

Extravasation of a Therapeutic Dose of ^{131}I -Metaiodobenzylguanidine: Prevention, Dosimetry, and Mitigation

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After the extravasation of a therapeutic dose of ^{131}I -metaiodobenzylguanidine that produced a radiation burn to a patient's forearm, we instituted a catheter placement verification protocol. **Methods:** Before therapy infusion, proper placement is verified by administering 37 MBq of $^{99\text{m}}\text{Tc}$ -pertechnetate through the catheter, and monitoring activity at the administration site and on the contralateral extremity. A dosimetric model describing both high-rate and low-rate dose components was developed and predicted that the basal epidermal layer received a radiation dose consistent with the observed moist desquamation radiation skin toxicity. **Results:** No extravasation incidents have occurred since the verification procedure was instituted. **Conclusion:** To protect against radiation injury from extravasation of therapeutic radionuclides, test administration of a small $^{99\text{m}}\text{Tc}$ dose with probe monitoring of comparable sites in both upper extremities appears to be an effective preventive measure.

Key Words: radiopharmaceutical therapy; skin radiation injury; extravasation dosimetry

J Nucl Med 2011; 52:1-5

DOI: 10.2967/jnumed.110.083725

As more intravenous radionuclide therapy procedures are performed, particularly using high-dose β -emitters, radiation accidents such as the one described here can occur. The nuclear medicine physician administering therapeutic radionuclides must recognize such unexpected events and have the expertise to estimate the extent and severity of potential complications.

A 76-y-old man with known metastatic carcinoid tumor received an intravenous infusion of 11.1 GBq of ^{131}I -metaiodobenzylguanidine over 15 min through an angiocatheter. The angiocatheter had been placed in the patient's left forearm 45 min before dose administration, which was uneventful. There was no evidence of extravasation of the dose and

no swelling; the patient felt no pain. However, after angiocatheter removal, forearm swelling was noted. The timing of the swelling led the physician to think that this was an allergic reaction, perhaps a local reaction to the tape used to anchor the intravenous catheter to the skin. The patient was given 50 mg of diphenhydramine intravenously.

Approximately 4 wk later, the patient called to let the nuclear medicine physician know that he had developed a "rash" on his left forearm at the site of the intravenous dose administration. The rash measured about 10 cm in length by 5 cm in width. He reported that his primary care physician had suggested that perhaps there had been extravasation of the dose at the time of the therapy administration and that this was a radiation burn. With the patient's concurrence, a next-day dermatology appointment was arranged with the Emory Clinic.

Telephone contact was maintained with the patient weekly for the next 3 wk until the dermatology follow-up appointment. The patient reported that the lesion was still "angry looking," red, or raw (Fig. 1) but that the dermatologist-prescribed high-dose steroid cream had eliminated the discomfort and itchiness of the lesion. The lesion continued to look angry and red for a couple of weeks and then became dry, with a scaly appearance. On his final visit to the dermatologist, he was told that the lesion would heal and he would have some permanent discoloration at the site. [Fig. 1]

Delayed nuclear medicine images obtained 7 d after the therapy demonstrated persistent activity at the site of extravasation (Fig. 2), with dimensions matching those of the radiation burn. [Fig. 2]

In reviewing with the patient the events that led to the skin lesion, he reported that the laboratory technologist who inserted the angiocatheter had made several attempts to insert the catheter.

Radiation injury after parenteral administration of radiopharmaceuticals is probably very rare, but several incidents have been described in the literature (1,2). In the oncologic nursing literature, the term *extravasation* denotes the exit in tissue of chemotherapy solutions (vesicants) that may produce extensive tissue damage, whereas *infiltration* describes the exit into the tissue of chemotherapy solutions

Received Oct. 7, 2010; revision accepted Apr. 25, 2011.
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FIGURE 1. Patient forearm, on follow-up visit (about 7 wk after therapy), with radiation skin injury demonstrating moist desquamation.

(irritants) that may produce a local reaction but do not induce extensive tissue damage (3). Radiation injury can lead to severe tissue damage. Thus, we propose that leakage into tissues of radiopharmaceuticals administered in therapeutic dosages should be consistently referred to as extravasation. This terminology is consistent with the language used previously in reporting radiopharmaceutical-induced radiation injury (2,4).

In this article, we present a simplified approach for estimating radiation dose in cases of extravasation and a method to prevent radiotracer therapy dose extravasation.

