Drug Dosing in the Obese Emergency Department Patient: How High Can You Go?

David E. Zimmerman, Pharm.D., BCCCP, BCPS
Assistant Professor of Pharmacy at Duquesne University
Emergency Medicine Clinical Pharmacist-UPMC Mercy Hospital
@DEZ_EM_Pharm
Disclosures

- **David E. Zimmerman**: ASHP: Author
- All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
Objectives

• Describe principles of pharmacokinetics that are involved for medication dosing in the obese patient in the emergency department.
• Evaluate the published literature that supports dosing recommendations.
• Given a clinical situation, recommend the appropriate dosing weight and dose for the medication dose.
EM Pharmacist’s PK Guide to the Galaxy
Drug Examples

**Sedative A**
- \( F = 1 \) (being given IV)
- \( V_d = 4 \text{ L/kg} \)
- Protein Binding = 60%
- Clearance = hepatic
- Elimination = renal

**Sedative B**
- \( F = 1 \) (being given IV)
- \( V_d = 2 \text{ L/kg} \)
- Protein binding = minimal
- Clearance = hepatic
- Elimination = renal

F, bioavailability; Vd, volume of distribution
ADME

- Absorption (F)
- Distribution (Vd)

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ADME

• Different weights for Vd parameters
  – Total body weight (TBW)
  – Ideal body weight (IBW)
  – Adjusted body weight (AdjBW)
  – Lean body weight (LBW)
    • LBW (female) = [1.07 x TBW(kg)] – [0.0148 x BMI x TBW (kg)]
    • LBW (male) = [1.1 x TBW(kg)] – [0.0128 x BMI x TBW (kg)]

ADME

• Metabolism

• Excretion/Clearance
  – Estimating renal clearance
  – Cockcroft-Gault

• Evaluate concomitant disease states affecting clearance

Drug Examples

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F, bioavailability; Vd, volume of distribution
RSI N’At
Rapid Sequence Intubation (RSI) Goals

- Adequately sedate and then paralyze for optimal intubating conditions
- Secure airway
- Prevent iatrogenic injury
Weight, hold up...we need a starting point

- How are we getting the patient’s weight?
  - Looking at the chart from last admission?
  - Weigh bed?
  - Asking them?
  - Estimating (i.e. guessing)
    - ED health care providers have been shown to underestimate obese patient’s weight

We know we under dose obese patients in RSI

- Obese patients were more likely to be underdosed with:
  - Succinylcholine (OR 63.7; 95% CI: 17.8-228.1)
  - Etomidate (OR 178.3; 95% CI, 37.6-844.7)

Etomidate

• Volume of distribution (Vd): 3-5 L/kg

• Protein binding: ~75% to albumin

• Rapid distribution from the central compartment

Etomidate

• Prospective “study” in obese patients undergoing laparoscopic surgery

• Received etomidate via syringe pump until goal bispectral index

• Obese vs. normal body weight patients required ~21 mg (p > 0.05)

Etomidate

• What happens if I give too much etomidate....waiting...waiting...still waiting...

• Use TBW until more evidence arrives
Ketamine

- Typical RSI dosing: 1.5-2 mg/kg
- Currently recommended dosing weight: TBW vs. LBW????
- PK parameters


# Ketamine

<table>
<thead>
<tr>
<th></th>
<th>Ectomorph n = 7</th>
<th>Mesomorph n = 5</th>
<th>Endomorph n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Fat</td>
<td>12.1 ± 3.3</td>
<td>22 ± 3.5</td>
<td>43.8 ± 12</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>53.9 ± 7.6</td>
<td>71.8 ± 8.6</td>
<td>91.7 ± 15.4</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>47.1 ± 6.6</td>
<td>56 ± 7.5</td>
<td>50.5 ± 9.2</td>
</tr>
<tr>
<td>Dose, mg</td>
<td>90 ± 12.6</td>
<td>105 ± 17</td>
<td>98 ± 18.6</td>
</tr>
<tr>
<td>Male/female</td>
<td>2/5</td>
<td>4/1</td>
<td>5/5</td>
</tr>
<tr>
<td>Dose/TBW, mg/kg</td>
<td>1.67</td>
<td>1.46</td>
<td>1.07</td>
</tr>
<tr>
<td>Dose/LBW, mg/kg</td>
<td>1.91</td>
<td>1.88</td>
<td>1.94</td>
</tr>
</tbody>
</table>

Kg, kilogram; LBW, lean body weight; mg, milligram; TBW; total body weight

Table adapted from: *Anesth Analg*. 1972;51(2):299-305
Clinical Considerations of Ketamine

• What happens if I do not give enough?

• What happens if I give too much?

