ADMINISTRATION OF DECORPORATION DRUGS TO TREAT INTERNAL RADIONUCLIDE CONTAMINATION

MEDICAL EMERGENCY RESPONSE TO RADIOLOGIC INCIDENTS

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Introduction

The possibility of radiologic accidents involving unsealed radioactive material is always present where radioactive materials are used. Such incidents are relatively unusual in the United States, where we take significant care to avoid them. When they do occur, they usually affect one or a few radiation workers, often in a controlled environment in which sophisticated expertise, materials and equipment are available for diagnosis and treatment. For this reason, most American physicians, including nuclear medicine physicians, radiologists, and emergency medicine physicians, have little or no education or experience with the medical management of internally contaminated individuals.

The possibility of terrorist acts involving radioactive material means that physicians who normally would never have occasion to treat internally contaminated patients might be called upon to do so. The purpose of this presentation is to review the detailed use of a number of drugs and procedures that will eliminate some or most internal radioactive contamination from the body.

Nature of Radiologic Incidents

Terrorist incidents could involve a radiological dispersion device (RDD) which could be a bomb (a so-called “dirty” bomb) or a method for dispersing radioactive material surreptitiously so that recognition of a contamination event might occur some time later, after significant spread of the radioactive material. It could involve the destruction of a place in which radioactive material is stored or used in sealed or unsealed form, and the consequent dispersion of that radioactive material. It could involve a nuclear weapon, although in this case, other problems such as external irradiation, blast, and burns would likely take precedence. In the event that the dispersion of radioactive material is associated with a non-nuclear explosion, ordinary injuries due to the explosion would have to be treated. Many of the most severely injured, who would be the closest to the

explosion, would also be among the most severely externally and internally contaminated with radionuclides. External contamination is generally removed with clothing removal and washing. Internal contamination will have to be ascertained along with the treatment of injuries due to the explosion, and after external contamination is removed.

Modes of Internalization of Radionuclides

Radioactive material may be inhaled, either as gases or particulates. Some will end up being swallowed, from mouth contamination, ciliary movement in the bronchial system that moves particulates to the mouth, or the eating or drinking of contaminated food. In addition, radioactive shrapnel from the destruction of a sealed source of radioactive material can become embedded in a wound.

The treatment of radioactive shrapnel is its surgical removal, as quickly as possible. The shrapnel should only be touched with instruments, not fingers, and should be placed in a lead container (called a “pig”) for shielding purposes.

Inhaled radioactive gases have varying amounts of absorption into the blood. Inhaled particulates that are not coughed out or swept out by cilia can be gradually solubilized to some extent, and then absorbed, or deposited eventually in the tracheobronchial lymph nodes, where they stay indefinitely. Radioactive material that is swallowed can be absorbed to some extent, depending upon what it is, and unabsorbed radioactive material is excreted in stool. Of material that is absorbed, some may be deposited in a variety of organs, and some may be excreted in urine.

Pharmacologic Mechanisms for Radionuclide Decorporation

A variety of rather simple pharmacologic concepts are exploited in order to rid the body of radioactive contamination (radionuclide decorporation).

If radionuclides are in the gastrointestinal tract, speeding up intestinal transit will favor excretion in the stool rather than absorption. A simple laxative thus becomes a radionuclide decorporation drug. Certain drugs will bind radionuclides in the gastrointestinal tract, making the radionuclides unavailable for absorption. Prussian blue, an unabsorbable dye, works this way for cesium and thallium, including radioactive isotopes of these elements. Flooding the gastrointestinal tract with stable counterparts of the radioactive material will compete with the radioactive material for absorption, and thereby cut down on the absorption of radionuclide. Ingesting calcium salts after strontium (Sr)-90 ingestion is an example of this (calcium is chemically similar to strontium).

Once the radionuclide enters the blood, one can try to block uptake in the target organ, such as by using non-radioactive potassium iodide to block radioiodide incorporation into thyroid hormone and subsequent storage in the thyroid gland. One can also use propylthiouracil to block the thyroid from taking up radioactive *or* non-radioactive iodide. One can change the chemical state to one that is less toxic, such as by alkalinizing

the urine after uranium ingestion with sodium bicarbonate. This produces uranium bicarbonate which is less nephrotoxic than other forms of uranium. Sometimes diuretics can be used to promote urinary excretion, such as after tritium (H-3) contamination. Chelating agents such as Ca-DTPA and Zn-DTPA may be parenterally administered to chelate a number of radioactive metals and promote their urinary excretion.