MATERIALS AND METHODS

Radiation Dose Model

Superficial veins are located in the dermis, the layer of skin between the epidermis and the fat-rich hypodermis. Thus, extravasation of hydrophilic radiopharmaceutical solution secondary to leakage from veins will spread through dermis, forming a relatively flat source (Fig. 3). Based on prior experience with

[Fig. 3]

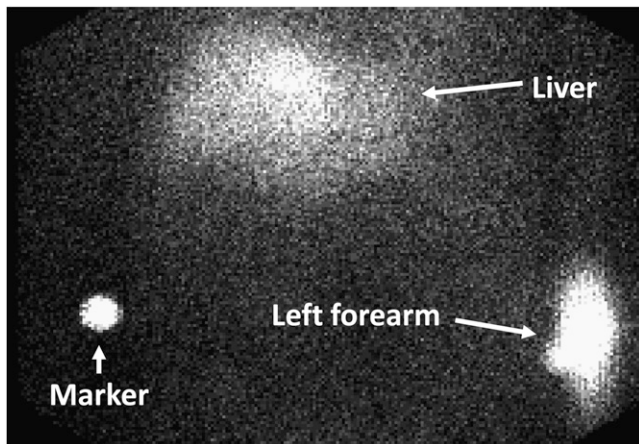


FIGURE 2. Posttherapy scan of abdomen, with arm at side, demonstrating persistent retention of radiotracer at site of extravasation (500 cps).

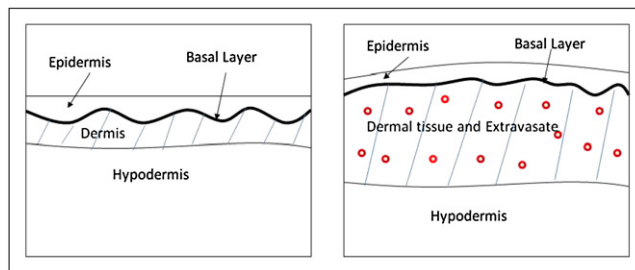


FIGURE 3. Putative distribution of radioactive source. Radioactive extravasate (O) mixed with dermis irradiates basal/germinative epidermal layer.

human and animal studies (5,6), we assume that the radiosensitive component of the skin is the basal (germinative) layer of epidermis, which is separated from the dermis by a thin but relatively impermeable basal membrane.

The dose to the epidermal basal layer has 2 components, photons (long range) and β -particles (short range).

When the dermal radioactive collection is thicker than the maximum β -particle range (3.45 mm for ^{131}I), the β -dose can be approximated as half of the charged particle equilibrium dose because a point on the basal layer receives β -particles only from half of the 4π solid angle surrounding it. The dose rate at charged-particle equilibrium, per the Fano theorem (7), is equal to the mass density of emitted β -energy, and therefore:

$$\text{Dose} = \frac{1}{2} \times \frac{E_{av} \times A}{\rho \times V}, \quad \text{Eq. 1}$$

where E_{av} is the average β -energy per decay (182 keV for ^{131}I), A is activity, V is the volume of distribution, and ρ is the basal layer's mass density, assumed to be 1 g/cm^3 .

As detailed in Appendix 1, for most radionuclides of therapeutic interest and reasonable source geometry, the photon dose rate represents less than 10% of the β -dose. Because this is significantly less than the level of uncertainty in extravasated material absorption kinetics, we discount the photon contribution to dose.

Preventive Methodology for Therapy Dose Injection

Conventional Approach. A 16- to 18-gauge angiocatheter connected to a 3-way stopcock is administered into an accessible peripheral vein. Patency is assessed by infusing a test dose of saline and checking for swelling at the injection site. Once patency has been confirmed, infusion of the therapy ^{131}I -metaiodobenzylguanidine dose is started (volume, 50–75 mL) and continued for 20–30 min until the infusion is complete.

Preventive Approach. After angiocatheter placement, a test dose of about 37 MBq (1 mCi) of $^{99\text{m}}\text{Tc}$ -pertechnetate (or other $^{99\text{m}}\text{Tc}$ -radiopharmaceutical) is administered via the indwelling angiocatheter. Counts are recorded using a γ -probe over the arm proximal to the venous access site and at a comparable contralateral site.

RESULTS

Dosimetry

In human models of extravasation using small volumes (5 mL), residual extravasate was still present at 42 min but

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was resorbed by 72 min (8). Given that in our patient, in the worst case, the treatment dose (50 mL) and the saline flush (10 mL) extravasated, a large amount of extravasate was likely present in the dermis for 60–120 min. The resulting extravasate thickness of 1.2 cm (60 mL/50 cm²), ensures that charged particle equilibrium is a reasonable assumption. The associated dose rate is:

$$\text{Dose rate} = \frac{11.1 \text{ GBq} \times 182 \text{ keV}}{2 \times 60 \text{ mL} \times 1 \text{ g/mL}} \quad \text{Eq. 2}$$

That is:

$$\text{Dose rate} = 0.16 \text{ Gy/min.} \quad \text{Eq. 3}$$

Thus, the patient received about 10–20 Gy during extravasate resorption.