• Dosing weight to use: TBW
  – Until further evidence is published
Propofol

• Clearance and Vd are better correlated with TBW than AdjBW
• Concerns with hemodynamic consequences
• Avoid unless hypertensive or available use of vasopressors
• Dosing weight to use: TBW

Succinylcholine

• In one study, comparing LBW vs. IBW vs. TBW
  – No difference in time of onset
  – Longer duration of action in TBW vs. IBW (8.5 vs. 5 mins)
  – 1/3 of patients in IBW group had intubating conditions rated as poor vs. none in TBW group

Succinylcholine

- In a retrospective review of 891 patients who received RSI in the ED:
  - Decrease first-pass success in patients > 120 kg
  - Under dosing of succinylcholine in patients > 120 kg
  - Bottom line: Use TBW

Rocuronium

• Onset: similar when dosed on TBW vs IBW

• Longer duration of action with TBW dosing

• If I give too much...what happens?

• Bottom line: IBW

<table>
<thead>
<tr>
<th>Height</th>
<th>IBW Female, kg</th>
<th>Dose Female, mg (0.6 mg/kg)</th>
<th>Dose Female, mg (1.2 mg/kg)</th>
<th>IBW Male, kg</th>
<th>Dose Male, mg (0.6 mg/kg)</th>
<th>Dose Male, mg (1.2 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5'</td>
<td>45.5</td>
<td>27.3</td>
<td>54.6</td>
<td>50</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>5'6”</td>
<td>59.3</td>
<td>35.6</td>
<td>71.2</td>
<td>63.8</td>
<td>38.3</td>
<td>76.6</td>
</tr>
<tr>
<td>6’</td>
<td>73.1</td>
<td>43.9</td>
<td>87.8</td>
<td>77.6</td>
<td>46.6</td>
<td>93.2</td>
</tr>
<tr>
<td>6’6”</td>
<td>86.9</td>
<td>52.1</td>
<td>104.2</td>
<td>91.4</td>
<td>54.8</td>
<td>109.6</td>
</tr>
</tbody>
</table>
Fentanyl

• Pharmacokinetics

• Fentanyl doses based upon TBW overestimates
  – PK mass (kg) = 52 / [1 + (196.4 x e^{-0.025(TBW)} – 53.66)/100]
  – A 200 kg person would have a PK mass of 109 kg
  – You would then use this “PK mass” for weight-based dosing

• In case you cannot do this math in your head (I can’t)....use fixed/capped doses and reassess

Morphine

- Pharmacokinetics

- Retrospective review, evaluated analgesic response following fixed dose of 4 mg IV
  - Analgesic response was not influenced by BMI

- Fixed, non-weight based!!

Hydromorphone

- Pharmacokinetics

- A secondary analysis of a previous prospective clinical trial failed to find any strong correlation between body weight and decrease in reported pain

- Guess what...Fixed, non-weight based!!

## Summary of Agents for RSI

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing Weight</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td>TBW</td>
<td>0.3 mg/kg</td>
</tr>
<tr>
<td>Ketamine</td>
<td>TBW</td>
<td>1.5-2 mg/kg</td>
</tr>
<tr>
<td>Propofol</td>
<td>TBW</td>
<td>1.5-2 mg/kg</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>TBW</td>
<td>1.5 mg/kg</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>IBW</td>
<td>1-1.2 mg/kg</td>
</tr>
</tbody>
</table>

IBW; ideal body weight; kg, kilogram; mg, milligram; TBW, total body weight
# Summary of Agents

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<td>Morphine</td>
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<td>Fixed, non-weight based</td>
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<tr>
<td>Hydromorphone</td>
<td>--------</td>
<td>Fixed, non-weight based</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>--------</td>
<td>Fixed, non-weight based</td>
</tr>
</tbody>
</table>
Drugs Examples

EMS brings in an unresponsive male who is not protecting his airway and RSI is needed. You reach into your RSI kit for a sedative and you remove Sedative A (or B). The patient is normotensive and in normal sinus rhythm. You estimate him to be 140 kg and his height to be 5’9”. Of course you are estimating because the patient is lying down on a stretcher, so you do not actually know the correct weight/height of the patient.
**Drug Examples**

<table>
<thead>
<tr>
<th>Sedative A</th>
<th>Sedative B</th>
</tr>
</thead>
<tbody>
<tr>
<td>- F = 1</td>
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<td>- Vd = 4 L/kg</td>
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<td>- Protein Binding = 60%</td>
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<td>- Clearance = hepatic</td>
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</tr>
<tr>
<td>- Elimination = renal</td>
<td>- Elimination = renal</td>
</tr>
</tbody>
</table>
Drug Examples

