IMPACT OF OBESITY ON DRUG DISPOSITION AND RESPONSE

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1949 - 2017

Tufts Post-Doc and Faculty
1979-1984
The Seventy-Kilogram Fantasy

1942
Co-morbid conditions:

- Hypertension
- Diabetes
- Cardiovascular disease
- Metabolic disorders (cholesterol, lipids)
- Depression
- Osteoarthritis
- Sleep apnea
Dr. Abernethy’s Research Questions:

- How do you measure obesity?
- How do you measure volume of distribution?
- What is the physiologic (not arithmetic) relation between volume of distribution, half-life, and clearance?
- How does obesity modify drug distribution? What is the relation to lipid solubility?
- How does obesity modify clearance?
- How does this influence pharmacologic treatment of the obese patient?

Additional questions: The influence of old age and gender
QUANTITATIVE MEASURES OF OBESITY

- Weight
- Weight-height combinations (Ponderal Index, BMI, etc.)
- Waist circumference
- Percent ideal body weight
- Skinfold thickness

- Hydrostatic weighing
- Bioelectric impedance
- DXA (Dual-Energy X-Ray Absorptiometry)
Percent ideal body weight

\[ \text{IBW (pounds)} = 100 + 5 (\text{Height} - 60 \text{ inches}) \] for women
\[ 110 + 5 (\text{Height} - 60 \text{ inches}) \] for men

\[ \% \text{IBW} = \left(\frac{\text{actual weight}}{\text{IBW}}\right) \times 100 \]
INITIAL CLINICAL QUESTION:

For a specific individual drug, how does degree of obesity influence drug distribution and clearance?

(Drug entity is fixed; degree of obesity is variable)
# VOLUNTEER SUBJECTS

(1979-1984)

<table>
<thead>
<tr>
<th>Category</th>
<th>Weight</th>
<th>% Ideal Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>65 kg (142 pounds)</td>
<td>99%</td>
</tr>
<tr>
<td>Obese</td>
<td>114 kg (251 pounds)</td>
<td>179%</td>
</tr>
<tr>
<td></td>
<td>(Max: 435 pounds)</td>
<td></td>
</tr>
</tbody>
</table>

(Male and female mixed in both groups)
STUDY DESIGN

19 drugs studied;
N = 20 to 40 subjects per study;
More than 600 total trials!

- Single intravenous dose, or
- Single oral dose, if F = 1
- Multiple blood samples
- Determine $T_{\frac{1}{2}}, V_d, \text{Clearance}$

Pharmacokinetic analyses done by Jerold S. Harmatz
How do you measure volume of distribution?

\[ V_d = \frac{X}{C} \]
$V_{d(ss)}$ vs. $V_{d(area)}$?

Neither is “dependent” on elimination; both are independent physiologic determinants of $T_{1/2}$

$V_{d(area)}$ used in all studies

J Clin Pharmacol 1983; 23: 391-400
J Clin Pharmacol 2022; 62: 1350-1363
N = 1299

$R^2 = 0.895$

J Clin Pharmacol. 2022; 62: 1350-1363
Intravenous diazepam

CONTROL SUBJECT
Male, 64 yr, 65 kg
\( V_d = 107 \text{ Liters} \)
\( T_{\frac{1}{2}} = 51 \text{ hours} \)
\( CL = 24 \text{ mL/min} \)

OBESE SUBJECT
Male, 61 yr, 197 kg
\( V_d = 747 \text{ Liters} \)
\( T_{\frac{1}{2}} = 277 \text{ hr} \)
\( CL = 31 \text{ mL/min} \)
Anesthesiology 1984; 61: 27-35

[Graph showing the plasma midazolam concentration over time for different doses and body weights.

- Female, 37 yr: 61 kg (0.97 x IBW), $t_{1/2} = 3.4$ hr
- Female, 36 yr: 136 kg (2.31 x IBW), $t_{1/2} = 8$ hr

5 mg Intravenous
10 mg Oral]
Midazolam \( V_d(\text{area}) \) (Liters) vs. Percent Ideal Body Weight for MALE (filled squares) and FEMALE (open squares). The coefficient of determination \( R^2 = 0.84 \).
Clearance and volume of distribution are independent of each other.
NORMAL-WEIGHT SUBJECT (A1, A2)  

Non-Lipophilic drug (A1, B1)

A1

\[
\begin{array}{c}
C \\
\end{array}
\]

\[
\begin{array}{c}
P \\
\end{array}
\]

A2

\[
\begin{array}{c}
C \\
\end{array}
\]

\[
\begin{array}{c}
P \\
\end{array}
\]

OBESE SUBJECT (B1, B2)

Lipophilic drug (A2, B2)

B1

\[
\begin{array}{c}
C \\
\end{array}
\]

\[
\begin{array}{c}
P \\
\end{array}
\]

B2

\[
\begin{array}{c}
C \\
\end{array}
\]

\[
\begin{array}{c}
P \\
\end{array}
\]

Anatomic

Pharmacokinetic
How do you measure lipid solubility?

**PARTITION COEFFICIENTS**
- octanol:water
- \( \log_{10}P \)

**REVERSE-PHASE HPLC RETENTION TIME**
- \( \log_{10} \) HPLC retention
NEXT CLINICAL QUESTION:

For a specific degree of obesity, how does lipid solubility across a series of drugs influence drug distribution and clearance?

(Degree of obesity is fixed; drug lipid solubility is variable)
<table>
<thead>
<tr>
<th>Category of lipophilicity based on $\log_{10}$ of high-pressure liquid chromatographic retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ($\leq 0.95$)</td>
</tr>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Antipyrine</td>
</tr>
<tr>
<td>Caffeine</td>
</tr>
<tr>
<td>Cimetidine</td>
</tr>
<tr>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Salicylate</td>
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</table>
Non-obese control subjects

Log$_{10}$ (Unbound Vd(area))

Log$_{10}$ HPLC RENTENTION

R$^2 = 0.65$

LogP

R$^2 = 0.79$
Clearance in Obesity

- No evident relation to $V_d$ or lipid solubility

- No consistent relation to degree of obesity

- Obesity effect may be related to clearance pathway:
  
  Renal
  Hepatic -- CYP
  Hepatic -- UGT
- Lipid solubility
- Loading dose
- Obesity
- Single dose; Multiple dose: accumulation, washout
- Maintenance dose
- CL [Independent]
- Vd [Independent]
- T_{1/2} [Dependent]
Diazepam, 2 mg daily (hs)

Last dose

Obese subjects
$T_{1/2} = 10.7$ days

Control subjects
$T_{1/2} = 2.9$ days

Abernethy DR et al: J Clin Pharmacol 1983; 23: 369
Patient efficacy/safety consequences of:

- Delayed washout of lipophilic drugs after chronic therapy in obese patients (sustained serotonergic effects,\(^1\) sustained/prolonged DDIs involving inhibitors\(^2,3\))

- Delayed attainment of steady-state with lipophilic drugs in obese patients\(^4\)

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Vortioxetine-MAOI Serotonin Syndrome Risk

- 21-day prohibition against starting on a MAO inhibitor (risk of serotonin syndrome)

- NDA PK studies excluded
  BMI ≥ 35 kg/m²

- ‘Safe’ concentration in normals not reached until 31 days in obese patients

- Product label should provide this information

Data from J Clin Psychopharmacol 2018; 38: 172-179
Mean washout half-life:
Controls: 31 hours
Obese: 58 hours

Consequences: Prolonged DDIs with lurasidone and ranolazine due to sustained CYP3A inhibition
WHAT IS THE DESTINATION?

- Mandated study of obesity for all new drug development

- Current labels MUST be updated to incorporate consequences of prolonged half-life of lipophilic drugs in obesity

- Understand the unexplained variance

- Can DXA be bypassed?