Additional irradiation resulted from persistent retained activity at the site of extravasation, probably because of incorporation of labeled ¹³¹I-metaiodobenzylguanidine in dermal cells. The total detected activity in the area of infiltration (at 8 d) was 500 cps. Assuming a camera sensitivity of about 10⁻⁴ cps/Bq, this would represent an activity of about 5 MBq. The 1-mm thickness of dermis is not sufficient to assume charged-particle equilibrium but is comparable to the ¹³¹I β-particle range. Thus, using a 0.5 dose reduction factor to account for the limited thickness of the source, the initial dose rate was:

$$\text{Dose} = \frac{1}{4} \times \frac{E_{av} \times A}{\rho \times V} \quad \text{Eq. 4}$$

We assume the activity to be distributed uniformly across the area extravasated, with a surface of 50 cm² and the previously assumed dermal thickness of 1 mm. Thus, per Equation 4:

$$\text{Dose rate}_{1 \text{ wk after therapy}} \sim 0.45 \text{ mGy/min.} \quad \text{Eq. 5}$$

As detailed in Appendix 2, under several assumptions of clearance kinetics the dose arising from low dose rate exposure will be:

$$D \sim 12 - 16 \text{ Gy.} \quad \text{Eq. 6}$$

Because of the very low dose rate, approximately 10% of the lowest dose rate systematically evaluated in radiotherapy (9), it is unlikely that this dose was the main cause of patient symptoms. However, in experiments of radiation injury to pig skin, a shallow dose–response curve was observed for moist desquamation when low-dose-rate irradiation was added to radiation delivered at a high dose rate (10). Therefore, persistent activity at the extravasation site—as an added radioactive insult to the acute radiation injury at the time of extravasation—likely contributed to our patient’s injury.

Therapy Dose Injection

The method used for the case presented here was the conventional approach. Afterward, the preventive approach was applied to all intravenous therapy administrations at Emory. Probe monitoring proximal to the angiocatheter and at a comparable site on the opposite arm has shown similar counts, 1,000–2,000/min, with variations of less than 5% between arms. In none of these subsequent cases has extravasation of injected dose occurred.

DISCUSSION

Recent incidents in which medical errors led to clinically apparent radiation injury have alerted the public and governmental agencies to problems with quality assurance (11–13) and have increased awareness of the need for specific measures to prevent radiation injuries.

The clinical course of skin radiation injury, its dependence on the radiation dose, and a description of the relevant pathology are summarized elsewhere (14). As radiation dose increases, the skin may develop erythema, dry desquamation, moist desquamation, and ultimately necrosis.

Extravasation of dose resulted in a radiation injury that led to moist desquamation of the skin in this patient, a finding that fits better with the higher dose estimates. Our assumed clearance rate is similar to previously measured clearance kinetics of extravasated radiopharmaceuticals in animal and human models (15,16).

In our model, the radiation dose to the basal epidermal layer is proportional to the administered radiopharmaceutical concentration. Therefore, administration of diluted solutions can reduce the dose from gross dermal extravasation of radiopharmaceuticals. From a radiation protection perspective, shielding a smaller volume is easier, but coinjection of normal saline for further dilution of extravasated radioactivity may be considered.

Increasing the resorption rate will also decrease the radiation dose. Clearance can be increased by elevating the injection site and applying warm packs or compression stockings. A modest reduction of 20% in radiation dose can decrease skin reaction from moist desquamation to dry desquamation.

Pharmaceutical intervention is another option for preventing severe damage. Amifostine has been used in radiation oncology to mitigate radiation injury to normal tissue, in particular in head and neck malignancies. Thus, amifostine could be considered if expertise in using this agent is available.

From this experience, the following cautions are recommended for all high-dose radionuclide therapy administrations.

- If venous access is difficult, with multiple sticks, do not use that access site to administer radionuclide therapy.
- Perform a test to ensure the absence of leakage at the venous access site. To date, our clinical protocol has prevented a repetition of the extravasation incident.

- If the patient reports pain at the injection site or if swelling is seen, stop the infusion and establish another access site.
- If extravasation occurs, try to mitigate toxic effects by elevating the arm, applying heat, and considering pharmaceutical intervention.