Sedative A-Which weight to use?  
A) TBW  
B) IBW  
C) AdjBW  
D) LBW  

Sedative B-Which weight to use?  
A) TBW  
B) IBW  
C) AdjBW  
D) LBW
KEY TAKEAWAYS

1) ALWAYS USE CLINICAL JUDGEMENT WHEN MAKING DOSING DECISIONS

2) ASSESS RISK VS. BENEFIT OF UNDER- OR OVERDOSING FOR EACH DRUG

3) FOR RSI, IT’S BETTER TO GIVE MORE!
References and Additional Readings


• Wulfsohn NL. Ketamine dosage for induction based upon lean body mass. *Anesth Analg.* 1972;51(2):299-305


References and Additional Readings

Mississippi Mud Redux

Craig Cocchio, Pharm.D., BCPS
EM Clinical Pharmacist
Residency Program Director, PGY-2 EM
CHRISTUS Trinity Mother Frances Hospital
Tyler, Texas
Male, mid 40s, LLE purulent cellulitis.

125 kg.

No comorbidities (currently diagnosed)
Choose your vancomycin dose

- A) Guideline based
- B) Two compartment
- C) Allometric dosing
- D) A gram q12
The ugly truth about vancomycin

Institutional dose limits/caps

Vd and Cl

Comorbidities limit penetration to sites of infection

Not all obese patients are equal

AUC:MIC ratio at the site of infection
Mississippi Mud

Not the formulation... it’s the pharmacokinetics
Vancomycin dosing

- Two compartment
- AUC:MIC
- Allometric
A dose divided cannot stand... or can it?

Single center, uncontrolled, prospective study

54 consecutive obese patients (>137% IBW)

Two compartment model loading dose

PMID: 25986008
## Divided loading dose

<table>
<thead>
<tr>
<th>IBW (Kg)</th>
<th>Percent IBW</th>
<th>CrCl (mL/min*)</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 83</td>
<td>≥ 137</td>
<td>&gt; 60</td>
<td>1 g q6h Max 20 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21-60</td>
<td>1 g q6h Max 17 mg/kg/dose</td>
</tr>
<tr>
<td>&gt; 83</td>
<td>≥ 137</td>
<td>≥ 21</td>
<td>15 mg/kg/dose q6h Max 1.5 g/dose</td>
</tr>
</tbody>
</table>

Level check prior to 3rd and 5th dose

*Based on IBW

PMID: 25986008
Who was included

58 year old male, 111 kg (± 31)
TBW 171% (± 37) of IBW
Normal renal function (SCr ~ 0.9 mg/dL)
What they found

• 89% between 10 – 20 mcg/mL within 12 hours
  – 3 patients > 20 mcg/mL
• 97% between 10 – 20 mcg/mL within 24 hours
  – 1 patient > 20 mcg/mL
• All AUC:MIC > 400
• No kidney injury

PMID: 25986008
We thought it was a good idea

• Retrospective chart review
  – Patients > 18 years of age
  – No missing data

• N=51
  – Vancomycin 2000 mg IV once
  – Vancomycin 1000 mg IV Q6H x 5 doses

• Study approved by CHRISTUS Institutional Review Board
What we looked at

**Primary Endpoint**
- Proportion of patients with a post loading dose trough between 10 – 20 mcg/mL

**Secondary Endpoints**
- Nephrotoxicity
- Time from order verification to administration
<table>
<thead>
<tr>
<th></th>
<th>Divided Loading Dose, (n=22)</th>
<th>Traditional Loading Dose (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, ±SD)</td>
<td>55 years, ± 12.0</td>
<td>60 years, ± 12.6</td>
</tr>
<tr>
<td>Gender (males, %)</td>
<td>17, 77%</td>
<td>20, 68%</td>
</tr>
<tr>
<td>Actual body weight (mean, ± SD)</td>
<td>146.75 kg, ± 53.6</td>
<td>120.46 kg, ± 31.8</td>
</tr>
<tr>
<td>BMI (mean, ± SD)</td>
<td>46.8 kg/m², 16.58</td>
<td>40.12 kg/m², 15.58</td>
</tr>
<tr>
<td>Baseline SCr (mean, ± SD)</td>
<td>1.19 mg/dL, ±0.5</td>
<td>1.25 mg/dL, ± 0.7</td>
</tr>
<tr>
<td>Indication (n, %)</td>
<td>Cellulitis- 17, 77%</td>
<td>Cellulitis- 12, 41%</td>
</tr>
<tr>
<td></td>
<td>Pneumonia- 5, 23%</td>
<td>Pneumonia- 16, 55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacteremia- 1, 3%</td>
</tr>
<tr>
<td>Vancomycin dose (mean, ± SD)</td>
<td>N/A</td>
<td>17.6 mg/kg, ± 4.1</td>
</tr>
</tbody>
</table>
What we found

