Correspondence

Effects of high dose orally administered paracetamol for heel prick pain in premature infants

To the Editor

I read the valued study by Badiee and Torcan,[1] on the effects of high dose orally administered paracetamol for heel prick pain in premature infants. I have 3 comments on the aforementioned study.

First, clinical and laboratory investigations of neonatal pain suggest that preterm neonates are more vulnerable to stress and painful procedures and have heightened responses to successive stimuli.[2] Preterm infants receiving intensive care are subjected to frequent invasive, and stressful procedures as well as more chronic environmental influences. Acute episodic pain may cause early neurologic injury. Repeated, and prolonged exposure to pain may alter subsequent psychokinetic development, as well as affect long-term neurodevelopmental, behavioral, and social-emotional outcome.[3] Surprisingly, despite the large numbers of painful and stressful procedures performed in intensive care units, the majority are not accompanied by suitable analgesia.[4]

Second, though Badiee, and Torcan,[1] addressed in their study inadequate analgesia by paracetamol for acute pain caused by heel prick in premature babies, the use of paracetamol to fill that objective necessitates cautious revision. Pharmacological studies on paracetamol in infants are generally limited. Most studies have focused on the administration of a single paracetamol dose, and the problem of cumulative toxicity with repeated dosing has not been addressed. The volume of serum paracetamol distribution seems to be age-independent, whereas its clearance is reduced in neonates, particularly in preterm babies. Neonates and infants are capable of forming the reactive intermediate metabolite that causes hepatocellular damage, particularly after multiple doses. They have an immature glucuronide conjugation system, but the rate constant for the sulfation metabolic pathway is larger than in older children, and, this is the most important route of metabolism.[5] Though the toxicity of paracetamol in premature babies generally appears to be low because of slow oxidative metabolism, and rapid glutathione synthesis,[6] it ought to be anticipated and appropriate diagnostic and therapeutic interventions are installed whenever necessary.

Third, several non-pharmacological measures have been promisingly shown to reduce acute procedural pain in infants, including skin-to-skin contact between a mother and her infant,[7] oral sucrose administration,[8] and breastfeeding.[9] Therefore, they could practically substitute pharmacological measures in terms of safety, and effectiveness, particularly in premature infants.

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Reply from the Author

There are many published articles that demonstrated the frequency of painful procedures, also the short and long term effects of these painful procedures in newborn infants. There are many non pharmacological methods for pain reduction in newborn infants, and oral sucrose is one of the most frequently used non pharmacological methods. However, concentrated solutions have high osmolarity, and could be dangerous for preterm infants. Recently Taddio et al,[10] showed that oral sucrose could not effectively prevent pain due to repeated heel-sticks in newborns. Also, repeated use of sucrose for analgesia may not prevent processing of remote hyperalgesia.[11] So, it seems important to find alternative methods for analgesia in neonates. Paracetamol is the most frequently used drug for treatment of mild to moderate pain in infants. We used only a single dose of 40 mg/kg before heel lancing, as a result, cumulative toxicity would not be a problem in our study. Anderson at al,[12] studied the pharmacokinetics of different formulations of paracetamol and found that a mean steady state target concentration of 10 mg/l at trough can be achieved by an oral dose of 25 mg/kg/day in premature neonates at 30 weeks postconception, 45 mg/kg/day at 34 weeks gestation, and 60 mg/kg /day at term. Allegaert et al,[13] looked at intravenous paracetamol in term and preterm infants. They demonstrated that a mean steady state through concentration of more than 10mg/l can be achieved with a loading dose of 40 mg/kg followed by a maintenance dose based on the gestational age. So I think, even use of these maintenance doses is safe for premature infants.

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