Lesson of the week

Perinatal asphyxia and inadvertent neonatal intoxication from local anaesthetics given to the mother during labour

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Do not assume that every case of neonatal encephalopathy is due to perinatal asphyxia

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In 1998, Edwards and Nelson discussed whether asphyxia at birth really is an important cause of neonatal encephalopathy and wondered how often neurological impairment in children is due to perinatal hypoxia-ischaemia and how often to entirely different causes.¹ We describe two cases of neonatal intoxication resulting from the administration of local anaesthetic to the mother during labour but which we initially diagnosed as perinatal asphyxia. We analyse here the major manifestations of acute poisoning in newborns and the clinical picture that could be misdiagnosed as perinatal asphyxia. Early and correct diagnosis is recommended for allowing adequate treatment and a positive outcome and for ruling out the medicolegal aspect of perinatal asphyxias (law courts often have to decide whether a child's neurological impairment is the result of mismanagement of labour, leading to asphyxia).

Case reports

Within minutes of birth, two full term neonates delivered vaginally presented sudden neurological and cardiac signs such as apnoea, bradycardia, seizures, and hypotonia. In both cases no evidence of fetal distress was noted, and the fetal monitoring was normal. They were transferred to our neonatal intensive care unit with a presumptive diagnosis of perinatal asphyxia.

Case 1

A 3550 g male infant was born after an uneventful pregnancy; episiotomy was performed after application of combined lidocaine (2.5%) and prilocaine (2.5%) cream. The Apgar score was high (9 at one minute, 9 at five minutes). Thirty minutes after birth, while still in the delivery room, the neonate suddenly developed apnoea, bradycardia, and hypotonia. He was intubated and mechanically ventilated.

His cardiorespiratory function gradually improved, and he was extubated 30 minutes later. However, at this stage he began to show the first signs of neurological involvement, characterised by generalised hypertonia, which required transfer to our neonatal intensive care unit. During transport (at age one and a half hours) he had tonic seizures.

On arrival, at 2 hours of age, opisthotonic posturing and dilated pupils (unreactive to light) were also observed. Routine laboratory examinations were normal, and an arterial blood gas analysis showed a mild metabolic acidosis (pH, 7.32; P_{O_2} , 64 mm Hg; P_{CO_2} , 34 mm Hg; base excess, -7.6 mmol/l). Phenobarbital 20 mg/kg was given intravenously and repeated twice at the dose of 5 mg/kg intravenously. Cranial ultrasonography, electrocardiography, and echocardiography at 10 and 12 hours of age were normal. Investigations for sepsis (white blood cell count,

Fig 1 The results of urine toxicology screening showing the evolution of prilocaine, lidocaine, and metabolite concentrations in the urine specimens during the first four days after birth: prilocaine and lidocaine were present in the first sample, with much higher concentrations in the second and decreasing concentrations as the lidocaine metabolites increased

platelet count, C reactive protein, serum procalcitonin); creatinine, IgM, and serum ammonia concentrations; and urine screening for amino acids were subsequently reported as negative or within normal limits. The two hour blood specimen showed a lidocaine level of 80 ng/ml and a high level of prilocaine. The first urine specimen showed low levels of lidocaine and prilocaine and even lower levels of lidocaine metabolites, which increased in the following samples (fig 1).

At age 48 hours polygraphic electroencephalography showed mild abnormalities (immaturity, with multifocal spikes and sharp transients). Spontaneous motor activity began to improve after the first 48 hours and seemed to be within normal limits between age 5 and 7 days. Phenobarbital was discontinued after five days' treatment, and the infant was discharged on day 8 with normal neurological assessment. The neurodevelopmental outcome at 12 months of age was normal.

Case 2

A 4010 g male infant was delivered at a gestational age of 40 weeks. A vacuum extractor was used, and episiotomy was performed after local injection of 10 ml of 2% mepivacaine solution. The Apgar score was 1 at one minute and 6 at five minutes. The infant needed intubation and ventilation, was floppy without spontaneous movement, and developed seizures 10 minutes after birth. Diazepam 0.5 mg/kg was administered intravenously, and he was transferred to our neonatal intensive care unit.