Radionuclides of Maximum Concern from RDD's

It is difficult to predict which radionuclides are most likely to be used in an RDD event, but based on accessibility and maximizing terrorist impact, it is not too hard to come up with some educated guesses. Strontium (Sr)-90, yttrium (Y)-90, cesium (Cs)-137, iridium (Ir)-192, cobalt (Co)-60, americium (Am)-241, iodine (I)-125 and 131, uranium (U)-234, 235, and 238, plutonium (Pu)-239, radium (Ra)-226, tritium (hydrogen-3 or H-3), phosphorus (P)-32 and palladium (Pd)-103 are possible candidates. There could always be mixtures of radionuclides, either because the original sealed sources contained a mixture, or because an exploded establishment contained a mixture, or because a terrorist sought to confuse responders and complicate the response situation.

When accidents occur involving radiation workers, one knows right away what radionuclide(s) is (are) involved. With an RDD event, the radionuclides used will have to be determined by radiologic health experts, either locally or through the Department of Energy (DOE). While some radionuclides are rather easily identified by a characteristic gamma ray spectrum, others are not. Hopefully, by the time patients appear in Emergency Departments, information will be available about the identity of some or all of the radionuclides used. This will permit the treating physicians to choose an appropriate decorporation regimen, if warranted by levels of internal contamination.

Note than in addition to knowing what radionuclides are involved, it is necessary to estimate the approximate level of internal contamination of the patient in order to know whether a decorporation treatment is necessary at all. Ascertaining the approximate contamination levels of patients will most likely be the responsibility of your nuclear medicine service. This is not an easy task, but we will assume, for the purposes of this presentation, that such knowledge is available to you.

It is also necessary to set the approximate upper limit of radionuclide contamination that can reasonably be ignored from a radiation safety point of view. These are value judgments that will depend upon the circumstances of the event and the resources available. One very conservative point at which to start would be the upper limit of radionuclide contamination permitted *each year* for radiation workers ("allowable levels of intake", or "ALI's"). While radiation workers are permitted fifty times more radiation dose each year than are members of the general public, the radiation doses allowed to workers are not associated with any measurable risk, and so it makes no medical sense to be concerned with lower doses, except perhaps for children. A comprehensive list of ALI's is to be found in 10 CFR Part 20, the radiation safety standard of the United States.

Decorporation Drug Access

Not all drugs used for decorporation are FDA-approved, although three that are extremely important (Prussian blue, Ca-DTPA, and Zn-DTPA) were recently approved by FDA pending an application by a manufacturer to produce the drug under current Good Manufacturing Practices. At least one manufacturer has been found for Prussian blue, and it is likely that a manufacturer will be found for the other two drugs. In any case, these drugs are available by prescription from at least one pharmacy in the United States who will fill prescriptions from all States and other countries as well. Other decorporation drugs are not FDA-approved for the decorporation indication (e.g., penicillamine). However, physicians may prescribe any drug for any indication, FDA-approved or not. You may want to check with your administration about your hospital's insurance policy regarding FDA-unapproved drugs and unapproved indications of FDA-approved drugs.

The Los Angeles County Dept. of Health Services Emergency Medical Services Agency has purchased a limited supply of a number of drugs useful for decorporation which hospitals would be unlikely to stock normally. *There should be an adequate number of doses stockpiled for needy patients, so long as the drugs are only used for patients who have been shown to require them.* Haphazard use and overuse of the drugs would rapidly deplete the stockpile and leave needy patients without access to necessary medication. Therefore, it is essential to be very professional about the decision to use these drugs in a particular patient. The stockpiled drugs include Prussian blue (500 mg capsules), Ca-DTPA (0.5 gm vials), Zn-DTPA (0.5 gm vials), Ca gluconate (20%, 10 ml vials), Na alginate (10 gm powder in 30 cc vial, add water to drink), D-penicillamine (250 mg capsules), ammonium chloride (500 mg capsules), Na bicarbonate (8.9%, 100 or 200 cc vials for intravenous use), and dimercaprol (British anti-lewisite, or BAL, 300 mg/vial for deep intramuscular injection suspended in peanut oil). While some other counties and hospitals in the United States have purchased supplies of Prussian blue, Ca-DTPA, and Zn-DTPA, physicians from counties other than Los Angeles need to check on which drugs are stockpiled, and where the stock is kept.

Alphabetical List of Radioelement and Decorporation Treatment Summary (see specific details under alphabetical list of drugs)

Americium: parenteral Ca-DTPA, Zn-DTPA.

Cesium: oral Prussian blue.

Cobalt: nothing too good, but oral penicillamine worth trying.

Iodine: KI *within about first 4 hours.* Consider PTU.

Iridium: unknown; try oral penicillamine.

Palladium: unknown; try oral penicillamine.

Phosphorus: oral Na phosphate or K phosphate.

Plutonium: parenteral Ca-DTPA, Zn-DTPA.

