Babies with Neonatal Abstinence Syndrome Have Electrographic Seizures and Altered Sleep on Amplitude-Integrated EEG

By R. Edwin Spitzmiller, DO; Tracy Morrison, RN, BSN; Robert White, MD

Abstract

This study examined amplitude integrated electroencephalogram (aEEG) characteristics in term neonates undergoing treatment for Neonatal Abstinence Syndrome (NAS). Twenty mothers consented to participate and eight infants with an estimated gestational age ≥ 37 weeks and undergoing treatment for NAS were placed on aEEG for the first 72 hours of life and then, when possible, for 48 hours every week thereafter until discharge. The average length of time for monitoring was 174 hours. Abnormal progression of cycling as well as presence of electrographic seizures was identified during the study period. The number of aEEG seizures identified ranged from two to a maximum of nine in one infant. The presence of aEEG seizure activity in addition to abnormal cycling patterns without physical manifestation of seizures may provide significant additional clinical information to withdrawal scores in infants with NAS.

Keywords: seizure, aEEG, neonatal abstinence syndrome, drug withdrawal

Introduction

Illicit drug use is prevalent in women during pregnancy. From 2000-2009, 16.2% of pregnant teens and 7.4% of pregnant women between 18 and 25 years used illicit drugs in the month before participation in drug use interviews. Concomitantly, rates of Neonatal Abstinence Syndrome (NAS) have increased in the United States from 1.3 per 1000 births in 2000 to 3.3 per 1000 births in 2009, with the approximate number of newborns with NAS in the US of 13,500. From 2000 to 2009, hospital charges for NAS increased from an estimate of $190 million to $720 million dollars when adjusted for inflation.¹

Background

The physical signs of withdrawal can be debilitating and include evidence of central nervous system and gastrointestinal dysfunction and neurologic excitability as described in Table 1.

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¹References

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Seizures may accompany the withdrawal process in as many as 2%-11% of infants withdrawing from opiates. Abnormal electroencephalogram (EEG) findings have been reported; however for more than 30% of these infants, no overt seizure activity was noted.\(^2,3\) The onset of withdrawal from opiates, including methadone, is typically within the first 24 hours to up to 72 hours of age, depending on the opiate used. First symptoms may also occur as late as 7 days after birth.\(^4,5\)

Traditionally, symptoms of NAS have been attributed to the abrupt cessation of drug use. However, recent evidence suggests there may be interplay of other genetic, epigenetic and environmental factors. Polysubstance abuse concomitant with psychological comorbidities within circumstances of abuse, poor nutrition, and lack of prenatal care appears to create significant risk for NAS.\(^6\)

Over time, understanding of the pathophysiology for infants presenting with NAS has expanded.\(^6\) Evidence suggests that fetal programming may play a significant role in whether infants will exhibit symptoms of withdrawal as a result of in utero stressors. Proposed is that the fetus adapts to the unfavorable intrauterine environment by alteration of physiologic systems as a response. In utero responses result in ex utero maladaption, manifested as symptoms of NAS.

In 1980, Dinges, et al., studied infants born to mothers on various amounts of narcotics. The authors performed a sleep study that recorded electroencephalogram, electrocorticogram, electromyogram, respiration, and behavioral activity to evaluate these newborns, and found that the opiate-exposed infants exhibited less quiet sleep and more active REM sleep than their non-exposed counterparts.\(^7\) In 1988, Pinto, et al., published a case series report on 13 infants with neonatal abstinence syndrome and examined their sleep at the end of their second week of life and then again in the fourth and fifth week after the abstinence syndrome was treated. Again, NAS babies demonstrated decreases in quiet sleep.\(^8\)

In contrast, Sarfi and colleagues examined the sleep patterns of three month-old babies who were born to mothers taking either methadone or buprenorphine as compared to a control group and found no differences between the groups at this age.\(^9\) However, in both reports, sleep was evaluated at only one point in time. In fact, there is no evidence describing the progression of aEEG background pattern, bandwidth and time to develop cycling in term infants born to a mother on opioids. Therefore, the goal of this study was to describe aEEG characteristics in the term neonate undergoing treatment for NAS.

