When Patients Outweigh the Mold: Pharmacotherapy in Pediatric Obesity

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Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.
Objectives

1. Interpret literature on pharmacokinetic alterations & specific dose adjustment tools in the obese population
2. Justify drug dosing for common & high-risk medications in overweight/obese pediatric patients
3. Evaluate dosing strategies for common agents used as continuous infusions
Background
Pediatric Obesity

• Definitions:

<table>
<thead>
<tr>
<th>BMI Percentile</th>
<th>CDC Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 85th</td>
<td>Healthy weight</td>
</tr>
<tr>
<td>85th - 94th</td>
<td>Overweight</td>
</tr>
<tr>
<td>≥ 95th</td>
<td>Obese</td>
</tr>
</tbody>
</table>

• Prevalence:
  - 17% of 2-19 years obese (2011-2014)
  - No significant difference between 2005-2006 & 2013-2014


## In-Patient Obese Admissions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%) or Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>1448 (50.9)</td>
</tr>
<tr>
<td>TCH Admissions</td>
<td>2010 (70.7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.8 ± 4.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.2 ± 31.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>134.7 ± 28.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 ± 7.1</td>
</tr>
<tr>
<td>BMI percentile</td>
<td>98.0 ± 7.1</td>
</tr>
</tbody>
</table>

2844 (18.8%) 15,119 admissions 2-17 years

TCH = Texas Children’s Hospital  
BMI = Body mass index

Top 25 Medications (n=28,234)

- Sedatives and analgesics: 36.0%
- Corticosteroids: 12.0%
- Gastrointestinal: 20.0%
- Antibiotics: 20.0%
- Other: 12.0%
PK Alterations in Obesity

• Distribution:
  - $\uparrow Vd_{ss}$ for lipophillic medications
  - $\downarrow Vd_{ss}$ for hydrophillic medications

• Excretion:
  - $\uparrow$ kidney size
  - $\uparrow$ glomerular filtration rate

$Vd_{ss} = \text{Volume distribution at steady state}$

Pro/Con Debate #1: Weight-based dosing adjustments
Pediatric Pharmacists should routinely use weight-based dosing adjustments.

A  TRUE
B  FALSE
Dose Adjustment Tools:

We should use drug adjustment tools
Dosing Strategies

- Continuous infusion dosing:
  - Fixed-dose (mcg/hr)
  - Weight-based dosing (mcg/kg/hr)

- Weight-based dosing:
  - Total body weight (TBW)
  - Body surface area (BSA)
  - Ideal body weight (IBW)
  - Adjusted body weight (ABW)
  - Lean body mass (LBM)

Body Composition

- **TBW = FM and FFM**
- **Fat-free mass:**
  - Consists of muscle, bone, vital organs, & ECF
  - Free-fat mass differs from LBM:
    - Lipids in CNS & bone marrow contained in LBM not FFM
    - Differences NOT appreciable
    - FFM interchangeable with LBM


- FM = Fat mass
- FFM = Free fat mass
- ECF = Extracellular fluid
- LBM = Lean body mass
## Body Composition Comparison

<table>
<thead>
<tr>
<th>Factor</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obese</td>
<td>Controls</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.3 ± 18.2</td>
<td>40.1 ± 12.1</td>
</tr>
<tr>
<td>Total body water (L)</td>
<td>29.7 ± 7.2</td>
<td>24.4 ± 8.5</td>
</tr>
<tr>
<td>Body volume (L)</td>
<td>65.0 ± 18.4</td>
<td>38.2 ± 11.4</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>26.3 ± 10.1</td>
<td>7.7 ± 3.6</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>39.0 ± 10.0</td>
<td>32.4 ± 11.4</td>
</tr>
<tr>
<td>FFM hydration (%)</td>
<td>76.5 ± 1.8</td>
<td>75.3 ± 1.7</td>
</tr>
</tbody>
</table>