- Primary outcome - troughs between 10 - 20 mcg/mL
- Divided loading dose 72.7 %, 16/22
- Traditional loading dose 58.6 %, 17/29
- Time to 1st dose of vancomycin
  - 92.48, ± 90.7
  - 173.93, ± 187.9
- Change in SCr from baseline
  - 0.06, ± 0.48
  - 0.18, ± 0.9
## Results

<table>
<thead>
<tr>
<th></th>
<th>Divided Loading Dose, (n=22)</th>
<th>Traditional Loading Dose, (n=29)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troughs between 10 - 20 mcg/mL</td>
<td>72.7 %, 16/22</td>
<td>58.6 %, 17/29</td>
<td>0.533</td>
</tr>
<tr>
<td>Time to 1\textsuperscript{st} dose of vancomycin</td>
<td>92.48, ± 90.7</td>
<td>173.93, ± 187.9</td>
<td>0.049</td>
</tr>
<tr>
<td>Change in SCr from baseline</td>
<td>0.06, ± 0.48</td>
<td>0.18, ± 0.9</td>
<td>0.59</td>
</tr>
</tbody>
</table>
Divide and conquer

Feasible in real world practice

Improved time to first dose antibiotics

Change in practice NOT protocol
Allometry – Body Size and Physiology

Body weight

mg/kg dose
<table>
<thead>
<tr>
<th>Est $\text{CL}_v$ (L/h)</th>
<th>LD (mg)</th>
<th>MD (mg)</th>
<th>$\text{AUC}_{0-24} \geq 400$ at 24 hr (%)</th>
<th>$\text{AUC}_{24-48} \geq 400$ at 48 hr (%)</th>
<th>Toxicity ($\text{AUC}_{48-72} \geq 700$) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2500</td>
<td>500 q24h</td>
<td>100</td>
<td>100</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>2500</td>
<td>1000 q24h</td>
<td>98</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>2500</td>
<td>1500 q24h</td>
<td>93</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2500</td>
<td>1000 q12h</td>
<td>99</td>
<td>100</td>
<td>0</td>
</tr>
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<td>8</td>
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<td>100</td>
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<td>2250 q12h</td>
<td>92</td>
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$\text{CL}_v = 9.656 - 0.078 \times \text{AGE} - 2.009 \times \text{SCR} + 1.09 \times \text{SEX} + 0.04 \times \text{TBW}^{0.75}$

AGE (years), SEX is 1 if male 0 if female

PMID: 30203073
Back to the methods

• What they did
  – Population PK study using per protocol data
  – Monte Carlo simulation to ↑ efficacy and ↓ toxicity

• How it’s translated
  – Empiric dosing nomogram for obese and super obese
  – \( CL_V \) described using a linear combination of age, serum creatinine, sex and allometrically scaled body weight

PMID: 30203073
Vancomycin TDM Protocol

- Patient-specific PK via Sawchuk–Zaske
- Steady state vancomycin peak and trough
- Loading dose target peak 30–40 mg/L, max 3000 mg
- Volume
  - 0.8 L/kg (BMI 30-39.9 kg/m^2)
  - 0.52 L/kg (BMI 40–49.9 kg/m^2)
  - 0.42 L/kg (BMI ≥50 kg/m^2)
- Matzke nomogram

PMID: 30203073
Study Population

- n = 346 obese and super obese adults
- Body weight (69.6–293.6 kg) and BMI (30.1–85.7 kg/m²)
- Average were middle aged (range 19–88 years), male
- Normal renal function average 1.0 mg/dL

PMID: 30203073
Monte Carlo Simulation

• 1000-subject Monte Carlo simulations within Pmetrics™

• First run, no LD
  – TDDs from 500 to 5000 mg in 1000 simulated subjects per
    patient in the original dataset

• Second run with LD

• CL rounded to nearest whole number

PMID: 30203073
<table>
<thead>
<tr>
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<td>100</td>
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</tr>
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\[ \text{CL}_v = 9.656 - 0.078 \times \text{AGE} - 2.009 \times \text{SCR} + 1.09 \times \text{SEX} + 0.04 \times \text{TBW}^{0.75} \]

AGE (years), SEX is 1 if male 0 if female

PMID: 30203073
It's not that complicated…
Male, mid 40s, LLE purulent cellulitis.

125 kg.

No comorbidities (currently diagnosed)
KEY TAKEAWAYS

Reality:
• Low quality data – no patient oriented outcomes

Solutions:
• Divided loading dose plus Crass Nomogram?
• Approach each patient individually
• We need more researchers
References


Further Reading