Respiratory Distress Syndrome: A Pharmacology Case Study

Jackie B. Martin, DNP, NNP-BC, CCNS

Neonatal Nurse Practitioner
Associate Nursing Educator
Pediatrix Medical Group

Neonatal Clinical Nurse Specialist
Carilion Memorial Hospital, Roanoke, VA
This case presentation will present a case history, the medications received by the infant with pharmacological information, and information on the pathophysiology and course of Respiratory Distress Syndrome.
Disclosures

- Relevant financial relationships
  - No financial affiliations or relationships to disclose

- FDA
  - Inhaled nitric oxide used for the prevention of chronic lung disease in preterm infants is an investigational medication.
  - The February 2002 AAP and CPS statement strongly discourages routine use of dexamethasone.
  - No other medication disclosures.
Maternal History

- Mother is 42 years old, Caucasian, gravida 1 para 0 abortion 0, at 25 weeks gestation
- Prenatal labs: A Neg, RPR- nonreactive, Rubella-immune, HIV-negative, HbsAg – negative, GBS unknown
- Uncomplicated pregnancy prior to today when she had a seizure at home
- Taken to the hospital by EMS
- She received one dose of betamethasone prior to her emergent C-Section which was performed due to Eclampsia.
Betamethasone

- Why was the mother given betamethasone?

**Pharmacologic Category:** Betamethasone is a systemic corticosteroid.

**Use:** Injections of corticosteroids promote fetal lung development in mothers who are at risk for preterm labor and birth. Steroids reduce the risk of respiratory distress syndrome (RDS) and reduce the risk of intraventricular hemorrhage.

- Betamethasone and dexamethasone are the two most commonly used steroids.

Betamethasone (continued)

**Administration:** The medication is given IM in 2 doses, 24 hours apart. Usual dosage is 0.6-0.9 mg/day divided into the 2 doses.

- For maximum effect the drugs should be given 24-48 hours prior to the birth of the baby.

- The drugs are best used between 24 and 34 weeks gestation

- Previously some physicians gave multiple doses until the birth of the baby, however, multiple doses are questionable due to the potential risks of using the drugs.

Betamethasone (continued)

**Adverse Reactions**

Cardiovascular: Congestive heart failure, hyper/hypotension.

Central Nervous System: Dizziness, headache, insomnia, increased intracranial pressure.

Dermatologic: Ecchymoses, facial erythema, fragile skin, hirsustism, petechiae.

Endocrine & metabolic: Cushing’s syndrome, diabetes mellitus, growth suppression, hyperglycemia, hypokalemia, sodium and water retention.

Betamethasone (continued)

Adverse Reactions Continued
Gastrointestinal: Abdominal distention, appetite increased, hiccups, indigestion, peptic ulcer, pancreatitis
Local: Injection site reactions

Side effects of corticosteroids in the infant include: psychomotor delays and behavioral problems.

Mechanism of Action: “Controls the rate of protein synthesis; depresses the migration of polymorphonuclear leukocytes, fibroblasts; reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation.”

Betamethasone (continued)

Pharmacodynamics/Kinetics

- Protein binding: 64%
- Metabolism: Hepatic
- Half-life elimination: 6.5 hours
- Time to peak, serum IV: 10-36 minutes
- Excretion: Urine (<5% as unchanged drug)

This infant was born at 25 weeks gestation. What can be expected from the lung function of an infant born at 25 weeks gestation?

- Stages of Lung Development
  - Embryonic Period
  - Pseudoglandular Period
  - Canalicular Period
  - Saccular Period
  - Alveolar Period
Stage I: Embryonic

- Week 4 of Gestation
  Laryngotracheal groove forms
  Single lung bud forms
  Division to the 2 primary bronchial buds

- Week 5 of Gestation
  Lobar bronchi form
  Lung buds grow

- Week 6 of Gestation
  Segmental bronchi form
Problems during the Embryonic Period

- Primary Lung Agenesis
- Laryngeal Clefts
- Tracheoesophageal Fistulas
Stage II: Pseudoglandular

Weeks 6-16
- Conducting Airways Form

Weeks 7-10
- Diaphragm Forms
- Intestinal Contents Move into the abdomen

Weeks 8-10
- Pulmonary Lymphatics
- Pleural Membranes
Problems in the Pseudoglandular Period

- Abnormalities in bronchial position and number
- Pulmonary Sequestration
- Diaphragmatic Hernia
Stage III: Canalicular

- **Week 17**
  Intra-acinar respiratory bronchioles develop
  Capillaries connect to pulmonary arteries

- **Weeks 18-28**
  Saccules arise from the ends of the bronchioles

- **Week 20**
  Granular pneumocytes form
Problems During the Cannalicular Period

- Deficiency in gas exchange in parts of the lungs
- Pulmonary Hypoplasia

Stage IV: Saccular

- Weeks 28-32
  - Decrease in interstitial tissue
  - Airspace walls become more compact
  - Increase in lung volume and surface area

- Weeks 32-36
  - Alveoli form
Stage V: Alveolar

- Alveoli start at 32-36 weeks
- At term there are about 50 million alveoli
- Reach adult number of 300 million alveoli at 3 years of age
Compliance