↑ volume, & FFM adjusting for age, sex, & height (p <0.0001)

TBW = Total body water
FM = Fat mass
FFM = Free fat mass

Dosing Considerations

• ↓ Percentage of lean tissue per TBW (kg)
• 30% ↓ in water content in adipose tissue
• Therapeutic alterations:
  - Altered concentrations
  - ↑ or ↓ efficacy
• Alterations in dosing:

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Hydrophilic</th>
<th>Lipophilic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose</td>
<td>↓ per TBW (kg)</td>
<td>↑ per TBW (kg)</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>↓ per TBW (kg)</td>
<td>↓ per TBW (kg)</td>
</tr>
</tbody>
</table>

### Types of Weight-Based Adjustments

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBW</td>
<td>Reflective of indirect assessment of LBM</td>
<td>(50% BMI for age) x (height in m²)</td>
</tr>
<tr>
<td>ABW</td>
<td>Reflective of LBM plus proportion of excess mass determined by cofactor</td>
<td>IBW + Pre-specified cofactor x (TBW – IBW)</td>
</tr>
<tr>
<td>LBM</td>
<td>Estimation of lean tissue mass minus adipose tissue</td>
<td>• LBM = IBW + 0.29 (TBW – IBW)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FFM (male) = ( \frac{9.27 \times 10^3 \times TBW}{6.68 \times 10^3 + [216 \times BMI]} )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FFM (female) = ( \frac{9.27 \times 10^3 \times TBW}{8.78 \times 10^3 + [244 \times BMI]} )</td>
</tr>
</tbody>
</table>

IBW = Ideal body weight  
ABW = Adjusted body weight  
LBM = Lean body mass  

Summary Pro: Use Adjustments

- Obese kids have altered body composition
- Weight-based dosing may lead to ↑ adverse events
- Utilize weight-based adjustments:
  - Validated approaches
  - Work in obese adults
Dose Adjustment Tools:
We should NOT use drug adjustment tools
Summary Con: Don’t Use Adjustments

- Outcomes
- Therapeutic Drug Monitoring
- Technology Limitations
Patient Outcomes

- No clear data on improved patient outcomes when adjusting medications for body habitus.

- Propofol use in morbidly obese pediatric patients
  - Patients required a lower dose for sedation

- Esophagogastroduodenoscopy, colonoscopy, or both
  - Airway obstruction (1%), cough (0.9%), and laryngospasm (0.6%).
  - 5 years old or younger, American Society of Anaesthesiologists greater than or equal to 2, esophagogastroduodenoscopy ± colonoscopy, and coexisting medical conditions of obesity and lower airway disease were independent predictors of higher adverse event

- TNA surgery
  - Weight < 14 kg (underweight) associated with complications

Top 25 Medications (n=28,234)

- Sedatives and analgesics: 36.0%
- Corticosteroids: 12.0%
- Gastrointestinal: 12.0%
- Antibiotics: 20.0%
- Other: 20.0%

Therapeutic Drug Monitoring

- Vancomycin
  - Obese (6.9 ± 4.30 μg/mL) versus nonobese children (4.8 ± 3.08 μg/mL; P = 0.052)

- Aminoglycosides
  - Higher values in obese pediatric patients
  - Monitoring is standard anyway
  - Dose limits and prescribing practices saw no differences

Therapeutic Drug Monitoring

- What about drugs with no monitoring?
  - Corticosteroids
  - Gastrointestinal medications
  - Analgesic / Sedative medications

- Risk versus Benefit

- Overdosing vs underdosing
# Technology Limitations

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<tr>
<td>LBM</td>
<td>Estimation of lean tissue mass minus adipose tissue</td>
<td><img src="#" alt="LBM calculation equations" /></td>
</tr>
</tbody>
</table>

Which one do you use?

Seriously, who is going to calculate this?

