Disaster Medicine and Public Health Preparedness

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Report from the Field

Cite this article: Keenan M, Behrens T, Bravenec S, *et al*. (2022) Americium inhalational exposure with successful chelation therapy. *Disaster Med Public Health Prep* **16**: 2185–2189. doi: https://doi.org/10.1017/dmp.2021.211.

First published online: 17 August 2021

Keywords:
Americium; Radiation Injuries; Chelation; Toxicology; DTPA

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Americium Inhalational Exposure with Successful Chelation Therapy

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Abstract

Americium is a man-made metal produced in very small quantities in nuclear reactors. Americium-241 is one of the radioactive isotopes of americium and has commercial applications, including use in smoke detectors. This is a case report of an occupational inhalation of americium-241, treated with both effective external decontamination and the use of diethylenetriamine pentaacetate to promote decorporation. This experience is significant because of the potential for americium or similar radionuclides to be used in "dirty" bombs or other radiological dispersion devices to cause large-scale radioactive contamination.

Introduction

Americium is a radioactive element that undergoes predominantly alpha decay, with some weak photon emissions.[1,2] The isotope americium-241 (Am-241) has a number of uses in industry, including in the production of smoke detectors. Alpha particles emitted during the decay of americium and other large radionuclides are capable of causing damage to biological tissues by depositing all of their energy within the space of 1–2 cells. Fortunately, they are also the most easily shielded type of ionizing radiation, with the stratum corneum being thick enough to absorb the particles before they cause damage to underlying cells.[3] Therefore, external contamination by americium is of little concern. However, external decontamination should be done, to the extent practical, to prevent inhalation, ingestion, or entry into a wound, if present. Contamination with americium may be problematic when the material is internalized by inhalation, ingestion, or through non-intact skin. Internal contamination with a radioactive element can progress to incorporation into different tissues depending on the type of radioactive element.[3] Thus, it is important to not delay treatment of internalized americium with the chelator diethylenetriamine pentaacetate (DTPA).[4] DTPA has been US Federal Drug Administration (FDA) approved for use in internal contamination with americium, plutonium, and curium since 2004.[5–7] The effectiveness of DTPA is shown in both animal studies and human contamination events.[4,8,9]

DTPA is available in 2 forms, trisodium calcium diethylenetriamine pentaacetate (Ca-DTPA) and trisodium zinc diethylenetriamine pentaacetate (Zn-DTPA).[4] While Ca-DTPA is more effective in decorporation, the benefits decrease with time and there is some increase in risk with repeated usage due to depletion of zinc, magnesium, manganese, and other trace metals, particularly if there are any underlying disease processes that may be exacerbated by depletion of these trace elements.[4,6,7] The recommendation is to switch to the Zn-DTPA form after the first dose of Ca-DTPA, or to use it as an alternative to Ca-DTPA in those patients who may have relative contraindications for Ca-DTPA.

The recommended routes of administration for DTPA are intravenous and inhalation via nebulization. In patients with asthma or, more broadly, with any underlying respiratory disease, the intravenous route of administration may be best. Some recommend the nebulization route of administration for inhalation of plutonium-238 or Am-241.[8,10,11] Further, these recommendations are supported by older animal studies that have demonstrated that administration of dry powder and liquid aerosol DTPA via pulmonary delivery decreased deposition of plutonium oxides with Am-241 in the lung, bone, and liver[1,8] and better availability for the nebulized administration for plutonium and americium inhalation.[10,12–16] Stradling et al. (2000) indicated that prompt and repeated aerosolized administration of Zn-DTPA "can reduce lung and body content of americium by up to about 45- and 30-fold, respectively, by 28d after exposure" when compared to prompt and repeated intravenous administration of Zn-DTPA.[17,18] Animal studies have also showed that inhalational Ca-DTPA, with subsequent doses of Zn-DTPA over 30 days, reduced pulmonary deposits of aerosolized plutonium to 2% of the control group.[5,6] The bioavailability of inhaled DTPA is determined both by the fraction of material deposited in the

alveolar region of the lungs and the rate at which the drug crosses the alveolar epithelial membrane. The literature reports a bioavailability of approximately 20–30% depending on the particle size and method of delivery, with a clearance half-life of less than 2 hours.[8,19]

Removal of inhaled pharmaceuticals from the lungs occurs across the epithelium into the blood, particularly in the alveolar tract, and via mucociliary clearance along the airway surfaces.[19] Older literature discusses bronchoalveolar lavage (BAL) as an alternative for extremely high burdens in the lungs. This has not been used clinically in decades, and canine models showed that the amount of Am-241 remaining in the lungs at 64 days was equal in both the BAL and intravenous routes of administration.[20]