The study was approved by the Institutional Review Board and was not funded by any organization or company.

### Methods

All infants with an estimated gestational age (GA) of >37+0 weeks born to mothers with known narcotic use, no prenatal care, or who had a positive maternal urine drug screen had urine and meconium analyzed for illicit drugs and methadone were invited to participate. They were monitored with abstinence scores using the modified Finnegan scoring system every 8 hours.

When a diagnosis of NAS was made, the baby was admitted to the Neonatal Intensive Care Unit (NICU). Informed parental consent for study participation was obtained. Each subject was assigned an individual study number and aEEG was started. Day of Life (DOL) was used to describe the number of 24 hour periods after birth with the day of birth as DOL 0.

Amplitude integrated EEG, was monitored using either the Natus Medical CFM-6000, manufactured by Olympic Medical, Seattle, Washington, USA, or the Natus Medical BRM3 manufactured by Xitek, Oakville, Ontario, Canada. The aEEG was initially placed by nurses for 72 hours and then reapplied by nurses every 7 days for a 48 hour period until discharge or withdrawal from the study. Initially the study was designed to include the use of hydrogel and/or needle electrodes, but the increased physical activity of infants with NAS precluded the use of the hydrogel electrodes due to the difficulty in obtaining artifact free tracings. To reduce measurement error,
only a small team of 12 experienced nurses was recruited for electrode needle insertion and maintenance. Verification of aEEG electrode application was accomplished through simulation so that each RN used the same application techniques.

All infants with NAS received standard of care according to NICU protocols. Education regarding the study was provided in staff meetings, by unit newsletter, and in person by the study nurses. Families were encouraged to ask questions and continue to fully participate in the care of their infants. There was always a study team member in house or on call to initiate study monitoring during the study period.

Infants with NAS were treated with methadone; with the dose and frequency modified based on Finnegan scores over the previous 24 to 48 hours. The Finnegan scoring system is a list of symptoms with accompanying numbers to reflect the severity of each system, and has been well-described and utilized. A score of 8 or more indicates the need for treatment.\textsuperscript{10,11} The American Academy of Pediatrics states the use of a scoring system is necessary as it results in more objective criteria to determine whether pharmacologic treatment is necessary to begin and whether the dose of the medication should be altered.\textsuperscript{4}

Reduction in methadone dose or frequency was not made more frequently than every 48 hours as was the care protocol for the NICU. Dosage adjustments were made at the discretion of the attending neonatologist based on Finnegan scores.

**Instrumentation**

The (aEEG) is a bedside monitor in which cerebral electrical activity is recorded from either 1 or 2 channels. The aEEG has been described in detail in several publications.\textsuperscript{12,13,14,15,16} Briefly, the electrical signal obtained is rectified, smoothed, and recorded on a semi-logarithmic scale. Interpretation is based on recognition of the background pattern as defined by the height of the upper and lower margins of the band, the width of the electrical band, the continuity of the signal, and the changes in the cyclical activity in the recording.\textsuperscript{12,13} This allows for easy interpretation at the bedside without extensive training.\textsuperscript{17}

**Data Analysis**

Normal sleep-wake cycling (SWC) is characterized by sinusoidal variations in the minimal and maximal amplitude of the aEEG which reflects patterns of alternating periods of sleep and wakefulness. A broad bandwidth represents discontinuous background activity during quiet sleep while a narrow bandwidth represents wakefulness and active sleep.\textsuperscript{15,18} The patterns on aEEG representing active sleep and wakefulness cannot be easily distinguished.\textsuperscript{19}
Since the aEEG monitoring system does not provide summation scores for monitored events, aEEG bandwidth of the aEEG tracing was calculated by drawing lines across the upper and lower margins of the band and subtracting voltage of the latter from that of the former. Sleep-wake cycling (SWC) was defined as a regular pattern of wider bandwidth alternating with narrower bandwidth pattern every 40–90 minutes. The quiet portion of the cycle time was found by counting the minutes from the beginning of the widened portion of the tracing to the end of the same portion. Seizures were defined as an abrupt up-stroke of the lower margin in the aEEG pattern with regularly occurring associated high amplitude spikes in the raw EEG for a minimum of 10 seconds.