---

IBW = Ideal body weight  
ABW = Adjusted body weight  
LBM = Lean body mass

Summary **Con**: Don’t Use Adjustments

- No data suggest improved outcome
- Obesity doesn’t always mean reduce the dose
- Calculations are labor intensive and have not had clinical evaluation
- Current guidelines prevent errors
Pediatric Pharmacists should routinely use weight-based dosing adjustments.

A  TRUE
B  FALSE
Pro/Con Debate #2: Dosing for high-risk meds (anti-coagulants)
Patient Case #1

- 9 year-old Male (68 kg; 147 cm) admitted for multiple bowel perforations:
  - Ulcerative colitis
  - Obesity (99th percentile for age, height, gender)
- HD 1: Transferred to PICU
- HD 12:
  - Abdominal ultrasound revealed portal vein thrombosis
  - Normal renal function

What dose of SQ enoxaparin should be used?

HD = Hospital day
Dosing Controversies for High-Risk Medications:

We *should* make empiric dose adjustments for anti-coagulants
Summary **Pro**: Use An Adjustment

- **Unfractionated Heparin**
  - Lower doses required in obese patients
  - Initial Doses: 17.4 vs 20.2 U/kg/hour; $P = 0.013$
  - Maintenance dose: 19.1 vs 24.3 U/kg/hour; $P = 0.033$
  - Xa: 0.45 vs 0.29 unit/mL; $P = 0.045$

- **Enoxaparin**
  - Anti-Xa: 0.67 ± 0.27 vs 0.53 ± 0.24 unit/mL, $P = 0.028$
  - Lower doses were required over time


Summary Pro: Use An Adjustment

- Warfarin
- Max Initial Dose of Warfarin: 0.2 mg/kg/dose (5 mg per day)
  - Initial and maximum doses of warfarin per kg significantly lower in obese patients (P<0.05).
- Time to therapeutic INR value was twice as long in obese patients
  - Median=6 [range, 4 to 28 d] vs median=3 [range, 1 to 10 d]; P<0.01.

Summary **Pro**: Use Adjustments

- Clinically relevant endpoints are different for obese patients
- Risk of overdosing
  - Increased monitoring
- Risk of increasing length of stay
Dosing Controversies for High-Risk Medications:

We should not use empiric adjustments (use total body weight) & follow therapeutic concentrations to adjust dosing.
Heparin & Warfarin

• Heparin:
  - Rarely used outside of CV surgery population
  - Titrate to effect due to post-operative bleeding

• Warfarin:
  - Drug interactions & PG affect dosing
  - Obese adults cap dose—5-10 mg

• Recommendations:
  - Dose using TBW & cap at adult dosing
  - Monitor vigilantly & titrate to effect

PG = Pharmacogenomics
TBW = Total body weight
# Enoxaparin Prophylaxis in Kids

<table>
<thead>
<tr>
<th>Patient</th>
<th>Weight (kg)</th>
<th>Enoxaparin Dose</th>
<th>Enoxaparin Dose (mg/kg/day)</th>
<th>Anti-Factor Xa Value (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>358.6</td>
<td>40 mg SQ daily</td>
<td>0.11</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td></td>
<td>338.6</td>
<td>40 mg SQ bid</td>
<td>0.24</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>336.4</td>
<td>60 mg SQ bid</td>
<td>0.36</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>324.5</td>
<td>90 mg SQ bid</td>
<td>0.55</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>324.5</td>
<td>95 mg SQ bid</td>
<td>0.59</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>302.3</td>
<td>100 mg SQ bid</td>
<td>0.66</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>285</td>
<td>100 mg SQ bid</td>
<td>0.7</td>
<td>0.29</td>
</tr>
<tr>
<td>2</td>
<td>277</td>
<td>40 mg SQ daily</td>
<td>0.14</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>277</td>
<td>40 mg SQ bid</td>
<td>0.29</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>277</td>
<td>45 mg SQ bid</td>
<td>0.32</td>
<td>0.13</td>
</tr>
<tr>
<td>3</td>
<td>81.5</td>
<td>40 mg SQ daily</td>
<td>0.49</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>81.5</td>
<td>40 mg SQ bid</td>
<td>0.49</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Prophylaxis anti-Xa range: 0.1-0.3 IU/mL