- The elasticity or distensibility of the lungs and chest wall

- Measured as change in volume divided by change in pressure

- Normal infants: 0.0002-0.0006 L/cmH2O

- RDS infants: 0.0005-0.001 L/cm H2O
Resistance

- **Airway Resistance:**
  Friction between gas molecules and the airway
  Nasal resistance is 50% of airway resistance in the neonate

- **Tissue Resistance:**
  Friction between lung tissue and the chest wall

- Resistance is inversely proportional to lung volume
Resistance (continued)

- Measured as change in pressure divided by change in flow

- Dependent on:
  - Airway resistance
  - Airway length
  - Flow rate
  - Gas density and viscosity

Normal infants: 20-40 cm H2O/L/s
Intubated infants: 50-150 cmH2O/L/s
Delivery History

- This 25 week gestation, female infant was delivered by emergent C-Section. Weight was 535 grams.
- The infant was placed in a prewarmed radiant warmer, wrapped in plastic wrap.
- Brief vital signs showed a HR < 100 bpm and occasional gasps with deep retractions, color cyanotic, tone limp.
- The infant was dried, bulb suctioned, stimulated and given blow by oxygen briefly with little response.
Delivery History (continued)

- PPV with bag and mask were provided while intubation equipment was assembled.
- One minute Apgar score was 2.
- The infant was intubated with a 2.5 ETT to 6.5cm at the lip without difficulty.
- Heart rate, oxygen saturation, and tone improved.
- For what type of respiratory distress is this infant most at risk?
Clinical Assessment for Respiratory Distress

- Respiratory Rate
- Retractions
- Nasal Flaring
- Grunting
- Cyanosis
Respiratory Rate

- Abnormal respiratory rate is associated with:
  - Mechanical pulmonary dysfunction
  - Acid base imbalance
  - ABG abnormalities

High rates are associated with increased dead space ventilation.

Low rates are associated with decreased alveolar ventilation.
Retractions

- Retractions occur due to a very soft chest wall and stiff lungs
Nasal Flaring

- Enlargement of the nostrils decreases airway resistance and work of breathing.
Grunting

- Normally vocal cords abduct in inspiration and adduct in exhalation.

- Exhalation through closed vocal cords causes the grunting sound.

- Grunting increases the ventilation/perfusion ratio due to increased airway pressure and increased lung volume.
Cyanosis

- Causes include:
  - Airway obstruction
  - Ventilation perfusion mismatch
  - Intrapulmonary shunting
  - Cardiac disease
Respiratory Distress Syndrome

- Our 25 week gestation infant is most at risk for Respiratory Distress Syndrome (RDS)

- RDS affects 10 of every 100 premature infants in the US, or about 40,000 babies, each year

- Approximately 50% of the neonates born at 26-28 weeks of gestation develop RDS
RDS Rates

- 71% in those 501-750 grams
- 54% in those 751-1000 grams
- 36% in those 1001 – 1250 grams
- 22% in those 1251-1500 grams
Risk Factors for RDS

- A sibling who had RDS
- Maternal Diabetes
- Cesarean delivery
- Delivery complications that lead to acidosis in the newborn at birth
- Multiple pregnancy (twins or more)
- Rapid labor
Pathophysiology of RDS

- The lungs are developmentally deficient in surfactant.
- Surfactant is comprised of lipids, proteins, and glycoproteins which are produced in Type II pneumocytes. The surfactant is packaged in lamellar bodies which unfold into a complex lining of the alveoli. This layer reduces the surface tension of the fluid that lines the alveolar walls. By reducing surface tension, surfactant prevents the alveoli from collapsing on exhalation.
- Microscopically, a surfactant deficient lung shows collapsed alveoli alternating with hyperaerated alveoli, vascular congestion and, hyaline membranes. Hyaline membranes appear as an amorphous material filling the alveolar spaces and blocking gas exchange.
Clinical Presentation of RDS

- Tachypnea
- Tachycardia
- Retractions
- Grunting
- Flaring
- Cyanosis
Functional Abnormalities

- Decreased compliance
- Increased resistance
- Ventilation/Perfusion abnormalities
- Impaired gas exchange
- Increased work of breathing
Delivery Room Care

- This 25 week gestation infant receives **surfactant** as a part of the hospital protocol for care of the < 28 week gestation infant with respiratory distress in the delivery room.

Type given: calfactant

What do you know about **surfactant**?
Surfactant Development

- Surfactant is a lipoprotein with 6 phospholipids and 4 apoproteins
- Dipalmitoyl phosphatidylcholine (DPPC), or lecithin, is the principle phospholipid
- Surfactant lowers the surface tension at the alveolar air-fluid interface
Surfactant Composition

Therapy: Surfactant

- The mortality rate of RDS decreased by approximately 50% during the last decade with the advent of surfactant therapy.

- Neonates with RDS who require assisted ventilation with a FiO2 of > 0.40 should receive surfactant as soon as possible.

