Gathering Kinetic Data for Internal Dosimetry in Nuclear Medicine

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and
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RADAR method (Health Phys 85(3):294-310, 2003):

\[ D = N \times DCF \]

N is the number of disintegrations that occur in a source region

DCF is the dose conversion factor, which gives the dose absorbed in a target per disintegration in a source
Determination of Kinetic Data

• Preclinical:
  – Some animal species
  – Extrapolation of results
  – Kinetic analysis
  – Human dosimetry
  – Animal dosimetry?

• Clinical:
  – Experiments
  – Kinetic analysis
  – Dosimetry
MIRD Pamphlet No. 16: Techniques for Quantitative Radiopharmaceutical Biodistribution Data Acquisition and Analysis for Use in Human Radiation Dose Estimates


Nuclear Physics Enterprises, Cherry Hill, New Jersey; University of Cincinnati, Division of Medical Physics, Cincinnati, Ohio; Radiation Dosimetry Systems of Oak Ridge, Inc., Knoxville, Tennessee; Oak Ridge Institute for Science and Education, Radiation Internal Dose Information Center, Oak Ridge, Tennessee; Veterans Affairs Medical Center 640/151, Palo Alto, California; Department of Nuclear Medicine, University of Michigan, Ann Arbor, Michigan; Gaithersburg, Maryland; Division of Radiation Research, Department of Radiology, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; Department of Radiology, George Washington University Medical Center, Washington, DC; Pacific Northwest National Laboratory, Richland, Washington; Department of Radiation Research, University of California Davis Medical Center, Sacramento, California; Department of Radiology, Vanderbilt University School of Medicine, Nashville, Tennessee

This report describes recommended techniques for radiopharmaceutical biodistribution data acquisition and analysis in human subjects to estimate radiation absorbed dose using the Medical Internal Radiation Dose (MIRD) schema. The document has been prepared in a format to address two audiences: individuals with a primary interest in designing clinical trials who are not experts in pling error analysis techniques and selected calculational examples. The utilization of the presented approach should aid in the standardization of protocol design for collecting kinetic data and in the calculation of absorbed dose estimates.

FIGURE D3. Error in residence time calculation when the rapid washout phase is neglected. For source regions exhibiting biphasic clearance, the magnitude of the residence time underestimate (when neglecting the rapid washout component) are functions of the ratio of the slow to rapid washout effective half-times ($T_{s2}/T_{s1}$) and the ratio of the fractional activity removed rapidly to that removed slowly ($A_{r}/A_{2}$). When the relative amount of activity rapidly removed from the region is small compared to the long-term retention component, the errors due to neglecting the rapid washout are minor. As the long-term retention component effective half-time becomes much larger than that of the rapidly removed component, the errors are minor regardless of how the activity was distributed between the two washout components. The foregoing does not account for errors in residence time determination due to neglecting noninstantaneous uptake.

FIGURE D4. Potential errors in source region determination when the long-term retention is neglected. The ratio of activity removed from the source region to the total uptake is $r$, where $r = A_{r}/(A_{1} + A_{2})$. $(1 - r)$ is equal to the fraction of the activity retained with a long effective removal half-time. It is clear from this figure that not determining the long-term retention component introduces large errors (underestimates) in the source region residence time calculations.
Kinetic Models - Calculations

\[ N = \int A(t) \, dt = \int A_0 e^{-\lambda t} \, dt \]

\[ N = \int_0^t A_0 e^{-\lambda t} \, dt = \frac{A_0}{\lambda} (1 - e^{-\lambda t}) \]
Metabolic Models: Patient-specific kinetic modeling

MIRD 16: Number and spacing of time points
Uncertainties
\[ D = \frac{k \tilde{A} \sum_{i} n_i E_i \phi_i}{m} \]
A: Individuals with a rapid clearance rate require a higher dose of radiation (in mCi).

B: Individuals with a slow clearance rate require a lower dose of radiation (in mCi).

Targeted total body radiation dose 75cGy for patients with platelets 150,000/mm³ or 65cGy for patients with platelet counts between 100,000 and 150,000/mm³.

Cumulative excretion of Ho-166 DOTMP in twelve subjects (6 ♀, 6 ♂) with multiple myeloma. Breitz et al. J Nucl Med 2006
..the combined uncertainties in any given radiopharmaceutical dose estimate are typically, at a minimum, a factor of 2 and may be considerably greater, in general because of normal human variability, and particularly in disease states.

