

## Local Anesthetics for Mothers—Could They Be the Cause of ‘Unexplained Neonatal Asphyxia’?

a report by

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Over the last century, the practice of pain relief in labor has become more and more common in industrialized countries thanks to numerous alternative methods, such as general anesthesia, local analgesic techniques in the form of epidural analgesia, paracervical blockage, and also the simple administration of local anesthetics (LA). It has consequently become a priority to assess the wellbeing of the fetus/neonate after these procedures to the mother. The pioneering work of Virginia Apgar represented the first attempt to convert the impression of the clinical condition of a newborn baby into a formally defined measurement.<sup>1</sup>

### Evaluating Fetal/Neonatal Well-being

Various methods of evaluating fetal/neonatal well-being have since been used from electronic fetal monitoring, umbilical cord blood gas analysis, biophysical profile score, fetal pulse oximetry, and fetal Doppler to the evaluation of newborn neurobehavior.<sup>2</sup> However, no tests exist that are capable of identifying the effects of maternally administered medications on the fetus/newborn or of conclusively assessing such effects on the clinical conditions of the newborn. Currently, the clinical observation of the neonate is still the major determinant in the correct evaluation of adverse neonatal effects from maternal analgesia, although LA toxicity appears to be difficult to detect clinically and the definitive diagnosis requires blood or urine-level monitoring.

### LA Toxicity

Any anesthetic administration to the mother may profoundly affect the fetus and newborn, reaching the neonate either through the placenta or via inadvertent direct injection into the fetal scalp or uterine blood vessels. Systemic absorption could also occur via the permeability of the skin. Both general anesthesia and the safer LA are capable of giving rise to serious deleterious effects, which, although rare, can be life-threatening for the neonate.

Despite being safer than general anesthesia, LA administered via both paracervical block and local

injection may still give rise to the acute onset of a serious clinical picture due to neonatal intoxication from LA administered to the mother during delivery. The clinical syndrome of LA intoxication was first described by Finster et al.,<sup>3</sup> and Sinclair et al.,<sup>4</sup> and includes total arrest of spontaneous respiration, hypotonia, seizures, and cardiac symptoms such as bradycardia or ventricular tachycardia at, or shortly after, birth.<sup>5,6</sup> Other specific signs are dilated pupils and fixed to light, and doll's eye manoeuvre (oculocephalic reflex).

Diagnosis is confirmed by determining the LA levels in liquor, blood and urine. Examples of 'Clinical In-touch Briefing' involve three full-term neonates who were admitted to our Neonatal Intensive Care Unit from different maternity wards following spontaneous vaginal deliveries after uneventful pregnancies. Interestingly, the admission diagnosis for each one was 'perinatal asphyxia'. The suspicion of drug intoxication in these infants arose from several anamnestic and clinical features, such as a symptom-free period after birth, plus the type of neurological depression and seizures, mild metabolic acidosis, and the mothers' obstetric history. In each infant, the author and colleagues demonstrated a state of neurological impairment deriving from neonatal intoxication due to maternal anesthetic used to relieve episiotomy pain, as previously described for two cases.<sup>7</sup> The correct diagnosis, obtained via a simple toxicological screening of a urine or blood sample, allowed for the infants to receive correct treatment, ruling out misdiagnosis that could have led to medical-legal problems.

The clinical and anamnestic features of the three cases are illustrated (see *Tables 1, 2 and 3*). Local infiltration of the perineum, and cream application to the perivaginal skin are simple and commonly used techniques to provide pain relief for episiotomy (one of the most frequently performed surgeries in women).<sup>8</sup> These treatments are commonly considered safe for the fetus/neonate because of the short time interval between the LA administration and the delivery of the baby, and because of the small amount of drugs required.<sup>9</sup> For these reasons the effects of LA on the fetus/neonate are considered negligible as evaluated by

**Table 1: Clinical and Anamnestic Features of Three Newborns with Suspected LA Toxicity**

<b>At or within minutes of birth</b>	
Sudden neurological and cardiac signs	Apnea, bradycardia, hypotonia, seizures
No evidence of fetal distress	Normal CTG
Presumptive diagnosis of perinatal asphyxia	Slight metabolic acidosis