There is poor gastrointestinal absorption of DTPA and fecal excretion is 3%.[1,5,6] Following the formation of stable chelates with metal ions, the material excreted by glomerular filtration into the urine is enhanced.[5,6] There are no listed US FDA contraindications for DTPA.[5,6] In patients with renal impairment, no dose adjustment is required.[5,6] However, based on technetium-99 metastable labeled DTPA for imaging in renal impairment, there is increased renal excretion of these chelates with hemodialysis, which may prove useful to increase the rate of elimination of the radio contaminant. As mentioned, nebulization of DTPA may exacerbate asthma and the authors advise care with any underlying pulmonary disease. Also, caution should be taken to maintain trace metal equilibrium, as discussed. Special population considerations include pregnant women, nursing mothers, and pediatrics.[21] Five patients being treated with Ca-DTPA for hemochromatosis died after receiving the medication for more than a day by intramuscular injection,[22,23] whereas other patients suffered no adverse effects.[23,24] A causal relationship between administration of Ca-DTPA and the fatal outcome in these patients has not been established, but in light of the low number of cases available for evaluation, caution is warranted. Other listed adverse events include injection site reactions, dermatitis, allergic reaction, headache, lightheadedness, chest pain, nausea and diarrhea, and a metallic taste. Of historical significance, one individual received 338 doses, administered over 6.5 years, with no recorded adverse events.[25,26]

To facilitate discussion of radioactive materials and radiation impacts on the body, some discussion of common radiation protection terminology is warranted. The amount of radioactive material present is described by the activity of the sample with SI units of becquerel (Bq) and traditional units of curie (Ci). Dose, or the amount of radiation absorbed by matter, is quantified by gray (Gy) or radiation absorbed dose (rad). Dose equivalent is used to describe the risk to the biologic tissue and is given in sievert (Sv) or roentgen equivalents man (rem).

In response to radiation exposure, the types of effects seen are described as deterministic and stochastic. Deterministic effects are those that occur at or above a specified dose. Any dose received above that threshold impacts the severity and time between irradiation and manifestation. Stochastic effects are those that occur with some probability after radiation exposure, such as radiogenic cancer. A higher dose increases the probability of a stochastic effect occurring but does not change the severity of that effect.[27] Deterministic effects are seen, in the extreme, with acute radiation syndrome with classic organ damage, notably the bone marrow, gastrointestinal tract, the cutaneous system, and the neurovascular systems. Deterministic effects are most commonly seen after radiotherapy, occupational incidents with more localized injuries, or *tissue reactions*, a term used to describe deterministic effects and some later effects directly attributable to the exposure.[28] Stochastic effects are the risks of cancer from the exposure.

The National Council on Radiation Protection and Measurements (NCRP) has published a set of clinical decision guides (CDGs) to help treatment staff make a determination whether decorporation therapy is warranted. A CDG is the magnitude of a 1-time intake of a radionuclide that would result in a 50-year integrated whole body dose of 0.25 Sv (25 rem), or a 30-day integrated dose of 0.25 Gy (25 rad) to the bone marrow or 1 Gy (100 rad) to the lungs. The total body values are established to limit the possible lifetime risk of stochastic effects, such as cancer, attributable to the radiation dose to less than 1.3%. Values for individual organ doses are set below the threshold for deterministic effects of bone marrow depression and pneumonitis.[11]

Narrative

A 54-year-old male health physics technician at a smoke alarm manufacturer was using a vacuum to clean areas contaminated with Am-241 in the facility. He noticed that the vacuum made a noise and then a cloud of material was blown in his face. He was wearing a Tyvek suit but no respiratory personal protective equipment. He closed his eyes, held his breath, and prevented anyone from entering the area. The patient removed all of his clothing, showered thoroughly, and blew his nose repeatedly.

For suspected intakes of radionuclides, the NCRP Report Number 161 provides a method for estimating the amount of material deposited in the lungs by correcting the activity detected on a pre-decontamination nasal swab for the detector efficiency. The resulting value is multiplied by 20, based on the assumption that activity in the nares is approximately 5% of the activity deposited in the lungs.[11]

Historically, nasal swabs using a cotton-tipped applicator have been used as triggers to determine whether further investigation into a potential inhalation event is warranted.[29] Nasal swabs were collected after the incident to establish an upper bound for the amount of material potentially deposited in the lungs. A Beckman LS6500 liquid scintillation counter was used to determine the amount of americium present on each swab. A swab collected prior to a decontamination shower exhibited 65 654 disintegrations per minute (dpm). After the decontamination shower, swabs exhibited 3305 dpm. Nasal swabs collected the following day exhibited 51.5 dpm.