In therapy applications, if patient-individualized dosimetry is performed, …the total uncertainty in an individual dose estimate can be reduced to a value of perhaps ~10%–20%.
BIOLOGY
Approval of a new medical imaging agent includes several phases:

- A *preclinical phase*, in which studies in an appropriate animal species are carefully planned and executed, to provide a preliminary assessment of the possible radiation doses expected in human subjects.

- *Phase 1 studies* of medical imaging agents, which are designed to obtain pharmacokinetic and human safety assessments, based on a single mass administration and escalating mass administrations of the drug or biological product.
Phase 2 studies of medical imaging agents include:

- “refining the agent's clinically useful mass dose and radiation dose ranges or dosage regimen (e.g., bolus administration or infusion) in preparation for phase 3 studies,
- answering outstanding pharmacokinetic and pharmacodynamic questions,
- providing preliminary evidence of efficacy and expanding the safety database,
- optimizing the techniques and timing of image acquisition,
- developing methods and criteria by which images will be evaluated, and
- evaluating other critical questions about the medical imaging agent.”
• *Phase 3 studies* are designed to confirm the principal hypotheses developed in earlier studies, demonstrating the efficacy of the compound and method employed, verify the safety of the use of the medical imaging agent, and validate the necessary instructions for use of the compound and for imaging in the population for which the agent is intended.
Animal Data Collection Methods

• Autoradiography
  – Animals are sacrificed and frozen into a block of carboxymethyl cellulose (CMC).
  – Slices are cut with a Cryostat Microtome where the knife an cuts approximately 30 µm slice of the animal.
  – The sections are then freeze dried and attached to x-ray film for exposure.
Animal Data Collection Methods

- **Necropsy**
  - Animals are sacrificed, then frozen and individual organs and tissues are dissected out from the carcass.
  - These are assayed for radioactivity content, typically using scintillation detectors.

- **Imaging**
  - microPET and microSPECT methods
  - Region of Interest (ROI) analysis of images, as in humans.
Extrapolation of Animal Data

- Animals – mice, rats, even primates – are NOT little humans.
- Extrapolating the organ/tissue data to humans is not an exact science.
- One may assume that the percent of the administered activity seen in any organ at a given time will be the same activity seen in humans; one may say that this is a ’direct extrapolation’.
Extrapolation of Animal Data

• One may assume that the percent of administered activity *per gram* in an organ will be the same in humans; due to the normally considerable differences in body and organ masses, this is likely to produce erroneous results.

• Crawford and Richmond [1981] and Wegst [1981] evaluated various extrapolation methods proposed in the literature.
Extrapolation of Animal Data

• One method of extrapolating animal data that has been applied by many is the % kg/g method (Kirschner et al. 1975).

• In this method, the animal organ data need to be reported as % of injected activity per gram of tissue, and this information plus knowledge of the animal total body weight (TB weight) are employed in the following extrapolation:
Extrapolation of Animal Data

\[
\left( \frac{\%}{\text{organ}} \right)_{\text{human}} = \left( \frac{\%}{g_{\text{organ}}} \right)_{\text{animal}} \times \left( k g_{TB\text{weight}} \right)_{\text{animal}} \times \left( \frac{g_{\text{organ}}}{k g_{TB\text{weight}}} \right)_{\text{human}}
\]
<table>
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<th>Source Organ</th>
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<th>3 hr</th>
<th>6 hr</th>
<th>16 hr</th>
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<td></td>
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<tr>
<td>% ID/organ</td>
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<td>3.55</td>
<td>2.82</td>
<td>1.02</td>
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<tr>
<td>(% ID/g)</td>
<td>38.1</td>
<td>36.6</td>
<td>30.8</td>
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<td>HUMAN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>% ID/organ</td>
<td>3.26</td>
<td>3.12</td>
<td>2.63</td>
<td>0.962</td>
<td>0.486</td>
</tr>
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</table>

\[
\frac{38.1 \%}{g} \times (animal) \times \frac{0.020 \, kg \times 299 \, g}{70 \, kg} = \frac{3.26 \%}{organ} \quad (human)
\]
Extrapolation of Animal Data

• Some also suggest adding a scaling in time, to account for the different metabolic rates of species of different size.

