ADJUSTING DOSES IN THE CRITICALLY ILL OBESE PATIENT: HOW BIG OF A DEAL IS IT?

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OBJECTIVES

Recognize pharmacokinetic alterations in obesity

Evaluate current literature on weight-based anticoagulation, antibiotic dosing and nutrition management

Design optimal dosing strategies for critically ill obese patients
OBESITY STATISTICS

https://www.cdc.gov/obesity/data/prevalence-maps.html
OBESITY STATISTICS

![Graph showing the percentage increase in BMI categories (BMI > 30, BMI > 40, BMI > 50) from 2000 to 2010.](image)

HOW DO WE MEASURE OBESITY?

- BMI
- BSA
- IBW
- ABW
- LBW
- PNWT

Clin Pharmacokinet
IMPACT ON DRUG CLEARANCE

Absorption
- Bariatric surgery

Distribution
- Augmented volume of distribution with lipophilic agents

Metabolism
- Increased CYP450 2E1 activity, phase 2 conjugation

Excretion
- Effect on glomerular filtration?
ANTICOAGULATION DVT Prophylaxis Novel Oral Anticoagulants
WHAT DO YOU RECOMMEND FOR DVT PROPHYLAXIS IN NORMAL WEIGHT TRAUMA PATIENTS?

A. Heparin 5000 units SC BID
B. Heparin 5000 units SC TID
C. Enoxaparin 40 mg SC daily
D. Enoxaparin 30 mg SC BID
A COMPARISON OF LOW-DOSE HEPARIN WITH LOW-MOLECULAR-WEIGHT HEPARIN AS PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM AFTER MAJOR TRAUMA


<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Dose</th>
<th>Injury Severity Score</th>
<th>DVT</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>129</td>
<td>30 mg SC BID</td>
<td>23.1</td>
<td>40 (31%)</td>
<td>5</td>
</tr>
<tr>
<td>Heparin</td>
<td>136</td>
<td>5000 units SC BID</td>
<td>22.7</td>
<td>60 (44%)</td>
<td>1</td>
</tr>
</tbody>
</table>

BMI-STRATIFIED ENOXAPARIN DOSING

***Extrapolated from bariatric surgery data***

2002: Scholten et al
- Group I: Enoxaparin 30 mg Q12hrs vs Group II: 40 mg Q12hrs (BMI 51.7 vs 50.3)
- Group I: 5.4% DVT complications vs Group II: 0.6% DVT complications (p < 0.01)

2008: Borkgren–Okonek et al
- Enoxaparin 40 mg Q12hrs for BMI ≤ 50
- Enoxaparin 60 mg Q12hrs for BMI > 50
- 74% of patients achieved target prophylactic peak range of 0.2 – 0.4 IU/mL
- Nonfatal VTE in 1/208 patients

HOW SHOULD WE MONITOR THESE PATIENTS?

Anti-Xa levels

SHOULD IT BE A PEAK OR A TROUGH?
Historically, enoxaparin dose adjustment have been based off of anti-Xa peaks drawn 4 hours after dose.

Recent data suggests troughs of > 0.1 IU/mL better correlate with adequate VTE prevention.
Design

- Prospective arm: enoxaparin 30 mg SC BID adjusted by anti–Xa troughs
- Historic cohort arm: enoxaparin 30 mg SC BID

Troughs

- Anti–Xa trough ≤ 0.1 IU/mL increased by 10mg
- 73/87 required adjustment; 57/87 increased to 40mg BID

Results

- VTE significantly lower for adjusted arm (1.1% vs 7.6%)
- No difference in transfusions or hematocrit

WHEN USING SC HEPARIN, WHAT SHOULD THE DOSE BE?