- Studies show that surfactant administration to extremely premature neonates in the delivery room improves outcome.
Composition and dosing schedule of commercially available surfactant preparations

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Origin</th>
<th>Surfactant protein B content</th>
<th>Concentration of phospholipids</th>
<th>Initial dose</th>
<th>Repeat dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poractant alfa</td>
<td>Porcine lung minces, lipid extraction with purification using liquid-gel chromatography</td>
<td>0.38% of PL</td>
<td>80 mg PL per mL</td>
<td>2.5 mL/kg (200 mg/kg PL)</td>
<td>1.25 ml/kg (100 mg/kg PL) every 12 h as needed up to 2 total doses</td>
</tr>
<tr>
<td>Calfactant</td>
<td>Calf lung lavage, lipid extraction</td>
<td>0.74% of PL</td>
<td>35 mg PL/mL</td>
<td>3 mL/kg (105 mg/kg PL)</td>
<td>3.0 ml/kg (105 mg/kg PL) every 12 h as needed up to 3 total doses</td>
</tr>
<tr>
<td>Beractant</td>
<td>Bovine lung minces, lipid extraction. Supplemented with DPPC, palmitic acid and tripalmitin</td>
<td>0.044% of PL</td>
<td>25 mg PL/mL</td>
<td>4 mL/kg (100 mg/kg PL)</td>
<td>Repeat same dose every 6 h as needed for total of 4 doses</td>
</tr>
</tbody>
</table>

PL: phospholipid; DPPC: dipalmitoylphosphatidylcholine.

Continued Patient Care

- The infant was placed on a T-piece resuscitator, shown to the parents, and placed in a warm incubator for transport to the NICU.

- Upon arrival in the NICU, the infant was placed in a warm isolette, on a ventilator.

- Umbilical catheters, arterial and venous were placed.

- A chest and abdominal x-ray were obtained.
Therapy: Assisted Ventilation

- Assisted ventilation decreases RDS-related mortality; however, early ventilators were associated with complications including:
  - Air Leaks
  - BPD
  - Airway Damage
  - Intraventricular Hemorrhage

Consider ventilation as a necessary physiologic support while the infant recovers from RDS.
The infant’s initial x-ray showed RDS

What is the radiology picture of RDS?
Chest radiographs of an infant with RDS show bilateral, diffuse reticular granular or ground-glass appearances, air bronchograms, and poor lung expansion.

- Air bronchograms represent aerated bronchioles superimposed on a background of collapsed alveoli
- The radiologic findings of RDS cannot be differentiated reliably from those of pneumonia, which is most commonly caused by group B beta hemolytic streptococci.
Chest X-ray Findings

Chest radiographs in a premature infant with respiratory distress syndrome before and after surfactant treatment. Left, Initial radiograph shows poor lung expansion, air bronchogram, and reticular granular appearance. Right, Repeat chest radiograph obtained when the neonate is aged 3 hours and after surfactant therapy demonstrates marked improvement.
Continued NICU Care

- Now that the infant is in the NICU and somewhat settled on the ventilator, other care is provided. Medications administered on admission included:
  - Phytonadione
  - Erythromycin Ophthalmic
  - Ampicillin
  - Gentamicin
Phytonadione (Vitamin K₁)

- **Therapeutic Category:** Nutritional Supplement

- **Use:** Prevention and treatment of hemorrhagic disease of the newborn caused by vitamin K deficiency.

- **Administration:**
  - Prophylaxis: 0.5-1 mg IM at birth
  - May repeat 6-8 hrs later as necessary.
  - Preterm infants < 32 weeks gestation:
    - BW < 1000 grams: 0.5 mg IM
    - BW < 1000 grams: 0.3mg/kg IM
  - Black Box warning: SubQ administration is preferred, but IM can be used where SubQ is not feasible.
  - Treatment of severe hemorrhagic disease: 1 to 10 mg IV slow push.

Phytonadione (continued)

Adverse Reactions/Precautions: Severe reactions, including death have been seen with IV administration in adults. These reactions have been like anaphylaxis.

Cardiovascular: Flushing, hypotension, cyanosis

Endocrine & Metabolic: Hyperbilirubinemia in infants receiving > than the recommended dose

Gastrointestinal: GI upset

Hematologic: Hemolysis, Hemolytic anemia

Local: Pain, edema, tenderness at injection site

Respiratory: Dyspnea

Phytonadione (continued)

**Mechanism of Action:** Promotes formation in the liver of clotting factors (II, VII, IX, X)

**Pharmacodynamics:** Onset of action: Blood coagulation factors increase within 6-12 hours after oral doses and within 1-2 hours following parenteral administration; after parenteral administration prothrombin time may become normal after 12-14 hours

**Pharmacokinetics:**
- Metabolism: Rapidly in the liver
- Elimination: In bile and urine


Erythromycin Ophthalmic

Pharmacologic Category: Antibiotic

Use: Prophylaxis of neonatal gonococcal or chlamydial conjunctivitis

Administration: 0.5-1 cm ribbon of ointment should be instilled into each conjunctival sac.

Adverse Reactions:
Ocular: Hypersensitivity, minor ocular irritation, redness

Mechanism of Action: “Inhibits RNA-dependent protein synthesis at the chain elongation step; binds to the 50S ribosomal subunit resulting in blockage of transpeptidation”.

Rule out Sepsis

Since the infant was premature, a 48 hour rule out sepsis is performed. A CBC and blood culture were obtained and antibiotics begun. The CBC is within normal limits for the infant’s gestational age. The blood culture is pending. Ampicillin and gentamicin were started.
Ampicillin

- **Therapeutic Category:** Antibiotic

- **Use:** A broad-spectrum antibiotic used in the treatment of susceptible bacterial infections caused by Group B streptococcus, pneumococci, Listeria monocytogenes, enterococci, and susceptible E Coli species.


