Chapter 4

TREATMENT OF INTERNAL RADIONUCLIDE CONTAMINATION

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INTRODUCTION

A variety of events pose the risk of internal radionuclide contamination. A nuclear detonation will result in the release of over 400 radioactive isotopes.[1] Of these, approximately 40 are considered potential human health hazards because of their long radiological half-lives or their ability to concentrate in critical organ systems. Accidents at or attacks on nuclear reactors can result in internal radionuclide contamination, either through direct exposure to the released isotopes or as a result of radioactive fallout. In noncombat situations, accidents with radioisotopes used in medical and industrial applications can also result in internal radionuclide contamination. In addition, since the terrorist attacks of September 11, 2001, concern about the use of radiological weapons against civilians or military personnel has increased, and these fears are no longer limited to nuclear fission devices delivered by rogue states or terrorist groups. Terrorist use of a radiological dispersal device, or "dirty bomb," is also now a critical concern.[2]

Radionuclide internalization, whether accidentally or from a deliberate attack, is a critical medical situation for which treatment decisions should not be delayed. Although there are a seemingly endless number of radioisotopes, this chapter will focus on those most widely used in medical and industrial applications, as well as those thought to be potential radiological dispersal device components.

Routes of Exposure and Normal Clearance Mechanisms

Radionuclides can be internalized through three major routes: inhalation, ingestion, and wound contamination. Although percutaneous absorption is another potential exposure route, it is only a significant internalization pathway for tritium, or when the epithelial layer of the skin is damaged. Regardless of the route of exposure, several factors govern the eventual health effects induced by the internalized radionuclide. Clearly, the amount of radionuclide internalized plays a major role in the end result of any exposure; equally important, however, are the chemical and physical properties of the radionuclide. These properties include solubility characteristics (particularly in biological fluids), particle size, speciation, and chemical reactivity. The energy and type of radiation (α, β, γ) emitted by the isotope will dictate the damage it has the potential to inflict. For high-energy, short-lived isotopes, the radiological half-life is of concern. More important for longer lived isotopes is the biological half-life; the time it takes, without therapeutic intervention, for the internalized radionuclide to be cleared from the body. The final important issue is the "critical organ," or final deposition site for the radionuclide if it is not cleared from the body. Together, these factors ultimately determine the health effect of the internalized radionuclide, as well as its potential to be therapeutically removed or "decorporated" from the body.

Inhalation is the primary route of exposure for internalized radionuclides, with their ultimate fate depending on the size of the inhaled particles as well as the solubility of the radionuclide. Approximately 25% of inhaled radionuclides are immediately exhaled.[3] Of the remaining 75%, particles less than 5 μm in diameter can reach the alveolar space, while particles greater than 10 μm tend to remain in upper areas of the lung.[4] Once deposited in the lung, the particle's solubility becomes important. Radionuclides such as tritium, phosphorus, and cesium are rapidly solubilized and enter the circulatory system. Less-soluble radionuclides, such as the oxides of plutonium, uranium, cobalt, and americium, will eventually be removed through the process of phagocytosis by the alveolar macrophages. Until that occurs, the radioactive particle will continue to irradiate the surrounding tissue. Research has shown that in most cases, the internalized radionuclide will have both soluble and insoluble components,[5,6] further complicating treatment decisions. Larger inhaled particles, unable to access the alveolar space, will be removed from the lung via mucocilliary clearance. However, many of the particles, once cleared, will be swallowed and thus enter the gastrointestinal (GI) tract.

In addition to swallowing after mucocilliary clearance, radionuclides can be ingested through contaminated food or liquids. Once ingested, absorption of radionuclides will depend on chemical form and solubility. The majority of radionuclides are poorly absorbed by the GI tract. Some exceptions include strontium, tritium, and cesium. The amount of damage inflicted will be determined by the transit time through the GI tract, with the greatest potential for damage occurring in the descending colon prior to the ingested radionuclide being excreted in the feces. GI transit times are affected by a variety of factors, including diet, fluid intake levels, and physical activity, but generally range from 1 to 5 days.[7]

Wound contamination is the final route of exposure to be considered. Wound radionuclide contamination

