January 10, 2020

Michael Layton, Director
Division of Materials, Safety, Security, State and Tribal Programs
Office of Nuclear Material Safety and Safeguards
Nuclear Regulatory Commission

Dear Michael,

As requested by Dr. Said Daibes, Lucerno is providing NRC with the abstract, a copy of the American College of Nuclear Medicine acceptance letter, and the poster that will be presented at the Society of Nuclear Medicine and Molecular Imaging and American College of Nuclear Medicine Mid-Winter meeting in two weeks.

Please note that the novel dosimetry method described in this poster is being submitted for publication in a medical physics journal at the request of the journal's editor. Lucerno will forward more information about the publication of this method once we hear from the journal.

We request that the contents of the poster not be shared outside of the NRC staff until after January 24, 2020. Thank you for your consideration of this request. As promised in our December communication, Lucerno will be forwarding you some additional patient extravasation dosimetry results later this month.

I am sorry that we were not able to meet while I was in Washington DC earlier this week. I will be returning on February 5, 2020 and if you are available, I would appreciate the opportunity to stop in and introduce myself.

Sincerely,

Ron Lattanze
Chief Executive Officer

Enclosures:
1. Submitted Abstract
2. Acceptance Notice
3. Poster

cc:
Chris Einberg
Lisa Dimmick
Said Daibes
Kellee Jamerson
Donna-Beth Howe
Novel Method to Calculate Equivalent Dose to Tissue in Cases of Radiopharmaceutical Extravasation

Josh Knowland, Jackson W. Kiser

Objectives:

Radiopharmaceutical extravasations can result in high concentrations of activity remaining within tissue near the injection site. This activity can expose the tissue to significant dose over time. Existing dosimetry methods do not accurately account for changes in extravasated activity or its volume over time. While it may be impractical to dynamically monitor changes in extravasated activity using a PET/CT or gamma camera, radiation detectors may be a practical alternative.

The Lara® System (Lucerno Dynamics, Cary, NC) consists of scintillation detectors for monitoring radiopharmaceutical injection quality. The system records decay-corrected time-activity curves (TACs) of the activity near the injection site. The objective of this work was to develop a new method of extravasation dosimetry that considers the radiopharmaceutical reabsorption rate as measured by topical scintillation detectors.

Methods:

Extravasation activity is quantified using static PET/CT images with a threshold of 10% of SUV_{MAX}. An exponential function is fit to decay-corrected TAC data using a least squares method. The decay constant for the exponential function is used as an estimate of reabsorption rate. This rate is used to estimate the initial extravasation activity by extrapolating the measured activity in the static images back to the time of injection. Initial extravasation tissue volume is estimated with two approaches: twice the injected radiopharmaceutical volume and the injected radiopharmaceutical volume plus the saline flush volume. Dose rates are calculated using IDACdose 2.1 software using spherical volumes of muscle tissue. Equivalent dose to the tissue is then calculated by multiplying dose rate with activity over time and integrating.

Results:

The method was used to calculate equivalent tissue dose for 2 cases of clinical extravasation of 18F-FDG and the results were compared to three existing methods of extravasation dosimetry. Injection site activities at the time of imaging were 1.6 mCi and 5.2 mCi. Estimated half-time reabsorption rates were 27.6 min and 55.9 min. Initial volumes ranged from 3.0 cm³ to 44.1 cm³. Dose rates ranged from 2.2 mSv/mCi-min to 28.5 mSv/mCi-min. Equivalent dose calculations fell within the range of other methods, but with a tighter spread of estimates The new method resulted in equivalent dose estimates of 0.7 Sv to 6.0 Sv (0.7-6.0 Gy) whereas existing methods estimated 0.9 Sv to 70.1 Sv (0.9 Gy to 70.1 Gy).

Conclusions:

A new method of dosimetry for diagnostic radiopharmaceutical extravasation was developed and tested. The method improved upon existing methods by incorporating measurements of activity near the injection site over time. The method demonstrates that tissue near the injection site can be exposed to significant equivalent dose in cases of extravasation.
December 4, 2019
Dear Dr. Kiser
On behalf of the American College of Nuclear Medicine, I am pleased to inform you that your abstract, Control ID: 47 (now poster 13) Novel Method to Calculate Equivalent Dose to Tissue in Cases of Radiopharmaceutical Extravasation has been accepted for poster presentation at the ACNM Annual Meeting. Poster must be mounted, by Thursday, January 23rd at 3:00pm (local time) and can be removed anytime between Noon and 6pm on Saturday, January 25, 2020. Poster board specifications are as follows: 6 feet wide & 4 feet tall.
Presentation Date: Friday, January 24, 2020
Presentation Time: 12:15-1:15 pm (local time)
The meeting will be held at the Tampa Marriott Water Street, Tampa, FL on January 23-25, 2020. The Ursula Mary Kocemba-Slosky, Ph.D. award, the ACNM best abstract award; along with the Young Investigators Awards, comprised of three $500 essay awards and two $750 travel grant awards, will be awarded during the ACNM new fellows induction ceremony and Awards Banquet on Friday night, January 24, 2020 @ 7pm. Tickets are sold separately and may be purchased at the registration desk based on availability ($150/person, Residents: $60/person).
In addition, you will be able to submit your full manuscript for publication consideration no later than April 20, 2020. The Clinical Nuclear Medicine Journal editorial board will assist in an expedited review the manuscripts and, if accepted, chosen manuscripts will be published in the Clinical Nuclear Medicine Journal - ACNM’s official publication. Authors of ACNM presentations may send their full manuscript to Clinical Nuclear Medicine through the on-line "Editorial Manager" manuscript management system http://www.editorialmanager.com/cnmi/. Please also forward a copy of your manuscript to Delicia Hurdle in the ACNM office at dhurdle@snmmi.org no later than April 20, 2020.
To take advantage of the early-bird rates, please register by December 12. The link to the registration site can be found here: MWM 2020 Registration. After December 12th, please visit the ACNM Annual Meeting website to register for the meeting and for information to make your hotel and travel reservations.
EPoster Information: Instructions on uploading your ePoster will be provided, on or about Friday, December 20, 2019. We would like to have as many posters available for viewing no later than Friday, January 17, 2020.
If you have questions regarding this correspondence, please contact Delicia Hurdle, Senior Program Manager at dhurdle@snmmi.org or 703-667-5121.
Thank you for your contribution to the ACNM Annual Meeting. We look forward to seeing you in Tampa!
Sincerely,

Erin Grady, MD, FACNM
ACNM President ACNM

Simin Dadparvar, MD
FACNM Scientific Abstract Committee
Novel Method to Calculate Equivalent Dose to Tissue in Cases of Radiopharmaceutical Extravasation

Josh Knowland, Lucerno Dynamics LLC, Cary NC and Jackson W. Kiser M.D., Carolin Clinic, Roanoke VA

Background

Radiopharmaceutical extravasation can result in high concentrations of activity remaining within tissue near the injection site resulting in significant dose over time (2-5).

An existing published technique for extravasation dosimetry assumes the entire injection is extravasated into tissue with a minimal volume (2,3). This technique assumes no movement or reabsorption of the activity over time—it decays entirely in situ.

A second technique improves upon the first by assuming the biological clearance of the radiopharmaceutical. The body will clear the radiopharmaceutical in the intravascular space through venous and lymphatic capillaries at a rate dependent on the concentration gradient between intravascular fluid and blood as well as the degree of vasculature in the local area. The extravasation activity peaks initially in time of 1-2 hours, but can be up to 8 or 10 hours based on vasculature (10). This assumption has been further confirmed by studies that intentionally extravasated saline and then monitored the rate of clearance over time (9-10). Assumed clearance rate can improve dose estimation accuracy, but the technique still assumes complete extravasation within an unchanging volume.

A third technique assumes radioactive decay and uses static nuclear images to measure extravasation volume and activity at imaging time. It still assumes an unchanging volume and no biological clearance.

These techniques result in a flawed estimate of a patient’s tissue dose. To improve dose accuracy for a particular patient, information is needed about the changes in extravasation activity and volume over time, which static imaging cannot provide (7,13-15). Serial images of the injection site or continuous measurement with a sternal counter or radiation monitor have been proposed to estimate the rate of biological clearance (5,6,8,10-15). In this work, we sought to develop a more accurate technique of injection site tissue dosimetry for cases of extravasated radiopharmaceuticals that we account for both biological clearance and volume expansion over time.

Methods

Estimation of the rate of biological clearance was made using topical injection site sensors (Lara®, Lucerno Dynamics). The sensors provide a measurement once per second and its output is representative of changes in local activity (9).

The time-activity curve (TAC) produced by Lara for ideal intravenous injections shows an initial bolus spike from the injection-arm sensor followed by an immediate reduction to a level consistent with that measured by the reference arm sensor. This indicates that the injected radiopharmaceutical is systemic with low probability of residual injection site activity.

An extravasation that leaves significant activity near the injection site results in an elevated TAC during subsequent sensor monitoring. Sensor output will decrease accordingly. Sensor output and the presence of residual activity at the injection site has been clinically validated using dynamic imaging (20).

The figure to the right shows examples of TAC from both ideal and non-ideal injections.

With the availability of TAC data for the injection site, one can improve on the existing extravasation dosimetry techniques.

Overall, the steps in our novel technique are:

1. Calculate the activity clearance rate using injection site TAC data with a least squares function.
2. Determine the imaging-time activity and volume using static imaging.
3. Extrapolate backwards to injection time using imaging time activity and the clearance rate to find initial extravasation activity.
4. Calculate both minimal and maximal initial extravasation volumes using injected radiopharmaceutical and saline volumes. Minimal volume is calculated as twice the injected radiopharmaceutical volume while maximal volume includes the entire volume of saline flush. We used the maximal if calculated volume was less than 0.1 cm³.
5. Determine the activity within the initial extravasation tissue volumes at imaging time using a nuclear medicine image data centered about the maximal voxel.
6. Calculate the activity over time within the initial extravasation extravasation tissue volume from the potential function to the initial activity.
7. Calculate the dose per unit time for the initial extravasation tissue volume based on published data for spherical volumes of muscle.

