Are Pediatric Patients Small Adults?

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Goals and Objectives

- Understand the history and evolution of pediatric dosing and labeling
- Understand the pharmacokinetics and pharmacodynamics of pediatric patients
- Explain how to appropriately dose pediatric medications

Background

- In 1991, about 81% of medications lacked dosing information for children
- Medication errors are more common in pediatric patients than in adults
- USP MedMarx® data of 2006-2007
  - 2.5% of pediatric medication errors resulted in patient harm
Why the pediatric knowledge gap?
- There was a belief that dosing could be calculated using body weight
- Conducting pediatric trials can be difficult
- There was a lack of pediatric legislation to incentivize drug companies to conduct pediatric trials

Impact of the pediatric knowledge gap
- Children are excluded from receiving potential lifesaving therapies
- Children receiving unapproved drugs based on adult studies resulting in negative outcomes
  - Example
    Chloramphenicol

Closing the Gap
"Over the past 15 years, we have evolved from a view that we must protect children from research to a view that we must protect children through research."
- Michelle Roth-Cline, MD PhD
## Regulation and Legislation

<table>
<thead>
<tr>
<th>Year</th>
<th>Regulation/Legislation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>Product labels include pediatric use section</td>
<td>Packaged insert pediatric section</td>
</tr>
<tr>
<td>1994</td>
<td>Pediatric Use Labeling Rule</td>
<td>Allowed labeling based on extrapolation of studies from adults; Required manufacturers of new drugs to conduct pediatric studies</td>
</tr>
<tr>
<td>1997</td>
<td>FDA Modernization Act (FDAMA)</td>
<td>Offered financial incentive for pharmaceutical companies to conduct pediatric studies</td>
</tr>
<tr>
<td>2002</td>
<td>Best Pharmaceutical for Children Act (BPCA)</td>
<td>Encouraged more studies in children; Promoted the development of treatments for children; Provided incentive for drug companies</td>
</tr>
<tr>
<td>2003</td>
<td>Pediatric Research Equity Act (PREA)</td>
<td>Required drug companies to study their products in children under certain circumstances; Drugs and biologics are included</td>
</tr>
</tbody>
</table>

### 2007 - Food and Drug Administration Amendment Act (FDAAA)

- Established Pediatric Review Committee (PeRC)
- Required
  - Development of age-appropriate formulation
  - New labeling mandates
  - Post-marketing safety reporting

### 2012 - Food and Drug Administration Safety and Innovations Act (FDASIA)

- Required
  - Sponsors to submit pediatric plans at end of Phase 2
  - Inclusion of neonates (birth-28 days)
- Allows
  - Extensions for deferred studies
  - Priority review for rare pediatric diseases
“There have been more studies conducted in children in the last five years than in the previous 30 years combined.”
-Ralph Kauffman, MD, Director of medical research at Children’s Mercy Hospital in Kansas City, MO.

Age Ranges of Pediatric Subgroups

<table>
<thead>
<tr>
<th>Pediatric subgroup</th>
<th>Approximate age range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn (Neonate)</td>
<td>Birth to 28 days of age</td>
</tr>
<tr>
<td>Infant</td>
<td>1 month to 2 years of age</td>
</tr>
<tr>
<td>Child</td>
<td>2 years to 12 years of age</td>
</tr>
<tr>
<td>Adolescent</td>
<td>12 years to 16-21 years of age</td>
</tr>
</tbody>
</table>

Pharmacokinetics
Pharmacokinetics is what the body does to the drug

- ABSORPTION
- DISTRIBUTION
- METABOLISM
- ELIMINATION
Absorption: Gastric pH

- Neonatal period the gastric pH is basic
  - Neonatal 6-8
  - Adult 2-3
- Gastric acid production reaches adult values around 3 years of age

