Pharmacokinetics and Dose Optimization of Anticoagulants in Children with Obesity

A Focus on Enoxaparin

09 November 2022

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Eshelman School of Pharmacy

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Disclosures and funding

• I am an employee and stockholder of Pfizer.

• UNC funding:
  • 1R01HD096435
  • 5T32GM122741
  • American Foundation for Pharmaceutical Education (AFPE) Fellowship
Objectives

• Understand why precise anticoagulant dosing is important
• Hypothesize how anticoagulant dosing may differ in patients with obesity
• Review current literature of anticoagulant dosing in children with obesity
• Focus on enoxaparin:
  • How to use real world data and modeling and simulation to better understand enoxaparin in children with obesity
Anticoagulants are a broad and varied drug class

- Vitamin K Reductase Inhibitors
  - warfarin

- Heparins
  - unfractionated heparin
  - enoxaparin
  - dalteparin
  - fondaparinux

- Direct Thrombin Inhibitors
  - argatroban
  - bivalirudin

- Direct-Acting Oral Anticoagulants
  - apixaban
  - edoxaban
  - rivaroxaban

- Vitamin K Reductase Inhibitors
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Anticoagulants have narrow therapeutic indices, often requiring dose monitoring

- Many are dosed based on body weight
- Dose monitoring in special populations

Surrogate Measurements
- INR
- aPTT
- ACT
- anti-Xa

Bleeding risk
- Treatment target range
- Prophylaxis target range

Thromboembolic risk
- Concentration

ACT: activated clotting time
INR: international normalized ratio
PTT: partial thromboplastin time
Patients with obesity may be at risk of supra-therapeutic anticoagulant exposure.

**Without Obesity**
- 1 mg/kg
- 70 kg patient: 70 mg dose

**With Obesity**
- 1 mg/kg
- 150 kg patient: 150 mg dose

Mathematically:

\[
\text{Concentration} = \frac{\text{Dose}}{\text{Volume}}
\]
Appropriate heparin dosing in adults with obesity is still debated

Studies supporting recommended dosing\textsuperscript{1-4}:

- A minority of adults with obesity received reduced dosing
- No significant difference in peak concentration
- No difference in bleeding events

Studies supporting reduced dosing\textsuperscript{5-8}:

- Many real world patients with obesity received reduced dosing
- Reduced dosing better achieved concentration in the target range
- Reduced dosing with obesity reduced bleeding events

See slide 31 for list of references.
### Appropriate anticoagulant dosing in children with obesity is unclear

#### Vitamin K Reductase Inhibitors
- Warfarin
  - ↓ Dosing with obesity\(^1\)\(^-\)\(^2\)

#### Heparins
- Unfractionated heparin
  - ↓ Dosing with obesity\(^3\)\(^-\)\(^4\)
  - No adjustment for obesity\(^5\)
- Enoxaparin
  - ↓ Dosing with obesity\(^6\)
  - No adjustment for obesity\(^7\)
- Dalteparin
  - No adjustment for obesity\(^8\)
- Fondaparinux
  - No published data

#### Direct Thrombin Inhibitors
- Argatroban
- Bivalirudin
  - No published data

#### Direct-Acting Oral Anticoagulants
- Apixaban
- Edoxaban
- Rivaroxaban
- Dabigatran
  - No published data

• Understanding pediatric anticoagulant dosing requires characterizing age, obesity status, and their interplay.

See slide 32 for list of references.
Appropriate anticoagulant dosing in children with obesity is unclear

### Vitamin K Reductase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing with obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>warfarin</td>
<td>↓</td>
</tr>
</tbody>
</table>

### Direct Thrombin Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing with obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>argatroban</td>
<td>No published data</td>
</tr>
<tr>
<td>bivalirudin</td>
<td></td>
</tr>
</tbody>
</table>

### Heparins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing with obesity</th>
<th>Adjustment for obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>unfractionated heparin</td>
<td>↓</td>
<td></td>
</tr>
<tr>
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<td>↓</td>
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</tr>
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### Direct-Acting Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing with obesity</th>
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</thead>
<tbody>
<tr>
<td>apixaban</td>
<td>No published data</td>
</tr>
<tr>
<td>edoxaban</td>
<td></td>
</tr>
<tr>
<td>rivaroxaban</td>
<td></td>
</tr>
<tr>
<td>dabigatran</td>
<td></td>
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</table>

See slide 32 for list of references.
Appropriate anticoagulant dosing in children with obesity is unclear