• Glazier [2015] showed that metabolic rates vary with body size in mammals, with slopes typically between 0.67 and 0.75.

• From this, one may scale the times at which the same metabolic removal may have occurred in two mammalian species:
where $t_{\text{animal}}$ is the time at which a measurement was made in an animal system, $t_{\text{human}}$ is the corresponding time assumed for the human data, $m_{\text{animal}}$ and $m_{\text{human}}$ are the total body masses of the animal species and of the human and $b$ is a scaling factor derived from the slope of the metabolic rate ratios.
Fig 3.1. Variation of metabolic rates with mammalian body size, from [Glazier 2015]
<table>
<thead>
<tr>
<th></th>
<th>5 min</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>1.5 hr</th>
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<tr>
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<td>15 min</td>
<td>30 min</td>
<td>60 min</td>
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<tr>
<td>Extrapolated human time scale</td>
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<td>1.1 hr</td>
<td>2.2 hr</td>
<td>4.3 hr</td>
<td>6.5 hr</td>
</tr>
</tbody>
</table>
\[ t_a = t_h \left( \frac{m_h}{m_a} \right)^{0.25} \]

\[ 5 \text{ min} \times \left[ \frac{70 \text{ kg}}{0.2 \text{ kg}} \right]^{0.25} = 22 \text{ min} \]
Extrapolation of Animal Data

• Sparks and Aydogan [1999] studied the success of animal data extrapolation for several radiopharmaceuticals, using direct extrapolation, and mass and/or time extrapolation.

• They found that no particular method was superior to any other, and that in many cases, extrapolated animal data significantly underestimated observed uptakes in human organs.
\[ \tau \text{ Ratios Using Time/Mass Extrapolation} \]

\[ \mu = 2.6 \quad \mu_g = 0.79 \]

\[ \sigma = 11 \quad \sigma_g = 3.5 \]

Mode = 0.18
Extrapolation of Animal Data

- So, in conclusion, choice of an animal species and extrapolation method are areas of freedom in designing an animal study, and results obtained from animal studies must be recognized as only preliminary estimates of the dosimetry for any radiopharmaceutical.
Acquisition of Kinetic Data: Human Subjects
Anterior View - $I_A$

Posterior View - $I_P$

Figure 1. Illustration of conjugate-view counting.

Figure 2. Plot of transmitted fraction for anterior view, posterior view, geometric mean, and geometric mean with scatter included.
Gamma Camera Data:
Activity Calibration Factor

- Objects are at unknown depth in body.
- We obtain projection images. We need to correct for attenuation.
- Geometric mean method, in principle, removes depth dependence.

\[ A_{ROI} = \sqrt{\frac{I_A I_P}{e^{-\mu_e t}} \frac{f_j}{C}} \]
Important Corrections

- Attenuation
- Scatter
- Dead time
- Radioactive decay
\[ e^{-\mu_e t_1} \times e^{-\mu_e t_2} = e^{-\mu_e (t_1 + t_2)} = e^{-\mu_e t} \]
Co-57 Transmission Scan – Attenuation Correction
Co-57 Transmission Scan – Attenuation Correction
Gamma Camera Data:
Scatter Correction

- Activity in our region of interest has counts from Compton scattered events – from the actual photopeak and possibly from higher energy peaks.
- Use of lower and upper “scatter windows” in the acquisition are used to correct for this.
SPECT Image Reconstruction

Reconstruction Matrix

Detector
(n detector elements)
Iterative Reconstruction

- Mostly used today

- MLEM/OSEM (Poisson)

- From an initial estimate calculate a projection from a model of the imaging system

- Compare with measured projections

- Update estimate image based on the error between measured and calculated projection

Courtesy Dr. Michael Ljungberg, Univ of Lund
Principles of the ML-EM algorithm

- Initial Image Estimate
- New Image Estimate
- More Iterations
- Update step
- More angles?
- Backproject error
- Error projection
- Comparing step
- Estimated Projections
- Forward Projection
- Measured Projections
- Ratio


Yes

Courtesy Dr. Michael Ljungberg, Univ of Lund
PET/SPECT – draw Volumes of Interest (VOIs)
\[ A_{ROI} = \sqrt{\frac{I_A I_P}{e^{-\mu_e t}} f_j C} \]

