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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**KEY WORDS**

adverse drug reaction, arrhythmia, tetracaine, extremely low birth weight

**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 non-pharmacological 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 omphalocele was evaluated and managed as per surgical protocol. Given the need for parenteral nutrition and inotropes, multiple lines were required. Because of the omphalocele, umbilical lines were not an option. There were multiple attempts at peripheral intravenous and peripherally inserted central catheter (PICC) lines with the use of sucrose and/or systemic opioids, without local anesthetic. On day 2 of life at 10:55 AM, Ametop was applied to both antecubital fossae before ultrasound-guided PICC insertion. This was in keeping with our unit pain guidelines for radiologically placed lines. The infant was connected to continuous electrocardiogram (ECG) and oxygen saturation monitors throughout.

Before the application of Ametop, the infant was in normal sinus rhythm with a PR duration of 80 ms, a narrow QRS complex with an age-appropriate QRS duration of 40 ms, and a heart rate of 151 beats per minute (Fig 1A).

At 11:15 AM, 20 minutes after Ametop application, there was a change in the QRS morphology to a right bundle branch pattern and prolongation of the QRS duration up to 80 ms with the heart rate continuing at 153 beats per minute (Fig 1B).

By 11:29 AM the QRS duration on the monitor had widened further to 120 ms. In addition, there was terminal slurring of the QRS complex, accompanied by prolongation of the PR interval up to 200 ms and the presence of Mobitz type I second-degree atrioventricular (AV) block (Wenckebach) with aberrantly conducted sinus beats (Fig 1C). During this time, the heart rate remained at ~150 beats per minute. At 11:50 AM, the infant developed bradycardia due to 2:1 AV block with rate-dependent normalization of QRS morphology. This was captured on 12-lead ECG best seen in lead V2 (Fig 1D) with a heart rate of 78 beats per minute and a blood pressure of 39/13 mm Hg. Because of the hypotension, a dose of atropine (5 µg/kg) was given intravenously. No effect was noted, so a second identical atropine dose was given at 11:57 AM. After the second dose of atropine, the patient developed a wide complex rhythm with a heart rate of 150 beats per minute seen in lead II on ECG (Fig 1E), but he remained hemodynamically stable. This new rhythm was regular with 1:1 AV conduction, and the QRS complex was broad with right bundle branch block morphology. Although the QRS axis changed from +67° to +247°, the QRS morphology was the same as seen before atropine administration with the Wenckebach rhythm (compare QRS morphology in Fig 1C and E). This suggests that the broad complex rhythm was an aberrantly conducted sinus rhythm and not ventricular tachycardia.

There was gradual improvement in the QRS morphology over time with a decrease in the width of the QRS complex to 80 ms by 12:05 PM, 50 minutes after the initial Ametop application, although the PR interval remained prolonged at 120 ms (Fig 1F).

An echocardiogram showed an anatomically normal heart with a patent foramen ovale and good biventricular systolic function. After this event, this infant had no further cardiac arrhythmias. A PICC line was secured by using systemic opioids and nonpharmacological measures 3 days later.

**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 anesthetic.
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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