On arrival, at 3 hours of age, he was hypotonic with tonic seizures of the upper extremities and bilaterally fixed, dilated pupils. A blood glucose strip showed a

More information about the toxicology screening used is on bmj.com

Fig 2 The results of blood toxicology screening showing the evolution of mepivacaine concentrations in the blood specimens during the first four days after birth

glucose concentration of 1.99 mmol/l. Glucose 10% at 2 ml/kg and phenobarbital 20 mg/kg were administered intravenously. Arterial blood gas study showed pH, 7.46; P_{O_2} , 64 mm Hg; P_{CO_2} , 29 mm Hg; base excess, -1.7 mmol/l. Initial laboratory studies, as well as investigations for sepsis (as for case 1), serum ammonia concentration, and urine screening for amino acid were all reported as negative or within normal limits. Chest radiography, electrocardiography, and cranial ultrasonography were normal. Spontaneous breathing started at 10 hours of age, and muscle tone improved; at 12 hours of age he was extubated.

A two hour venous blood specimen sent for toxicology screening showed a high plasma concentration of mepivacaine, which disappeared after a few days (fig 2). The infant's scalp was carefully examined, but no sign of injection was seen. Tone quality and spontaneous motor activity began to improve after the first 48 hours and seemed to be normal between 5 and 7 days of age. Polygraphic electroencephalography at 12 hours of age showed moderate abnormalities (moderate electroencephalography immaturity with prevalence of trace alternant and multifocal spikes), which were slightly reduced at 7 days of age. The infant was discharged on day 9. Phenobarbital was discontinued after two weeks, with no recurrence of seizures. The neurodevelopmental outcome at 12 months of age was normal.

Discussion

Local infiltration of the perineum and cream application to the skin around the perivaginal skin are simple and common techniques for pain relief from episiotomy. Small amounts of the anaesthetic are thought to reach the fetus because of the short interval between local infiltration and delivery.²

Intoxication of newborns by lidocaine given to the mother during delivery was first described by Sinclair and colleagues in 1965.³ Detailed clinical features including apnoea, hypotonia, seizures, and cardiac symptoms such as bradycardia or ventricular tachycardia were reported in 1991.⁴ Other specific typical signs are dilated pupils fixed to light and eyes fixed in the "doll's eye manoeuvre" (oculocephalic reflex).⁵ Such toxic effects have been described with lidocaine levels as low as 3 γ /ml,⁶ which are very close to the levels found in cord blood of normal neonates.²⁻⁶ Diagnosis is

confirmed by determining anaesthetic levels in liquor, blood, and urine.

In our two cases the neonates developed symptoms of intoxication at different times, probably because of different types of absorption. In the first case the blood specimen showed high lidocaine levels and the urine specimens showed growing levels of lidocaine and prilocaine over the next two days, with the appearance of metabolites. As no lidocaine injections were reported in the medical record we assume that the drug was absorbed transcutaneously. This kind of absorption was indisputable for prilocaine because this drug is available in Italy only as a cream. In the second case the first blood specimen showed high levels of mepivacaine, which could have reached the fetus via placental transfer or via injection inadvertently directed into the fetal scalp, with levels decreasing over the next three days.

In both cases the clinical pictures were not typical for intrapartum asphyxia. The slight acidosis soon after birth or later, after cardiorespiratory resuscitation, was not a sufficient basis for an experienced clinician to justify the seizures. Hypoxic-ischaemic encephalopathy is not usually associated with a period without symptoms soon after birth in a neonate with a high Apgar score (case 1) before the onset of hypotonia, tonic seizures, arrest of spontaneous respiration, or with fixed dilated pupils and eyes fixed in the oculocephalic reflex.⁴ All these signs can be assumed to be caused by intoxication from local anaesthetic.

Both neonates arrived at our neonatal intensive care unit with a diagnosis of acute perinatal asphyxia, which was not consistent with the clinical picture above. Only the suspicion of involvement of other pathogenetic factors (such as neonatal intoxication) led us to make a correct diagnosis. Delay of appropriate treatment may worsen the outcome, and the medicolegal aspect of "unexplained perinatal asphyxias" can be ruled out with appropriate diagnosis. High levels of anaesthetic in blood, urine, and cerebrospinal fluid are essential for the diagnosis. If neonatal intoxication is suspected, an early urine specimen for toxicology screening is the cheapest and easiest way to secure a correct diagnosis. More studies are needed to understand how often this kind of aetiology occurs in neonatal encephalopathy.

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