Liquid scintillation counters are nearly 100% efficient in detecting alpha particles. Using this efficiency, and the methods described in NCRP Report 161, the amount of americium deposited in the lungs was estimated to be 22 kBq or (5.9×10^{-7} Ci).[11] This amount of material places an upper bound on the 30-day absorbed dose to the lung of 13.86 milligray (0.0139 Gy) and an upper bound on the 50-year committed effective dose of 0.594 Gy. The estimated intake exceeds the CDG of 9.3×10^{3} Bq (2.5×10^{-7} Ci) for Am-241, indicating that medical treatment should be considered but is not high enough to suggest the possibility of deterministic effects.[11] It is important to note that this estimate method carries a great deal of uncertainty and is intended only to guide initial treatment.

After initial radiological assessment, the work site contacted the Radiation Emergency Assistance Center/Training Site (REAC/TS). Based on the early estimation of Am-241 in the lungs, REAC/TS recommended treating the patient with Ca-DTPA. Unfortunately, the medication was not available at the treating hospital. REAC/TS coordinated with the Veterans

https://doi.org/10.1017/dmp.2021.211 Published online by Cambridge University Press

Health Administration (VHA) Medical Emergency Radiological Response Team (MERRT) to inquire about access to the medication in their pharmacy cache.[30] The chelator was located at another facility and delivered.

The patient presented to the emergency department (ED) on post-exposure day (PED) 2, with the ED seemingly the easiest and fastest way to arrange treatment. At the time of presentation, the patient's vital signs were stable. The patient reported a past medical history significant for insomnia, depression, migraines, hypertension, and hyperlipidemia. The patient did not have a significant surgical, family, or social history. The patient reported no medications, except for a home regimen of vitamins, and had no drug allergies. The patient was asymptomatic and the physical exam was unremarkable.

The recommendations from NCRP 161 specify that the calcium form of DTPA is the best chelator for the first dose and is most effective when given within the first 24 hours after an intake. Due to the high level of activity on the initial nasal swabs, and as it was the only form available, Ca-DTPA was used despite it being greater than 24 hours since exposure.

As briefly discussed in the introduction, DTPA may be given intravenously or by nebulization. More research exists in animal models regarding the comparison of the 2 routes of administration. There is no clear and stated most efficacious route of administration to choose, given the many variables that must be taken into account: (1) route of internalization, that is, inhalation versus wound; (2) chemical and physical properties of material(s) internalized; (3) suspected amount or significance of intake; (4) time from actual internalization; and (5) individual's medical history.

In consultation with REAC/TS, the treating physician administered nebulized Ca-DTPA. Nebulization was chosen based on direct delivery of the chelator into the lungs, lack of underlying respiratory disease, and the level of contamination still present in the patient's nares on PED 2. Particulates in the nares clear rapidly; thus, elevated levels of contaminant day(s) after exposure are suggestive of a significant inhalation event. As discussed above, this was a significant inhalation event, and direct delivery to the lungs was considered to be the best route of administration, given the persistence of contaminant in the nares. There was no sign of a deviated septum, obvious nasal polyps, or other pathology that might lend to increased retention in the nares.

The patient was instructed to take a multivitamin due to the potential for the chelator to deplete trace minerals. The patient subsequently returned on PEDs 3–6 for Ca-DTPA nebulizer treatments. Dosing was 1 g in 10 mL normal saline via standard nebulizer. It was recommended to switch to Zn-DTPA when available. On PED 7, Zn-DTPA was received from the manufacturer and the patient received 1 nebulized dose. Based upon recommendations from the private consulting company's physician, the patient received an additional 5 doses of Zn-DTPA intravenously on PEDs 8, 10, 12, 14, and 16. The dose was 1 g in 10 mL saline administered slow IV push or diluted in a 100 mL bag of saline to be run over several minutes. The decision to change to IV administration was made to account for the decrease in lung burden and the corresponding increase in systemic americium due to translocation of inhaled material from the respiratory tract into systemic circulation as shown in Figure 1.

Throughout treatment, the patient remained largely asymptomatic. He did experience some slight muscle cramping and intermittent shortness of breath. Lab work was performed each time to monitor his electrolytes and trace minerals. EKGs were obtained at each visit to monitor his QT interval, prolongation of which can result from hypomagnesemia, which, in turn, may result from the chelation of magnesium. These tests remained normal during treatment.