<table>
<thead>
<tr>
<th>Implications for drug therapy</th>
<th>Drug example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased absorption of basic drugs</td>
<td>Codeine</td>
</tr>
<tr>
<td>Increased absorption of acid-labile drugs</td>
<td>Penicillin G, Erythromycin, Amoxicillin</td>
</tr>
<tr>
<td>Decreased absorption of weak acidic drugs</td>
<td>Phenytoin, Phenobarbital</td>
</tr>
</tbody>
</table>

Absorption: Gastric Emptying

- Gastric emptying time is prolonged
  - Longer Time to Cmax
  - Inconsistent or slower absorption
  - Reaches adult function by 7-9 months of age
- Gastroesophageal reflux (GER)
  - May provide greater gastric volume of liquid available for reflux
  - No data to prove this yet

Absorption: Intramuscular

- Neonates
  - Reduced muscle mass, contractions, and oxygenation
  - Unpredictable absorption
- Infant, child, and adolescent: IM drugs are well absorbed due to increase in muscle mass
Absorption: Percutaneous

- Increased skin hydration
- Thinner stratum corneum
- Larger body surface area

- Creams have a higher absorption than ointments

Absorption: Rectal

- Effective in older infants and children
- Good alternative for patients with nausea, vomiting, seizures, or unable to tolerate oral medications

Body Composition

- Greater total body water
- Greater extracellular fluid volume
  - Larger volume of distribution for hydrophilic drugs requiring larger doses
- Less adipose tissue
  - Smaller volume of distribution for lipophilic drugs requiring smaller doses


Changes in body composition with growth and aging

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Hydrophilic Drugs</th>
<th>Lipophilic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Neomycin</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Phlebotomy</td>
<td>Propofol</td>
<td>Phenobarbital</td>
</tr>
</tbody>
</table>

Examples of hydrophilic drugs:
- Aminoglycosides
- Vancomycin
- Linezolid
- Phenobarbital

Examples of lipophilic drugs:
- Diazepam
- Propofol
- Phlebotomy

VS

Protein Binding

- Decreased albumin and α1-acid glycoprotein
  - Adult values by 10-12 months of age
- Lower binding capacity
  - Adult-like binding by 3-6 months of age
- Competitive binding by endogenous substances
- Risk of hyperbilirubinemia

Protein Binding

<table>
<thead>
<tr>
<th>Implications for drug therapy</th>
<th>Drug examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased free fraction of drug and enhanced pharmacological effects</td>
<td>Beta-lactam antibiotics, Warfarin, Digoxin, Phenytoin</td>
</tr>
<tr>
<td>Enhanced displacement leading to hyperbilirubinemia</td>
<td>Sulfamethoxazole (high affinity)</td>
</tr>
</tbody>
</table>

Membrane Permeability

- Blood-brain barrier (BBB) is not fully mature and drugs may gain access to the central nervous system and cause toxicity

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<th>Drug examples</th>
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</thead>
<tbody>
<tr>
<td>Low CNS penetration in adults</td>
<td>Amphotericin, Gentamicin, Clindamycin, Cefazolin</td>
</tr>
<tr>
<td>High CNS penetration in adults</td>
<td>Caffeine, Cefazoline, Ceftriaxone, Imipenem, Acyclovir</td>
</tr>
</tbody>
</table>
Metabolism

- Infants metabolize drugs slower than adult
- **Phase I Reactions**
  - Oxidation, reduction, hydrolysis, and hydroxylation
  - Cytochrome P450 reaches adult values by 10 years of age
- **Phase II Reactions**
  - Glucuronidation, sulfation, methylation, and acetylation
    - Glucuronidation starts ~2 months of age

Drug Elimination

- **Renal elimination increases with maturity**
  - Decreased renal blood flow
- **Tubular secretion**
  - Lower at birth
- **Schwartz equation**
  - Estimates GFR in pediatric patients
  - Cockcroft and Gault equation recommended for 18 and older

