

PHARMACOKINETICS OF PHENOBARBITAL IN NEONATES ON EXTRACORPOREAL MEMBRANE OXYGENATION

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Objectives: The use of extracorporeal membrane oxygenation (ECMO) is associated with changes in drug pharmacokinetics. This study characterizes the pharmacokinetics of phenobarbital and provides dosing recommendations in neonates on ECMO.

Methods: Therapeutic drug monitoring (TDM) data were available from 13 critically - ill neonates (birth bodyweight (bBW): 3.21 (2.65-3.72) kg; postnatal age (PNA) at start of treatment: 2 (0-7) days; gestational age: 38 (38-41) weeks) receiving veno-venous or veno-arterial ECMO, yielding 5, 31, and 19 phenobarbital concentrations before, during and after ECMO, respectively. Population pharmacokinetic analysis was performed using NONMEM 7.3.0. Maturation functions based on bBW and PNA for clearance (CL) and based on actual BW for distribution volume (Vd) were obtained from literature. Additionally, kidney and liver function markers and flow and speed of ECMO were evaluated for their predictive properties regarding the PK of phenobarbital.

Results: In a one-compartment model, CL and Vd for a typical neonate of median bBW (3.21 kg) at median PNA (2 days) off ECMO were 0.0096 L/h (RSE = 11%) and 2.72 L (16%), respectively. During ECMO, CL was linearly increasing with time. Furthermore, phenobarbital CL initially decreased after decannulation compared to CL during ECMO, and subsequently increased driven by the maturation function. Changes in Vd during ECMO could not be identified, possibly due to sparse data collection shortly after the ECMO start. Simulations showed that optimal dosing includes a LD of 20 mg/kg and a MD of 4 mg/kg/day divided in 2 doses with an increase of 0.25 mg/kg every 12 h during ECMO treatment.

Conclusions: Continuously decreasing phenobarbital exposure during ECMO, resulting from the time-dependent increase in CL, increases the risk of therapeutic failure over time. Due to high remaining unexplained variability, frequent and repeated TDM over time is highly recommended.