See the accompanying screen shots from the monitors used during the study. Below each screen shot is the tracing type and the definition of each tracing for definitions and screen images from the two monitors used. All infant tracings were reviewed by the two physician investigators. In the event of a disagreement, all aspects of the tracing measurement or interpretation were discussed until an agreement between the two reviewers was reached.

Results

Twenty mothers between May 1, 2009 and April 30, 2011 were approached to participate in the study and fourteen consented to participation of their infants. Infants were enrolled in the study for 5 to 66 days with a mean of 27.4 days, a standard deviation of 18.5 days and a median of 15 days. The average length of monitoring was 174 hours with a range of 95 – 344 hours. Subjects not included for analysis were one infant determined to be 36 weeks gestation by exam and ten babies were withdrawn from monitoring prior to discharge at the request of their parent(s). After request, the IRB granted permission to use the data obtained from early study withdrawal babies for analysis. Five infants had recordings for less than 72 hours; therefore, information from these tracings was not used in the final analysis. Three babies were monitored until discharge. For the final analysis, aEEG results were used for analysis from a total of 8 infants, as described in Figure 1.

All eight babies had background patterns consistent with continuous normal voltage (CNV) on Day One of monitoring. The bandwidth ranged from 10 to 15 microvolts (µV) with a mean of 12 µV. Seven of the eight (88%) babies had electrographic seizure activity, without clinically apparent seizures. The seizures were not treated due to retrospective review of the tracings. The number of aEEG seizures seen ranged from 1 to a maximum of 9 seizures in 1 baby.

<table>
<thead>
<tr>
<th>ID</th>
<th>EGA (weeks+days)</th>
<th>BW (grams)</th>
<th>Postmenstrual age at time of entry (days)</th>
<th>Length of stay (days)</th>
<th>Total duration of monitoring (days)</th>
<th>Total number of seizures</th>
<th>Average NAS per day of monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>#2</td>
<td>40+2</td>
<td>3455</td>
<td>0</td>
<td>81</td>
<td>5</td>
<td>0</td>
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<tr>
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<td>40+2</td>
<td>3410</td>
<td>2</td>
<td>71</td>
<td>4</td>
<td>3</td>
<td>13, 15, 12, 7, 7, 6</td>
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<tr>
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<td>39+3</td>
<td>2935</td>
<td>2</td>
<td>36</td>
<td>9</td>
<td>2</td>
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<tr>
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<td>38+6</td>
<td>3120</td>
<td>1</td>
<td>34</td>
<td>4</td>
<td>2</td>
<td>8, 6, 5</td>
</tr>
<tr>
<td>#9</td>
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<td>2635</td>
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</tr>
<tr>
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<td>23</td>
<td>7</td>
<td>9</td>
<td>8, 4, 6, 8, 3, 3, 3, 4, 5</td>
</tr>
</tbody>
</table>

Evidence of cycling was seen on DOL 1 in 3 babies, DOL 2 in 3 babies, and DOL 3 in 2 babies. There was no change in cycling for the duration of monitoring in 5 babies; however, in 3 babies the pattern changed over time, with prolonged active sleep/awake pattern in the first 24 hours, which then normalized over a period of days to weeks. All babies spent more time in either awake or active sleep than in quiet sleep during monitoring. The average awake/active sleep period was approximately 67% of the total recorded time which is summarized in Table 2. There did not appear to be a correlation between the presence of seizure activity and the timing of the appearance of a normal sleep-wake cycling pattern or the total awake time and the NAS scores.

Discussion

To our knowledge, the current descriptive study is the first study to document abnormal quiet-active cycling as well as the presence of...
subclinical seizure activity on aEEG in term newborns undergoing treatment for NAS.

We found the basic and predominant background tracing to be continuous normal voltage in all subjects. One of the most surprising findings, however, was the number of seizures seen on aEEG. As described, 88% of the babies had at least one aEEG seizure during the monitoring period without a physiological manifestation. One infant had up to 9 seizures without overt clinical evidence. This is the first time electrographic seizures via aEEG monitoring have been described in the infant with NAS.