Ampicillin (continued)

**Administration:**
**Dose:** 25 to 50 mg/kg per dose.

**Route:** IV slow push or IM

**Dosing for meningitis and severe group B streptococcal sepsis:**
100 mg/kg/dose

<table>
<thead>
<tr>
<th>PMA (weeks)</th>
<th>Postnatal (days)</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 29</td>
<td>0 to 28</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>30 to 36</td>
<td>0 to 14</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&gt;14</td>
<td>8</td>
</tr>
<tr>
<td>37 to 44</td>
<td>0 to 7</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&gt;7</td>
<td>8</td>
</tr>
<tr>
<td>45</td>
<td>ALL</td>
<td>6</td>
</tr>
</tbody>
</table>
Ampicillin (continued)

**Adverse Reactions/ Precautions:**

- Central Nervous System: CNS excitation or seizure activity with large doses.
- Gastrointestinal: Diarrhea (20%), vomiting, glossitis, pseudomembranous enterocolitis, oral candidiasis
- Hematologic: Eosinophilia, hemolytic anemia, thrombocytopenia, neutropenia, prolongation of bleeding time
- Renal: Interstitial nephritis

Ampicillin (continued)

**Mechanism of Action:** Ampicillin binds to one or more penicillin-binding proteins during the active multiplication phase of bacterial cell wall synthesis, interfering with the synthesis and causing cell wall death.  

**Pharmacokinetics:**

Half life:
- Neonates < 7 days of age: 4 hours

Clearance: Primarily renal and inversely related to postnatal age. 

Gentamicin

**Therapeutic Category:** Antibiotic, Aminoglycoside

**Use:** Used in combination with β-lactam antibiotics as empiric therapy for sepsis in newborns. Treatment of bacterial infections caused by aerobic gram-negative bacilli such as Pseudomonas, E.Coli, Klebsiella, Proteus, Seratia, and gram-positive staphlococcus. Also used for the treatment of bone, CNS, respiratory tract, skin and soft tissue infections.

Administration:

IV- on syringe pump over 30 minutes.

IM- associated with variable absorption

Dosing Chart for Gentamicin

<table>
<thead>
<tr>
<th>PMA (weeks)</th>
<th>Post-natal (days)</th>
<th>Dose (mg/kg)</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 29*</td>
<td>0 to 7</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>8 to 28</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>≥ 29</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>30 to 34</td>
<td>0 to 7</td>
<td>4.5</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>≥8</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>≥35</td>
<td>ALL</td>
<td>4</td>
<td>24</td>
</tr>
</tbody>
</table>

*or significant asphyxia, PDA, or treatment with indomethacin

Gentamicin (continued)

Adverse Reactions/Precautions:

**Black Box Warning:** Aminoglycoside therapy has been associated with possible neurotoxicity, ototoxicity, and nephrotoxicity.

Neuromuscular & Skeletal: neuromuscular blockade

Otic: damage is usually irreversible.

Renal: Risk of toxicity with impaired renal function, dehydration, high dosages, or prolonged therapy.

Gentamicin (continued)

**Mechanism of Action:** Gentamicin binds to 30S and 50S ribosomal subunits, which inhibits cellular initiation of bacterial protein synthesis and results in a defective bacterial cell membrane.

**Pharmacokinetics:**
- Distribution: increased in neonates with fever, edema, ascites, fluid overload. Decreased in patients with dehydration:
  - $V_d$ Neonates: 0.45 + 0.1 L/kg
  - Protein binding: < 30%
  - Half-life:
    - Neonates: < 1 week: 3-11.5 hours
    - 1 week to 1 month: 3-6 hours

Gentamicin (continued)

Time to peak serum concentration:
   IM: Within 30-90 minutes
   IV: 30 minutes after 30-minute infusion

Elimination: Clearance is directly related to renal function; eliminated almost completely by glomerular filtration of unchanged drug with excretion into urine.

Clearance:
   Neonates: 0.045 + 0.01 L/hour/kg

Gentamicin Special Considerations

- If treating for more than 48 hours, measure serum concentrations.

- The peak concentration should be obtained 30 minutes after the end of the infusion.

- The trough concentration should be obtained just prior to the next dose.

- Therapeutic serum concentrations:
  - Peak: 5 to 12 mcg/ml
  - Trough: 0.5 to 1 mcg/ml

Patient Care

- The infant’s blood gases were initially good, but as the day progressed she required more respiratory support and placement on the high frequency oscillating ventilator. She did not tolerate this well and became agitated requiring pain medication and sedation. **Fentanyl** and **midazolam** were provided. She also became hypotensive requiring pressure support - normal saline boluses x 2, then **dopamine** was started.
Fentanyl

**Pharmacologic Category:** Analgesic, Narcotic; General Anesthetic

**Usage:** Sedation, relief of pain; adjunct to general or regional anesthesia

**Dosing:**
- **Sedation and Analgesia:** 0.5 to 4 mcg/kg per dose, repeat as required q 2-4 hrs.
  - Route: slow IV push
- **Infusion Rate:** 1 to 5 mcg/kg per hour. May rapidly develop tolerance with constant infusion.
- **Anesthesia:** 5 to 50 mcg/kg/per dose.


Fentanyl (continued)

Adverse Reactions/ Precautions:

- Cardiovascular: Bradycardia, cardiac arrhythmia, hypertension, hypotension, tachycardia

- Renal: Urinary retention may occur with continuous infusions.

- Respiratory: Apnea, hypoxia, respiratory depression.

