Cardiovascular pharmacotherapy in special population: Morbid obesity

Krittin Bunditanukul Pharm.D, BCPS, FACP
Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University
Case

• ชายไทยอายุ 61 ปี น้ำหนัก 150 kg สูง 170 ซม. (BMI 48.7 kg/m²)
• CC: Shortness of breath and chest pain
• Spiral CT scan: Confirmed pulmonary embolism
• Which anticoagulant should we use and which dose?
Thailand obesity rate 2014: 5.9 (3.9-9.5)
Cardiovascular pharmacotherapy in special population: Morbid obesity

- Obesity is not only associated with an increase in fat but also in lean body weight (LBW) which is the weight devoid of all adipose tissue.
- The percentage of fat mass per kg of total body weight increase more than LBW in obese patient.
Cardiovascular pharmacotherapy in special population: Morbid obesity

- Dosages of many medications are determined using patient weight, clinicians may have reservations about weight based dosing in obese patients due to the increased possibility of toxicities with larger doses.
- The practice of “capping” doses for obese patients may increase the risk that suboptimal dosing regimens may lead to treatment failure.
Physiologic change in obesity

- ↑ Cardiac output, blood volume
- No change in serum albumin but ↑ alpha-1 acid glycoprotein
- ↑ Liver size
- Fatty infiltrate may effect drug metabolism
- ↑ LBM, adipose tissue
- ↓ Peripheral blood flow
- ↑ Kidney size, glomerular filtration
Measure of body size

- **BMI**: descriptor of body shape
- **IBW**: rarely use for drug dosing and dose not consider BW
- **ABW**: very little evidence for guide dosing
- **BSA**: use mostly in cancer
- **LBW**: fat-free mass less evidence
<table>
<thead>
<tr>
<th>Size descriptor</th>
<th>Formula</th>
</tr>
</thead>
</table>
| **BSA**         | Du Bois and Du Bois:  
|                 | $\text{TBW (kg)}^{0.425} \times \text{HT (cm)}^{0.725} \times 0.007184$  
|                 | Mosteller:  
|                 | $\sqrt{(\text{HT (cm)} \times \text{TBW (kg)})/3600}$  
|                 | Schlich:  
|                 | Men: $0.000579479 \times W^{0.38} \times HT^{1.24}$  
|                 | Women: $0.000975482 \times W^{0.46} \times HT^{1.08}$  
| **BMI**         | $\frac{\text{TBW (kg)}}{\text{HT (m}^2\text{)}}$  
| **IBW**         | Men: $45.4 \text{ kg} + 0.89 \times (\text{HT [cm]} - 152.4)$  
|                 | Women: $49.9 \text{ kg} + 0.89 \times (\text{HT [cm]} - 152.4)$  
| **LBW**         | Men: $1.10 \times \text{TBW} - 0.0128 \times \text{BMI} \times \text{TBW}$  
|                 | Women: $1.07 \times \text{TBW} - 0.0148 \times \text{BMI} \times \text{TBW}$  
|                 | Based on BIA: $(9270 \times \text{TBW})/(A + B \times \text{BMI})$  
|                 | Men: $A = 6680; B = 216$  
|                 | Women: $A = 8780; B = 244$  
| **ABW**         | Calculate IBW and then increase final estimate by a certain proportion (usually 40%)  

PK of drug in obese

- Drug absorption and oral bioavailability are not change, except SC route.
- CL and Vd often change in obesity but the magnitude and direction are vary.
- Increase phase II metabolism while phase I is depend on type of CYP used.
- Renal clearance is higher.
- Cicr is very biased in obese when use TBW.
PK of drug in obese

- Highly lipophilic drugs have increased Vd in patients with excess adipose tissue, and therefore may require higher bolus doses to rapidly achieve therapeutic plasma concentrations.

- Higher blood volume in obese patients may increase bolus dose requirements even for hydrophilic medications, while maintenance dosing of lipophilic medications must account for the potential for prolonged elimination half-life given the depot effect of adipose.
The American College of Chest Physicians (ACCP) practice guidelines recommend weight-based dosing of UFH over fixed dosing in obese patients.
Figure 1. Hours required to achieve therapeutic anticoagulation (partial thromboplastin time >60 s). N=84.
Figure 3. Gap between recommended and actual initial continuous heparin doses. Histogram shows number of patients receiving initial continuous heparin doses that fell below or above the recommended dose (18 units/kg/h) by the indicated amounts (units/h). N=84.
Enoxaparin

- Because obese patients have a lower proportion of lean body mass compared to their TBW, there are concerns about potential overdosing with the weight-adjusted therapeutic dose of LMWH and underdosing with the standard prophylactic dose of LMWH.
Fig 1. Mean anti-Xa and anti-IIa activity–versus–time profile in 24 obese volunteers and 24 nonobese volunteers after subcutaneous enoxaparin injection, 1.5 mg/kg, on day 1. IU, International units.
### Table 3. Recurrence of Venous Thromboembolism and Attendant Risk Factors for All Treated Patients and Evaluable Patients