The SWC was not consistent in these infants. Some of the babies developed a regular SWC from the time the aEEG was first placed, and then became irregular; other babies did not develop a regular SWC pattern until much later. There did not appear to be any distinct correlation between the NAS scores the development of regular SWC. These findings are consistent with the literature; however this is the first time it has been described using aEEG.

There are 5 conscious states of the term newborn: wakefulness, drowsiness, active sleep, quiet sleep, and indeterminate sleep. To properly determine the sleep/wake state of the newborn, Kidokoro et al., concluded that one must use physiological parameters such as rapid eye movement, body movements, and respirations in addition to the aEEG. The development of the sleep cycle of the normal newborn infant has been well reviewed. An infant at 39-41 weeks’ gestation spends approximately 65% of its time in active sleep, which steadily decreases as the infant ages. The two-month-old spends approximately 55% of its sleep time in active sleep. It is possible that if more babies remained enrolled for the duration of their hospitalization, there would have been an even higher percentage of time in active sleep/awake.

Polydrug-exposed infants have been shown to have more total awake time, less total sleep time and more arousals during active sleep than non-exposed infants. Although the babies in our study did spend about 67% of the time either in active sleep or awake, this figure represents an average. We did not differentiate based on the age of the baby or whether the baby was asleep or awake. Several of the tracings showed prolonged active sleep/awake time in the earlier part of the study, which then transitioned to a normal cycle over time.

Polydrug-exposed infants have been shown to have more total awake time, less total sleep time and more arousals during active sleep than non-exposed infants. One study utilized aEEG sleep recordings for 2 hours at two time points while the other observed respiratory control and behavior overnight on postnatal days 3, 4 and 5. Both studies involved babies exposed to polydrug abuse including cocaine.

The presence of abnormal cycling should be considered in the treatment of the withdrawing infant. In our study, four of the eight infants had periods of normal cycling interpersed with periods of prolonged active phase. The presence of these prolonged active patterns, when paired with physical signs of wakefulness, could be used to determine medication adjustments during treatment.

The incidence of visible seizures in the newborn is 1 to 3.5 per 1000 live births. Electrographic-only seizures are not uncommon; one report quotes 80% of electrographic seizures were not associated with clinical findings and they occurred in 1% of 1200 neonates considered high risk for seizures. Although clinically apparent seizures are known to occur during opiate withdrawal we observed solely electrographic-only seizures.

**Implications**

One limitation of this study is the small number of infants enrolled. Our results need to be duplicated on a larger scale. Another limitation was the inability to monitor all infants until discharge due to parental withdrawal of consent in the later stages of their treatment. A third limitation is that we did not specifically evaluate the amount of active sleep time, awake time or time in quiet sleep; rather, we compared active sleep/awake versus quiet sleep. While there has been no study validating aEEG for quantification of sleep-wake cycling, Kidokoro et al. state the presence of cycling on aEEG corresponds to the presence of alternate changes of continuous and discontinuous patterns on conventional EEG. Since the aEEG trace is the result of a filtered, amplified, rectified, smoothed and compressed raw EEG displayed on an semilogarithmic scale, it is the best way to follow cycling for a prolonged period while a baby is in the NICU. Our findings of electrographic-only seizures and the abnormal SWC patterns are the first to be described. These findings should be considered an additional, previously undescribed manifestation of NAS, with possible implications for treatment. More studies with larger numbers of subjects need to be done.

**Conclusion**

The aEEG may be a useful adjunct tool in the evaluation of the full-term neonate who is exhibiting signs of NAS. Some of these babies have less sleep – wake cycling and many babies exhibit electrographic-only seizure activity, the significance of which is yet to be established. More studies with larger numbers of infants are needed to answer these questions.

“The aEEG may be a useful adjunct tool in the evaluation of the full-term neonate who is exhibiting signs of NAS. Some of these babies have less sleep – wake cycling and many babies exhibit electrographic-only seizure activity, the significance of which is yet to be established. More studies with larger numbers of infants are needed to answer these questions.”