## Enoxaparin Treatment in Kids

<table>
<thead>
<tr>
<th>Data</th>
<th>Obese (n = 30)</th>
<th>Non-obese (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD or Number (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.6 ± 4.4</td>
<td>11.4 ± 4.3</td>
<td>NA</td>
</tr>
<tr>
<td>Initial dose (mg/kg)</td>
<td>0.93 ± 0.16</td>
<td>0.98 ± 0.19</td>
<td>0.22</td>
</tr>
<tr>
<td>Therapeutic dose (mg/kg)</td>
<td>0.81 ± 0.12</td>
<td>1.1 ± 0.14</td>
<td>0.005</td>
</tr>
<tr>
<td>Dose changes:</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Increases</td>
<td>26 (38%)</td>
<td>35 (52%)</td>
<td></td>
</tr>
<tr>
<td>Decreases</td>
<td>42 (62%)</td>
<td>32 (48%)</td>
<td></td>
</tr>
<tr>
<td>Supratherapeutic anti-Xa concentration:</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Patients</td>
<td>21 (70%)</td>
<td>14 (47%)</td>
<td></td>
</tr>
<tr>
<td>Concentration (IU/mL)</td>
<td>1.12 ± 0.17</td>
<td>1.08 ± 0.08</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Both groups required dose ↑’s & ↓’s

Question other affects on clearance

Summary Con: Use TBW

- Case series suggest ↑ dosing for prophylaxis
- ↓ dosing needed for treatment in obese group:
  - Similar age groups
  - All groups needed dose adjustments
  - Unclear affect of other factors on clearance
- Data unclear so dose using TBW & monitor anti-Xa concentrations

TBW = Total body weight
What Dose of SQ Enoxaparin Should be Used?

A. Use ABW & monitor anti-Xa concentrations
B. Use IBW & monitor anti-Xa concentrations
C. Use LBM & monitor anti-Xa concentrations
D. Use TBW & monitor anti-Xa concentrations

Patient Case # 1 Summary:

- 9 year-old
- Wt = 68 kg
- Normal renal function
Pro/Con Debate #3: Continuous infusion dosing
PICU Obese Admissions (n=834)

Represent 12.8% of all PICU admissions

## Continuous Infusions in Obese Kids (n=94)

<table>
<thead>
<tr>
<th>Rank Order</th>
<th>Agent</th>
<th>Number (%)</th>
<th>Rank Order</th>
<th>Agent</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fentanyl</td>
<td>12 (12.8)</td>
<td>11</td>
<td>Furosemide</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>2</td>
<td>Regular insulin</td>
<td>12 (12.8)</td>
<td>12</td>
<td>Cisatricurium</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>3</td>
<td>Milrinone</td>
<td>12 (12.8)</td>
<td>13</td>
<td>Nitropruside</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>4</td>
<td>Epinephrine</td>
<td>11 (11.7)</td>
<td>14</td>
<td>Norepinephrine</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>5</td>
<td>Midazolam</td>
<td>10 (10.6)</td>
<td>15</td>
<td>Propofol</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>6</td>
<td>Dopamine</td>
<td>6 (6.4)</td>
<td>16</td>
<td>Vasopressin</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>7</td>
<td>Dobutamine</td>
<td>5 (5.3)</td>
<td>17</td>
<td>Aminophyllline</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>8</td>
<td>Remifentanl</td>
<td>5 (5.3)</td>
<td>18</td>
<td>Amiodarone</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>9</td>
<td>Aminocaproic acid</td>
<td>4 (4.3)</td>
<td>19</td>
<td>Morphine</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>10</td>
<td>Dexmedetomidine</td>
<td>4 (4.3)</td>
<td>20</td>
<td>Phenylephrine</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

