



Commentary

Towards personalized medicine in preterm newborns: Morphine analgesia predicted by genotype



Sinno.H.P. Simons*

Division of Neonatology, Department of Paediatrics, Erasmus UMC, Sophia Children's Hospital, Rotterdam, the Netherlands

After preterm birth, newborns are exposed to repetitive stressors and painful events during their treatment at the neonatal intensive care unit [1]. Respiratory support, surgical interventions, infections, skin breaking and other painful procedures all contribute to the cumulative amount of distress in the early life of preterm infants. Appropriate analgesia to protect these vulnerable patients is obligatory, but remains an important challenge.

Randomised controlled trials showed that the routine use of morphine in the first week of life is not beneficial on the short term outcome of preterm ventilated newborns [2,3], and effects on the long term are partly unclear [4,5]. Today, most units treat the preterm newborns pain based on the individual needs based on pain assessment scores. Neonatologists are reluctant to prescribe sedatives and analgesics because of fear for side effects on the developing brain. The use of morphine is highly dependent on treatment centre and local policy [1].

Neonatal analgesia and morphine use is complicated by the fact that pain is difficult to assess. Large inter-individual variability morphine pharmacokinetics and in the effects of analgesics add to this. The amounts of morphine needed to maintain adequate analgesia in preterm newborns vary widely. Predetermination of appropriate dosing and drugs for individual preterm infants would be a great step forward in the medical care of these patients.

Grunau, Carleton and colleagues now published their study in *EBioMedicine* on the genotypic variance in genes related to morphine biotransformation and their association with the amounts of morphine needed during the neonatal period of life and on the behavioural long-term outcome of these infants [6]. Pharmacogenetics, the study of genetic polymorphisms on the pharmacokinetics and dynamics, has only been of limited value for neonatal care up till now. This is partly caused by the fact that maturational effects are very large and therefore generally accepted as the most important factors in neonatal clinical pharmacology [7]. Pharmacokinetics and dynamics of morphine are highly influenced by post-natal maturation. Activity of metabolizing enzymes, but also opioid receptor expression and related pain sensitivity importantly change with age [8]. The system is however very complex and most data are derived from animal models. Further understanding

of neonatal pain and analgesia is essential. Non-maturational covariates are important, but data are largely lacking [9].

Morphine is importantly metabolized by glucuronidation. UGT2B7 is the most important metabolizing enzyme, although less active in newborns. It is therefore quite unexpected that the genetic variance of the UGT1A6, and not the UGT2B7, enzyme was found to be associated with the morphine exposure and long-term behavioural outcome. A clear explanation for this fails and as no pharmacokinetic data were available in the current study this remains unclear. Further research on the role of UGT1A6 in neonatal morphine biotransformation is needed. Polymorphic expression of the so called COMT gene has been related to opioid analgesia before, but the relation to externalizing behavioural problems is new. Again, the detected association is clear, but the relationship and exact mechanism of action needs to be unravelled.

Nevertheless, better understanding of who benefits from neonatal morphine and who does not, would be of great advantage. This is of special relevance in preterm infants, who are very vulnerable for side-effects and toxicity that may have life consequences. Higher neonatal morphine exposure, although always related to severity of illness, is associated with cerebellar changes on MRI and with long term behaviour [10]. The new genetic targets provided by the current study can provide new ways to better predict the effects of opioid analgesia in newborns. Better prediction of the individual infant's morphine needs and its long-term consequences, based on genotype would be highly interesting. It could provide the next step for personalized neonatal pain medicine with an optimally balanced treatment for each individual preterm infant.

Disclosure

The author declared no conflicts of interest.

References

- [1] Carbajal R, Eriksson M, Courtois E, et al. Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study. *Lancet Respir Med* 2015;3(10):796–812.
- [2] Anand KJ, Hall RW, Desai N, et al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet* 2004;363(9422):1673–82.
- [3] Simons SHP, van Dijk M, van Lingen RA, et al. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. *JAMA* 2003;290(18):2419–27.

DOI of original article: <https://doi.org/10.1016/j.ebiom.2019.01.042>.

* Corresponding author at: Erasmus UMC, Sophia Children's Hospital, Room SK-4113, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands.

E-mail address: s.simons@erasmusmc.nl.

<https://doi.org/10.1016/j.ebiom.2019.02.003>

2352-3964/© 2019 Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

- [4] de Graaf J, van Lingen RA, Simons SHP, et al. Long-term effects of routine morphine infusion in mechanically ventilated neonates on children's functioning: five-year follow-up of a randomized controlled trial. *Pain* 2011;152(6):1391–7.
- [5] de Graaf J, van Lingen RA, Valkenburg AJ, et al. Does neonatal morphine use affect neuropsychological outcomes at 8 to 9 years of age? *Pain* 2013;154(3):449–58.
- [6] Chau CMY, Ross CJD, Chau V, et al. Morphine biotransformation genes and neonatal clinical factors predicted behaviour problems in very preterm children at 18 months. *EBioMedicine* 2019. <https://doi.org/10.1016/j.ebiom.2019.01.042>.
- [7] van den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental changes in pharmacokinetics and pharmacodynamics. *J Clin Pharmacol* 2018;58(Suppl. 10):S10–25.
- [8] Nandi R, Fitzgerald M. Opioid analgesia in the newborn. *Eur J Pain* 2005;9(2):105–8.
- [9] Allegaert K, Simons SHP, Tibboel D, Krekels EH, Knibbe CA, van den Anker JN. Non-maturational covariates for dynamic systems pharmacology models in neonates, infants, and children: filling the gaps beyond developmental pharmacology. *Eur J Pharm Sci* 2017;109S:S27–31.
- [10] Zwicker JG, Miller SP, Grunau RE, et al. Smaller cerebellar growth and poorer neurodevelopmental outcomes in very preterm infants exposed to neonatal morphine. *J Pediatr* 2016;172 [81–7 e2].