Fentanyl (continued)

**Mechanism of Action:** Interacts with opiate receptors decreasing pain impulse transmission at the spinal cord level and higher in the CNS, thus increasing the pain threshold, altering pain reception and inhibiting ascending pain pathways.

**Pharmacodynamics:** May have respiratory depression lasting longer than the analgesic effect

Onset of action:
- I.M.: 7-15 minutes
- I.V.: almost immediate

Duration:
- I.M.: 1-2 hours
- I.V.: 30-60 minutes

**Pharmacokinetics**

Newborn Clearance: may be correlated to gestational age and birth weight.

Midazolam

- **Therapeutic Category:** Sedative/Hypnotic, anticonvulsant

- **Usage:** Conscious sedation, treatment of refractory seizures, anxiolysis, and amnesia prior to a procedure or before anesthesia
Midazolam (continued)

Administration:

Sedation:
IV: 0.5 to 0.15 mg/kg over at least 5 minutes. Repeat as needed q2-4hrs.
Continuous IV infusion: 0.01 to 0.06 mg/kg per hour (10 to 60 mcg/kg/hour). May need to be increased with development of tolerance and/or increased clearance.
Intranasal: 0.2 to 0.3 mg/kg per dose using 5-mg/ml injectable form.
Sublingual: 0.2 mg/kg per dose using 5-mg/ml injectable form mixed with a small amount of flavored syrup.
Oral: 0.25 mg/kg per dose using Versed® oral syrup.

Anticonvulsant: Loading dose: 0.15 mg/kg (150 mcg/kg) IV over at least 5 minutes, followed by
Maintenance Infusion: 0.06 to 0.4 mg/kg per hour (1 to 7 mcg/kg per minute).

Midazolam (continued)

Adverse Reactions/ Precautions:

**Black Box Warning**: Midazolam has been associated with respiratory depression and arrest when used for sedation in a non-critical care setting. Rapid administration of midazolam has been associated with severe hypotension and seizures in neonates. Nasal administration may cause a burning sensation.

Midazolam (continued)

**Mechanism of Action:** “Depresses all levels of CNS, including the limbic and reticular formation, by binding to the benzodiazepine site on the gamma-aminobutyric acid (GABA) receptor complex and modulating GABA, which is a major inhibitory neurotransmitter in the brain.”

**Pharmacodynamics:**

Onset of Action:
- I.M.: within 5 minutes
- I.V.: within 5 minutes
- Intranasal: within 5 minutes

Duration:
- I.M.: Mean: 2 hours, up to 6 hours
- I.V.: 20-30 minutes
- Intranasal: 30-60 minutes

Note: Full recovery may take more than 24 hours

Midazolam (continued)

Pharmacokinetics:

- **Distribution**: $V_d$:
  - Preterm infants ($n=24$; GA: 26-34 weeks; PNA: 3-11 days)
    - Median 1.1L/kg (range: 0.4-4.2 L/kg)

- **Half-life, elimination**: Increased with acute renal failure.
  - Preterm Infants ($n=24$; GA: 26-34 weeks; PNA: 3-11 days)
    - Median: 6.3 hours (range: 2.6-17.7 hours)
    - Neonates: 4-12 hours; seriously ill neonates: 6.5-12 hours

Midazolam (continued)

Pharmacokinetics (continued)
- Elimination: 63-80% excreted as alpha-hydroxy-midazolam glucuronide in urine; 2-10% in feces, < 1% eliminated as unchanged drug in the urine.
- Clearance:
  - Preterm (n=24; GA: 26-34 weeks; PNA 3-11 days):
    - Median: 1.8 mL/minute/kg
    - (range: 0.7-6.7 mL/minute/kg)
  - Neonates < 39 weeks GA: 1.17 mL/minute/kg
  - Neonates > 39 weeks GA: 1.84 mL/minute/kg

Nursing Implications: Abrupt discontinuation after prolonged use may result in withdrawal symptoms.

Dopamine

Therapeutic Category: Adrenergic Agonist Agent; Sympathomimetic

Uses: In low doses, increases renal perfusion. Treats hypotension by increasing cardiac output, blood pressure, and urine flow which persists after adequate fluid volume is replaced.

Dosage:
2 to 20 mcg/kg per minute continuous IV infusion. Begin at a low dose and titrate per effects. Use a large vein for IV, a central line is preferred.

### Dopamine Titration Chart


<table>
<thead>
<tr>
<th>Concentration (mcg/mL)</th>
<th>Dose (mcg/kg/min)</th>
<th>IV Rate (mL/kg/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>2.5</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>0.9</td>
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<tr>
<td></td>
<td>10</td>
<td>1.2</td>
</tr>
<tr>
<td>800</td>
<td>2.5</td>
<td>0.19</td>
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<tr>
<td></td>
<td>5</td>
<td>0.38</td>
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<tr>
<td></td>
<td>7.5</td>
<td>0.56</td>
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<td></td>
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<td>0.75</td>
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<tr>
<td>1000</td>
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<td>0.3</td>
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<td></td>
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<td>0.6</td>
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<td>1600</td>
<td>2.5</td>
<td>0.094</td>
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</table>
Dopamine (continued)

Adverse Reactions/Precautions:

**Black Box Warning:** Tissue sloughing may occur with IV infiltration. To prevent necrosis and sloughing of the infiltrated area, the area should be injected with a saline solution containing phentolamine mesylate as soon as possible.¹

