Population pharmacokinetics of Phenobarbital in neonates and infants

Amélie Marsot[1], Renaud Vialet[2], Audrey Boulamery[1], Bernard Bruguerolle[1], Nicolas Simon[1].
[1]Laboratoire de Pharmacologie Médicale et Clinique APHM, Université de la Méditerranée, Marseille, France; [2]Département de Réanimation Pédiatrique, Hôpital Nord, Marseille, France.

INTRODUCTION

- Phenobarbital, antiepileptic drug, is used for treatment of neonatal seizures and prevention of neonatal hyperbilirubinemia.
- Two described pharmacokinetic population models in this population, intravenous administrations in neonates in 1985 [1] and oral and rectal administrations in neonates and infants in 2005 [2].
- Pharmacokinetic population approach derived from routine clinical data.

Table 1. Demographic data

Variable	*Mean*	*+/- SD*	*Range*
Number of patients	27	-	-
Male/female	19/8	-	-
Body weight (kg)	4.4	2.5	1.2 - 10.0
PNA (days)	98.2	156.8	0 - 466
Total phenobarbital dose (mg)	194.4	115.2	40.0 - 450.0

*PNA : Postnatal age

METHODS

- Administration of phenobarbital by 30-min infusion to 27 neonates and infants hospitalized in a pediatric intensive care unit.
- These patients received a 20mg/kg loading dose of phenobarbital and daily maintenance doses of 5mg/kg.
- Determination of concentrations by immunoassay method.
- Pharmacokinetic analysis was made by using a non linear mixed-effect population model.
- Data analysis included calculation of indicators of performance :
  - **P**erformance **E**rror : $PE=(C_m-C_p)/C_p$
  - **MeD**ian **P**erformance **E**rror (bias),
  - **MeD**ian **A**bsolute **P**erformance **E**rror (precision).

*C_m : Measured concentration, C_p: Predicted concentration

RESULTS

- A one-compartment open model with intravenous bolus administration and first-order elimination was used to describe the pharmacokinetics of phenobarbital.
- Clearance and volume of distribution were not significantly affected by sex and PNA.
- Bias and precision were presented in Table 2.
- The pharmacokinetic parameters were listed in Table 3.
- The half-life calculated from the pk parameters estimated was 115 h.
- Validation of our model by an internal method : bootstraping.

Table 2. Accuracy of pharmacokinetic model.

%	*Value*		
MDPE	**-9.5**		
Range	-74.4	to	131.7
95% CI	0.5	to	16.2
MDAPE	**30.1**		
Range	3.9	to	131.7
95% CI	0.3	to	10.7

Figure 2. Visual Predictive Check

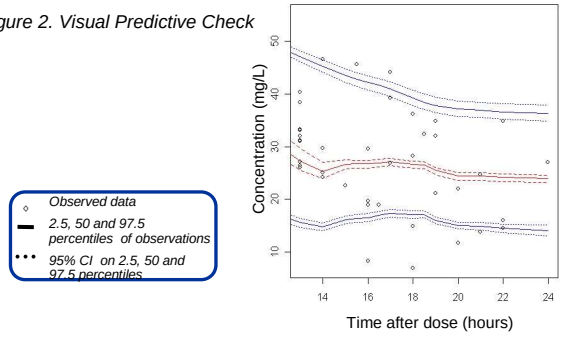

Figure 3. Normalized predictive distribution errors (npde) versus time (a) and versus predicted concentrations (b).

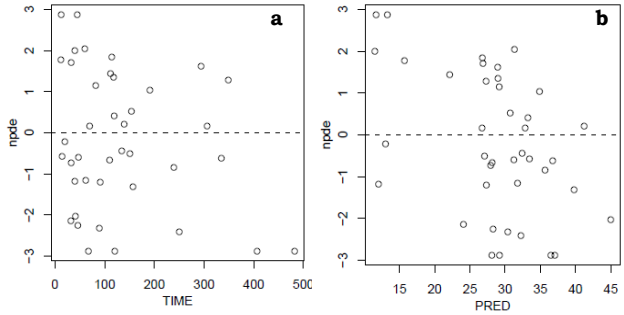

Table 3.Mean pharmacokinetic parameters estimates.

Parameters	*NonMEM Estimates*	*% RSE*	*95% CI*
CL (L/h) = θ_1x(WT/70)$^{0.75}$	***0.04***	-	-
θ_1 *(L/h/70kg)*	0.36	10.4	0.51 - 0.74
V_d (L) = θ_2x(WT/70)	**6.35**	-	-
θ_2 *(L/70kg)*	106.00	15.1	73.28 - 126.37
Interindividual variability of V_d	0.60	25.0	0.379 - 0.680
Intraindividual variability	0.42	27.9	0.262 - 0.572

WT: Body weight

CONCLUSION

- The pharmacokinetic parameters of intravenous phenobarbital in neonates and infants were estimated, the predictive performance was acceptable with a small bias.
- These intermediate results should be confirmed by the inclusion of new patients.

References: [1] Grasela et al. Neonatal population pharmacokinetics of phenobarbital derived from routine clinical data. Dev Pharmacol Ther 1985.

[2] Yukawa et al. Population pharmacokinetic investigation of phenobarbital by mixed effect modelling using routine clinical pharmacokinetic data in Japanese neonates and infants. J Clin Pharm Ther 2005.