To estimate the rate of biological clearance within a patient, the Lara system identifies the likely presence of excess radiotracer near the injection site and time data for the injection site, an image could be constructed.

Results

Below are the dosimetry results for three clinical cases of diagnostic radiotracer extravasation using the proposed technique.

<table>
<thead>
<tr>
<th>Case Study</th>
<th>Equivalent Dose to Extravasated Tissue (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14547</td>
<td>3,100 - 70,100</td>
</tr>
<tr>
<td>15170</td>
<td>2,300 - 27,500</td>
</tr>
<tr>
<td>16414</td>
<td>43,000 - 154,000</td>
</tr>
</tbody>
</table>

- **Case 1**
  - **Injection**:
    - **Radiotracer Activity**: 9.99 mCi
    - **Biological Clearance Half-Life**: 27.6 min
  - **Sensor Output**:
    - **Saline Flush Volume**: 0.0 mL
    - **Dose Rate**: 5.95 mSv/mCi-min
    - **Time Before Imaging**: 62 min
    - **Total Equivalent Dose**: 1,500 mSv

- **Case 2**
  - **Radiotracer Activity**: 14 mL
  - **Biological Clearance Half-Time**: 2.0 min
  - **Total Equivalent Dose**: 7,000 mSv

- **Case 3**
  - **Radiotracer Activity**: 2.3 mCi
  - **Biological Clearance Half-Time**: 2.0 min
  - **Total Equivalent Dose**: 1,500 mSv

<table>
<thead>
<tr>
<th>Case Study</th>
<th>Radiotracer Activity (mCi)</th>
<th>Biological Clearance Half-Time (min)</th>
<th>Total Equivalent Dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14547</td>
<td>9.99</td>
<td>27.6</td>
<td>1,500</td>
</tr>
<tr>
<td>15170</td>
<td>14.00</td>
<td>2.0</td>
<td>7,000</td>
</tr>
<tr>
<td>16414</td>
<td>2.30</td>
<td>2.0</td>
<td>1,500</td>
</tr>
</tbody>
</table>

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- **Case 3**
  - **Radiotracer Activity**: 2.3 mCi
  - **Biological Clearance Half-Time**: 2.0 min
  - **Total Equivalent Dose**: 1,500 mSv

Conclusions

We have described and demonstrated a novel technique for calculating equivalent dose to tissue in the case of radiopharmaceutical extravasation.

The technique differs from existing techniques by accounting for the ways in which both the extravasation activity and volume change over time. Inclusion of dynamic time-activity data results in a more accurate rate of estimation of equivalent dose to the initially extravasated tissue volume.

The table below compares our novel technique’s results to existing techniques.

- **Technique 1** assumes that the entire injection is extravasated into a volume of tissue equal to its injection volume. Furthermore, it assumes no reabsorption and no movement of the radiopharmaceutical. Dose was calculated using static saline flush calculation.
- **Technique 2** assumes a biological clearance half-time of 120 minutes and 80% extravasation into a volume equal to the injected radiopharmaceutical volume plus the injected radiopharmaceutical volume plus the saline flush volume.
- **Technique 3** uses activity and volume from static images and accounts for physical decay, but assumes no biological clearance.

Nuclear medicine practitioners may reject technique 1 as implausible because the assumption of 100% extravasation with no biological clearance is easily refuted by static images. If all activity decays near the injection site, no image could be constructed.

Neither technique 2 nor 3 accurately account for changes over time. Technique 2 assumes biological clearance with a half-time of 120 minutes. However, the example cases presented here show that 18F-FDG can clear faster than that. An assumed clearance half-time of 120 minutes would over estimate the dose in these examples, in the 18F-MDP case, biological clearance was essentially non-existent, so an assumed clearance rate would underestimate the dose.

Tissue dose is dependent on not only the radiopharmaceutical radiation type and energy, but also how it is administered and how it clears. For example, 18F-MDP extravasations may lead to higher than anticipated tissue dose. First, many 18F-MDP procedures are performed as a “straight stick” with no saline flush, leading to very small initial volumes with high specific activity. Secondly, the molecular chain of Tc99m-MDP is shorter than other radiopharmaceuticals which leads to more rapid biological clearance and Tc99m has a significantly longer physical half-life than other diagnostic radiopharmaceuticals.

Along with the impact that extravasations can have on diagnosis and subsequent treatment (11), there is evidence that the radiation dose to injection site tissue can cause both deterministic (1,2,3,4) and stochastic (12) harm.

We propose that patient care teams should be aware of and prepared for the possibility of extravasation when using radiopharmaceuticals. Furthermore, they should monitor each procedure for extravasation and evaluate the extravasation dose geometry. We have demonstrated a method of dosimetry that may be more accurate than existing methods due to inclusion of dynamic time-activity data.