### Vitamin K Reductase Inhibitors

| Warfarin | ↓ Dosing with obesity$^{1-2}$ |

### Direct Thrombin Inhibitors

| Argatroban | Bivalirudin | No published data |

### Heparins

<table>
<thead>
<tr>
<th>Unfractionated heparin</th>
<th>↓ Dosing with obesity$^{3-4}$</th>
<th>No adjustment for obesity$^{5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>↓ Dosing with obesity$^{6}$</td>
<td>No adjustment for obesity$^{7}$</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>No adjustment for obesity$^{8}$</td>
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### Direct-Acting Oral Anticoagulants

| Apixaban | Edoxaban | Rivaroxaban | Dabigatran | No published data |

See slide 32 for list of references.
Children with obesity may have altered warfarin exposure

**Methods:** Retrospective chart review children 1-12 years old (n = 184)

<table>
<thead>
<tr>
<th>Category</th>
<th>Odds for elevated INR value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>0.24 (0.06-0.86)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Odds ratio (95% confidence interval)

**Methods:** Retrospective chart review of children 2-18 years old

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With Obesity (n = 10)</th>
<th>Without Obesity (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial warfarin dose (mg/kg)</td>
<td>0.06 ± 0.02</td>
<td>0.11 ± 0.04</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Maximum warfarin dose (mg/kg)</td>
<td>0.09 ± 0.04</td>
<td>0.13 ± 0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Supratherapeutic INR value</td>
<td>1 (10%)</td>
<td>14 (70%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Time to therapeutic INR (days)</td>
<td>6 (4-28)</td>
<td>3 (1-10)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Values presented as mean ± standard deviation, n (%), or median (range).
Appropriate anticoagulant dosing in children with obesity is unclear

<table>
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</tbody>
</table>

↓ Dosing with obesity\(^1\)\(^-\)\(^2\)
No adjustment for obesity\(^3\)\(^-\)\(^4\)
↓ Dosing with obesity\(^5\)
No adjustment for obesity\(^6\)
No adjustment for obesity\(^7\)
No published data
Children with obesity receiving heparin exhibit supratherapeutic anti-Xa levels

**Methods:** Retrospective BMI-based sub-analysis of children 2-19 years old

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With Obesity (n = 22)</th>
<th>Without Obesity (n = 34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to therapeutic anti-Xa (h)</td>
<td>4 (2-17)</td>
<td>12 (4-96)</td>
<td>0.02</td>
</tr>
<tr>
<td>First anti-Xa (IU/mL)</td>
<td>0.61 (0.09-2.23)</td>
<td>0.24 (0.09-1.02)</td>
<td>0.01</td>
</tr>
<tr>
<td>Supratherapeutic first anti-Xa level</td>
<td>10 (45.5%)</td>
<td>3 (8.8%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Any supratherapeutic anti-Xa level</td>
<td>17 (77.3%)</td>
<td>12 (35.3%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Major bleed</td>
<td>1 (4.5%)</td>
<td>1 (2.9%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Initial aPTT</td>
<td>101 (40-250)</td>
<td>67 (34-250)</td>
<td>0.07</td>
</tr>
<tr>
<td>Supratherapeutic first aPTT</td>
<td>11 (57.9%)</td>
<td>6 (18.8%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Any supratherapeutic aPTT</td>
<td>16 (84.2%)</td>
<td>21 (65.6%)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Note: Data are presented as n (%) or median (range). P-values result from chi-square, Fisher’s exact, or Wilcoxon rank sum test.
## Appropriate anticoagulant dosing in children with obesity is unclear

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<td><strong>↓ Dosing with obesity(^1)(^2)</strong></td>
<td>bivalirudin</td>
</tr>
<tr>
<td></td>
<td>No published data</td>
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<tr>
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<td>rivaroxaban</td>
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<td>dalteparin</td>
<td><strong>No adjustment for obesity(^8)</strong></td>
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</table>

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See slide 32 for list of references.
Appropriate enoxaparin dosing in children with obesity is unclear

Reduced dosing of enoxaparin for venous thromboembolism in overweight and obese adolescents: a single institution retrospective review

Stephanie Hoffman MD¹ | Chi Braunreiter MD²,³

- 12-18 year-olds (n = 30) with obesity and overweight
- Compared reduced (< 0.9 mg/kg) versus recommended dosing
- Both regimens achieved equivalent concentrations
- No adverse outcomes

Comparison of Anti-Xa Levels in Obese and Non-Obese Pediatric Patients Receiving Treatment Doses of Enoxaparin