Cardiovascular: Ectopic heartbeats, tachycardia, vasoconstriction, cardiac conduction abnormalities, hypertension

Central Nervous System: anxiety

Genitourinary: Decreased urine output with high doses

Ocular: Dilated pupils²

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Dopamine (continued)

Mechanism of Action: Low dose dopamine is mainly dopaminergic which stimulates and produces renal and mesenteric vasodilation. Moderate doses stimulate both dopaminergic and beta –adrenergic receptors and produce cardiac stimulation and increased renal blood flow. High doses of dopamine stimulate alpha-adrenergic receptors primarily producing vasoconstriction and increased blood pressure.¹

Pharmacokinetics:
Serum half-life is 2-5 minutes
Clearance is variable.²

Patient Care

- Four days after birth, the infant was trialed on conventional ventilation but failed and was placed back on the HFOV.

- This time ventilator support was gradually weaned, and at two weeks of age, she was given a caffeine load in preparation for extubation. The extubation failed due to an inability to oxygenate the infant, so she was reintubated and placed on a conventional ventilator.
Caffeine Citrate

Therapeutic Category: CNS stimulant, respiratory stimulant

Usages: Treatment of neonatal apnea

Administration:
- Loading Dose: 20 to 25 mg/kg IV over 30 minutes (or po)
- Maintenance dose: 5 to 10 mg/kg per dose slow IV push or PO q 24 hours- started 24 hours after loading dose


Caffeine Citrate (continued)

**Adverse Reactions/Precautions:**

Cardiovascular: functional cardiac symptoms such as arrhythmias, tachycardia, extrasystoles
Central Nervous System: restlessness, agitation, irritability, jitteriness
Endocrine & Metabolic: hypo- or hyperglycemia
Gastrointestinal: vomiting, possible NEC
Genitourinary: increased urinary output
Neuromuscular & skeletal: tremors or twitches

Caffeine Citrate (continued)

**Mechanism of Action:** Increases the respiratory center output, chemoreceptor sensitivity to CO2, smooth muscle relaxation, and cardiac output. Stimulates central inspiratory drive, and improves skeletal muscle contraction.

**Pharmacokinetics:**
- Distribution: $V_d = 0.8-0.9$ L/kg
- Half-life: 72-96 hours (range 40-230 hours)
- Elimination: 86% excreted unchanged in urine
- Clearance: 8.9 mL/hour/kg (range 2.5 -17)

Patient Care

- At three weeks of age, the infant’s respiratory condition worsens. Her chest x-ray shows patchy infiltrates. She develops a metabolic acidosis and requires sodium bicarbonate. She is also given a dose of furosemide.

- Her course continues to worsens and she is placed on inhaled nitric oxide with a “white out” x-ray and her parents agree to a trial of dexamethasone due to her failing respiratory status. She is given a two week course of the dexamethasone.
Sodium Bicarbonate

**Therapeutic Category:** Alkalinizing Agent

**Usages:** Treatment of metabolic acidosis caused by renal or GI losses. Not recommended in neonatal resuscitation guidelines. Use only after adequate ventilation is established.

**Administration:** 1 to 2 mEq/Kg IV over at least 30 minutes. Recommended dilution: 0.25 mEq/mL  
Maximum Concentration: 0.5 mEq/mL  
Can also give by continuous IV infusion or PO.

Sodium Bicarbonate (continued)

Adverse Reactions/Precautions:

Cardiovascular: IVH with rapid injection in neonates.

CNS: tetany

Endocrine & Metabolic: hypocalcemia, hypokalemia, hypernatremia, metabolic alkalosis

Gastrointestinal: gastric distension

Local: tissue necrosis at IV site

Respiratory: pulmonary edema

**Mechanism of Action:** Bicarbonate buffers hydrogen ions, leading to increased production of carbon dioxide and water, raising blood and urinary pH.

**Pharmacodynamics:**
- Onset of action: rapid
- Duration IV: 8-10 minutes

**Pharmacokinetics:**
- Elimination: reabsorbed by kidney and <1% is excreted in urine

Furosemide

**Therapeutic Category:** Loop diuretic, antihypertensive

**Usage:** Management of edema associated with heart failure, hepatic or renal disease. May also improve pulmonary function. Used alone or in combination with antihypertensives in treatment of hypertension.

**Administration:**
- Initial dose: 1 mg/kg IV slow push, IM, or PO
- May increase to max of 2 mg/kg per dose IV or 6 mg/kg per dose PO.
- Dosing intervals initially:
  - Preterm infant: q 24 hours
  - Full term infant: q 12 hours
- Consider alternate day therapy for long-term use

Furosemide (continued)

Adverse Reactions/ Precautions:

Cardiovascular: orthostatic hypotension
Central nervous system: vertigo
Endocrine & metabolic: hypokalemia, hyponatremia, hypomagnesemia, hypocalcemia, hyperglycemia, hypochloremia, alkalosis
Hematologic: anemia, thrombocytopenia, agranulocytosis
Hepatic: ischemic hepatitis, jaundice
Otic: potentially ototoxic
Renal: nephrocalcinosis, hypercalciuria

Furosemide (continued)

**Mechanism of Action:** Inhibits reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule, interfering with the chloride-binding cotransport system. Causes major urinary losses of sodium, potassium, chloride, calcium and magnesium.¹

**Pharmacodynamics:**
- Peak effect: IV is 1 to 3 hours
- Duration: Approximately 6 hours
- Half-life: may be as long as 67 hours in the most preterm infant²

Inhaled Nitric Oxide

**Therapeutic Category:** Selective pulmonary vasodilator

**Uses:** treatment of hypoxic respiratory failure associated with pulmonary hypertension in the term or near-term infant. Use in preterm infants is controversial. Do not use in infant dependent on right-to-left cardiac blood flow.