<table>
<thead>
<tr>
<th></th>
<th>Time</th>
<th>organ # pixels</th>
<th>organ cts/pixel</th>
<th>View</th>
<th>bkgd # pixels</th>
<th>bkgd cts/pixel</th>
<th>Net cts/pixel</th>
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<td>Time (cts)</td>
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\[ A(t) = 0.0832 \exp(-0.0422 t) \]
Kinetic Analysis

In general, there are three levels of complexity that our analysis can take:

- Direct integration
- Least Squares Analysis
- Compartmental Models
Trapezoidal integration – manually calculate the area of the trapezoids, add, assume physical decay after last point.
Regression analysis – Fit a function (usually a sum of exponentials) through data, correct biological removal for physical decay, integrate.

\[ A(t) = A_1 \exp(-a_1 t) + A_2 \exp(-a_2 t) \]
Compartmental Analysis
Use of SAAM II for Biokinetic Analysis
RADAR method (Health Phys 85(3):294-310, 2003):

\[ D = N \times DCF \]

N is the number of disintegrations that occur in a source region.

DCF is the dose conversion factor, which gives the dose absorbed in a target per disintegration in a source region.
Area under any time-activity curve:

Number of disintegrations occurring in the source region

Units: Bq-hr, Bq-s, μCi-hr, etc.

Also: Bq-hr/Bq (administered), Bq-s/Bq, μCi-hr/μCi, etc.
**Example** Consider the following data set.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Activity (MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>0.5</td>
<td>72</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>
Trapezoidal Method

\[ A = \sum_{i} \left( \frac{x_i + x_{i+1}}{2} \right) \Delta t \]
Trapezoidal Method: Each interval is treated separately, and the parts are added:

\[ A_1 = (100 + 72) \times 0.5/2 = 43 \text{ MBq-hr} \]
\[ A_2 = (72 + 35) \times 0.5/2 = 26.75 \text{ MBq-hr} \]
\[ A_3 = (35 + 24) \times 1.0/2 = 29.5 \text{ MBq-hr} \]
\[ A_4 = (24 + 20) \times 2.0/2 = 44 \text{ MBq-hr} \]
\[ A_5 = (20 + 15) \times 2.0/2 = 35 \text{ MBq-hr} \]
\[ A_6 = (15 + 12) \times 4.0/2 = 54 \text{ MBq-hr} \]

Total = 232 MBq-hr
Least Squares Analysis - In general, the approach is to minimize the sum of the squared distance of the data points from the fitted curve. The curve will have the form:

$$A(t) = a_1 \exp(-\lambda_1 t) + a_2 \exp(-\lambda_2 t) + ...$$
The method looks at the squared difference between each point and the solution of the fitted curve at that point, and minimizes this quantity by taking the partial derivative of this expression with respect to each of the unknowns \( a_i \) and \( b_i \) and setting it equal to zero. Once the ideal estimates of \( a_i \) and \( b_i \) are obtained, the integral of \( A(t) \) from zero to infinity is simply:

\[
\int_0^\infty A(t) \, dt = \frac{a_1}{\lambda_1} + \frac{a_2}{\lambda_2} + \cdots
\]
For the above example, a computer fit of the data yielded the following fit:

\[ A(t) = 18.6 \exp(-0.039t) + 81.4 \exp(-1.23t) \]

(Time was given in hours; therefore the units on the rate constants are hr\(^{-1}\). The activity units are MBq.) The cumulative activity for this system, integrating from zero to infinity, then is:

\[ \tilde{A} = \frac{18.6}{0.039} + \frac{81.4}{1.23} = 477 + 66 = 543 \text{ MBq-hr} \]
This does not agree well with the estimate given by the trapezoidal method. The reason for this is that this integration goes from zero to infinity and the trapezoidal method estimates cut off the integration at \( t=10 \) hours. Evidently, a significant amount of the area under the curve (about half!) exists beyond \( t=10 \) hours. So this shows the importance of estimating the area under the curve beyond the end of the data set.
Conclusions

• Dosimetry based on data gathered in animals are required for new drug approval.
• Dosimetry based on extrapolated data from animals is generally not very reliable.
• Imaging studies with human subjects can provide reasonably accurate dose estimates for radiopharmaceuticals, but involves several important steps in order to be performed correctly.