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PAEDIATRICS

Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial

K. J. S. Anand[1]*, B. J. Anderson[2], N. H. G. Holford[3], R. W. Hall[1], T. Young[4], B. Shephard[5], N. S. Desai[6] and B. A. Barton[7] for the NEOPAIN Trial Investigators Group

[1]Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR, USA. [2]Division of Anaesthesiology and [3]Division of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, New Zealand. [4]University of North Carolina at Chapel Hill and Wake Medical Center, Raleigh, NC, USA. [5]Tufts University School of Medicine, Boston, MA, USA. [6]University of Kentucky Medical Center, Lexington, KY, USA. [7]Maryland Medical Research Institute, Baltimore, MD, USA

**Corresponding author: Arkansas Children's Hospital, Rm S-4417, 800 Marshall Street, Slot 900, Little Rock, AR 72202, USA. E-mail: anandsunny@uams.edu*

Background. Relationships between plasma morphine concentrations and neonatal responses to endotracheal tube (ETT) suctioning are unknown in preterm neonates.

Methods. Ventilated preterm neonates (n=898) from 16 centres were randomly assigned to placebo (n=449) or morphine (n=449). After an i.v. loading dose (100 μg kg^{-1}), morphine infusions [23–26 weeks postmenstrual age (PMA) 10 μg kg^{-1} h^{-1}; 27–29 weeks 20 μg kg^{-1} h^{-1}; and 30–32 weeks 30 μg kg^{-1} h^{-1}] were established for a maximum of 14 days. Open-label morphine (20–100 μg kg^{-1}) was given for pain or agitation. Morphine assay and neonatal response to ETT suctioning was measured at 20–28 and 70–76 h after starting the drug infusion and at 10–14 h after discontinuation of the study drug. The concentration–effect response was investigated using non-linear mixed effects models.

Results. A total of 5119 data points (1598 measured morphine concentrations and 3521 effect measures) were available from 875 neonates for analysis. Clearance was 50% that of the mature value at 54.2 weeks PMA ($CLmat_{50}$) and increased from 2.05 litre h^{-1} 70 kg^{-1} at 24 weeks PMA to 6.04 litre h^{-1} 70 kg^{-1} at 32 weeks PMA. The volume of distribution in preterm neonates was 190 litre 70 kg^{-1} (CV 51%) and did not change with age. There was no relationship between morphine concentrations (range 0–440 μg litre^{-1}) and heart rate changes associated with ETT suctioning or with the Premature Infant Pain Profile.

Conclusions. A sigmoid curve describing maturation of morphine clearance is moved to the right in preterm neonates and volume of distribution is increased compared with term neonates. Morphine does not alter the neonatal response to ETT suctioning.

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There are limited reports of either morphine pharmacokinetics (PK) or pharmacodynamics (PD) in preterm newborns. Chay and colleagues[1] described a relationship between morphine concentrations and the sedation required to tolerate artificial ventilation in 19 neonates, both preterm and term. Morphine produced sedation in 50% of patients at concentrations of 125 μg litre^{-1} and adverse effects at >300 μg litre^{-1}. PK parameter estimates were not significantly different between preterm and term neonates.[1] Scott and colleagues[2] investigated the relationship between morphine concentrations and heelstick-induced acute pain in neonates (n=48, 24–39 weeks PMA). Pain, assessed by the Neonatal Facial Coding System, was unrelated to morphine concentration. Morphine clearance increased from 2.27 (SD

1.07) ml min^{-1} kg^{-1} at 24–27 weeks PMA to 7.8 (SD 2.67) ml min^{-1} kg^{-1} at 36–39 weeks PMA.[2]

We had the opportunity to examine morphine PK–PD data in preterm neonates enrolled in the NEOPAIN randomized trial,[3] with a larger sample size limited to the lower gestational ages (23–32 weeks). We have previously reported models describing morphine kinetics in term infants.[4] The data from that study has been pooled with the NEOPAIN data[3] and a new model developed in order to broaden the range of the maturation models. This current analysis uses a population-based approach that included body size, expressed by weight, as the primary covariate in an effort to disentangle age-related factors from size-related factors.[5 6]