TABLE 4-1

ISOTOPES OF CONCERN

Element	Isotopes of Concern	Source	Radiation Type	Critical Organ(s)
Americium	^{241}Am	Smoke detectors, fallout	α, γ	Bone, liver, lung
Cesium	^{137}Cs	Radiotherapy units	β, γ	Total body (especially kidney)
Cobalt	^{60}Co	Radiotherapy units, commercial irradiators	β, γ	Total body (especially liver)
Iodine	^{131}I	Fallout, reactor accidents	β, γ	Thyroid
Iridium	^{192}Ir	Radiography source (material testing, brachytherapy)	β, γ	Spleen
Phosphorus	^{32}P	Medical research	β	Bone
Plutonium	^{238}Pu, ^{239}Pu	Nuclear weapons, reactors	α, γ	Bone, liver, lung
Polonium	^{210}Po	Antistatic devices	α	Spleen, kidney
Radium	^{226}Ra	Radioluminescent dials in old equipment	α, β, γ	Bone
Strontium	^{90}Sr	Radioisotope thermoelectric generators, medical uses	β, γ	Bone
Tritium	^{3}H	Medical research	β	Total body
Uranium	^{235}U, ^{238}U	Fuel rods, nuclear weapons, armor-piercing munitions (depleted uranium)	α, β, γ	Kidney, bone

can occur as a result of isotopes entering open wounds (eg, as dust or liquid) or as embedded fragments of a radionuclide. As with other routes of exposure, the physiochemical properties of the radionuclide are of prime importance when determining the effect of the internalized isotope. Research with intramuscularly injected radionuclides has shown that even those considered insoluble can be solubilized in vivo.[8–10] This was shown in studies investigating the health effects of embedded fragments of depleted uranium, where solubilization and urinary excretion of the uranium was found within 48 hours after implantation of the solid metal into the leg muscles of laboratory rodents.[11] These results point to the complex nature of radionuclide internalization as a result of embedded fragments and the potential difficulties involved in treating them.

Isotopes of Concern

As noted previously, there are hundreds of natural and manufactured radioisotopes that could result in internal contamination. However, in reality, only a handful are likely candidates for internalization due to their widespread use or potential incorporation into radiological dispersal devices (Table 4-1).

ASSESSING CONTAMINATED PERSONNEL

By the time contaminated patients reach a medical care facility, they should have undergone an external decontamination procedure, usually at or near the site of the radiological event; however, it is safer to assume no decontamination has occurred unless told otherwise. Medical staff should work closely with health physics personnel in initially assessing potentially contaminated personnel. While external decontamination is essential to prevent the spread of radiological contamination, it should not take priority over the initiation of immediate lifesaving measures. If not already completed, external decontamination procedures should be undertaken before assessing the patient for internal radiological contamination. Decontamination procedures decrease external radiation levels, allowing for a more accurate determination of internal radionuclide contamination (methods to determine internal contamination depend on the

suspected radionuclide, physical form of the radionuclide [ie, liquid, solid, gas], and route of exposure, and are beyond the scope of this chapter). In addition, thorough external decontamination procedures will prevent accidental radionuclide internalization during patient assessment and treatment. Those decontamination procedures need not be exhaustive; simply removing the patient's outer clothing and shoes can reduce external contamination by 90%.[12] Additional decontamination procedures, including washing the skin and hair with soap and water, further decrease external contamination levels; however, open wounds need to be covered to prevent the unintentional internalization of external contamination during decontamination procedures. The logistics involved in establishing a decontamination area are beyond the scope of this chapter, but several excellent sources of information are available.[13–17]

Initial Determination of Radioactive Contamination

Information from the accident or attack scene (preferably in the form of a firsthand account from the patient) will provide the first information on the radioisotopes involved. However, in many cases, the exact isotope and route of exposure will not be known. Although the identity of a radioactive contaminant, especially one that has been internalized, could take days to determine, several simple assessments can determine whether the contaminant is a β or γ emitter, and may also indicate a possible exposure route. Thus, as a preliminary step, a thorough body survey with a Geiger-Müller meter incorporated into the external decontamination procedure is recommended. A general survey may be done when the patient arrives for triage and may be repeated after contaminating clothing has been removed and skin washed. Survey details are generally reported by body area (for more information, see Chapter 3, Triage and Treatment). A Geiger-Müller meter is capable of detecting β- and γ-emitting isotopes, but not those emitting α particles. The first scan should be made with the shield of the Geiger-Müeller meter open to detect the presence and location of β and γ contamination. The second scan should be conducted with the shield closed. Results from this scan will indicate what proportion of the contamination is due to γ-emitting isotopes alone. Radioactive contamination by α emitters should also be determined. However, because of the difficulties involved with such measurements, these procedures require the assistance of experienced personnel. Special consideration should be given to the mouth and nasal regions, as well as to the areas around wounds. In addition to a body survey, swabs of each nostril should be taken, stored in sealed tubes to prevent unintentional contamination, and analyzed by health physics staff for radioactive contamination to help identify the potential contaminant and indicate whether clinically significant inhalation exposure has occurred.