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**Author Contributions**

Ed Spitzmiller wrote the majority of the manuscript and Tracy Morrison wrote the majority of the methods section. Robert White contributed valuable editorial advice and wrote smaller sections as well as serving a reviewer of aEEG tracings.

**Declaration of Conflicting Interests**

None of the authors have any conflicting interests to declare.
Funding

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Ethical Approval

This study was approved by the institutional review board at Miami Valley Hospital.

References


Unusual Presentation of Adrenal Hemorrhage in a Newborn

By Jamie K. Overbey, DO and Cynthia Schultz, MD

Disclaimer: The views expressed herein are my own and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government.

Presentation and Clinical Course

A female infant was born at 39+6 weeks EGA via spontaneous vaginal delivery to a 25-year-old gravida two now para two mother. The infant’s birth weight was 3892 grams which is appropriate for gestational age. The pregnancy itself was uneventful; however, the delivery was complicated by the presence of thick meconium and rupture of membranes for 19 hours. The infant was vigorous at birth and required routine NRP. APGAR scores were seven and eight at one and five minutes, respectively. There was no ABO incompatibility noted between the mother and the infant.

Initially, the infant transitioned well with the mother, but by seven hours of life, the infant was noted to be tachypneic to 90 breathes per minute with decreased muscle tone throughout. Although there were no identified maternal infectious risk factors, the infant’s presentation was initially suspicious for sepsis. Therefore, blood cultures were obtained and intravenous ampicillin and gentamicin were started. Upon admission to the Neonatal Intensive Care Unit (NICU), the infant’s hemoglobin and hematocrit were 10.4 and 30, respectively. This initially raised questions, but the following physical examination finding raised greater concern. During the physical examination, the infant experienced one episode of bilious emesis. At that time, malrotation was suspected and further workup was pursued. An upper GI study suggested a strong suspicion for malrotation and a surgical consultation was requested (Image 1). During surgery, a large volume of blood loss was noted and malrotation was quickly ruled out. After further exploration, a left adrenal hemorrhage was identified. While in the operating room, the patient received 10ml/kg of packed red blood cells for blood loss. Post-operatively, the patient received another 10ml/kg of packed red blood cells to correct a hematocrit of 27 and 10ml/kg of fresh frozen plasma to correct an INR of 1.7. Antibiotics were discontinued after 48 hours of negative cultures. Patient was briefly on parenteral nutrition but obtained full feeds by Day of Life Five with no evidence of intolerance and was discharged home shortly thereafter.

Discussion

Adrenal hemorrhage in neonates is a rare diagnosis; however, it is not completely uncommon. The newborn in this case with adrenal hemorrhage presented in such a way that a surgical emergency toppled the differential diagnosis list. The abnormal upper GI findings were reported to be secondary to a mass effect on the bowel from the adrenal hematoma. A review of pertinent literature regarding adrenal hemorrhage presentations follows. The clinical presentation depends on the volume of the bleed. Small bleeds are often asymptomatic; whereas larger bleeds often result in abdominal, flank, or scrotal masses.1 Adrenal hemorrhages are often found incidentally on radiographic studies. Although adrenal hemorrhages can be identified by abdominal ultrasound, there is documentation of a case presenting as abdominal calcification noted on abdominal radiography. Other clinical findings include a decreasing hematocrit from blood loss or unexplained jaundice secondary to the reabsorption and breakdown of red blood cells in the hematoma.2 Although rare, some infants do present with adrenal insufficiency, as this is often a complication of bilateral adrenal hemorrhage. Right-sided adrenal hemorrhage is the most common because of its anatomical location between the liver and the spine allowing it to become trapped and therefore hemorrhage.1 Upon review of the literature, it appears that bilateral adrenal hemorrhages are second most common in frequency, and, therefore, the least common are left adrenal hemorrhages.

This case demonstrates an unusual presentation of a neonatal adrenal hemorrhage. Although bilious emesis often indicates malrotation with midgut volvulus, physicians should now add adrenal hemorrhage to the differential diagnosis of a newborn with this presentation.

