Population Pharmacokinetics of Pentobarbital in Neonates, Infants, and Children after Open Heart Surgery

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Objectives To determine the pharmacokinetics of pentobarbital in neonates, infants, and young children with congenital heart disease after open-heart surgery.

Study design Thirty-five subjects (3.0 days-4.4 years) after open-heart surgery who received pentobarbital as standard of care were enrolled. Serial pharmacokinetic blood samples were obtained. A population-based, nonlinear mixed-effects modeling approach was used to characterize pentobarbital pharmacokinetics.

Results A two-compartment model with weight as a co-variate allometrically expressed on clearance (CL), intercompartmental clearance, central (V1) and peripheral volume of distributions, bypass grafting time as a co-variate on CL and V1, and age and ventricular physiology as co-variates on CL best described the pharmacokinetics. A typical infant (two-ventricle physiology, 6.9 kg, 5.2 months, and bypass grafting time of 60 minutes) had a CL of 0.12 L/hr/kg, V1 of 0.45 L/kg, and peripheral volume of distributions of 0.98 L/kg. The bypass grafting effect was poorly estimated. For subjects <12 months age, an age effect on CL remained after accounting for weight and was precisely estimated.

Conclusions Pentobarbital pharmacokinetics is influenced by age and weight. Subjects with single-ventricle physiology demonstrated a 15% decrease in clearance when compared with subjects with two-ventricle physiology. *(J Pediatr 2011;159:414-19)*.

See editorial, p 361

The barbiturate pentobarbital is the oxygen analogue of thiopental. Pentobarbital has a potent effect on γ-aminobutyric acid-sensitive chloride channels and is a potent central nervous system depressant. Pentobarbital enters the brain more rapidly than phenobarbital or diazepam and is a very potent anti-epileptic medication.[1] Pentobarbital is an ideal drug when sedation is the primary goal. It has been recommended as a sedative agent for diagnostic imaging studies.[2-7] It has respiratory depressant and hypotensive adverse effects in some patients. Pediatric populations who may benefit from the favorable pharmacodynamic effects of pentobarbital are neonates, infants, and children with congenital heart disease after corrective surgery who require sedation to tolerate the conditions of the immediate postoperative period. Tracheal intubation and mechanical ventilation are frequently required in the postoperative period for some of these patients. Fresh cardiac suture lines mandate that patients remain adequately sedated to decrease the risk of postoperative bleeding. These patients frequently have sufficient residual narcotic from intraoperative administration and are pain free, but require additional sedation to remain still to accept a chest tube, trans-thoracic lines, a foley catheter, and a strange environment.

Although pentobarbital pharmacology has been well studied in adults, limited pediatric pharmacokinetic (PK) and pharmacodynamic data are available to guide therapy, particularly in neonates, infants, and children with congenital heart disease, who exhibit a wide range of anatomy and physiology, from ventricular septal defects to single ventricle physiology. The impact of immature drug-metabolizing enzyme systems, altered physiology, and intraoperative procedures such as cardiopulmonary bypass grafting and hypothermic circulatory arrest on pentobarbital drug disposition has not been studied. Understanding the clinical pharmacology of pentobarbital is necessary to allow for rational drug administration in this critically ill pediatric subpopulation. Therefore, the primary objective of this study was to describe the PKs of pentobarbital in neonates, infants, and children after open-heart surgery.

CL	Clearance
FOCE-I	First-order conditional estimation with interaction
PK	Pharmacokinetic
Q	Intercompartmental clearance
$t^{1/2}$	Elimination half-life
Vd	Volume of distribution
V1	Volume of central compartment
V2	Volume of peripheral compartment

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Methods

After institutional review board approval and written informed parental consent, neonates, infants, and children with congenital heart disease undergoing open-heart surgery with adequate hepatic function and who received pentobarbital for sedation as standard of care in the postoperative period were eligible for enrollment. Doses of pentobarbital were administered at the discretion of the clinical team. PK samples, consisting of 1 mL blood, were drawn immediately before and after the bolus dose, and at 30 minutes, 60 minutes, 2 hours, 4 to 6 hours, 12 to 18 hours, 18 to 24 hours, 36 to 48 hours, and 56 to 72 hours after the bolus. For patients who received two consecutive boluses, the sampling scheme was identical, except PK samples were obtained after each bolus and the 56- to 72-hour PK sample was not obtained. For subjects who received ≥3 consecutive boluses, PK samples were obtained after the first 3 bolus doses, and then 15 minutes, 30 minutes, 2 hours, 4 to 6 hours, 12 to 18 hours, and 36 to 48 hours after the last bolus. Plasma was separated with centrifugation and stored at −80°C. Pentobarbital plasma concentrations were determined by using a validated high-performance liquid chromatography-tandem mass spectrometry assay with a lower limit of quantitation of 0.05 mcg/mL. The intraday accuracy and precision (co-efficient of variation) ranged from 97.6% to 113.2% and 0.8% to 6.0%, respectively. The interday accuracy ranged from 104.2% and 105.7%, and the precision (co-efficient of variation) was ≤7.3%.