<table>
<thead>
<tr>
<th>Age</th>
<th>Creatinine Clearance (mL/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>5-10</td>
</tr>
<tr>
<td>1-2 weeks preterm</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>

GFR = k x height (cm) x serum creatinine

Outdated Formulas Don’t Use

- **Young’s rule (children 1-12 years of age)**
  \[(\text{age in years}) \times (\text{adult dose}) / (\text{age} + 12)\]

- **Clark’s rule (infants and children)**
  \[(\text{Weight in pounds}) \times (\text{adult dose}) / 150\]
Dose According to Body Weight

- Kilograms should be the standard nomenclature for weight
  - Prescriptions
  - Medical records
  - Staff communication

- Do an independent double check when converting weight
  - 1 kg = 2.2 lbs.

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Dose According to Body Weight

- Weigh patient at admission
  - Including outpatient settings
  - Within four hours of an emergency situation

- As a final double check ask the parent for the weight and age of the patient

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Prescriptions

- Require prescriber to include
  - Calculated dose and the dosing determination to facilitate an independent double-check
  - Weight in kilograms
  - Indication
  - Duration
  - Concentration of medication (mg/mL)
Prescriptions

- Pay close attention to dosing
  - Often expressed as mg/kg/day or mg/kg/dose
- Orders written in “mg” preferred than “mL”
  - Double check units
  - Milligrams may facilitate the double checking of the pharmacist
  - Milliliters on the labeling may facilitate the administration by the parent/caregiver

Choosing the Correct Medication

- Medications are available in multiple concentrations
  - Separate concentrated adult medications from pediatric medications
- Dosing varies by indication
  - Clarify with prescriber diagnostic information if not provided
  - When looking up resources make sure to choose the right diagnosis
- Different formulations
  - Tablet vs liquid
  - Cream vs ointment

Appropriate Dosing

- Appropriate devices for liquid administration
  - Dosing Cup
  - Oral syringe with colored cap
  - Medicine dropper
  - Dosing spoons
  - Oral dosing syringe for infants


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Dose Calculation Steps

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<tr>
<th>Step</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Convert pounds to kg</td>
</tr>
<tr>
<td>Step 2</td>
<td>Drug reference</td>
</tr>
<tr>
<td>Step 3</td>
<td>Calculate independent dose</td>
</tr>
<tr>
<td>Step 4</td>
<td>Compare prescribed dose to calculated dose</td>
</tr>
</tbody>
</table>

* Contact prescriber if clarification needed

Step 1

- Convert pounds to kg
  - 2.2 lbs. = 1 kg
  - 24 lbs. = 2.2 lbs. = 10.909 kg
  - \( \frac{X \text{ kg}}{1 \text{ kg}} \) = 10.909

Step 2

- Drug reference
  - Micromedex
  - NeoFax
  - Clinical Pharmacology
  - Lexicomp
  - Mosby’s Pediatric Drug Consult
Step 3
- Calculate dose
  - Dose may vary depending on indication
  - Maximum doses might be expressed as per day or per dose

Step 4
- Compare to prescribed dose
  - Is prescription written mg/kg/dose or mg/kg/day
  - Is prescription written in mg or mL

Step 5
- Contact prescriber to clarify, if needed
  - Dose
  - Duration
  - Dosing intervals
  - Indication
  - Concentration
  - Age and weight if the parent/caregiver does not know
Example of an Incomplete Prescription

Step 1: Convert pounds to kg
22 lb x 1 kg/2.2 lb = 10 kg

Step 2: Drug reference
For 8.2 kg to 10.8 kg: 75 mg/dose
May repeat every 6-8 hours
(Maximum 4 doses/day)

Step 3: Calculate dose
75 mg/dose x 4 doses/day = 300 mg/day

Step 4: Compare the prescribed order
10 kg x 30 mg/kg = 300 mg/day

Contact provider to clarify, if needed
- Clarify with prescriber:
  - Per day or per dose
  - Concentration
  - Infant vs children Motrin
  - Duration of treatment