References


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Image 1. In this patient, the duodenal-jejunal junction at the Ligament of Treitz, does not cross midline, as would be expected in a normal upper GI study.
INOMAX® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems.

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INOMAX® Important Safety Information

- INOMAX is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood
- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation even in neonates with no apparent response to nitric oxide for inhalation

Please see Brief Summary of Prescribing Information on adjacent page.
**INOMAX (nitric oxide gas)**

**Brief Summary of Prescribing Information**

**INDICATIONS AND USAGE**

**Treatment of Hypoxic Respiratory Failure**

INOMAX*® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of INOMAX have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies.

Monitor for PaO₂, methemoglobin, and inspired NO₂ during INOMAX administration.

**CONTRAINDICATIONS**

INOMAX is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

**WARNINGS AND PRECAUTIONS**

**Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation**

Wean from INOMAX. Abrupt discontinuation of INOMAX may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOMAX therapy immediately.

**Hypoxemia from Methemoglobinemia**

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOMAX; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOMAX to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOMAX, additional therapy may be warranted to treat methemoglobinemia.

**Airway Injury from Nitrogen Dioxide**

Nitrogen dioxide (NO₂) forms in gas mixtures containing NO and O₂. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If the concentration of NO₂ in the breathing circuit exceeds 0.5 ppm, decrease the dose of INOMAX.

If there is an unexpected change in NO₂ concentration, when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO₂ analyzer should be recalibrated. The dose of INOMAX and/or FiO₂ should be adjusted as appropriate.

**Heart Failure**

Patients with left ventricular dysfunction treated with INOMAX may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOMAX while providing symptomatic care.

**ADVERSE REACTIONS**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOMAX doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOMAX, a result adequate to exclude INOMAX mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOMAX and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOMAX and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOMAX than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

**OVERDOSAGE**

Overdose with INOMAX will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO₂. Elevated NO₂ may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO₂ levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOMAX.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

**DRUG INTERACTIONS**

No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. INOMAX has been administered with dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOMAX on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

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Despite reported reductions in rates of CLABSI,\textsuperscript{1,2,3} infection and sepsis remain important and feared complications within the NICU.\textsuperscript{4}

HeRO monitoring has been shown to predict infection in the NICU.\textsuperscript{5} In a 3000-patient Randomized Controlled Trial, researchers reported a 22\% reduction in mortality through HeRO monitoring of Very Low Birth Weight (VLBW) NICU patients.\textsuperscript{6}

While the benefit of HeRO monitoring to VLBWs is now well-studied, the question remains as to the benefit to other NICU patients, especially feeder-growers.

Approximately ten years ago I received a phone call from a venture capitalist friend who was at the time Chairman of the WV Symphony Board, of which I was a member. He was also (and still is) a venture capitalist always looking for small companies to invest in, with the hope that such companies would eventually become profitable. He asked my opinion about a system which was non-invasive, that was hooked up to a baby’s monitor, which somehow would analyze the heart rate and come up with a real-time tracing that would give a “snapshot” of the beat-to-beat variability, which could be visualized over days at a time. The hypothesis was that since normal “beat-to-beat variability” was evidence of fetal well-being, and that “loss of this beat-to-beat variability,” was associated with “fetal distress” in utero, perhaps a baby that was becoming ill due to bacteremia or sepsis may have the same pattern of “loss of beat-to-beat variability” which could be an early warning sign for us in the neonatal unit. This hypothesis was originally conceived by a neonatologist and a cardiologist at the University of Virginia, and the technology was created by MPSC (Medical Predictive Sciences Corp) and tested in a pilot at Wake Forest University on a small scale.\textsuperscript{7}

The system was called HeRO, and I was asked to offer an opinion re the efficacy of such a system, as these investors were looking at the company as a proposed venture.