Ashley A. Richard, PharmD¹, Shelly Kim, PharmD¹, Brady S. Moffett, PharmD, MPH¹, Lisa Bomgaars, MD², Donald Mahoney, Jr., MD², and Donald L. Yee, MD²

- 2-18 year-olds (n = 60) with and without obesity
- Mean therapeutic dose was 26% lower with obesity
- Concentrations were 21% higher with obesity
- Minimal bleeding for either group

Appropriate enoxaparin dosing in children with obesity is unclear

Use of Real-World Data and Physiologically-Based Pharmacokinetic Modeling to Characterize Enoxaparin Disposition in Children With Obesity

Jacqueline G. Gerhart¹, Fernando O. Carreño¹, Matthew Shane Loop¹, Craig R. Lee¹, Andrea N. Edginton², Jaydeep Sinha¹,³, Karan R. Kumar⁴,⁵, Carl M. Kirkpatrick⁶, Christoph P. Hornik⁴,⁵ and Daniel Gonzalez¹,⁶ on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee⁷

OBJECTIVE:

Use real world data to characterize differences in enoxaparin disposition in children with and without obesity.

OBJECTIVE: Use real world data to characterize differences in enoxaparin disposition

1. Prepare real world dataset for analysis.
   - Data cleaning and formatting
   - Data quality control checks

2. Use real world data to develop a PBPK model to better understand mechanistic drivers of enoxaparin concentration.
   - Developed in adults
   - Scaled to children

3. Use the PBPK model to do dosing simulations in order to optimize dosing in children with obesity.
   - Evaluate recommended dosing
   - Explore body size metrics

✓ Extensive dataset of real world patients
✓ Mechanistic characterization of exposure differences

PBPK: physiologically-based pharmacokinetic
Observed concentrations came from pediatric electronic health record data

Inclusion criteria

- Children 2 – 17 years old
- Receiving enoxaparin for treatment or prophylaxis

Exclusion criteria

- Renal dysfunction (eGFR < 30 mL/min or 90 mL/min/1.73m² or CrCl < 75 mL/min/1.73m²)
- Serum creatinine > 4 mg/dL
- Elevated bilirubin levels (≥ 6 mg/dL)
- On hemodialysis, ECMO, VAD, or dialysis
- Pregnancy
- Neoplasms
- No height or anti-Xa concentration reported

Data

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites</td>
<td>9</td>
</tr>
<tr>
<td>Subjects</td>
<td>596</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>1,098</td>
</tr>
<tr>
<td>Anti-Xa Samples</td>
<td>2,825</td>
</tr>
</tbody>
</table>


CrCl: creatinine clearance
ECMO: extracorporeal membrane oxygenation
eGFR: estimated glomerular filtration rate
VAD: ventricular assist device
Children with and without obesity have significantly higher enoxaparin concentrations.

Concentration

\[ p = < 0.001 \]

\[ n = 415 \quad n = 104 \]

Dose-Normalized Concentration

\[ p = 0.003 \]

\[ n = 415 \quad n = 104 \]

Note: 20 and 18 upper outliers omitted from left and right figures, respectively, for better visualization.

BMI: body mass index
Conc: concentration
IU: international units

PBPK offers advantages for characterizing drug disposition in children with obesity

Virtual population

Physicochemical properties

System information

PBPK: physiologically-based pharmacokinetic

Key enoxaparin PBPK model parameters

**Drug Properties**
- Average molecular weight: 4500 g/mol
- logP: -10.0
- 1 mg enoxaparin ≈ 100 IU anti-Xa

**Absorption**
- Bioavailability: 100%
- $k_a$ (1/h): 0.60

**Distribution**
- Bound to anti-thrombin in plasma:
  - $K_D = 2.5 \mu M$
  - $k_{off} = 2.1/h$

**Metabolism**
- **Heparinase**:
  - Intrinsic clearance = 151 mL/min

**Excretion**
- **Renal clearance**:
  - GFR ($f_{e, urine}$ ≈ 40%)

---

PBPK modeling captures observed concentrations from children without and with obesity

**Representative concentration versus time profile for children 2-6 years old with obesity.**

<table>
<thead>
<tr>
<th></th>
<th>Children without Obesity</th>
<th>Children with Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFE</td>
<td>0.87</td>
<td>0.82</td>
</tr>
<tr>
<td>Within 90% PI (%)</td>
<td>75.2%</td>
<td>77.2%</td>
</tr>
<tr>
<td>Above 90% PI (%)</td>
<td>20.6%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Below 90% PI (%)</td>
<td>4.2%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

PBPK model-estimated changes in enoxaparin disposition with obesity

Above target range:
- 8.9% children without obesity
- 22.5% children with obesity

