THE NOTION BEHIND NEONATE DOSING

Eric Okazaki, Pharm.D.
PGY-1 Pharmacy Resident
St. Alphonsus Regional Medical Center
ISHP Fall Conference 2014

Introduction:
Why do we do the things we do?
Introduction

- Standard concentrations
- Separate medications
- Label medications
- Double Checks

Goal

- Provide information that will enhance the thought process (generate questions) for each action.

<table>
<thead>
<tr>
<th>Event</th>
<th>Guidelines</th>
<th>Action</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication ordered</td>
<td>ISMP, JACHO, Policies and Procedures act as guides</td>
<td>Carry out the action according to guidelines</td>
<td>Patient Safety</td>
</tr>
</tbody>
</table>
Goal

- Provide information that will enhance the thought process (generate questions) for each action.

- Event
  - Medication ordered

- Guidelines
  - ISMP, JACCHO, Polices and Procedures to provide direction

- Thought
  - Understand the WHY behind the directions

- Action
  - Carry out the action understanding the guidelines

- Result
  - Enhanced Patient Safety

Objectives

- CONCEPT:
  Explain the basics principles that describe how the body handles medication when it enters the body (ADME properties).

- CONCEPT:
  Point out the differences between neonate and adult physiology.

- APPLY:
  Use these concepts to review medications used in the Neonatal Intensive Care Unit.

- DISCUSS:
  Review how these concepts will allow us to question/think about our actions—improve results (patient safety)
Concept: ADME

Pharmacokinetics: The timeline of events that represents the manner in which the body deals with medications.

Explained in 4 steps: **ADME properties**

(A): **Absorption**—Getting the drug into the body

(D): **Distribution**—Getting the drug to its action site

(M): **Metabolism**—Breaking down the drug into metabolites

(E): **Excretion**—Removing the drug and its metabolites
Concept: ADME

Absorption: The process by which the drug gets into the body and into circulation.

- Oral Route = Mouth, Stomach, Intestine
- Topical Route = layers of the skin
- Rectal Route = lower 2/3 of rectum
- IV Route = immediate

Image from: [www.paradoja7.com](http://www.paradoja7.com/human-circulatory-system-pictures/human-circulatory-system-pictures/)

Concept: ADME

Distribution: The process by which the drug gets to its sites of activity in the body.

- Properties of the drug determine where it can and cannot “spread”
  - Hydrophilic, lipophilic, protein bound, molecule size, charge, etc.
  - $V_d = $ Volume drug distributes in body

- Drug properties stay constant, our bodies are different

Image from: [www.paradoja7.com](http://www.paradoja7.com/human-circulatory-system-pictures/human-circulatory-system-pictures/)
Concept: ADME

Metabolism: The process by which the drug is broken down in the body.

- Phase I and II enzymes break down drugs in preparation for excretion from the body.
- Original form of the drug is altered into a metabolite which may or may not be active.
- Not all drugs are metabolized in the body.

Excretion: The process by which the body removes the drug.

- The drug and the metabolites are removed from the body usually as urine or feces.
- Not everything is completely removed.
Neonates are not small adults, they are not small children, their bodies are different: *Human growth is not a linear process!*

- Physiological changes occur dynamically
  - Hours: cardiopulmonary physiology
  - Weeks: renal/hepatic function
  - Months: gastric function
  - Years: musculoskeletal development

*These changes impact ADME properties!*

**Concept: Physiology + ADME**

**Absorption: Getting the drug into the body**

**GI tract**
- Reduced acid production, less acidic
- GI emptying is irregular
- Gastro-esophageal reflux
- Splanchnic blood flow decreased
- Longer GI absorption times in neonates
- Increased rectal absorption (hepatic/contractions)

**Topical**
- Greater hydration, greater perfusion of the skin
- Greater surface area: mass ratio

**Intramuscular**
- Less skeletal muscle blood flow

**Intravenous**
- Vein size, irritability, concentrations, location
Concept: Physiology + ADME

Distribution: Getting the drug into the body

- Neonates have greater extracellular and total body water spaces
- Greater body water composition
- Limited volume requirements
- Less plasma proteins (i.e. albumin)
- Increased endogenous substances (i.e. bilirubin)
- Greater BSA: Mass ratio
- Less lean mass

