USTUR Whole Body Case 0269: i.v. Ca-EDTA and Ca-DTPA Therapy

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Resource for Internal Actinide Dosimetry and Bio-molecular Effects
USTUR Whole Body Case 0269: Evaluating Pu Removal Mechanisms for i.v. Ca-EDTA and Ca-DTPA

Scope

1. Some personal background “perspective” -
   • Where am I coming from?

2. Overview of Pu-biokinetic research “methodology” –
   • Well illustrated by USTUR Case 0269.

3. Interim results of modeling Ca-EDTA and Ca-DTPA action in USTUR Case 0269.
Where Does ACJ Come From: My Research Pathway!

Royal Free Hospital School of Medicine, London, UK (1965-69)

NRPB, UK (1970-1988)


USTUR/COP/WSU Richland, WA (2004-2010?)

From Laboratory Rat to Human!
USTUR Case 0269 – Historical Perspective

- **Since the late 1950s**, Ca-DTPA (trisodium calcium diethylenetriaminepentaacetate) has been used in the U.S. atomic weapons program to “decorporate” serious (infrequent accidental) internal uptakes of plutonium, americium, californium and curium.
  - Historical accounts of Ca-DTPA decorporation therapy in major U.S. radiation accidents (1958 through 1987) have been published.
    - See [http://www.orau.gov/reacts/calcium.htm](http://www.orau.gov/reacts/calcium.htm) for sources.

- **Case 0269 - accidental exposure in 1956!**
  - Pre-dates published accounts.
  - Served as a key “test bed” for various “potential” decorporation drugs.
  - Results influenced early selection of Ca-DTPA as the “drug of choice.”
USTUR Case 0269 – Early Medical History

- Exposed (at Hanford) by accidental inhalation of a fine “mist” of freshly-separated solution of $^{239}\text{Pu(NO}_3\text{)}_4$:
  - Recognized immediately as a “serious internal exposure” – warranting “decorporation” therapy.
  - Urine and fecal sampling started immediately.
  - Intravenous injection of Ca-EDTA (only drug available at the time) started on second day.
  - All of the above signify a remarkably high standard of prompt medical care!

- This person was one of the earliest “registrants” of the National Plutonium Registry – founded in 1968 by the Hanford Environmental Health Foundation (HEHF) under contract with the U.S. Atomic Energy Commission (AEC).
  - National Plutonium Registry was “progenitor” of what is now the USTUR.
USTUR Case 0269 – The Exposure

• Pre-dated the International Commission on Radiological Protection’s (ICRP’s) earliest recommended reference “permissible” exposure value for internal plutonium.
  ▪ In 1959, for “soluble” Pu, the ICRP recommended a “Maximum Permissible Burden” \((\text{in Bone})\) of 40 nano-curries \((1.48 \text{kBq})\).

• Air sample (running when accident occurred) had \(^{239}\text{Pu}\) activity of \(7 \times 10^6 \text{ dpm} \approx 120 \text{kBq}\).
  ▪ \(\approx 80 \times \text{the [1959] MPB!}\)
  ▪ \(\text{Nasal smear } 10^5 \text{ dpm} \approx 1.1 \text{ MPB}!\)

• The person was “removed” from further work with plutonium.
  ▪ No subsequent exposures.
USTUR Case 0269 – Early “Decorporation” Treatment

• Within a day of the accident, patient treated with i.v. Ca-EDTA:
  ▪ 1 g per injection – per day.
  ▪ Injection regimen ~ 1-week-on, 1-week-off.
  ▪ Continued for following 6 months.

• Oral administration of Ca-EDTA – and various other “experimental” chelating agents – attempted over following years.

• Intravenous Ca-DTPA:
  ▪ 869 d – 0.2 g × 2
  ▪ 870 d – 0.4 g × 2
  ▪ 871 d – 0.6 g × 2
  ▪ 872 → 952 d – 0.8 g × 2 per day – intermittently.
  ▪ 954 → 963 d – 1.0 g × 2 per day – intermittently.
  ▪ 1031 → 1642 d – 1.0 g × 1 per day – intermittently.
Molecular Structure of Ca-EDTA


FIGURE 19.2A. (Left) Possible structural formula of EDTA and its complex with calcium. (Redrawn from Foreman 1954. Reprinted with permission of the University of Utah Press, Salt Lake City, Utah, copyright 1954.)

FIGURE 19.2B. (Right) Alternative structure for the calcium chelate with EDTA. (Redrawn from Foreman 1954. Reprinted with permission of the University of Utah Press, Salt Lake City, Utah, copyright 1954.)
USTUR Case 0269 – Bioassay Monitoring

- $^{239/240}$Pu in urine:
  - Followed over 33 years.
  - Collected both during and between decorporation treatments.
  - Total of 391 $^{239/240}$Pu-in-urine results.

- $^{239/240}$Pu in feces:
  - Followed over 31 years.
  - Collected both during and between decorporation treatments.
  - Total of 92 $^{239/240}$Pu-in-feces results.