**Administration:**
Should be used only after optimal mechanical ventilation and surfactant use.

Begin at 20 ppm. Infants who respond begin to do so within 15 to 20 minutes. The iNO concentration is decreased slowly as oxygenation improves.

Inhaled Nitric Oxide (continued)

Adverse Reactions/Precautions:

Do not stop iNO abruptly as this can cause a worsening in oxygenation and increased pulmonary artery pressures.

Hematologic: methemoglobinemia and elevated NO2 levels at doses > 20 ppm, prolonged bleeding times.

Respiratory: pulmonary injury related to increased levels of nitrogen dioxide

**Inhaled Nitric Oxide (continued)**

**Mechanism of Action:** Selective pulmonary vasodilatation that decreases extrapulmonary right-to-left shunting. iNO binds to the heme component of guanyl cyclase leading to production of cyclic GMP, thus relaxing pulmonary vascular smooth muscle. iNO redirects blood from poorly aerated to better aerated air spaces improving oxygenation as well.

**Monitoring:**
Continuous oxygenation, blood pressure, and heart rate monitoring are needed.

Dexamethasone

**Therapeutic category:** Systemic corticosteroid, anti-inflammatory agent.

**Uses:** Anti-inflammatory used to facilitate extubation and improve lung function in neonates with BPD to facilitate ventilator weaning.

**Administration:**
DART trial protocol: 0.075 mg/kg per dose Q 12 hours for 3 days, 0.05 mg/kg per dose Q 12 hours for 3 days, 0.025 mg/kg per dose Q 12 hours for 2 days, and 0.01 mg/kg per dose Q 12 hours for 2 days. Slow IV push or PO

Dexamethasone (continued)

Adverse Reactions/Precautions:

- Cardiovascular: edema, hypertension
- Central nervous system: headache, vertigo, seizures,
- Dermatologic: skin atrophy
- Endocrine & Metabolic: glucose intolerance, hypokalemia, alkalosis
- Gastrointestinal: nausea, vomiting
- Ocular: Increased ocular pressure, glaucoma
- Other: psychomotor delay and behavioral problems

Dexamethasone (continued)

**Mechanism of Action:** “Stabilizes lysosomal and cell membranes, inhibits complement-induced granulocyte aggregation, improves integrity of alveolar-capillary barrier, inhibits prostaglandin and leukotriene production, rightward shifts oxygen-hemoglobin dissociation curve, increases surfactant production, decreases pulmonary edema, relaxes bronchospasm.”

Dexamethasone (continued)

**Pharmacodynamics:**
- Duration: 72 hours for metabolic effects

**Pharmacokinetics:**
- Metabolism: in the liver
- Elimination: in urine and bile

Patient care

- By one month of age, the infant has chronic pulmonary changes on chest x-ray and is declared as having chronic lung disease.

- Chronic Lung Disease is defined as a need for supplemental oxygen at:
  - 28 days of life
  - 36 weeks CGA
  - X-ray changes consistent with lung injury
By five weeks of age, the infant has weaned nicely from ventilator support with the assistance of the dexamethasone.

She is loaded with caffeine (previously discussed) and placed on a maintenance dose and extubated to SiPAP.

She was also placed on an albuterol metered dose trial, but showed no improvement and it was discontinued.
Albuterol

**Therapeutic Category:** Adrenergic Agonist Agent, antiasthmatic, beta$_2$-adrenergic agonist agent bronchodilator$^1$

**Usage:** Bronchodilation/ prevention and relief of bronchospasm. Treatment of hyperkalemia.$^{1,2}$

**Administration:**
- Bronchodilation: 0.1 to 0.5 mg/kg per dose Q2 to 6 hours by nebulizer.
- 1 MDI actuation per dose (approx. 0.1 mg or 100 mcg) Q2 to 6 hours via MDI.
- Oral: 0.1 to 0.3 mg/kg per dose Q6-8 hours PO.
- Treatment of hyperkalemia: 0.4 mg/kg per dose q 2hours via nebulizer.$^2$

Albuterol (continued)

Adverse Reactions/Precautions:
- Cardiovascular: tachycardia, arrhythmias, palpations, hypertension
- Central Nervous System: irritable behavior, hyperactivity, insomnia
- Dermatologic: angioedema, urticaria
- Endocrine & metabolic: hypokalemia
- GI: nausea, vomiting, unusual taste, hoarseness with inhalation only
- GU: Dysuria
- Neuromuscular & skeletal: tremor, weakness, muscle cramping
- Respiratory: irritation of oropharynx, coughing

Albuterol (continued)

**Mechanism of Action:** Relaxes bronchial smooth muscle by action on specific beta$_2$-adrenergic receptors with little effect on heart rate.