Optimizing recommended weight-based enoxaparin dosing

Recommended Dosing

- Treatment: 1 mg/kg BID
- Prophylaxis: 0.5 mg/kg BID

Body Size Metrics

- Total bodyweight (currently recommended)
- Fat-free mass (FFM)

\[
\begin{align*}
FFM (males) &= 0.88 + \left(\frac{0.12}{1 + \left(\frac{age}{13.4}\right)^{-12.7}}\right) \times \left[\frac{(9270 \times weight)}{6680 + (216 \times BMI)}\right] \\
FFM (females) &= 1.11 + \left(\frac{-0.11}{1 + \left(\frac{age}{7.1}\right)^{-1.1}}\right) \times \left[\frac{(9270 \times weight)}{8780 + (244 \times BMI)}\right]
\end{align*}
\]

Goal: Match exposure between children with and without obesity.
Weight-based dosing results in differences in enoxaparin concentration with obesity and age

Treatment Dosing

Prophylaxis Dosing


iU: International units
Fat-free mass dosing equalizes enoxaparin concentration with obesity and age

**Treatment Dosing**

- **Nonobese**
- **Obese**

**Prophylaxis Dosing**

IU: international units

Future directions: Anticoagulant pharmacodynamics

- **Pediatric** anticoagulant trials
  - Direct thrombin inhibitors, DOACs

- **Dose-response** relationship
  - Adults versus pediatric patient populations

- **Obesity-induced** changes in the coagulation cascade

DOACs: direct-acting oral anticoagulants

Conclusions: Results to-date highlight the importance of childhood obesity in anticoagulant dosing

- Most anticoagulant pediatric obesity data published are for warfarin, heparin, or enoxaparin.

- Taken together, these studies generally suggest that children with obesity might receive lower anticoagulant doses, are more likely to have a supratherapeutic concentrations, and take longer to achieve therapeutic concentrations relative to children without obesity.

- Dose monitoring of anticoagulants can allow for dose adjustments with obesity.

- Children with obesity have statistically significantly higher enoxaparin concentrations. Fat-free mass dosing leads to more comparable 4-hour enoxaparin exposure.

- Age and obesity status should be considered in enoxaparin dose selection for children.

Acknowledgements

- Jaydeep Sinha, PhD
- Fernando Carreño, PhD
- Matthew Loop, PhD
- Carl Kirkpatrick, PhD
- Ben Urick, PharmD, PhD

- PTN Data Repository
  - Christoph Hornik, MD, PhD, MPH
  - Karan Kumar, MD, MS

- UNC Gonzalez Lab members

- Project advisors
  - Danny Gonzalez, PharmD, PhD
  - Craig Lee, PharmD, PhD
  - Andrea Edginton, PhD
  - Bob Dupuis, PharmD
  - Jian Wang, PhD

- Funding:
  - 1R01HD096435; 5T32GM122741, AFPE fellowship
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References* - Slide 7


*References are not intended to be a comprehensive list.


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Obesity and weight may impact appropriate anticoagulant dosing in adults

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<tr>
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<tbody>
<tr>
<td>warfarin</td>
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<tr>
<td>↑ absolute dose with obesity¹⁻⁴</td>
<td>Use recommended weight-based dose²⁶⁻²⁷</td>
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</tbody>
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<td>Use recommended weight-based dose¹⁵⁻¹⁹</td>
<td>Use recommended absolute dose³¹⁻³³</td>
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<tr>
<td>↓ absolute dose with obesity²⁰</td>
<td>No published data</td>
</tr>
<tr>
<td>Use weight-based dose with obesity²¹⁻²³</td>
<td></td>
</tr>
<tr>
<td>Use ideal weight-based dose with obesity²⁴</td>
<td></td>
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<td>fondaparinux</td>
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</table>

↓ weight-based dose with obesity²⁵

See slides 34-37 for list of references.


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Scaling the adult PBPK to children

Scaling to Children

- Adult PBPK Model
  - Scale protein binding
  - Scale clearance
  - Scale anatomy/physiology
- Pediatric PBPK Model

Expanding to Children with Obesity

- **Organs**
  - Blood flow
  - Weight
- **Renal Clearance**
  - Glomerular filtration rate
- **Protein Binding**
  - Albumin
  - AAG
  - Hematocrit
- **Hepatic Clearance**
  - Liver clearance
  - Metabolism

PBPK model-estimated changes in enoxaparin disposition with obesity


CL: clearance
PBPK: physiologically-based pharmacokinetic
$V_d$: volume of distribution