Evaluating Contaminated Patients

After a patient has been identified by health physics staff as being internally contaminated, the next step is to positively identify the contaminants so that the body burden (the total amount of a substance in an individual's body) and dose estimates can be calculated. It should not be assumed that there is only a single radionuclide present unless proven by radioanalysis. Measuring and identifying external patient contamination is the first step in this process and should have been initiated during the decontamination procedure. Swabs, including nasal, obtained during decontamination; fluids used to cleanse wounds (as much as can reasonably be collected by personnel using standard precautions and personal protective equipment); tissue and fluid samples from wound debridement; and wound dressings (the number of which and the time period covered depend on radioanalytical results obtained by health physics staff) should all be analyzed for radiation contamination using appropriate radioanalytical techniques.[18] Urine and fecal samples should also be collected, depending on the identity and form of the nuclide and the recommendations of the health physics staff, and analyzed to provide an indication of the excretion pattern of the internalized radionuclide. Although this information can be used to calculate body burden, it is only an estimate of the amount of internal contamination present. More sensitive in-vivo measurements provide a more accurate assessment of dose. For example, whole-body counters can be used to measure radiation given off by the body; however, these are only useful for radionuclides that emit γ rays.

Treatment Decisions

If internal radionuclide contamination is likely and a tentative identification of the isotope and extent of contamination can be made, treatment decisions must follow. Most treatment protocols for internal radionuclide contamination carry some risk; therefore, it is imperative that, prior to initiation, the potential risk of the treatment be weighed against the possible benefit. In most cases, the benefits of treatment far outweigh the risks, and potential treatment risks can usually be successfully managed.

TREATING INTERNAL RADIONUCLIDE CONTAMINATION

The first step in dealing with internal radionuclide contamination is to remove sources of potential contamination. As discussed above, external decontamination procedures are vital in reducing the risk of additional internal contamination events. Isotope-specific pharmacological treatments can begin once thorough external decontamination is performed. Agents used to treat internal radionuclide contamination can be loosely grouped into four categories: uptake-reducing agents, blocking or diluting agents, mobilizing agents, and chelating agents.[19] These are not mutually exclusive groupings; the action of many compounds can span two or more of the categories. More importantly, no single compound works for all radionuclides, illustrating the need for competent radioanalytical support to identify the radiological contaminant. (Table 4-2)

Uptake-Reducing Agents

One of the keys to a successful treatment outcome is to reduce or eliminate the uptake of internalized radionuclides before they can reach the critical organ. Simple procedures, such as irrigation of the nasal passages and mouth, should not be overlooked as treatment options. For exposure due to ingestion, emetics (eg, ipecac) and laxatives or purgatives (eg, castor oil) can be considered in order to reduce the time the radionuclide spends in the GI tract.

Ion exchangers can also be used to reduce radionuclide uptake in the GI tract. Ferric hexacyanoferrate (Prussian blue) is approved by the US Food and Drug Administration (FDA) for the treatment of internal cesium and thallium contamination. This insoluble compound is taken orally but is not absorbed by the GI tract. Once in the GI tract, it binds preferentially to cesium and thallium (radioactive and nonradioactive forms) with very high affinity. This changes and increases the rate of elimination from primarily urinary to fecal. Other ion exchangers and absorption compounds that may be useful in reducing the uptake of ingested radionuclides are sodium polystyrene sulfonate and activated charcoal. Although both compounds are used for other indications, neither is FDA-approved specifically for treating internalized radionuclides. Oral administration of calcium- and aluminum-containing antacids to decrease the GI uptake of radioactive strontium and radium has also been suggested.[20,21]