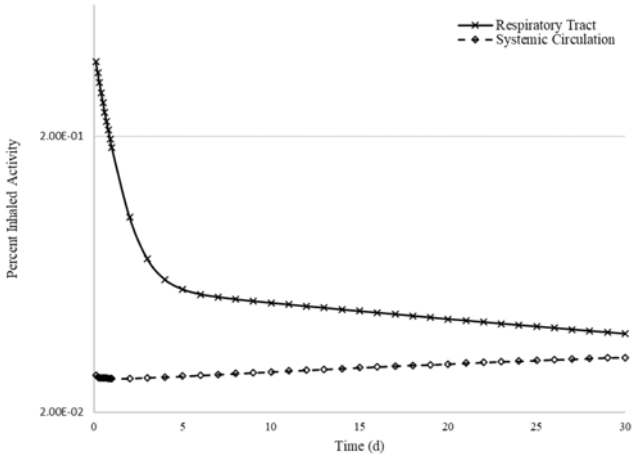


Figure 1. Percent of inhaled activity remaining in the respiratory system and systemic circulation as a function of time.

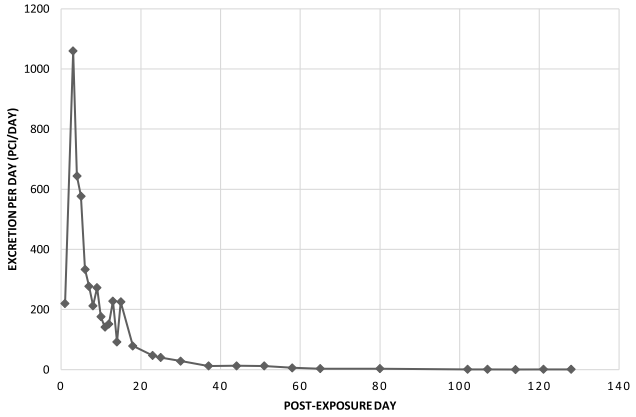


Figure 2. Radioactivity (pCi) in 24-hr urine samples over time.

The patient's progress was monitored with urine radiobioassay. Analysis of 24-hour urine specimens was performed by General Engineering Laboratories in Charleston, South Carolina (Figure 2). The bioassays were interpreted to help the consulting/treating physicians and health physicists decide when to cease chelation therapy. There is no protocol to guide cessation other than balancing the diminishing returns in the urine bioassays with continued chelation.

Intakes of radionuclides can be assessed through the collection of excreta samples or by use of radiation detection instruments that measure photons emitted by radionuclides in the body. Am-241 emits photons with energies less than 60 keV that are detectable with sensitive instrumentation that is not widely available.[31] However, modeling has shown that inhaled Am-241 is detectable only if the contaminated individual inhaled thousands-fold more material than the CDG, making handheld Geiger-Mueller detectors inappropriate for screening for internalized americium.[32]

The energy deposited in an organ by internalized radioactive material cannot be measured directly and is calculated by modeling how the material moves through body organs and how much of the material undergoes radioactive decay while in each of those organs. An initial urine sample was collected prior to the administration

https://doi.org/10.1017/dmp.2021.211 Published online by Cambridge University Press

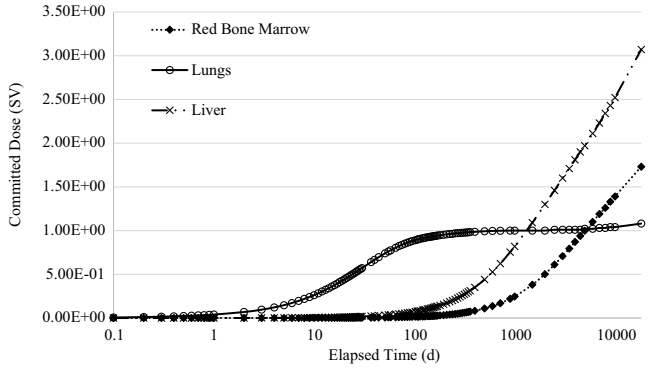


Figure 3. Variation of committed organ dose with time.

of DTPA. Using this value in the biokinetic models for Am-241 dioxide published by the International Commission on Radiation Protection (ICRP), the amount of material deposited in the lungs could be estimated more precisely.[29,32] All biokinetic and dosimetric calculations were performed using the AIDE software package.[33] Based on 8.12 Bq (219.55 pCi) in the 24-hour urine sample, an estimated 4590 Bq (124 nCi) was deposited in the lungs. Left untreated and assuming a 5-μm particle size, the amount of Am-241 estimated to have been deposited in the lungs would deliver a committed effective dose equivalent (CEDE), or dose to the total body, of 1.24 Sv.[34,35] It would deliver a committed dose equivalent (CDE), or dose to an individual organ, of 1.08 Sv to the lungs, 1.73 Sv to the red bone marrow, 3.07 Sv to the liver, and 50.8 Sv to the bone surface, which are the 2 limiting organs for this nuclide.[34,35] Note that, as shown in Figure 3, a committed dose is delivered over a period of 50 years rather than instantaneously.

