Published in final edited form as:

Paediatr Anaesth. 2014 November ; 24(11): 1189–1190. doi:10.1111/pan.12525.

The addition of tramadol to a standard IV acetaminophen/morphine analgesia protocol in neonates: purposeful or just polypharmacy ?

Karel Allegaert^{1,2} and John N van den Anker^{3,4,5}

¹Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium ²Department of Development and Regeneration, KU Leuven, Belgium ³Departments of Pediatrics, Pharmacology, Physiology and Integrative Systems Biology, George Washington University School of Medicine and Health Sciences, Washington, USA ⁴Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands ⁵Department of Pediatric Pharmacology, University Children's Hospital Basel, Switzerland

dear editor,

With great interest we have read the paper of Olischar *et al.* about the addition of tramadol to the routine use of acetaminophen and morphine for the treatment of postoperative neonatal pain. The investigators, using a placebo-controlled randomized control trial design, studied the potential opioid sparing effects of adding tramadol (2 mg.kg⁻¹, q6h or placebo) to a standard IV acetaminophen (10-15 mg.kg⁻¹, q6h) and morphine (continuous, start at 20 µg.kg⁻¹.h⁻¹ on admission) analgesia protocol in postoperative neonates (1). Analgosedation was assessed every hour and based on these assessments the amount of morphine was adjusted and, if the dose exceeded 40 µg.kg⁻¹.h⁻¹, midazolam was added (1). The primary outcome variable was the extubation rate 96 h after admission and secondary outcome variables were morphine exposure, midazolam exposure, hourly pain scores, and seizure activity. Based on the findings of this study, the investigators concluded that there was no benefit of adding tramadol to their multimodal analgo(sedative) protocol and expressed their concern about the use of polypharmacy in this setting (1). We fully agree that treatment modalities - including polypharmacy using newer compounds – have been introduced in neonatal intensive care units without sufficient evidence to support its use. On the other hand, we also like to share our doubts about the scientific evidence behind the doses applied for 'old, well known' drugs like morphine, and would like to focus the reader's attention on the limitations of any currently applied assessment tool to quantify analgosedation in neonates (2).

Using a consecutive study approach, Krekels *et al.* recently documented that a maintenance dose of 5 µg.kg^{1.5}.h⁻¹ in neonates with a postnatal age of less than 10 days resulted in

Correspondence Karel Allegaert, MD PhD, Neonatal Intensive Care Unit, University Hospital, Herestraat 49, 3000 Leuven, BELGIUM, Tel 00-32-16-343850; Fax 00-32-16-343209, karel.allegaert@uzleuven.be.

Conflict of interest:

IRB approval:No

effective analgesia after major surgery (3). With the use of the same morphine dosing regimen, the same investigators, also demonstrated that in a placebo-controlled randomized study that IV acetaminophen resulted in an additional 66 % decrease in morphine exposure in postoperative neonates (4). If we try to translate these new morphine dosing guidelines to the current study, it is very plausible that both groups were overexposed to opioids, masking potential differences between the two study groups. This explanation is further supported by the limited validity of any currently available pain assessment tool: we are not yet able to discriminate sufficiently between analgesia and sedation, as also reflected in the analgo-sedation protocol of the current study, using midazolam as co-medication (1,2).

The trend for opioid reduction is mainly driven by the emerging animal experimental observations and associations between exposure to analgesedatives, neuro-apoptosis and neurocognitive outcome, and is, as such, worthwhile (5). We therefore encourage clinicians, but also ethics committees and other stakeholders, to accept to concept to conduct dose-finding studies for pain management in neonates to further improve adequate (i.e. effective, so neither over- nor underexposure) administration of analgesedatives in neonates (2). When based on much lower initial maintenance doses of morphine (or even as rescue), multimodal analgesia approaches may be one of the ways to reach this ultimate goal.

Acknowledgments

Karel Allegaert was supported by the Fund for Scientific Research, Flanders (Fundamental Clinical Investigatorship 1800214N). Johannes van den Anker is supported by NIH grants (R01HD048689, K24DA027992, U54HD071601) and FP7 grants TINN (223614), TINN2 (260908) and GRIP (261060).

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