Change to mL
75 mg = 50 mg = 1.875 mL per dose
1.25 mL

Example of a Complete Prescription

<table>
<thead>
<tr>
<th>Patient name</th>
<th>John Doe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td>Miami, FL</td>
</tr>
<tr>
<td>Date</td>
<td>01-01-15</td>
</tr>
<tr>
<td>Rx</td>
<td>MoXm1n1n</td>
</tr>
</tbody>
</table>
Example of a Complete Prescription

<table>
<thead>
<tr>
<th>Step</th>
<th>Function</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1:</td>
<td>Convert pounds to kg</td>
<td>11.5 kg</td>
</tr>
<tr>
<td>Step 2:</td>
<td>Drug reference</td>
<td>80—90 mg/kg/day PO in divided doses every 12 hours</td>
</tr>
<tr>
<td>Step 3:</td>
<td>Calculate the dose</td>
<td>$11.5 \text{ kg} \times 80 \text{ mg/kg/day} = 920 \text{ mg/day}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$11.5 \text{ kg} \times 90 \text{ mg/kg/day} = 1035 \text{ mg/day}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum 875 mg/dose if given every 12 hours</td>
</tr>
<tr>
<td>Step 4:</td>
<td>Compare the prescribed order</td>
<td>1035 mg/day $+ 2 \text{ (BID)} = 517.5 \text{ mg/dose BID}$</td>
</tr>
<tr>
<td>Contact prescriber to clarify, if needed</td>
<td>No need to clarify</td>
<td></td>
</tr>
<tr>
<td>Change to mL</td>
<td>517.5 mg = 400 mg = 6.468 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5 mL every 12 hours</td>
<td></td>
</tr>
</tbody>
</table>

OTC Example

A parent approaches you and asks for help on how much Tylenol® to give their 3 year old son:
- 25 lbs.
- Experiencing fever

| Step 1: | Convert pounds to kg | 11.363 kg |
| Step 2: | Drug reference | 10 to 15 mg/kg/dose PO every 4 to 6 hours. Max single dose 15 mg/kg/dose Max daily dose 75 mg/kg/day |
| Step 3: | Calculate dose | $11.363 \text{ kg} \times 10 \text{ mg/kg/dose} = 113.63 \text{ mg}$ |
| | | $11.363 \text{ kg} \times 15 \text{ mg/kg/dose} = 170.45 \text{ mg}$ |
| | | Max single dose = 170.45 mg |
| | | Max daily dose = 852.225 mg |
| Step 4: | Compare the prescribed order | N/A |
| Change to mL | Available: 160 mg/5 mL |
| | You can recommend 12 mg/kg/dose every 4 to 6 hours. |
| | $11.363 \text{ kg} \times 12 \text{ mg/kg/dose} = 136.356 \text{ mg}$ |
| | Maximum daily dose = 818.136 mg |
| | $136.356 \text{ mg} = 100 \text{ mg} = 4.26 \text{ mL per dose}$ |
| | $4.26 \text{ mL} = 4 \text{ mL} = 20 \text{ mL every 4-6 hours as needed for pain}$ |
Conclusion

- Legislation and regulation have helped decrease the pediatric knowledge gap by encouraging and requiring studies in pediatric patients
- The pharmacokinetic and pharmacodynamics processes are not at the adult capacity in pediatrics and they must be considered when dosing
- When calculating a pediatric dose, it is important to know the requirements of a prescription, and the steps for calculating a dose

Pediatric patients are not just small adults

Quiz: Question #1

True or False

Historically, approximately 81% of listed medication labels lacked dosing information for children.
Quiz: Question #2

True or False

The Cockcroft and Gault equation can be used to estimate clearance in patients 16 years and older.

Quiz: Question #3

True or False

In pediatric patients, it is appropriate to dose medications based on patient’s weight in pounds.