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Unfractionated Heparin Group</th>
<th>Once-Daily Enoxaparin Group</th>
<th>Twice-Daily Enoxaparin Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treated patients, n</td>
<td>290</td>
<td>298</td>
<td>312</td>
<td>900</td>
</tr>
<tr>
<td>Recurrent venous thromboembolic event, n (%)*</td>
<td>12 (4.1)</td>
<td>13 (4.4)</td>
<td>9 (2.9)</td>
<td>34 (3.8)</td>
</tr>
<tr>
<td>Deep venous thrombosis (lower extremity), n</td>
<td>7</td>
<td>11</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Deep venous thrombosis (upper extremity), n</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary embolism, n</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Deep venous thrombosis and pulmonary embolism, n</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Evaluable patients, n</td>
<td>235</td>
<td>247</td>
<td>258</td>
<td>740</td>
</tr>
<tr>
<td>Recurrent venous thromboembolic event, n (%)†</td>
<td>10 (4.3)</td>
<td>11 (4.5)</td>
<td>8 (3.1)</td>
<td>29 (3.9)</td>
</tr>
<tr>
<td>Risk factors for recurrent thromboembolism for all treated patients (occurrences/patients at baseline), n/n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>3/122 (2.5)</td>
<td>10/137 (7.3)</td>
<td>5/146 (3.4)</td>
<td>18/405 (4.4)</td>
</tr>
<tr>
<td>Pulmonary embolism at baseline</td>
<td>4/88 (4.5)</td>
<td>5/94 (5.3)</td>
<td>5/105 (4.8)</td>
<td>14/287 (4.9)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0/44 (0.0)</td>
<td>1/54 (1.9)</td>
<td>2/59 (3.4)</td>
<td>3/157 (1.9)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>4/44 (9.1)</td>
<td>4/40 (10.0)</td>
<td>3/46 (6.5)</td>
<td>11/130 (8.5)</td>
</tr>
<tr>
<td>Cancer</td>
<td>3/45 (6.7)</td>
<td>6/49 (12.2)</td>
<td>3/47 (6.4)</td>
<td>12/141 (8.5)</td>
</tr>
</tbody>
</table>

* Treatment difference was 0.2% (95% CI, −3.04% to 3.49%) for once-daily enoxaparin compared with heparin and −1.2% (CI, −4.2% to 1.7%) for twice-daily enoxaparin compared with heparin.
† Treatment difference was −0.2% (CI, −3.45% to 3.84%) for once-daily enoxaparin compared with heparin and −0.6% (CI, −4.49% to 2.18%) for twice-daily enoxaparin compared with heparin.
Table 2.
Recommended Weight-Based Anticoagulant Dosing at Saint Vincent Hospital

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Dosage</th>
<th>BMI (kg/m²) Required for Dosage Adjustment</th>
<th>Weight (kg) Required for Dosage Adjustment</th>
<th>Dosage Adjustment Based on $CL_{cr}$ (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal Renal Function</td>
</tr>
<tr>
<td>Enoxaparin Prophylaxis</td>
<td>30 mg subcutaneously every 12 hr or 40 mg subcutaneously daily</td>
<td>≥35</td>
<td>&gt;150</td>
<td>$CL_{cr} &gt; 50$: 0.5 mg/kg subcutaneously daily</td>
</tr>
<tr>
<td>Enoxaparin Treatment</td>
<td>1 mg/kg subcutaneously every 12 hr or 1.5 mg/kg subcutaneously daily</td>
<td>≥35</td>
<td>&gt;150</td>
<td>$CL_{cr} ≥ 30$: 1 mg/kg subcutaneously every 12 hr or 1.5 mg/kg subcutaneously daily (as written on original order); do not cap dose</td>
</tr>
<tr>
<td>Heparin Prophylaxis</td>
<td>5000 units subcutaneously every 8 or 12 hr</td>
<td>30–50</td>
<td>&gt;100</td>
<td>5000 units subcutaneously every 8 hr</td>
</tr>
<tr>
<td>Heparin Treatment</td>
<td>For DVT/PE: 80 units/kg by i.v. bolus, then 18 units/kg/hr by i.v. infusion For ACS: 60 units/kg by i.v. bolus, then 12 units/kg/hr by i.v. infusion</td>
<td>&gt;30</td>
<td>&gt;100</td>
<td>Use ABW for dosing; do not cap dose</td>
</tr>
</tbody>
</table>

**ABW** = **IBW** + 0.4(TBW – IBW)

**IBW male** = 50 + (2.3 x ส่วนสูงเป็นนิ้วที่เกินจาก 150 ซม.)

**IBW female** = 45.5 + (2.3 x ส่วนสูงเป็นนิ้วที่เกินจาก 150 ซม.)
Other medications

- Lipophilic BBs: may need higher dose to achieve steady state.
- Verapamil: may prolong elimination and the effect may slightly reduce.
- Amiodarone, digoxin, propranolol: may need more supplemental dose.
- Warfarin: may require higher dose of warfarin to maintain a therapeutic INR.
- NOACs: Cmax and AUC may lower
Thank you