- **35%** for sedation, analgesia, and NMB
- **40%** for hemodynamic support

Patient Case #2

- 11 year-old Male (81.5 kg; 165 cm) admitted for septic shock secondary to pneumonia:
  - Ulcerative colitis
  - Obesity (99th percentile for age, height, gender)

- **HD 1**: Admitted to PICU
- **HD 2**:
  - Intubated in PICU
  - Team wishes to initiate fentanyl infusion

**What dose of fentanyl should be used (mcg/kg/hr or mcg/hr)?**

HD = Hospital day
Dosing Strategies for Continuous Infusions:

We should use non-weight based dosing
Summary Pro: Non-weight Based Dosing

- Overdosing Risk
- Titration
- Other medications
Summary Pro: Non-weight Based Dosing

- Fentanyl
- 1 mcg/kg/hr = 81.5 mcg/hr
- Severe pain, intermittent: 25-35 mcg
- Infusion: 25 to 100 mcg bolus followed by an initial rate of 25 to 200 mcg/hour
Summary Pro: Non-weight Based Dosing

- Titration of continuous infusions
- Difficult due to multiplying scale
- Titrating by 10%
  - 1.1 mcg/kg/hour, 1.2 mcg/kg/hour...
  - Used to larger increments
Summary Pro: Non-weight Based Dosing

- Other medications:
  - Vasopressin
  - Norepinephrine

- Weight, as a pharmacokinetic variable, is not as relevant once patients achieve adult size.
Summary

- Initiation and titration using weight based dosing will result in greater than expected changes in dose.

- Pharmacokinetics don’t support the inclusion of weight as a variable once a patient has reached ‘adult’ size.

- Adult patients receive adult doses at adult hospitals regardless of weight.
Dosing Strategies for Continuous Infusions:

*We should use fixed-dosing or weight-based dosing depending on the patient or drug*
Not A Straightforward Answer

• Depends on degree of lipophilicity & compartment type (zero, 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd})

• Variability in weight-based clearance vs clearance differences based on age

Lim SY, et al. (Unpublished data)
Fentanyl Clearance: Obese vs Controls

Lim SY, et al. (Unpublished data)

N = 4,376

11-30% ↓ clearance in all obese groups
Fentanyl Pharmacokinetics

- $V_{dss}$ values $\uparrow$ 50% in obese vs non-obese children > 10 years
- $C_{ss}$ using weight-based dosing in obese vs non-obese children:
  - 4 YO: 25%
  - 9 YO: 77%
  - 15 YO: 50%

$V_{dss}$ = Volume of distribution at steady state

$C_{ss}$ = Steady state concentration

Lim SY, et al. (Unpublished data)
4 YO: 1 mcg/kg/hr

9 YO: 1 mcg/kg/hr

15 YO: 1 mcg/kg/hr

15 YO: 50 mcg/hr

Lim SY, et al. (Unpublished data)
Summary Con: Always Fixed-Dosing

- Not one-sized fits all answer
- Use weight-based dosing based on TBW
- Utilize pharmacodynamic target & adjust dosing:
  - Sedation scores
  - Mean arterial pressure
  - Urine output (mL/kg/hr)

TBW = Total body weight
What Dosing Units Should Be Used (mcg/kg/hr OR mcg/hr)?

A. Use mcg/kg/hr based on TBW
B. Use mcg/kg/hr based on IBW
C. Use mcg/kg/hr based on ABW
D. Use mcg/hr
D. None of the above

Patient Case # 2 Summary:

- 11 year-old
- Wt = 81.5 kg
- Intubated & placed on fentanyl infusion
Key Takeaways

1. Number of obese children hospitalized children are ↑’ng
2. Dosing in obese children is NOT straightforward
3. Consider pharmacokinetic analysis & employ monitoring with pharmacodynamic targets
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