth. 2005;15(7):560-565.
2. El-Tahtawy et al. J Clin Pharmacol. 2006;46(4):433-442.
3. Foracchia et al. Comput Meth Programs Biomed. 2004;74(1):29-46.
4. Johnson et al. Clin Pharmacokinet. 2006;45(9):931-956.