Methods

Study design

Preterm neonates were eligible for the NEOPAIN trial, if they were born between 23 and 32 weeks of gestation and required intubation before 72 h of age. Morphine infusion was started within 8 h of intubation. Neonates with major congenital abnormalities, birth asphyxia (5 min Apgar score $\leq$3 or cord pH $\leq$7.0), intrauterine growth restriction ($\leq$5th percentile) or maternal opioid addiction, and those participating in other clinical trials were excluded. Written parental consent was obtained for all 898 neonates enrolled from 16 neonatal intensive care units (NICUs) and all clinical personnel were blinded to the study drug code. The NEOPAIN protocol and consent forms were approved by local ethics committees at each participating site, by an external ethics committee at the coordinating centre, and by an independent data and safety monitoring board. Randomization via an automated telephone response system was stratified according to participating NICUs and gestational age (23–26, 27–29, or 30–32 weeks PMA) to ensure equal representation in the morphine (n=449) and placebo (n=449) groups.

After an i.v. loading dose (100 μg kg^{-1} infused over 1 h), morphine infusions (23–26 weeks of gestation 10 μg kg^{-1} h^{-1}; 27–29 weeks 20 μg kg^{-1} h^{-1}; and 30–32 weeks 30 μg kg^{-1} h^{-1}) were continued as long as clinically justified (maximum 14 days). Open-label morphine (20–100 μg kg^{-1} up to every 6 h) could be given, based on clinical judgement (placebo group 242/443 and morphine group 202/446).

Study procedures

The neonatal response to endotracheal tube (ETT) suctioning was assessed by means of the Premature Infant Pain Profile (PIPP). This assessment was performed before starting morphine, during morphine infusion (at 20–28 h), and 10–14 h after stopping morphine infusion. Heart rate recorded before and after ETT suctioning was also available for analysis.

Arterial blood samples (1 ml) were collected for morphine assay at 20–28 and 70–76 h after starting the drug infusion and at 10–14 h after discontinuation of the study drug. These blood samples were collected into pre-chilled tubes containing sodium-EDTA, plasma obtained by immediate centrifugation and stored at −20°C before analysis.

Morphine analysis

All analyses were performed on a Hewlett-Packard model 5972B positive ion electron impact quadrupole mass spectrometer interfaced with a model 5890 gas chromatograph, a model 6890 autosampler, and a Gateway model E-4200 computer using HP ChemStation Software (version B.01.00). Each batch processed during the study contained a set of six calibrators, viz., 500, 250, 125, 62.5, 31.25, and 15.62 ng ml^{-1}, and four controls, viz., 400, 200, 30, and 0 (drug-free plasma) ng ml^{-1}. Duplicate controls were analysed in a randomized fashion in each of the 42 batch runs during the 12 month period required for specimen processing to assess precision and accuracy of the method. If the determined concentration was >500 ng ml^{-1}, the specimen was appropriately diluted and reprocessed. The lower limit of quantitation was assumed to be 15.62 ng ml^{-1} (low calibrator) and the limit of detection was shown by dilution of the low calibrator to be 1.95 ng ml^{-1}.

To 200 μl of patient plasma specimens, calibrators, or controls were added 25 μl of d_3-morphine internal standard solution and 400 μl of ammonium carbonate buffer followed by brief vortex mixing. This mixture was slowly added under reduced pressure to a 50 mg C-8 solid phase column (Varian Bond Elut) that had been pre-washed with 2×1 ml methanol, 1 ml water, and 1 ml of ammonium carbonate buffer under reduced pressure. Once the mixture was adsorbed to the top of the solid phase column, the reduced pressure was removed to accomplish equilibration for 2 min. The column was washed with 1 ml of ammonium carbonate buffer followed by 1 ml of methanol under reduced pressure. The methanol elute was stored at 4°C until GC-MS analysis.

For GC-MS analysis, the methanol elute was evaporated to dryness under nitrogen at 50°C. To the residue was added 20 μl ethyl acetate (Aldrich) and 30 μl *N,O-bis*(trimethylsilyl)trifluoroacetamide (BSTFA, Pierce), the solution was then vortex mixed and heated in a sand bath at 75°C for 15 min. After cooling to room temperature, the resultant solution was transferred to an autosampler vial for GC-MS analysis. An ethyl acetate blank was processed after each specimen analysis. The gas chromatograph was equipped with a capillary column (12 m×0.2 mm ID, 0.33 μm film thickness) containing an HP-1 cross-linked methyl silicone gum and operated using a programme with an initial temperature of 130°C (2 min) that was increased