A. Heparin 5000 units SC TID
B. Heparin 7500 units SC TID
Safety and Efficacy of High-Dose Unfractionated Heparin for Prevention of Venous Thromboembolism in Overweight and Obese Patients

Mishna Joy,¹ Eileen Tharp,¹ Heather Hartman,¹ Sara Schepcoff,¹ Jennifer Cortes,¹ Adam Sieg,¹ Mark Mariski,¹ Yeunju Lee,¹ Meghan Murphy,¹ Ghazaleh Ranjbar,¹ Sherouk Sharaf,¹ Gin Yau,¹ Huimahn Alex Choi,² and Sophie Samuel,¹,§
¹Department of Pharmacy, Memorial Hermann–Texas Medical Center, Houston, Texas; ²Department of Neurosurgery & Neurology, University of Texas Medical School, Houston, Texas

- **Study**
  - Heparin 7500 units vs 5000 units Q8H in patients >100kg

- **Efficacy**
  - Similar incidence of VTE across each BMI category

- **Safety**
  - More bleeding & transfusions required in the high-dose arm

Pharmacotherapy 2016;36(7):740-748.
UPDATE TO CHEST GUIDELINES FOR VTE

NOACs are now suggested over warfarin for initial & long-term treatment of VTE in patients without cancer.

Does this hold true for obese patients?

Still a relatively data-free zone!
ANTICOAGULATION TAKEAWAYS

#1: Enoxaparin should be dose optimized aggressively to reduce VTE in high-risk trauma patients

#2: New literature suggests anti-Xa troughs correlate better with VTE prevention than anti-Xa peaks

#3: Caution should be exercised in the morbidly obese with dosing NOACs until more data becomes available
Lipophilic

↑ Vd

Hepatic

↓ Vd

Renal

Hydrophilic

Cephalosporins

Carbapenems

Aminoglycosides

Vancomycin

Tigecycline

Fluoroquinolones

Macrolides
Information provision for antibacterial dosing in the obese patient: a sizeable absence?

- **No advice provided**
- **Advice suggests that no dosing adjustment is necessary** (tigecycline)
- **Caution that dose may need to be altered** (daptomycin and vancomycin)
- **Specific dosing strategy suggested** (aminoglycosides, glycopeptides, lipoglycopeptides, tobramycin and teicoplanin)
# Pharmacokinetics of Intravenous Linezolid in Moderately to Morbidly Obese Adults

Amira A. Bhalodi, a Pavlos K. Papasavas, b Darren S. Tishler, b David P. Nicolau, a,c Joseph L. Kuti a

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## TABLE 2 Comparison of AUCτ and C_{max} between moderately obese and morbidly obese participants by noncompartmental methodology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (^b)</th>
<th>Moderately obese (BMI, 30–39.9 kg/m(^2)) ((n = 10))</th>
<th>Morbidly obese (BMI, 40–54.9 kg/m(^2)) ((n = 10))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants ((n = 20))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(\tau)</td>
<td>119.8 ± 46.24</td>
<td>130.3 ± 60.1</td>
<td>109.2 ± 25.5</td>
<td>0.32</td>
</tr>
<tr>
<td>(C_{max})</td>
<td>19.8 ± 4.00</td>
<td>20.9 ± 5.0</td>
<td>18.8 ± 2.6</td>
<td>0.237</td>
</tr>
</tbody>
</table>

\(a\) AUC\(\tau\), AUC calculated from 0–12 h after the 5th dose; \(C_{max}\), observed maximum concentration.  
\(b\) Values are reported as mean ± SD.

HOW DO YOU CURRENTLY DOSE ACYCLOVIR IN OBESE PATIENTS?

