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Model-based clinical dose optimization for phenobarbital in neonates: An illustration of the importance of data sharing and external validation

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ABSTRACT

Background: Particularly in the pediatric clinical pharmacology field, data-sharing offers the possibility of making the most of all available data. In this study, we utilize previously collected therapeutic drug monitoring (TDM) data of term and preterm newborns to develop a population pharmacokinetic model for phenobarbital. We externally validate the model using prospective phenobarbital data from an ongoing pharmacokinetic study in preterm neonates.

Methods: TDM data from 53 neonates (gestational age (GA): 37 (24–42) weeks, bodyweight: 2.7 (0.45–4.5) kg; postnatal age (PNA): 4.5 (0 – 22) days) contained information on dosage histories, concentration and covariate data (including birth weight, actual weight, post-natal age (PNA), postmenstrual age, GA, sex, liver and kidney function, APGAR-score). Model development was carried out using NONMEM® 7.3. After assessment of model fit, the model was validated using data of 17 neonates included in the DINO (Drug dosage Improvement in NeOnates)-study.

Results: Modelling of 229 plasma concentrations, ranging from 3.2 to 75.2 mg/L, resulted in a one compartment model for phenobarbital. Clearance (CL) and volume (V_d) for a child with a birthweight of 2.6 kg at PNA day 4.5 was 0.0091 L/h (9%) and 2.38 L (5%), respectively. Birthweight and PNA were the best predictors for CL maturation, increasing CL by 36.7% per kg birthweight and 5.3% per postnatal day of living, respectively. The best predictor for the increase in V_d was actual bodyweight (0.31 L/kg). External validation showed that the model can adequately predict the pharmacokinetics in a prospective study.

Conclusion: Data-sharing can help to successfully develop and validate population pharmacokinetic models in neonates. From the results it seems that both PNA and bodyweight are required to guide dosing of phenobarbital in term and preterm neonates.

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1. Introduction

Rational dosing guidelines for drugs in neonates are urgently needed. However, datasets from prospective clinical trials in children are scarce and both the number of included children and the number of samples per child are usually very small (Knibbe et al., 2011). To overcome this problem data-sharing is of utmost importance and can help to make the most out of all available data (Knibbe et al., 2011; Ince et al., 2009; Knibbe and Danhof, 2011). Existing data can be utilized to determine the optimal design of prospective trials but it may also aid dose finding in ongoing trials in case the collected data is not (yet) sufficient to draw valid conclusions (Ince et al., 2009; Krekels et al., 2015).

Besides that, the application of advanced data analysis techniques, namely the population pharmacokinetic modelling approach, allows handling sparse and infrequently collected samples (Knibbe and Danhof, 2011). Moreover, it offers the possibility to quantify inter-individual variability and to identify covariates that determine the pharmacokinetics of drugs along the whole pediatric life-span and can thereby be used to optimize drug dosing (Brussee et al., 2016; De Cock et al., 2011).

Phenobarbital remains the traditional first-line treatment for seizures in neonates although evidence to favour one antiepileptic agent over the other is lacking (Blume et al., 2009). Using phenobarbital alone, only around 50% of seizures can be effectively controlled (Painter et al., 1999; Tulloch et al., 2012). As persistence of seizures might cause permanent functional and structural damage to the brain and existing brain damage might be worsened (Wirrell et al., 2001; Rennie and Boylan, 2003), safe and efficacious treatment is of primary importance. The optimal dosage of phenobarbital in term and preterm neonates remains a topic of discussion. The therapeutic effect is dose dependent with a suggested therapeutic range between 15 and 40 mg/L (Gilman et al., 1989). At higher concentrations sedation and feeding difficulties might occur (Ouvrier and Goldsmith, 1982). The Dutch National Children's Formulary recommends a loading dose of 20 mg/kg and a maintenance dose of 2.5–5 mg/kg/day (Dutch National Children's Formulary, 2016). However, pharmacokinetic data is sparse in term (Ouvrier and Goldsmith, 1982; Donn et al., 1985; Heimann and Gladtke, 1977; Marsot et al., 2014; Yukawa et al., 2011) and preterm (Marsot et al., 2014; Yukawa et al., 2011; Oztekin et al., 2013) newborns.