I said that I thought it was far-fetched, and that I did not believe that the system would help us in our quandary of trying to diagnose infection in newborns. I explained that our armamentarium of tests was not very helpful, for the most part, unless a baby was clearly overwhelmed with infection, in which case the tests were merely confirmatory, but not predictive. Blood cultures took time, and many times the yield was poor; the complete blood count (WBCs and differential) were equivocal and the acute phase reactants (C reactive protein) lagged behind sometimes for greater than 24 hours before becoming positive. Other tests such as IL6, IL8, Haptoglobins, and others were simply not available quickly, and could take up to 3 days for the results to be available. My friend asked if I would be willing to try this system in my unit, free of charge, for a few months, and then offer an opinion. I agreed.

The system was installed in the NICU and I began the process of observing the tracings on all my babies. I was taught by the staff at MPSC that “normal” beat-to-beat variability was equated to a HeRO score of $<1$. If the score was 1 and suddenly started to rise to multiples of 1, that this was associated with a “flat” tracing, or loss of variability. I was also taught that there were some conditions such as a Patent Ductus Arteriosus, or a post-operative state, or an infant who was critically ill, that were associated with a high HeRO score. It became obvious to me early on, that new admissions that were sick with RDS, or PPHN or congenital anomalies requiring surgery all had high HeRO scores, and that the system really had no utility for me there. And it wasn’t very helpful in “early onset” sepsis at all. I really could not judge length of therapy in a newborn who was started on antibiotics at birth, because the scores were affected by too many other concomitant conditions. So I still relied on blood counts and the C-reactive protein values at...
24 hours to help me gauge therapy in early onset infection.

One afternoon as I was examining the HeRO tracings, there was one that caught my eye. It was a “feeder/grower” lying in a crib waiting to be discharged the next day. There was an indwelling Broviac catheter which had just been “heparin-locked”, and the surgeon that inserted it was on her way to remove it before discharge. The HeRO score had tripled in a period of 3 hours. I examined the baby, and she was normal-looking, was nipple feeding and seemed perfectly fine. I sent a C-reactive protein which came back within an hour. The value was 110. Normal values in our institution were <10. I sent an immediate blood culture which had just been “heparin-locked”, and the next day, the blood culture came back positive for Klebsiella sp. Needless to say, the baby was treated with IV antibiotics for another 10 days.

This was not an isolated incident. I have had many more instances over the years where the HeRO system has diagnosed “late-onset” infection in my babies, and has preceded the rise in CRP and procalcitonin on many occasions. I have relied on this system to help me to decide regarding antibiotics in babies with symptomatology that is not clear-cut, and in my opinion, has saved lives. The infant described above could have been discharged home, and may have succumbed to her infection.

Until there are new methods devised or lab investigations that are more precise in diagnosing infection, it is my opinion that the HeRO system is an invaluable tool in the management of our infants, especially those that are chronic feeding and growing infants that are always prone to developing indolent, slow-growing bacterial infections.

References

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Neonatology Today (NT) is the leading monthly publication that is available free to qualified Board Certified (BC) neonatologists and perinatologists. Neonatology Today provides timely news and information to BC neonatologists and perinatologists regarding the care of newborns, and the diagnosis and treatment of premature and/or sick infants. In addition, NT publishes special issues, directories, meeting agendas and meeting dailies around key meetings.

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Discovery Laboratories, Inc. (NASDAQ: DSCO), a specialty biotechnology company dedicated to advancing a new standard in respiratory critical care, today announced the U.S. Food and Drug Administration (FDA) has agreed to the Company’s updated product specifications for SURFAXIN® (lucinactant) Intratracheal Suspension for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS. The Company has initiated manufacturing of SURFAXIN for its planned commercial introduction in the fourth quarter of 2013. SURFAXIN is the first FDA-approved synthetic, peptide-containing surfactant available for the prevention of RDS in premature infants and the only approved alternative to animal-derived surfactants currently used today.

“We are pleased that the FDA has agreed with our updated product specifications and are appreciative of the process that has lead to this decision”, said John G. Cooper, Chief Executive Officer of Discovery Labs. “SURFAXIN represents the first milestone in our goal of transforming the treatment of RDS and is an important medical advancement for the neonatology community and parents of preterm infants who will soon have an effective alternative to animal-derived surfactants for the prevention of RDS.”

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