Arrhythmia Associated With Tetracaine in an Extremely Low Birth Weight Premature Infant

abstract

Infants in NICUs undergo a variety of painful procedures. The management of pain has become an integral part of newborn infant care with the use of both systemic and topical agents to provide analgesia and anesthesia for procedural pain. Tetracaine and prilocaine-lidocaine are the 2 topical anesthetics most frequently used. Tetracaine belongs to an ester group of local anesthetics available as a topical 4% gel (Ametop, Smith and Nephew, Canada). The major side effects reported when using topical anesthetics are cutaneous reactions. There are no definite reports of systemic toxicity in the published literature. We present a recent case of an extremely low birth weight premature infant who developed a clinically significant arrhythmia after topical tetracaine was applied before the insertion of a peripherally inserted central catheter. The infant had no other identifiable cause for the resulting bradycardia that occurred only after Ametop was applied. The cardiac symptoms resolved with treatment. This case highlights a significant potential adverse event when using topical tetracaine.

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ABBREVIATIONS
AV—atrioventricular
ECG—electrocardiogram
ELBW—extremely low birth weight
PICC—peripherally inserted central catheter

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There is evidence that exposure to prolonged or repeated noxious stimuli has adverse consequences on the newborn both in the short- and long-term. This has resulted in procedural pain management becoming an integral part of neonatal care. The current standard of care includes pharmacological and nonpharmacological approaches for pain management. Topical anesthetics have now become widely accepted for use in the neonatal population. Two topical anesthetics, Ametop (tetracaine, Smith and Nephew, Canada) and EMLA (lidocaine-prilocaine, AstraZeneca, Canada), have both been shown to be effective in children and infants when used for venipuncture, vaccination, and intravenous cannulation. Some practitioners may be reluctant to use EMLA because of concerns regarding the risk of methemoglobinemia, although this is only with repeated doses, and its prolonged onset of action. Adverse effects reported in the literature include cutaneous reactions such as blanching and erythema. We are not aware of any previous case reports describing definite systemic or cardiac effects related to Ametop in the pediatric or neonatal literature.

CASE PRESENTATION

The case involved a 24 weeks gestational age male infant with an antenatal diagnosis of Beckwith-Wiedemann syndrome. The infant was born after spontaneous onset of premature labor with a birth weight of 900 g (>97th percentile) in keeping with the diagnosis of Beckwith-Wiedemann syndrome. The infant was intubated and ventilated immediately after birth. Apgar scores were 2 and 8 at 1 and 5 minutes, respectively. A septic workup was completed, and intravenous ampicillin and tobramycin were started. The initial clinical assessment showed that the infant had premature skin consistent with his gestational age and an omphalocele. The omphalocele was evaluated and managed as per surgical protocol.

The case of this infant highlights the importance of pain management in the neonatal population. The use of topical anesthetics such as Ametop can provide effective pain relief during procedures without the risk of systemic adverse effects. The case also underscores the need for vigilance in monitoring infants for potential cardiac arrhythmias, especially in the presence of systemic opioids and nonpharmacological measures.

DISCUSSION

To our knowledge, this is the first confirmed systemic adverse event associated with tetracaine in a neonate. The event occurred soon after the drug was applied, and this infant had no other attributable cause for the bradycardia. Studies using Ametop in the neonatal population have included infants between...
the ages of 24 and 42 weeks of gestation with no reports of any major side effects. In pediatric studies, the most common adverse effect is minor local erythema. This same effect has not been seen as frequently in neonatal studies. Lemyre et al did report one 25 weeks gestational age infant who became bradycardic after Ametop was applied. However, a nasogastric tube was also inserted at that time that was thought to explain the transient bradycardia. A second case report by Taddio et al reported a severe skin reaction and bradycardia after Ametop application in a 27 weeks gestational age infant. They concluded that the associated bradycardia was unlikely to be secondary to a drug effect, because there was the presence of a pneumothorax on further evaluation. The bradycardia did not respond to drugs but resolved only after the pneumothorax was drained.

The primary mechanism of action of local anesthetics is blockade of voltage-gated sodium channels. The more highly lipophilic local anesthetics have a faster rate of interaction with the sodium channel receptor. Ametop is the most lipophilic of the ester-type anesthetics.

In our case, the application of topical Ametop to this premature extremely low birth weight (ELBW) infant resulted in prolongation of AV conduction and intraventricular conduction delay with the right bundle branch of ventricular conduction tissue affected more than the left-sided bundle (most likely owing to the smaller size of the right bundle in comparison with the left). These observations are consistent with the effect of Ametop as a sodium channel blocker. These effects resolved spontaneously over time.

Despite the fact that the manufacturer has not endorsed the use of this product in premature infants, we have been using Ametop for PICC insertions for over a year in our unit in both term and premature infants. This is the first case we have seen with systemic side effects. However, we rarely use topical anesthesia in infants of this gestational age within the first week of life. The majority of infants at this gestational age in our unit are managed with umbilical catheters after birth and then transitioned to PICC lines after the first 7 to 10 days of life when their skin is more mature. Skin maturation in the premature infant is accelerated after birth and is similar to that of a term infant by 2 to 3 weeks of postnatal life.

Premature infants born at the lower gestational ages only have a 2- or 3-cell-layer epidermis with little or no developed stratum corneum. This immature skin barrier is characterized by increased water content, permeability, and blood supply. This could potentially place the newborn ELBW at risk for increased absorption of any topical
agent if used at this stage. The theoretical risk of increased cutaneous absorption may explain the complications we saw in this infant. Furthermore, the infant had the gel applied to both arms, increasing the surface area exposed.

Based on this case, we reevaluated our topical anesthetic pain guidelines to limit the use of Ametop to infants >27 weeks’ gestation and >14 days of age. When we initially developed our guidelines for procedural pain management, a literature review at that time did not reveal any severe side effects in the studies that evaluated Ametop in neonates, and our own NICU experience with its use had been favorable.

Since this case, however, a more extensive review is ongoing and we may consider removing Ametop and evaluate using EMLA for premature infants if the exposure will be limited to a 1 time dose.

We would advise health care professionals to be cautious when using any topical analgesics in ELBW infants within the first few weeks of life and to ensure continuous ECG monitoring in this population when topical anesthetics are used. However, we still advocate that units continue to adopt guidelines aimed at reducing noxious stimuli to newborns, including those born preterm.

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