Pharmacokinetics of Morphine and its Metabolites in Neonates with Hypoxic-Ischemic Encephalopathy During and After Therapeutic Hypothermia

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Background: Morphine is a routinely used drug in neonates undergoing therapeutic hypothermia (TH) as treatment for hypoxic-ischemic encephalopathy (HIE). Pharmacokinetics (PK) and optimal dosing of morphine in this population, however, are still largely unknown.

Objective: To examine the effect of hypothermia on the PK of morphine in neonates with HIE and to develop PK based dosing guidelines.

Results

Table 1: Patient characteristics

Parameter	N = 244
Gestational age (wk; mean ± sd)	38.8 ± 1.6
Birth weight (g; mean ± sd)	3,428 ± 613
Male (n, %)	150 (61.5)
pH (median, IQR)*	6.96 (6.80 – 7.09)
Base Excess (mmol/L, median, IQR)*	-17 (-12 – -21.9)
Lactate (mmol/L, median, IQR)*	13.6 (9.0 – 18.2)
Thompson score (median, IQR)#	9.5 (8.0 – 12.0)
Mortality (n, %)	58 (23.8)

*Value measured in umbilical cord blood or, if unavailable, from arterial or venous blood within 1h after birth

#Highest score before start of hypothermia

Morphine was administered as continuous infusion with or without a loading dose. Morphine plasma levels ranged between 10 and 371 µg/L (Figure 1).

Figure 1: Observed morphine plasma concentrations

Methods: Data was collected in two multicentre prospective cohort studies. (Near-)term neonates who received morphine while treated with TH for HIE were eligible for inclusion. Once daily plasma samples were obtained during both hypothermia and normothermia. Morphine concentrations were analyzed using an LC-MS/MS method. Pharmacokinetic analyses were performed using NONMEM (version 7.3).

Results (continued)

A population pharmacokinetic model was developed; morphine clearance was dependent on gestational age, postnatal age and body temperature. Morphine clearance during hypothermia was reduced by 15.8% compared to normothermia. A loading dose of 50 µg/kg followed by continuous infusion of 5 µg/kg/h resulted in morphine plasma concentrations in the desired range (10-40 µg/L, Figure 2).

Figure 2: Simulated morphine plasma concentrations of the proposed dosing regimen

Conclusion

- Clearance of morphine is reduced in neonates during hypothermia compared to normothermia.
- A relatively low dose of 5 µg/kg/h preceded by a loading dose of 50 µg/kg is recommended to avoid morphine overexposure.
- Due to high interpatient variability, higher doses might be necessary in individual patients.