Blocking or Diluting Agents

The terms "blocking" or "diluting" agent can, in most cases, be used interchangeably. These compounds reduce the uptake of a radionuclide by saturating binding sites with a stable, nonradioactive element, thereby diluting the deleterious effect of the radioisotope. For example, potassium iodide is the FDA-recommended treatment to prevent radioactive iodine from being sequestered in the thyroid. Speed is essential when administering potassium iodide; delay in treatment (> 4 hours postexposure) results in a greater uptake of radioactive iodine in the thyroid, lessening this treatment's effectiveness. Nonradioactive strontium compounds may also be used to block the uptake of radioactive strontium. In addition, elements with chemical properties similar to the internalized radionuclide are often used as blocking agents. For example, calcium, and to a lesser extent phosphorus, can be used to block uptake of radioactive strontium. Isotopic dilution techniques are also included in this category. For example, internal tritium contamination may be treated by forcing fluids to reduce the time the isotope remains in the body.

Mobilizing Agents

Mobilizing agents are compounds that help release deposited radionuclides by increasing the natural rate of elimination. One example is ammonium chloride, which, when given orally, results in acidification of the blood and increased elimination of internalized radiostrontium. Sodium bicarbonate , given orally or intravenously, is used to increase urinary pH; such increases in alkalinity are useful in preventing the deposition of internalized uranium as it passes through the kidney.

Chelating Agents

A chelating agent is a compound that binds with a metal to form a stable, preferably less toxic, complex that facilitates excretion of the metal.[22] Chelating agents such as ethylenediaminetetraacetic acid (EDTA), desferrioxamine, dimercaptosuccinic acid (succimer), D-penicillamine, and 2,3-dimercaptopropanol (dimercaprol, British anti-Lewisite) have been used for many years as antidotes for acute heavy metal poisoning. In some cases, laboratory research has indicated that these compounds may also be useful in chelating radionuclides; however, chelation therapy can have a number of undesired side effects. Many chelating agents are chemically toxic and lack specificity for the target metal. This can lead to the depletion of metals essential for normal homeostasis. For example, EDTA, a compound often recommended for chelating lead

and mercury, can also decrease metabolic calcium to dangerously low levels. Chelating agents can also have the unintended side effect of redistributing toxic metals to previously uncontaminated tissues. For example, the chelator 2,3-dimercaptopropanol, once tested as an antidote for arsenic poisoning, was subsequently shown to move arsenic into the brain, an area that arsenic alone would not have been able to penetrate.[23] In some cases, chelation has been shown to enhance the toxicity of a metal. EDTA readily chelates iron, but it does so in a manner that permits the iron to catalyze reactions that result in oxidative stress, leading to greater damage than if chelation therapy had not been used.[24] Despite the potential pitfalls with the use of chelating agents, they represent the most promising avenue of therapeutic intervention in decorporating

TABLE 4-2

INTERNAL RADIONUCLIDE CONTAMINATION TREATMENT OPTIONS*

Targeted Radionuclide	Compound(s)	Dosage[1,2]
Americium	DTPA (calcium and zinc salts)†	Adults: IV 1 g in 5 mL IV push over 3–4 min, or IV infusion over 30 min, diluted in 250 mL of dextrose (5% in water), lactated Ringer's, or normal saline Children (< 12 y): 14 mg/kg IV as above, not to exceed 1 g
Cesium	Prussian blue†	Adults: 3 g three times daily orally Children (2–12 y): 1 g three times daily orally
Curium	DTPA (calcium and zinc salts)†	See americium
Iodine	Potassium iodide†	Adults: 130 mg/day orally Children (3–18 y): 65 mg/day orally Infants (1 mo–3 y): 32 mg/day orally Neonates (birth–1 mo): 16 mg/day orally
Phosphorus	Phosphate, dibasic potassium, and sodium salts	Adults: 1–2 tablets (250 mg phosphorus per tablet) orally four times per day with a full glass of water each time, with meals and at bedtime Children (> 4 y): 1 tablet orally 4 times daily
Plutonium	DTPA (calcium and zinc salts)†	See americium
Polonium	2,3-Dimercaptopropanol	Deep IM injection only, 2.5 mg/kg four times a day for 2 days, then twice a day on day 3, then daily for 5–10 days
Radium	Ammonium chloride	Ammonium chloride: 1 g three times daily for up to 6 days
	Calcium carbonate	Calcium carbonate: 0.5–1.0 g orally twice per day
	Calcium gluconate	Calcium gluconate: 10 g orally
	Sodium alginate	Sodium alginate: 5 g orally twice per day for 1 day, then 1 g four times daily with water
Strontium	Aluminum compounds (hydroxide, phosphate)	Aluminum hydroxide: 60–100 mL orally once for adults; children: 50 mg/kg, not to exceed adult dose
	Ammonium chloride Calcium carbonate Calcium gluconate Sodium alginate	Ammonium chloride, calcium carbonate, calcium gluconate, sodium alginate: see radium
Thallium	Prussian blue†	See cesium
Uranium	Sodium bicarbonate	Isotonic sodium bicarbonate, 250 mL slow IV infusion or 2 bicarbonate tablets orally every 4 h until urine pH reaches 8–9; continue for 3 days