**Table 2: Neonatal and Clinical Features of Three Newborns with Suspected LA Toxicity**

	<b>Case 1</b>	<b>Case 2</b>	<b>Case 3</b>
wsGA	39	40	41
Apgar Score	9I:9V	1I:6V	5I:5V
Anesthesia for episiotomy	Lidocaine (2%) prilocaine (2,5%) cream EMLA(r)	Local injection of 10ml of 2% mepivacaine Mepiforan(r)	local injection of 10ml of 2% mepivacaine Mepiforan(r)
Onset	30s	At birth	At birth
Clinical features	30s after birth: apnea, bradycardia, hypotonia Later: Generalized hypertonia, tonic seizures, opisthotonic posturing and dilated pupils	At birth: Required CPR 10s after: Floppy without spontaneous movements; seizures	At birth: No spontaneous breathing efforts, seizures, hypotonia; needed RCP Later: Seizures
Laboratory tests	normal	normal	normal
Cerebral ultrasonography	negative	negative	negative
Extubation	30s	12h	48h
Resolution	22h	48h	48h

**Table 3: Arterial Blood Gases of Three Newborns with Suspected LA Toxicity on Arrival at Neonatal Intensive Care Unit**

<b>Case</b>	<b>Arterial blood gases</b>		
	<b>1</b>	<b>2</b>	<b>3</b>
Hours of age	2	3	3
pH	7.32	7.46	7.29
pO <sub>2</sub>	64	64	61.8
pCO <sub>2</sub>	34	29	40.7
BE	-7.6	-1.7	-6.8

acid-base status, Apgar scores, and neonatal neurobehavioral assessments. However, the drug can reach the fetus via a placental transfer, through direct injection into the uterine vessels, or via accidental direct injection into the fetal scalp. The placental drug transfer involves numerous mechanisms, such as passive diffusion, facilitated transport, active transport, and

perinocytosis offering easy access to the LA. In one study, the placental transfer of lidocaine following local perineal infiltration was documented.<sup>9</sup> Lidocaine was detected in maternal plasma as early as one minute after injection, and peak plasma concentrations occurred within three to 15 minutes; the drug and its active metabolites persisted in neonatal urine for at least 48 hours after delivery. In another paper, following different methods of administration, detectable LA drug concentrations, but rarely toxic levels (3mg/ml), were demonstrated in stored cord blood samples from 200 deliveries.<sup>10</sup> Since LAs are weak bases, with pKA values close to physiological pH, their concentration is at a peak in acidic media, when they would be in the ionized state. Therefore, they have a low degree of ionization in the maternal blood. However, in a slightly acidotic fetus, increasing amounts of LA will traverse the placenta, and revert to the ionized form leading to ion trapping in the fetus.<sup>11</sup> The result is an accumulation of LA in the fetus/neonate with a slow elimination.

Percutaneous absorption causing severe lidocaine intoxication has also been described, but through lesioned skin when lidocaine cream was used as a LA.<sup>12</sup> Neonatal skin permeability to lidocaine was studied *in vitro* using excised skin from 24 infants, 25–40 weeks gestational age and 0–seven days postnatal age.<sup>13</sup> The authors found that while preterm infants showed a marked increase in absorption, mature skin was relatively impermeable to lidocaine and suggested that there was a negligible risk of toxicity due to systemic absorption. Nevertheless, in one of cases observed by the author and colleagues, percutaneous absorption was the only possible pathway as the anesthetic was not available in Italy in any form other than cream at that time.