CONCLUSION

Extravasation is a potentially serious complication for a variety of intravenous radionuclide therapies. This risk can be mitigated if the special precautions described in this report are taken.

APPENDIX 1

Because diffusion in the dermis progresses more easily along some directions than others, elliptic source geometry might be closer to reality than circular source geometry. However, for reasons of ease we chose to ignore this effect, and we assume a circular shape for the radioactive source.

To obtain an estimate of the radiation dose due to photons absorbed at a point, we start with the dose rate due to a radioactive disk of radius R_0 , thickness t , and volumetric density of activity a at height h along the axis of the disk. Ignoring attenuation, for the distances involved, the dose due to a thin disk of thickness dh at distance h from the point of interest can be written as the sum of contributions from an annulus of radius R and thickness dR :

$$d(\text{dose rate}) = dh \times \int_0^{R_0} \Gamma \times a \times \frac{1}{R^2 + h^2} \times 2\pi R \times dR, \quad \text{Eq. 1A}$$

where Γ is the dose rate constant for the photons of interest. Then, the total dose rate at a point on the surface of the disk is:

$$\text{Dose rate} = \int_0^t \Gamma \times a \times \ln\left(\frac{R_0^2}{h^2} + 1\right) \times dh. \quad \text{Eq. 2A}$$

For $R_0 \gg h$ this approximates as:

$$\text{Dose rate} = \int_0^t 2 \times \Gamma \times a \times (\ln R_0 - \ln h) \times dh. \quad \text{Eq. 3A}$$

We obtain:

$$\text{Dose rate} = 2 \times \Gamma \times a \times t \times (1 + \ln(R_0/t)). \quad \text{Eq. 4A}$$

Our photon dose model has neglected the absorption phenomena. However, once the distances in consideration exceed the mean photon path length in tissue, $\lambda = 1/\mu$, any further increase in photon dose is attenuated by these absorption phenomena. Assuming a radius $R_0 = 1/\mu$ for the source that participates with dose, the ratio of the photon dose to β -dose can be written as:

$$\frac{\text{Dose rate}_{\text{photon}}}{\text{Dose rate}_{\beta}} = 4 \times \frac{\Gamma \times t \times \rho \times (1 + \ln(1/\mu t))}{E_{\text{avg}}^{\beta}}. \quad \text{Eq. 5A}$$

Among the radioisotopes of major therapeutic interest, only ^{131}I , ^{153}Sm , and ^{177}Lu have significant γ -emissions, and ^{90}Y , ^{89}Sr , and ^{32}P can be regarded as pure β -emitters. The ratio between the 2 doses is tabulated in Table 1A, for isotopes with a γ -emission component for infiltrate–tissue mixtures of 0.5-, 1-, and 1.5-cm thickness. The table also includes the ratio of photon dose to β -dose for positron emitters of major interest. For the positron emitters, a source (infiltrate) radius of 10 cm is assumed (because of 511-keV photon energy, $1/\mu$ would exceed the limits of human anatomy).

For a source thickness of 1.5 cm of ^{131}I and ^{18}F , the photon-to- β -dose ratio was verified using Monte Carlo simulation. The system was modeled in Monte Carlo N-particle code as a unit-density ellipsoid with the activity surrounded by concentric ellipsoids of varying thickness. Dose was scored in the ellipsoidal shells, with the midpoint of a shell constituting the distance from the contained source. Enough histories were performed to maintain the uncertainties in the reported values to about 3%–4%.

APPENDIX 2

We assume that the persistent extravasated activity is cleared with a monoexponential kinetic:

$$\lambda = \lambda_P + \lambda_B, \quad \text{Eq. 6A}$$

where λ_P reflects physical decay and λ_B reflects biologic clearance.

TABLE 1A
Ratio of Photon Dose to β -Dose

Collection thickness (cm)	^{131}I	^{153}Sm	^{177}Lu	^{18}F	^{68}Ga	^{124}I
0.5	4.5%	1.3%	0.7%	10.5%	1.5%	7.2%
1	7.5%	2.0%	1.1%	17.4%	2.5%	11.9%
1.5	9.8%*	2.6%	1.5%	22.9%*	3.3%	15.6%

*Results verified by Monte Carlo simulation.

For β^- emitters, collections are assumed to have radius $1/\mu$, where μ is mass attenuation coefficient for dominant photon energy. For positron emitters, collections are assumed to have radius of 10 cm.