The population PK analysis was conducted with NONMEM software (ICON Development Solutions, Ellicott City, Maryland) version VI, level 1.1 All models were run with the first-order conditional estimation with interaction (FOCE-I) method. S-Plus software version 6.2 (Insightful, Data Analysis Products Division, Seattle, Washington) was used for goodness-of-fit diagnostics and graphical displays. The goodness-of-fit from each NONMEM run was assessed by using the examination of these criteria: visual inspection of diagnostic scatter plots (observed versus predicted concentration, observed and predicted concentration versus time, and weighted residual versus predicted concentration or time), the precision of the parameter estimates as measured with asymptotic standard errors derived from the co-variance matrix of the estimates, successful minimization with at least 3 significant digits in parameter estimates, changes in the Akaike Information Criterion (minimum value of the objective function plus two times the total number of parameters), and changes in the estimates of inter-individual and residual variability for the specified model. No formal sample size estimation was performed. However, earlier work[8] has demonstrated that a population of 30 subjects is sufficient for the estimation of a clearance in a typical population when the inter-individual variability is <75%. Because of this information and clinical feasibility, we deemed a sample size of 35 subjects as adequate.

One- and two-compartment models were investigated. A two-compartment disposition model was deemed optimal to define the pentobarbital plasma concentration profile on the basis of results from the model building process and previously published data. Models were parameterized by clearance (CL, in L/hr), inter-compartmental clearance (Q, in L/hr), volume of central compartment (V1, in L), and volume of peripheral compartment (V2, in L). The impact of weight on all pharmacokinetic variables was investigated by using an allometric model:

$$TVP = \theta_{\mathrm{TVP}} * \left(\mathrm{WT_i}/\mathrm{WT_{ref}}\right)^{\theta\mathrm{allo}}$$

in which TVP is the typical value of a model parameter, described as a function of individual body weight; θ_{TVP} is an estimated parameter describing the typical PK parameter value for an individual with weight equal to the reference weight; $\mathrm{WT_i}$ is an individual subject's body weight; $\mathrm{WT_{ref}}$ is the reference metric (6.9 kg for this analysis); and θ_{allo} is an allometric power parameter fixed at a value of 0.75 for clearances, and a value of 1 for volumes on the basis of physiologic consideration of size impact on metabolic processes.[9,10]

An exponential variance model was used to describe the variability of PK variables across individuals in the form:

$$\mathrm{P_i} = \theta_{\mathrm{k}}\exp(\eta_{\mathrm{ki}})$$

in which $\mathrm{P_i}$ is the estimated parameter value for the individual subject i; θ_{k} is the typical population value of parameter k; η_{ki} are the inter-individual random effects for individual i and parameter k. Models were explored with various inter-individual random effect co-variance structures. Inter-individual variability was initially estimated for clearance and then for the additional variables.

Additive, proportional, and combined (additive and proportional) residual error models were considered during the model-building process. Ultimately, a proportional error model was used to model random residual variability according to:

$$\mathrm{C_{ij}} = \left(\mathrm{C_{Pij}} * \left(1+\epsilon_{\mathrm{ijP}}\right)\right)$$

in which $\mathrm{C_{ij}}$ is the observed concentration j in individual i; $\mathrm{C_{Pij}}$ is the individual predicted concentration; and ϵ_{ijP} is the proportional residual random error.

Once the final base model was selected, a full co-variate modeling method, as implemented in Ravva et al,[11] was constructed to estimate effects of co-variates on pentobarbital disposition. Co-variate effects were pre-defined on the basis of clinical interest, earlier knowledge, and physiologic plausibility. Contrary to step-wise hypothesis testing, the full-model approach is advocated when the goal of the analysis is effect estimation and avoids the problem of selection bias, which is particularly problematic in small data sets.[9,10] The full model included effects of age, weight, total cardiopulmonary bypass grafting time, and ventricular physiology (single- or two-ventricle). Age was considered as an additional co-variate on clearance. Total bypass grafting time was evaluated as a co-variate on clearance, on the basis of the hypothesis that a longer bypass grafting time would impair clearance immediately postoperatively. The effect of total bypass grafting