In this analysis, we utilize therapeutic drug monitoring (TDM) data collected between 1997 and 2003 in the neonatal intensive care unit of the Maastricht University Medical Centre (study 1) to build a population pharmacokinetic model for phenobarbital in term and preterm newborns. We validate the model with data originating from an ongoing PK study (DINO-study: Drug dosage Improvement in preterm NeOnates, NL47409.078.14) (study 2). This study collects pharmacokinetic data of phenobarbital and eight other frequently used off-label drugs in preterm neonates to increase the knowledge on the pharmacokinetics and pharmacodynamics using sparse sampling and limited sample volumes to minimize the burden on the individual child. Using this approach, we illustrate that data sharing and external validation can lead to model-based clinical dose optimization, particularly in neonates where ethical and practical constraints limit the possibilities to perform studies.

2. Methods

2.1. Model development dataset (TDM data, study 1)

TDM data (study 1) were obtained from the database of the Maastricht University Medical Centre between 1997 and 2003 with approval from the medical ethical committee (MEC 02-204.3). Neonates younger than 35 days at the start of phenobarbital treatment were included. A total of 229 samples from 53 neonates (28 male, 25 female) were available for analysis. First dose and consecutive doses (intravenous as well as oral) varied between 4 and 40.7 mg/kg and 1.3 and 20 mg/kg, respectively, and the study period ranged from 4 to 85 days (Table 1). The median first dose was 20 mg/kg, 17 children received a first dose that was higher than 25 mg/kg. The median maintenance dose was 3.9 mg/kg. Covariates were retrieved from the patient's records.

Table 1
Patient characteristics (median (range)) of the TDM dataset (study 1) and the prospective validation dataset from the DINO study (study 2).

	TDM data (study 1)	Prospective data (study 2)
Gestational age [weeks]	37 (24–42)	25 (24–31)
Birthweight [kg]	2.6 (0.45–4.4)	0.94 (0.58–2.2)
Postnatal age (at the day of inclusion) [days]	4.5 (0–22)	15 (1–76)
Duration on study[a] [days]	12 (4–85)	5 (1 – 20)
Actual bodyweight [kg]	2.7 (0.45–4.5)	1.07 (0.63–4.7)
APGAR-Score at 5 min	3 (0–9)	8 (1–9)
First Dose [mg/kg]	20 (4–40.7)	10.8 (2 – 22)
Maintenance Dose [mg/kg]	3.9 (1.3–20)	10.8 (1.2–20)
Samples after intravenous dosing [n]	226	56
Samples after oral dosing [n]	16	6

[a] Defined as the time between the first and the last blood sample contributing to the analysis.

2.2. External model validation dataset (prospective data, study 2)

The DINO-study (NL47409.078.14, MEC-2014-067, study 2) prospectively studies a total of nine drugs including phenobarbital used as standard of care in preterm infants born before 32 weeks of gestation aiming at evidence-based individualized dosing regimen and is still ongoing. From September 2014 to September 2016, 61 blood samples from 17 children (7 female, 10 male) containing phenobarbital were evaluable for the analysis (Table 1).

2.3. Bioanalytical analysis

Phenobarbital concentrations of the model development dataset (study 1) were determined using a fluorescence polarization assay (Steijns et al., 2002) on the COBAS INTEGRA 700 (Roche Diagnostics; Basel, Switzerland) using COBAS INTEGRA reagent system cassettes at the pharmacy of Maastricht University Medical Centre. Fluorescein-labelled phenobarbital binds an antibody and the emitted light is polarized due to the reduction in freedom of rotation. In case phenobarbital is present in the patients serum it reduces the extent of fluorescence polarization due to antibody binding (Steijns et al., 2002). The test range of the assay was 0.6–60 mg/L (coefficient of variation (CV) intra-assay: 0.8–2.8%, CV inter-assay: 2.9–6.5%).

Phenobarbital concentrations of the validation dataset (study 2) were determined using a particle-enhanced turbidimetric inhibition immunoassay (Petinia) on the Architect C4000 (Abbott Diagnostics; Hoofddorp, The Netherlands) using Architect C4000 reagent system cassettes at the pharmacy of the ErasmusMC, Rotterdam. The assay is based on competition between drug in the sample and drug coated onto a microparticle for antibody binding sites of the phenobarbital antibody reagent. The test range is 2.0–80 mg/L (CV intra-assay: 0.9–4.8%, CV inter-assay CV: 3.2–4.8%). A recent method comparing different immunoassays for phenobarbital found a Pearson correlation coefficient of 0.989 between a COBAS and an Architect system (Shipkova et al., 2014).

2.4. Population pharmacokinetic analysis

The analysis was performed using NONMEM® version 7.3 (ICON Development Solutions, Ellicott City, MD, USA), supported by Perl-