At 1 wk after the extravasation incident, an activity of about 5 MBq was detected at the extravasation site. The associated dose rate was about 0.45 mGy/min. Assuming constant source geometry, the dose rate to the skin basal layer decreases exponentially:

$$\text{Dose rate}(t) = \text{Dose rate}(t_1) \times e^{-\lambda(t-t_1)}, \quad \text{Eq. 7A}$$

where we account for the evaluation of the dose rate at time t_1 rather than time t_0 .

Then, the total dose is:

$$D = \int_0^{\infty} \text{Dose rate}(t_1) \times e^{-\lambda(t-t_1)} \times dt, \quad \text{Eq. 8A}$$

which yields:

$$D = \text{dose rate}(t_1) \times \frac{e^{\lambda t_1}}{\lambda} \quad \text{Eq. 9A}$$

The minimum for the dose (as a function of λ) is when:

$$\lambda = \frac{1}{t_1}. \quad \text{Eq. 10A}$$

Given a dose rate of 0.45 mGy/min 1 wk after extravasation, the minimum dose will be 12 Gy.

Dosimetric studies of MIBG therapy demonstrated a triexponential clearance, with the late clearance component having a half-life of 100 h (17). Using this value for the biologic clearance half-life yields a total dose for the late clearance component of 15 Gy.

Assuming no biologic clearance, ($\lambda_B = 0$) yields a slightly higher value of 16 Gy.

DISCLOSURE STATEMENT

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ACKNOWLEDGMENTS

We gratefully acknowledge Dr. Michael Stabin for helpful discussions about the dosimetric model and for independent verification of photon/ β -dose ratios. No potential conflict of interest relevant to this article was reported.

REFERENCES

- Breen SL, Driedger AA. Radiation injury from interstitial injection of iodine-131-iodocholesterol [letter]. *J Nucl Med.* 1991;32:892.
- Williams G, Palmer MR, Parker JA, Robin J. Extravasation of therapeutic yttrium-90-ibritumomab tiuxetan (Zevalin): a case report. *Cancer Biother Radiopharm.* 2006;21:101–105.
- Hadaway L. Infiltration and extravasation. *Am J Nurs.* 2007;107:64–72.
- DeNardo GL. "Right place, wrong place": extravasation of therapeutic drug for molecular targeted radiotherapy. *Cancer Biother Radiopharm.* 2006;21:85–86.
- Hall EJ. *Radiobiology for the Radiologist.* Philadelphia, PA: Lippincott Williams & Wilkins; 2000:339–360.
- Snyder RS. The skin. In: Bloom W, ed. *Histopathology of Irradiation from External and Internal Sources.* New York, NY: McGraw Hill; 1948:32–69.
- Attix FH, Roesch WC. Basic concepts of dosimetry. In: Attix FH, Roesch WC, Tochilin E, eds. *Radiation Dosimetry.* New York, NY: Academic Press, 1968:2–42.
- Yucha CB, Hastings-Tolsma M, Szeverenyi NM. Effect of elevation on intravenous extravasations. *J Intraven Nurs.* 1994;17:231–234.
- Turesson I. Radiobiological aspects of continuous low dose-rate irradiation and fractionated high dose-rate irradiation. *Radiother Oncol.* 1990;19:1–15.
- Millar WT, Hopewell JW. Effects of very low dose-rate $^{90}\text{Sr}/^{90}\text{Y}$ exposure on the acute moist desquamation response of pig skin. *Radiother Oncol.* 2007;83:187–195.
- Balter S, Hopewell JW, Miller DL, Wagner LK, Zelefsky MJ. Fluoroscopically guided interventional procedures: a review of radiation effects on patients' skin and hair. *Radiology.* 2010;254:326–341.
- Shope TB. Radiation-induced skin injuries from fluoroscopy. *Radiographics.* 1996;16:1195–1199.
- Kuehn BM. FDA Warning: CT scans exceeded proper doses. *JAMA.* 2010;303:124.
- Koenig TR, Wolff D, Mettler FA, Wagner LK. Skin injuries from fluoroscopically guided procedures. I. Characteristics of radiation injury. *AJR.* 2001;177:3–11.
- Castronovo FP Jr, McKusick KA, Strauss HW. Dosimetric consequences of radiopharmaceutical infiltrations. *Invest Radiol.* 1994;29:59–64.
- Castronovo FP Jr, McKusick KA, Strauss HW. The infiltrated radiopharmaceutical injection: dosimetric considerations. *Eur J Nucl Med.* 1988;14:93–97.
- Flower MA, Fielding SL. Radiation dosimetry for ^{131}I -mIBG therapy of neuroblastoma. *Phys Med Biol.* 1996;41:1933–1940.