## Conclusion

As local infiltration of the perineum and cream application represent the simplest and most commonly used techniques for providing pain relief, a certain amount of the anesthetic may reach the fetus via placental transfer, accidental direct injection into the fetal scalp, and transcutaneous absorption. This event is commonly thought to be infrequent and of low intensity. However, although rare, neonatal LA intoxication is a possibility that neonatologists should bear in mind when treating depressed newborns, particularly since misdiagnosis of asphyxia could be common and have negative effects on the outcome. A symptom-free period after birth in a neonate with a high Apgar score before the onset of hypotonia, tonic seizures, and arrest of spontaneous respiration, may help in reaching a correct diagnosis. Fixed dilated pupils are frequent in LA intoxication and they are not usually present in hypoxic-ischemic encephalopathy. The absence of metabolic acidosis soon

after birth or later, following cardio-respiratory resuscitation, may be an indication of LA intoxication. The demonstration of high anesthetic levels in blood and urine is essential in making a correct diagnosis, and can be easily ruled out with a toxicological screening, which is an easy and inexpensive method. Delay of appropriate therapy may intensify the negative outcome if hypoxic complications occur, and such ‘unexplained perinatal asphyxias’ could be dangerous on medico-legal grounds.

Therapy for neonatal LA intoxication will depend on the time of recognizing the intoxication, as the half-life of the drug in the blood is approximately eight to 10 hours. Vigorous ventilatory support is essential.

Anticonvulsant drugs are of questionable value. The control of seizures is best performed by the removal of the drug; accomplished more effectively by diuresis with acidification of the urine than by exchange transfusion.

LAs given during labor are normally safe, if not beneficial, for the infant. However, as episiotomy is a very common procedure in modern obstetric care, greater awareness of the danger of acute intoxication from maternal LA of the newly born must be kept in mind. Moreover, LA administration to the mother either by local infiltration or cream application should be considered similar to any other anesthetic technique as it may result in significant neonatal drug exposure. ■

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### References

1. Apgar V, “A proposal for a new method of evaluation of the newborn infant”, *Curr Res Anesth Analg* (1953);32: pp.260–267.
  2. Littleford J, “Effects on the fetus and newborn of maternal analgesia and anesthesia: A review”, *Can J Anesth* (2004),51(6): pp.586–609.
  3. Finster M, Poopers PJ, Sinclair JC, et al., “Accidental intoxication of the fetus with local anesthetic drug during caudal anesthesia”, *Am J Obstet Gynecol* (1965);92: pp.922.
  4. Sinclair JC, Fox HA, Lentz JF, et al., “Intoxication of the fetus by a local anesthetic”, *N Engl J Med* (1965);273: pp.1173.
  5. Kim WY, Pomerance JJ, Miller AA, “Lidocaine intoxication in a newborn following local anesthesia for episiotomy”, *Pediatrics* (1979);64(5): pp.643–645.
  6. De Praeter C, Vanhaesebrouck P, De Praeter N, et al., “Episiotomy and neonatal lidocaine intoxication”, *Eur J Pediatr* (1991);150(9): pp.685–686.
  7. Pignotti MS, Indolfi G, Ciuti R, et al. “Perinatal asphyxia and inadvertent neonatal intoxication from local anaesthetics given to the mother during labour”, *BMJ* (2005);330: pp.34–35.
  8. Cleary Goldman J, Robinson JN, “The role of episiotomy in current obstetric practice”, *Semin Perinatol* (2003);27: pp.3–12.
  9. Philipson EH, Kuhert BR, Syracuse CD, “Maternal, fetal and neonatal lidocaine levels following local perineal infiltration”, *A J Obstet Gynecol* (1984);149: pp.403–407.
  10. Walson PD, Ott MA, Carter DE, “Lidocaine and mepivacaine in cord blood”, *Pediatr Pharmacol* (1982);2: pp.341–348.
  11. D’Alessio JG, Ramanathan J, “Effects of maternal anesthesia in the neonate”, *Semin Perinatol* (1998);22(5): pp.350–362.
  12. Lie FL, Vermeer BJ, Edelbrock PM, “Severe lidocaine intoxication by cutaneous absorption”, *J Am Acad Dermatol* (1990);23: pp.1026–1028.
  13. Barrett DA, Rutter N, “Percutaneous lignocaine absorption in newborn infants”, *Arch Dis Child* (1994),71(2): pp.F122–F124.
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