- $^{239/240}$Pu in blood:
  - Several measurements - during decorporation treatment.
USTUR Case 0269 – Whole-Body Donation

• Died in 1994 - at age 79 y:
  ▪ **38 y after plutonium intake.**

• Cause of death **NOT** related to internal actinide exposure:
  ▪ Extensive carcinomatosis secondary to prostatic carcinoma.

• Autopsy – full whole-body dissection carried out for radiochemical analysis of tissues.
  ▪ Radiochemical analyses completed in 1996 – by **USTUR laboratory (WSU, Pullman)**.
Scientific Bases of Early Pu Chelation Therapy

- **Mid-late 1950s** - USAEC treating physicians were guided only by “professional intuition”:
  - Ca-EDTA in common use to remove heavy metals (e.g. treat Pb poisoning) – *human experience*.

- **Caveat** - no practical knowledge of how Ca-EDTA “worked” to decorporate Pu (and other transuranium elements).
  - How much Pu is “removed”?
  - From which tissues?
  - Is Pu removable from *Bone* – the assumed “critical” tissue?

- **Experimental animal studies** were started (in U.S. and Europe) to address these questions.
Pu Decoration Studies in Rodents (U.S.)

• Early 1960s - USAEC program of “animal studies” – effectiveness of EDTA, DTPA (and other chelators) in rodents:
  - Argonne National Laboratory (Fried, Schubert et al.)
  - Battelle Northwest Laboratory (Smith, Bair et al.)
  - University of Utah Medical School (Lloyd et al.)
  - New York University (Cohen et al.).


Pu Decorporation Studies in Rodents (U.K.)

- Early 1960s – Medical Research Council supported actinide chelation studies at the Institute of Cancer Research, Sutton, Surrey (Drs. David Taylor and David Sowby).

Problems in Extrapolating from Animals to Man

Prompt i.v. DTPA Reduces Dose to Osteogenic Stem Cells

- James and Taylor (1971).
**Even Delayed DTPA Flushes Pu from Bone Marrow**

### Table 1. Plutonium-239 concentration in the epiphyseal marrow of the femur*

<table>
<thead>
<tr>
<th>Time in days post $^{239}$Pu injection</th>
<th>$^{239}$Pu concentration (nCi cm$^{-3}$ μCi$^{-1}$)</th>
<th>Untreated</th>
<th>DTPA at 7, 8, 9, 10, 11 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$4.7 \pm 0.8$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>4</td>
<td>$4.8 \pm 0.3$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>21</td>
<td>$4.6 \pm 1.1$</td>
<td>$0.8 \pm 0.3$</td>
<td>$-$</td>
</tr>
</tbody>
</table>

* Expressed in units of nanocuries per cm$^3$ microcurie of injected activity $\pm$ S.D. of mean values from different animal specimens.
Autoradiographic Visualization of Bone Growth/Chelation Dynamics

Key

i.v. injection of citrate-buffered (monomeric) $^{239}$Pu(NO$_3$)$_4$ – 5 µCi/kg

a. 1-d untreated
b. 21-d untreated
c. DTPA at 7 d
d. DTPA at 30 min
e. From [b]
f. From [c]
Why is Chelation Therapy for Internal Actinides Still of Interest in 2004?

- And it's only taken 50 years to get round to it!
Getting to the “New Science” Part – Essential Tools!


ICRP 67 Pu Biokinetic Model (1993) – Tissue Uptake/Retention
Where Does (Current) Data for Late Pu Excretion Data Come From?

Rundo et al. (1976) traced two of Wright Langham’s original group of “terminally ill” patients injected with soluble Pu(NO₃)₄ at Los Alamos - 27 years earlier (HP-3 & HP-6).

Their Pu excretion was still measureable!
ICRP 67 Pu Biokinetic Model – Potential Chelation Pathways
CASE 0269 Software Toolbox – 1. IMBA Expert™ USDOE-Edition
Case 0269 Software Toolbox – 2. Algorithm for Solving Large Model

Requirements

1. Solve model in time steps – corresponding to urine/fecal sampling interval.

2. Vary ALL parameter values.

3. Evaluate “goodness-of-fit” to urine/fecal data.

4. Fast cycle time – for iterative “parameter seeking”.

ICRP 66 HRTM (1994) – Competitive Clearance Mechanisms
Case 0269 – $^{239/240}$Pu-in-Urine Data

- **Key**
  - Untreated
  - i.v. Ca-EDTA
  - Oral Ca-EDTA
  - Zr-Citrate
  - i.v. Ca-DTPA

- **Approx. 8X untreated**
- **Approx. 50X untreated**

- **Graph Details**
  - Y-axis: Urinary excretion rate, dpdm/d
  - X-axis: Time since inhalation, d

- **Approx. 8X untreated**
- **Approx. 50X untreated**
Case 0269 – $^{239/240}$Pu-in-Feces Data

**Graph Description:**
- **Y-axis:** Fecal excretion rate, dpm/d
- **X-axis:** Time since inhalation, d

**Key Points:**
- Untreated
- i.v. Ca-EDTA
- i.v. Ca-DTPA
- Zr-citrate
"Fitted" $^{239}$Pu Activity Measured in Lungs (@14,054 d)
Case 0269 – IMBA Expert™ Analysis

- Exclude urinary and fecal data clearly influenced by chelation.
- Analyze simultaneously:
  - urinary and fecal bioassay data
  - lung (and lymph node) Pu contents at time of death
  - “Find best fit” – by varying aerosol and absorption parameter values required to minimize $\chi^2$.