A. Total body weight
B. Adjusted body weight
C. Lean body weight
D. Ideal body weight
A PROSPECTIVE, CONTROLLED STUDY OF ACYCLOVIR PHARMACOKINETICS IN OBESE PATIENTS

Morbidly obese >190% IBW

Acyclovir 5mg/kg over 60 min

Ideal Body Weight (BW)

Normal weight 80–120% IBW

Acyclovir 5mg/kg over 60 min

Total BW

Antimicrob Agents Chemother 2016;60(3):1830
ACYCLOVIR IN OBESE PATIENTS: RESULTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Morbidly obese (n = 7)</th>
<th>Normal Weight (n = 7)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>285</td>
<td>303</td>
<td>0.55</td>
</tr>
<tr>
<td>Cmax (mg/liter)</td>
<td>5.8</td>
<td>8.2</td>
<td>0.031</td>
</tr>
<tr>
<td>AUC (mg*hr/liter)</td>
<td>15.2</td>
<td>24</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Conclusion: Adjusted BW dosing for morbidly obese would provide similar AUC to normal weight patients.
ANTIMICROBIALS TAKEAWAYS

#1 – Linezolid 600mg IV Q12h may not hit the AUC target in patients > 150kg

#2 – Acyclovir should be dosed based on adjusted BW for morbidly obese patients with BMI > 40
NUTRITION SUPPORT

Protein requirements
Permissive underfeeding
Catabolic response similar to normal weight patients

Endogenous lipids become main energy source when protein is not enough

Increased net protein oxidation & higher daily muscle mass degradation

If eating more calories led to increased muscle, we would all look like this

https://en.wikipedia.org/wiki/Bodybuilding
PERMISSIVE UNDERFEEDING

Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults
Yaseen M. Arabi, M.D., Abdulaziz S. Aldawood, M.D., Samir H. Haddad, M.D., Hasan M. Al-Dorzi, M.D., Hani M. Tamim, M.P.H., Ph.D., Gwynne Jones, M.D., Sangeeta Mehta, M.D., Lauralyn McIntyre, M.D., Othman Solaiman, M.D., Maram H. Sakkijha, R.D., Musharaf Sadat, M.B., B.S., and Lara Afesh, M.S.N., for the PermiT Trial Group*

Initial Trophic vs Full Enteral Feeding in Patients With Acute Lung Injury
The EDEN Randomized Trial

Protein: >2–2.5 g/kg IBW

Caloric goal: 11–14 kcal/kg ABW or 22–25 kcal/kg IBW

Benefits: glycemic control, preservation of lean body mass
**Intervention:**
- 21–25 kcal/kg IBW
- >2g/kg IBW of protein

**Results:**
- Similar nitrogen balance in both age groups
- Similar clinical outcomes
ASSESSMENT QUESTIONS
YOU ADMIT A 27 Y/O FEMALE TRAUMA PATIENT WITH LONG BONE FRACTURES THAT WEIGHS 164KG AND HAS A BMI OF 51. YOU ARE CONCERNED THAT HER DOSE OF LOVENOX IS INSUFFICIENT FOR HER WEIGHT. YOU DECIDE TO:

A. Check an aPTT
B. Check daily lower extremity Doppler ultrasound to assess for DVT
C. Check an anti–Xa peak
D. Check an anti–Xa trough
DOSING ACYCLOVIR FOR A MORBIDLY OBESE PATIENT USING IDEAL BODY WEIGHT IS THE OPTIMAL DOSING STRATEGY TO USE

A. True
B. False
THE ICU TEAM IS WORRIED ABOUT OVERFEEDING THEIR PATIENT (230KG, BMI=76) WHEN INITIATING NUTRITION THERAPY. YOU RECOMMEND:

A. Eucaloric, high-protein diet
B. Hypocaloric, high-protein diet
C. Eucaloric, low-carbohydrate diet
D. Hypocaloric, low-carbohydrate diet
Patient weight is paramount for enoxaparin dosing for DVT prophylaxis & for appropriate use of NOACs

Consider lipophilicity of antimicrobials when determining adequate dosing in obese ICU patients

Nutrition support for obese, critically ill patients requires high-protein regimens to prevent wasting
ADJUSTING DOSES IN THE CRITICALLY ILL OBESE PATIENT: HOW BIG OF A DEAL IS IT?

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