Administration of DTPA enhanced the excretion rate of Am-241 from the body. Based on the post-treatment data, the patient only received a CEDE of 0.046 Sv, CDE to the liver of 0.12 Sv, and CDE to the bone surface of 1.9 Sv. As a comparison, a typical chest CT delivers 0.007 Sv and chest X-ray delivers 0.0001 Sv.[1] However, these are instantaneous doses, whereas the dose due to the americium is delivered over a period of 50 years.

Discussion

The management of a patient contaminated with radioactive material is multi-faceted. Contamination with radioactive material is itself not immediately life-threatening, and medical or trauma emergencies should be addressed first.[1,3,18] Simple measures may be taken to minimize further patient exposure or internalization and mitigate the spread of external contamination to health care providers and the treatment area. Mitigation for internal contamination includes the awareness that bodily fluids, such as perspiration, urine, and feces may be contaminated. Treatment in the ED should follow standard protocols as for any medical or trauma patient. Once stable, the patient should be decontaminated, if external contamination persists. Ideally, this will occur in the prehospital setting, but health care providers should be mindful that this may not have occurred. A detailed review of proper decontamination techniques is beyond the scope of this report, but may be reviewed at the REAC/TS website.[36,37]

Internal contamination is a medical urgency, as the soluble portion of americium that gains systemic access may incorporate into bone within hours.[8] One of the largest obstacles in managing an internal contamination incident is access to the medications. Prior to DTPA becoming a New Drug Application (NDA) medication, REAC/TS managed the stockpile for DTPA as the principal investigator (PI) in researching its safety/efficacy and in conjunction with co-PIs at other US Department of Energy (DOE) sites. The Strategic National Stockpile (SNS) does carry Zn-DTPA; however, as there may be singular or limited numbers of persons contaminated, the standard caches and push packs are not usually opened for these small events. Many DOE National Laboratories, as well as some Veterans Administration Medical Centers, may stock small amounts of DTPA, but there may be delays or impediments to obtaining US Government medications/countermeasures for the private sector treating physician. Many regional health care coalitions are teaming with their state and regional health departments to keep small quantities of these countermeasures for internal contamination that may be distributed to a local health care facility or treating physician. If there is no dedicated occupational health care provider for the company or site of an incident, it is reasonable to assume that care may be sought in an ED, an urgent care center, or with a primary health care provider. Both forms of DPTA are prescription medications, although pharmacies and most vendor managed inventories will not carry them. A prescription/order from the treating physician may be made to the US distributor for DTPA*; however, this will be needed on rare occasions, unless the facility is dedicated to care of a company/site that handles radiological materials. Thus, it is more efficient/cost-effective to have the state health department team with local health departments and the regional health care coalitions for management of small amounts of DTPA (and Prussian Blue, a countermeasure for cesium and thallium) with the caches/push packs but "outside" of the stockpile proper.

In the case described, the effectiveness of external decontamination is exhibited by the difference in the nasal swabs before and after the decontamination shower. The nasal swabs demonstrated a drop from 65 654 dpm before to 3305 dpm after the shower – only 5% of the original measurement. The effectiveness of the chelation therapy may be best observed by comparing the urine bioassays PED 1 versus PED 3, with an increase in excretion of americium (pCi/day) from 219.55 to 1059.92 after receiving the first dose of DTPA on PED 2. No reports are found in the literature regarding development of cancer in humans following acute-, intermediate-, or chronic-duration inhalation of americium. Animal studies indicate a possibility of developing osteosarcoma following a single intake without treatment of between 3.4 and 10 times higher than the patient in this case.[38]

There is concern that americium or a similar radionuclide could be used in a "dirty" bomb or other radiological dispersal device. It is important for disaster specialists to know the basics of management of a radioactive exposure or contamination, and to know what available resources exist to help care for these patients.[37]

Conflict(s) of Interest. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this paper.

*Golden State Medical Supply, 805-477-9866, 8:30 AM–5:30 PM Pacific Time or https://gsms.us.

https://doi.org/10.1017/dmp.2021.211 Published online by Cambridge University Press

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