Concept: Physiology + ADME

Metabolism: Breaking down the drug into metabolites

- Phase I and II enzymes are rapidly changing:
  - CYP3A7 enzyme predominant in fetal liver
  - CYP2E1 surges hours after birth
  - CYP2C9 and CYP2C19 appear at 1 week
  - CYP1A2 is a late bloomer at 1-3 months
  - Glucuronidation is decreased

  ...and many more

* Hepatic metabolism is increased in ages < 10 years compared to adults
Concept: Physiology + ADME

Excretion: Removing the drug and its metabolites

- Nephrogenesis occurs between 9 – 36 weeks
- Filtration: Low renal blood flow (5-6%, adult 15-25%)
- Tubular reabsorption: Less in neonates
- Tubular secretion: Greater in neonates

<table>
<thead>
<tr>
<th>Age</th>
<th>Creatinine clearance (mL/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterms</td>
<td>5-10</td>
</tr>
<tr>
<td>1-2 weeks preterms</td>
<td>10-12</td>
</tr>
<tr>
<td>Neonates</td>
<td>10-15</td>
</tr>
<tr>
<td>1-2 weeks of age</td>
<td>20-30</td>
</tr>
<tr>
<td>6 months</td>
<td>73</td>
</tr>
<tr>
<td>Adults</td>
<td>73</td>
</tr>
</tbody>
</table>

Image from: [http://classes.midlandstech.edu/carterp/Courses/bio211/chap25/chap25.htm](http://classes.midlandstech.edu/carterp/Courses/bio211/chap25/chap25.htm)

Concept: Physiology + ADME

- Gastric Function
- Integument
- Body Composition
- Metabolic Function
- Renal Function
Examples: Absorption

Lidocaine/Prilocaine (EMLA)  
(Topical Absorption)

**Caution:** EMLA dosing is restricted by age (<37 weeks) and weight, systemic toxicity

**Reason:**
* Neonates (preterm) absorption is improved
* BSA to weight ratio
* Metabolism (CYP3A4)


Examples: Distribution/Metabolism

Ceftriaxone  
($V_d$ and Metabolism)

**Caution:** Hyperbilirubinemia, risk of kernicterus, and calcium interaction

**Reason:**
* Increased bilirubin levels
* Decreased plasma proteins
* Displacement of bilirubin
* Decreased UGT metabolism

Examples: Metabolism

Caffeine Citrate
(Metabolism)

**Caution:** Used in apnea of prematurity, delayed onset of side effects

**Reason:**
* Metabolism by CYP1A2
* Longer half-life, renal excretion

---

Examples: Metabolism

Benzyl Alcohol
(Metabolism)

**Caution:** “Gasping Syndrome”

**Reason:**
* Multiple items may contain benzyl alcohol
* Glycine-conjugation
* 99 mg/kg
Examples: Excretion

Gentamicin
(Excretion)

<table>
<thead>
<tr>
<th>PMA (weeks)</th>
<th>Postnatal (days)</th>
<th>Dose (mg/kg)</th>
<th>Interval (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 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>

Caution: Dosing needs to be adjusted per changes in renal function

Reason: * Body water distribution
* Improving renal function

ADME “CASE”

Lasix (furosemide) is a diuretic used in the neonate population. Tertiary medication resources caution its use in neonates <32 weeks due to accumulation and variable availability in the body. What is actually happening?

* ECW 44.5% in neonates, 18.7% in 10-15 yo
* ECW at (Day 1): 1,473 mL, (Day 2): 516 mL
* Binding to albumin
* Metabolized into inactive metabolites
* GFR 2-4 ml/min in neonate, 120 ml/min in adults
* Renal tubule function
How does this Apply?

• What does this mean in the community setting?

• What does this mean in the hospital setting?

• What does it impact?
  • Drug delivery
  • Pulling of stock
  • Medication preparation
  • Product labeling
  • Double check

Recap:

• The body’s ability to absorb, distribute, metabolize, and excrete a drug is based on the patient’s physiology

• Most drugs are prepared and studied for use based on adult physiology

• Dosing for neonates is not based on a straight linear percent reduction of the adult dose

• Knowing the differences in physiology can help us utilize ADME principles to deliver appropriate neonate dosages
Recap:

- Not all doses are going to be smaller than adults
- Notice the route
- Notice the formulations
- Notice the volumes
- Notice the concentrations
- Notice the decimals
- **ASK QUESTIONS!**

Remember…

Understand why, ask questions…

...Become a Puppet-master!

**What questions do you have?**
References: