Human ADME Study Design Considerations in Healthy Subjects and in Patients

Daria Stypinski BSc (Pharm), PhD
Clinical Pharmacology Sciences
Nov 18, 2015
Learning Goals and Outline

What is a human ADME study?
- Mass balance in the context of an ADME study
- Why are they required and what information do they provide?

How is a human ADME study conducted?
- Standard designs and special considerations
- Results and interpretation

Expansions of ADME protocols
What is Mass Balance?

Human Absorption, Distribution, Metabolism and Elimination (ADME)
hADME = clinical ADME = AME = mass balance study

**Mass Balance: What comes in ≈ What comes out**

\[
\begin{align*}
R^{-14}C-O-R' & \rightarrow R'-OH + R^{-14}C-OH \\
\text{Phase 1} & \quad \text{Phase 2} \\
\end{align*}
\]

Further metabolism

\[
(14CO_2 + R-OH)
\]

**Recovery goal > 90% Administered Dose**

Drug Dose = Urine (Drug + Metabolites) + Feces (Drug + Metabolites) + Any Vomited Dose (PO)

- Sometimes collect: toilet tissue, exhalate (i.e. CO₂)
- Generally not collected: sweat, tears
Role of hADME in Drug Development

Conducted to identify the major route of drug removal from the body

- Does the mass balance study suggest renal or hepatic as the major route of elimination?
  - Is a renal or hepatic study required?

Conducted to quantify and identify the major metabolites in the body

- What are the characteristics of drug metabolism?
  - FDA guidance on Safety Testing of Drug Metabolites
    - Additional safety testing prior to Phase III? (if > 10% of parent systemic exposure)
  - FDA guidance on Drug Interaction Studies
    - Need for in vitro or in vivo metabolite DDI? (if ≥25% of parent or active)
hADME Data to Support Objectives

Mass balance in excreta
- % dose in feces + % dose in urine

PK in circulation (drug, metabolites, total radioactivity)
- Plasma (drug, metabolites, total RA) ± WB partitioning ± ETR

Metabolic profiling in excreta and circulation
- Identification and relative abundancies

Routes and rates of excretion & relative contributions to CL
# Standard Study Design Outline

<table>
<thead>
<tr>
<th>1 Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single oral dose</td>
</tr>
<tr>
<td>Subjects: 6-8 healthy males</td>
</tr>
<tr>
<td>Confinement: planned + early release criteria + contingency for extension</td>
</tr>
<tr>
<td>PK (blood, urine, feces) and safety assessments</td>
</tr>
</tbody>
</table>
hADME Design Considerations

Population
- Healthy or Patients

Route of administration

Dose
- API dose
- Radioactive dose

Sample collection and data analysis
## Choice of Subjects

### Standard ADME in healthy subjects
- Most practical approach if safety favorable
- 6-8 males
- Women of non-childbearing potential (WNCBP) - if indication only in females

### ADME in patients
- Based on safety or scientific considerations
- 4-6 patients
- Individual subject recruitment

### Microdose ADME in healthy subjects
- Safety limits pharmacologically active dose in healthy
- 6-8 males (WNCBP as per indication)
- Microdose PK must be predictive of active
hADME Design Considerations

Population

- Healthy or Patients

Route of administration

Dose

- API dose
- Radioactive dose

Sample collection and data analysis
Route of Administration

Oral
- Same as clinical
  - Oral solution or filled capsule

Vascular
- Same as clinical

Inhalation
- 3-period, PO and IV radiolabeled, inhalation cold
hADME Design Considerations

Population:
- Healthy or Patients

Route of administration

Dose
- API dose
- Radioactive dose

Sample collection and data analysis
Dose: Active Pharmaceutical Ingredient (API) and Radiation

API dose: goal for same PK as at therapeutic dose

- Therapeutic or equivalent
- Microdose (predictive of therapeutic dose PK)

Radiation dose: lowest possible

- 21 CFR 361.1:
  - “…the subject receives the smallest radiation dose with which it is practical to perform the study…”
- FDA sets limits for maximum exposure to:
  - Reproductive organs
  - Bone marrow
  - Lens of the eye
Dosimetry Report: What is it and What is Needed

Estimates radiation exposure to various tissues in human body

- Required when dose > 500 nCi (in NE)

Minimum requirements:

- Proposed radioactive dose
- Animal mass balance
- Organ biodistribution study [i.e. (Q)WBA]
Most Common vs Most Appropriate

Industry standard/most common dose: 100 μCi (US)

- Radiation safety:
  - dosimetry usually favorable
- Regulatory compliance:
  - is it more radioactivity than needed?
- Practicality:
  - is it enough? Can all objectives be achieved at this dose?
Determining the Minimum Radioactive Dose

- Proportionality ratio:
  \[
  \frac{C_{\text{max}}}{\text{API Dose}} = \frac{\text{LLOQ}}{X}
  \]
  
  \(X\) = amount of radioactivity needed to just detect the \(C_{\text{max}}\)

- Example:
  \(C_{\text{max}}\) (16 mg dose) = 15.4 ng/mL
  LLOQ ~ 110 DPM/mL
  \(X = 51.5 \mu\text{Ci}\)
Plasma PK and Radioactive Dose

- Problem for total radioactivity PK in plasma
- Problem for metabolic profiling in plasma
- Potential problem for mass balance (if long terminal $t_{1/2}$)

### Plasma Total Radioactivity (nM equivalents)

<table>
<thead>
<tr>
<th>AN</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>0001</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>157.774</td>
<td>319.459</td>
<td>217.754</td>
<td>156.470</td>
<td>122.568</td>
<td>100.141</td>
<td>77.844</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0002</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0003</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>179.940</td>
<td>284.254</td>
<td>157.774</td>
<td>82.929</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0004</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0005</td>
<td>0.00</td>
<td>65.978</td>
<td>0.00</td>
<td>0.00</td>
<td>89.057</td>
<td>258.175</td>
<td>131.695</td>
<td>92.448</td>
<td>73.541</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0006</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>75.757</td>
<td>112.919</td>
<td>117.744</td>
<td>106.399</td>
<td>95.968</td>
<td>85.015</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

### Plasma API (nM)

<table>
<thead>
<tr>
<th>AN</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>0001</td>
<td>0.00</td>
<td>0.00</td>
<td>50.647</td>
<td>144.042</td>
<td>280.561</td>
<td>160.445</td>
<td>90.619</td>
<td>76.906</td>
<td>47.309</td>
<td>25.811</td>
<td>17.020</td>
<td>9.237</td>
<td>5.133</td>
<td>1.413</td>
</tr>
<tr>
<td>0002</td>
<td>0.00</td>
<td>0.00</td>
<td>13.532</td>
<td>35.275</td>
<td>42.589</td>
<td>26.175</td>
<td>19.842</td>
<td>20.562</td>
<td>19.577</td>
<td>17.376</td>
<td>15.854</td>
<td>10.077</td>
<td>6.019</td>
<td>3.227</td>
</tr>
<tr>
<td>0003</td>
<td>0.00</td>
<td>0.00</td>
<td>7.096</td>
<td>8.416</td>
<td>21.447</td>
<td>63.840</td>
<td>139.034</td>
<td>226.742</td>
<td>83.451</td>
<td>101.575</td>
<td>70.803</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0004</td>
<td>0.00</td>
<td>20.605</td>
<td>86.742</td>
<td>139.727</td>
<td>140.336</td>
<td>108.711</td>
<td>69.610</td>
<td>47.643</td>
<td>40.917</td>
<td>22.122</td>
<td>14.562</td>
<td>12.562</td>
<td>7.275</td>
<td>2.718</td>
</tr>
<tr>
<td>0005</td>
<td>0.00</td>
<td>51.499</td>
<td>28.669</td>
<td>37.797</td>
<td>66.003</td>
<td>185.658</td>
<td>83.974</td>
<td>48.854</td>
<td>36.311</td>
<td>21.155</td>
<td>18.564</td>
<td>10.677</td>
<td>6.037</td>
<td>5.628</td>
</tr>
<tr>
<td>0006</td>
<td>0.00</td>
<td>20.141</td>
<td>51.470</td>
<td>61.653</td>
<td>84.453</td>
<td>84.745</td>
<td>81.288</td>
<td>75.559</td>
<td>57.855</td>
<td>44.248</td>
<td>36.964</td>
<td>22.280</td>
<td>16.059</td>
<td>5.428</td>
</tr>
</tbody>
</table>
Options When 100 µCi is Not Enough

Dose > 100 µCi

Microtracer ADME and AMS

LSC until BLQ then AMS

↑ Count time for plasma and whole blood

↑ Aliquot size for plasma and whole blood

Urine and feces → LSC
Plasma and whole blood → AMS
<table>
<thead>
<tr>
<th>WHEN TO CONSIDER MICROTRACER DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosimetry not favorable</strong></td>
</tr>
<tr>
<td>▪ Recalculate dosimetry if &gt; 500 nCi</td>
</tr>
<tr>
<td><strong>Missing data for a dosimetry report</strong></td>
</tr>
<tr>
<td>▪ Dose ≤ 500 nCi</td>
</tr>
<tr>
<td><strong>Option for long t_{1/2} drugs</strong></td>
</tr>
<tr>
<td>▪ Dilution in excreta reduces recovery</td>
</tr>
</tbody>
</table>
Study Design Considerations with Microtrace Dose

<table>
<thead>
<tr>
<th>Same basic ADME design</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Single therapeutic dose or equivalent</td>
</tr>
<tr>
<td>- 6-8 Males (or WNCBP if indicated)</td>
</tr>
<tr>
<td>- Standard safety, PK assessments</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Main difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Delayed data analysis (long sample preparation time for AMS)</td>
</tr>
<tr>
<td>- No early release criteria</td>
</tr>
<tr>
<td>- No evaluation for possible extension</td>
</tr>
</tbody>
</table>
Final Product

Therapeutic or equivalent dose:
- Extemporaneous compounding required

Microdose:
- Less extemporaneous compounding

Precision more important than accuracy
- Easier to backtrack with dosing solution than capsules

<table>
<thead>
<tr>
<th>Subject #</th>
<th>API Dose (mg)</th>
<th>Total Radioactivity (DPM)</th>
<th>Total Radioactivity (µCi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61.2</td>
<td>227805770</td>
<td>102.6</td>
</tr>
<tr>
<td>2</td>
<td>61.3</td>
<td>228209397</td>
<td>102.8</td>
</tr>
<tr>
<td>3</td>
<td>61.3</td>
<td>228336002</td>
<td>102.9</td>
</tr>
<tr>
<td>4</td>
<td>60.8</td>
<td>226566519</td>
<td>102.1</td>
</tr>
<tr>
<td>5</td>
<td>61.1</td>
<td>227396170</td>
<td>102.4</td>
</tr>
<tr>
<td>6</td>
<td>61.1</td>
<td>227620931</td>
<td>102.5</td>
</tr>
</tbody>
</table>

Specific activity in each mL of dosing solution = 7858778 DPM/2.11 mg
hADME Design Considerations

Population:
- Healthy or Patients

Route of administration

Dose
- API dose
- Radioactive dose

Sample collection and data analysis
Confinement, Duration of Sampling and $t_{1/2}$

Recovery goal > 90% Administered Dose

- Short $t_{1/2}$
  - 7 days if predominantly urinary excretion
  - 14 days if predominantly fecal excretion
- Long $t_{1/2}$
  - 21 days with potential extensions
- Include:
  - Early release criteria (i.e. 2 consecutive days with < 1% dose)
  - Contingency for study extension (i.e. confinement, returns, at-home collections)

%Recovery vs $t_{1/2}$ with release criteria of <1% dose over 24 hr

Dilution Effects and Long $t_{1/2}$

Dilution effects may result in $<< 80\%$ recovery

If conventional radioactive dose:

- Confinement $2-3 \times t_{1/2}$, then weekly (or QOW) 24 hr returns
  - Mass balance from excretion rate vs time plots
  - AMS for samples from return visits

If microtracer radioactive dose:

- Same approach, with all radioactivity determined using AMS
Data Analysis and Results: Mass Balance Data

% Dose Administered (Total RA in Dose – any vomited) ≈ % Urine (Total RA) + % Feces (Total RA)

- If 100% >>recovery<<80% verify precise dose to each subject and $t_{1/2}$ estimates (i.e. from renal excretion of total radioactivity)
Plasma Exposure Logistics

- SA incorrect
- Calculation error
- Radiochemistry or stability

- LOQ differences
- $t_{1/2}$ of total RA is in the “distribution” phase

- LOQ differences
Metabolic Profiling vs. PK

For plasma, urine and feces, pooling is across samples accounting for > 85% RA for the given matrix.

Pooled samples = cannot do traditional PK analysis on these data
Qualitative, but only semi-quantitative = will not match the PK data exactly
Expansions of hADME Protocols
Most Common: Absolute Bioavailability Arm

Part 1, hADME (N = 6)

Part 2, absolute BA (N ≥ 3)

- PO and IV in 1 Period
- Dose PO 1st (therapeutic dose)
- At PO $T_{\text{max}}$ administer $^{14}$C-labeled IV microdose
  - Timing of IV & PO samples
  - IV dosing window
- PO dose drives IV dose PK
Other Types of Expansions:

1\textsuperscript{st} dose $^{14}$C ADME followed by MD

- To supplement PK data for therapeutic dose
- No time or dose-dependent PK

Site of action PK

- When plasma PK does not reflect site of action PD
  - I.e. biopsy, CSF, specific cell types

Dual isotope approach

- PK & ADME with AMS and PD with PET
**Learning Goals and Summary**

**What is a human ADME study**
- PK study conducted to:
  - identify the major route of removal from the body (hepatic or renal)
  - characterize metabolites and their relative abundancies

**How is a human ADME study conducted**
- Standard design
- Special considerations
  - Population
  - Route of Administration
  - Dose
  - PK characteristics

**Expansions of ADME protocols**
Thank you