**Pharmacodynamics:**
- Nebulization/oral inhalation:
  - Peak bronchodilation: 0.5 to 2 hours nebulization
  - Duration: 2 to 5 hours
- Oral:
  - Onset of action: 30 minutes
  - Duration: 4 to 8 hours
  - Peak serum concentration: 3 to 4 hours

Albuterol (continued)

**Pharmacokinetics:** (adult)

Metabolism: by the liver
Half-life:
  - Oral: 2.7-5 hours
  - Inhalation 3.8 hours
Elimination: 30% appears in urine as unchanged drug

Patient Care Continued

- At two months of age, off the dexamethasone, the infant’s FiO2 requirement is increasing and her CO2 is climbing, so the parents agree to a second shorter course of dexamethasone (previously discussed). She is also trialed on a fluticasone inhaler with nystatin prophylaxis.
Fluticasone Inhaler

Therapeutic Category: Adrenal corticosteroid; anti-inflammatory agent; corticosteroid, inhalant

Usages: Long-term chronic control of persistent bronchial asthma: not indicated for relief of acute bronchospasm.

Administration:
Oral inhalation:
Initial: 88 mcg twice daily- maximum dosage
  Swab mouth with nystatin after inhalation to decrease chance of oral candidiasis.

Fluticasone Inhaler (continued)

**Adverse Reactions/Precautions:**

Central Nervous System: dizziness, fatigue, fever, headache, insomnia

Dermatologic: angioedema, facial edema, rash, urticaria

Endocrine & metabolic: Cushing’s syndrome, growth suppression, hyperglycemia, reduction of growth velocity

GI: diarrhea, nausea, vomiting

Local: Burning, irritation, growth of Candia in mouth, nares or throat

Neuromuscular & skeletal: decreased bone density, osteoporosis

Ocular: cataracts, glaucoma, IOP increased

Respiratory: congestion, nasal discharge, respiratory infection

Miscellaneous: rare anaphylactic reaction

Mechanism of Action: “Controls the rate of protein synthesis, depresses the migration of polymorphonuclear leukocytes and fibroblasts, reverses capillary permeability, and stabilizes lysosomal membranes at the cellular level to prevent or control inflammation.”

Pharmacodynamics:
- Oral inhalation: effects due to local rather than systemic absorption
- Onset of action: variable
- Maximum effect: 1-2 weeks
- Duration after discontinuation: several days

Nystatin

**Therapeutic Category:** Antifungal agent

**Usages:** Treatment of mucocutaneous candidal infections. Prophylaxis against fungal infections in high risk infants.

**Administration:**
- **Topical:** apply ointment or cream to affected area Q6hours. Continue to treat for 3 days after symptoms subside.
- **PO:** 1 ml (preterm) to 2 mL (term) of 100,000 units/mL suspension divided and applied with swab to each side of mouth Q6 hours. Continue to treat for 3 days after symptoms subside.
- **Prophylaxis:** 1 ml of 100,000 units/mL suspension orally or instilled into stomach via oro/nasogastric tube 3 times per day.


Nystatin (continued)

**Adverse Reactions/Precautions:**
- Dermatologic: contact dermatitis, pruritus, rash
- GI: Nausea, vomiting, diarrhea
- Local: irritation, burning, pain

**Mechanism of action:**
Changes the cell wall of the fungal cell membrane by binding to sterols thus allowing for leakage of cellular contents

**Pharmacodynamics:** relief within 24-72 hours

**Pharmacokinetics:**
- Absorption: poorly GI, not absorbed through mucous membranes
- Elimination: in feces unchanged

At 2 ½ months of age, the infant had a setback due to apnea and bradycardia requiring SiPAP. She gradually improved and weaned to a high flow nasal cannula. She was trialed on chlorothiazide, but had no marked improvement with a significant metabolic alkalosis and the drug was discontinued.
Chlorothiazide

**Therapeutic Category:** Antihypertensive agent, diuretic, thiazide

**Usage:**
Treatment of mild to moderate edema and mild to moderate hypertension. May improve pulmonary function in patients with BPD.

**Administration:**
Diuresis: 10 to 20 mg/kg/dose Q 12 hours PO

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Chlorothiazide (continued)

**Adverse Reactions/ Precautions:**

- Cardiovascular: hypotension, arrhythmia
- CNS: dizziness, vertigo
- Dermatologic: rash, photosensitivity
- Endocrine & Metabolic: hypokalemia, hyperglycemia, hypochloremic alkalosis, hyperlipidemia, hypomagnesemia
- GI: nausea, vomiting, diarrhea, cramping
- GU: hematuria
- Renal: interstitial nephritis, renal failure
- Respiratory: pulmonary edema

Chlorothiazide (continued)

**Mechanism of Action:** “Inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium, chloride, potassium, bicarbonate, magnesium, phosphate, calcium (transiently) and water.”

**Pharmacodynamics:**
- Diuresis: oral–within 2 hours
- Duration: oral–6-12 hours

**Pharmacokinetics:**
- Absorption: poor
- Half-life: about 5 hours
- Elimination: excreted unchanged in urine

Patient Care Continued

- At 3 months of age the infant had gradually weaned to a low flow nasal cannula and plans were put into place for discharge.
- A Pediatric pulmonary consult was obtained.
- The infant was discharged on home oxygen, flow 0.4 lpm and FiO2 100%, and a home monitor.
Patient Care Continued

- Discharge Medications included:
  - Fluticasone – inhaler
  - Nystatin oral

(previously discussed)

Thank you for participating in this continuing education activity.