Result:

Intake = 58 kBq
AMAD = 2 µm
$f_1 = 0.0005$
$s_p = 10 \text{ d}^{-1}$
$s_{pt} = 100 \text{ d}^{-1}$
$s_t = 0.02 \text{ d}^{-1}$
$f_b = 8\%$
$S_b = 2 \times 10^{-4} \text{ d}^{-1}$
"Best Fit" – Predicted vs. Measured Pu-in-Urine

**Assumes**

1. No treatment.

2. ICRP-Recommended parameter values in ICRP67 biokinetic model ("hard wired" in software).
“Best Fit” – Predicted vs. Measured Pu-in-Feces
Method Used to “Fit” Parameter Values
Fitted “Enhancement” Factors – Ca-EDTA (Interim)

- EDTA Flush Build-up Time Constant (Tissues) = 145
- EDTA Excretion Build-up Time Constant (Urine) = 240

- EDTA Excretion Enhancement Factor (to Urinary Path) = 5.100
- EDTA Excretion Enhancement Factor (to Bladder) = 14.900
- EDTA Tissue Uptake Factor = 1.000
- EDTA Liver Clearance Factor = 1.370
- EDTA Marrow Clearance Factor = 1.370
- EDTA ST0 Clearance Factor = 1.370
- EDTA ST1 Clearance Factor = 1.370
- EDTA ST2 Clearance Factor = 1.370
Fitted “Enhancement” Factors – Ca-DTPA (Interim)

DTPA Flush Build-up Time Constant (Tissues) = 1000000
DTPA Excretion Build-up Time Constant (Urine) = 1000000
DTPA Excretion Enhancement Factor (to Urinary Path) = 1.000
DPTA Excretion Enhancement Factor (to Bladder) = 15.500
DTPA Tissue Uptake Factor = 0.000
DTPA Liver Clearance Factor = 18.000
DTPA Liver Blood Factor = 1.000
DTPA Liver Fecal Factor = 1.000
DTPA Marrow Clearance Factor = 18.000
DTPA ST0 Clearance Factor = 1.440
DTPA ST1 Clearance Factor = 1.440
DTPA ST2 Clearance Factor = 1.440
DTPA Bone Surface Clearance Factor = 6.660
Ca-EDTA: Interim Model of Pu-in-Urine Excretion
Ca-DTPA: Interim Model of Pu-in-Urine Excretion
Ca-DTPA: Interim Model of Pu-in-Feces Excretion
## Case 0269: Tissue Radiochemistry Results

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Measured Tissue Content, kBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Body</td>
<td>2.280</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.0267</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>0.00019</td>
</tr>
<tr>
<td>Liver</td>
<td>0.937</td>
</tr>
<tr>
<td>Skeleton</td>
<td>1.178</td>
</tr>
<tr>
<td>Muscle, Skin, etc.</td>
<td>0.141</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.00169</td>
</tr>
</tbody>
</table>
## Case 0269: Interim USTUR Model Predictions

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Measured</th>
<th>USTUR Model Ca-EDTA + Ca-DTPA</th>
<th>USTUR Model Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Body</td>
<td>2.280</td>
<td>2.289</td>
<td>4.225</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.0267</td>
<td>0.0267</td>
<td>0.0267</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>0.00019</td>
<td>0.00021</td>
<td>0.00021</td>
</tr>
<tr>
<td>Liver</td>
<td>0.937</td>
<td>0.814</td>
<td>1.623</td>
</tr>
<tr>
<td>Skeleton</td>
<td>1.178</td>
<td>1.213</td>
<td>2.183</td>
</tr>
<tr>
<td>Muscle, Skin, etc.</td>
<td>0.141</td>
<td>0.228</td>
<td>0.383</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.00169</td>
<td>0.00166</td>
<td>0.00317</td>
</tr>
</tbody>
</table>
Summary

Graphical General Biokinetic Model for Inhaled Plutonium
Summary

Mathematical

Specific Rate Matrix for Individual Person

Pu Systemic Biokinetics
Objective

Solve Rate Matrix for Every USTUR Whole-Body Case — i.e., Define Human Population Distribution!
Summary

Future

Solve Extended Rate Matrix for USTUR Whole-Body Cases with Significant $^{241}$Am in-growth
Finale

Future

It’s All in the Genes!

GENE EXPRESSION MAP (GEM)