DTPA: diethylenetriamine pentaacetic acid
IM: intramuscular
IV: intravenous
*Always take into account the possibility of essential metal depletion when initiating treatment. This list contains potential treatment options and should in no way be considered exhaustive.
†Approved for use by the US Food and Drug Administration.
Data sources: (1) National Council on Radiation Protection and Measurements. *Management of Persons Contaminated with Radionuclides*. Bethesda, MD: National Council on Radiation Protection and Measurements; 2009. NCRP Report 161. (2) Armed Forces Radiobiology Research Institute. Medical management of radiological casualties. 3rd ed. Bethesda, MD: AFRRI; June 2010. AFRRI Special Publication 10-1. http://www.usuhs.mil/afrri/outreach/pdf/3edmmrchandbook.pdf. Accessed March 17, 2011.

internal radionuclide contamination.

Two formulations of a chelating agent have been approved by the FDA for the treatment of internal contamination with plutonium, americium, and curium. The calcium (Ca) and zinc (Zn) salts of diethylenetriamine pentaacetic acid (DTPA) were approved for use in 2004. Ca-DTPA has been shown to be almost 10 times more effective than Zn-DTPA at chelating the transuranics (plutonium, americium, and curium) when given early after radionuclide exposure. However, this advantage is lost by 24 hours after exposure, when Ca-DTPA and Zn-DTPA are equally effective chelating agents. Because of this property, and the fact that Ca-DTPA has more adverse side effects than Zn-DTPA, standard practice is to start with Ca-DTPA for initial chelation therapy and switch to less-toxic Zn-DTPA to continue more protracted therapy regimens. In either case, depletion of essential trace metals should be monitored and mineral replacements given as needed.

Although not FDA-approved for treating internal radionuclide contamination, the off-label use of D-penicillamine for cobalt and iridium contamination, EDTA for cobalt, and dimercaprol for polonium should be considered in the absence of other options.[25]

Treating Contaminated Wounds

Radionuclides internalized as a result of wound contamination are eliminated in the same way as those internalized via other exposure pathways. In most cases, thorough irrigation and cleaning of the wound is sufficient. In some situations, adding a chelating agent to the irrigation solution facilitates radionuclide removal from the wound site. For wound contamination with plutonium, americium, or curium, standard chelation therapy with Ca-DTPA and Zn-DTPA should be initiated.

Wounds containing embedded radioactive fragments pose a unique treatment dilemma. In many of these situations, treatment with chelating agents is not indicated because of the potential to solubilize excessive amounts of metal from the embedded fragment and distribute it throughout the body. In these cases, it may be necessary to surgically remove the embedded fragment. Special precautions may be required depending on the radionuclide, including protective shielding for the surgical staff. Surgically removed fragments should be placed in lead containers and appropriately shielded. The facility's health physics staff is essential in helping deal with these situations in the safest manner possible.

SUMMARY

Radiological contamination remains a threat to civilians and military personnel alike. Because radionuclides may be internalized through inhalation, ingestion, and wound contamination, treatment methods vary, and each treatment option carries with it some risk. Internal radionuclide contamination treatment procedures are currently an area of much research, particularly in the field of chelating agents.[26–28] It is important that healthcare professionals are aware of treatment advances (please refer to the references for additional information[29–31]).

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