Radium: oral calcium to reduce gastrointestinal absorption and increase urinary excretion. Alginates are also useful to reduce gastrointestinal absorption.

Strontium: intravenous calcium gluconate, oral ammonium chloride for acidification. Alginates are useful to reduce gastrointestinal absorption.

Tritium: force water to promote diuresis.

Uranium: Ca-DTPA and Zn-DTPA within *4 hours only.* Na bicarbonate to alkalinize urine.

Yttrium: parenteral Ca-DTPA, Zn-DTPA.

Alphabetical List of Decorporation Drugs

Ammonium chloride: This orally administered salt causes acidification of the blood, and is useful for the removal of strontium from the body, especially when combined with intravenous calcium gluconate. Ammonium chloride is given p.o., 1-2 gm q.i.d., for up to 6 consecutive days. Check blood pH or serum CO_2 which will be lowered due to acidification. While best results occur if given quickly after intake, some effect is seen if used up to two weeks afterwards. If used promptly with calcium gluconate, radiostrontium levels can diminish 40-75 %. Nausea, vomiting, and gastric irritation are common. Avoid in patients with severe liver disease.

Calcium (oral): A variety of oral calcium supplements are available. One commonly used one is Tums^{R}. There are numerous others. Calcium is an alkaline earth, as are strontium, barium, and radium, and a mass effect from calcium can interfere with absorption of the other alkaline earths, and compete with their deposition in bone. In the event of internal contamination with Sr-90 or Ra-226, generous doses of oral calcium preparations should be beneficial.

Ca-DTPA: This is a powerful and stable chelating agent, which has been used primarily to remove plutonium and americium. It chelates transuranic (Z>92) metals (plutonium, americium, curium, californium, and neptunium), rare earths such as cerium, yttrium, lanthanum, promethium, and scandium), and some transition metals (such as zirconium and niobium). In normal, healthy, non-pregnant adults with normal bone marrow and renal function, the dose to use is 1 gm in 250 ml normal saline or 5% dextrose in water, iv over 1 hour. No more than 1 dose per day should be used, and the dose should *not* be fractionated. May use for several days to a week in most cases without toxic effects. Toxicity is due to chelation of needed metals, such as Zn and Mn. Toxicity includes nausea, vomiting, chills,

diarrhea, fever, pruritus, muscle cramps, and anosmia. After a couple of doses, the less toxic Zn-DTPA should be used instead. Zn-DTPA should be used exclusively in pregnant patients, if available. The same dose and dose schedule is used for Zn-DTPA as for Ca-DTPA. While the DTPA compounds are best used as quickly as possible after internal contamination, they are effective if given later, but therapy may go on for months or even years. The DTPA compounds are only effective if the metals one wishes to chelate are in ionic form. They are useless for highly insoluble compounds.

Calcium gluconate: Intravenous calcium gluconate is indicated for Sr-90 contamination, and probably Ra-226 contamination as well. Five ampoules, each containing approximately 500 mg calcium, may be administered in 0.5 liter D5W over a 4 hour period. This treatment may be administered daily for 6 consecutive days. It is contraindicated in patients who have a very slow heart rate, those on digoxin preparations, and those on quinidine.

Dimercaprol (British antilewisite, BAL): This agent effectively chelates radioactive and stable nuclides of mercury, lead, arsenic, gold, bismuth, chromium, and nickel. It is quite toxic, however, with about 50% of patients given 6 mg/kg IM developing reactions. These include systolic and diastolic hypertension, tachycardia, nausea, vomiting, chest pain, headache, and sterile abscess at the injection site. The dose to use is 2.5 mg/kg (or less) q4h x 2 days, then bid for 1 day, and then qd for days 5-10. It is available as 300 mg/vial for deep IM use (suspension in peanut oil).

D-Penicillamine: This drug chelates nuclides of copper, iron, mercury, lead, gold, and possibly other heavy metals. The chelated metals are excreted in the urine. While this drug is relatively non-toxic, it probably has only limited usefulness for radionuclide decorporation, saving perhaps only 1/3 of the total radiation absorbed dose that would have occurred without treatment. The adult dose is 250 mg p.o. qd between meals and at bedtime. May increase to 4 or 5 g qd in divided doses. Be very cautious if patient has a penicillin allergy.

Potassium iodide: Useful for blocking radioiodine uptake by the thyroid, but needs to be administered almost immediately after intake. It is virtually useless after 12 hours following a contamination event. Adult dose is 130 mg p.o. ASAP and repeat dose daily as long as the contamination lingers in the environment. For children 4 to18y, the dose is 65 mg p.o.; 1 month to 3y, 32.5 mg, and <1 month, 16.25 mg mixed with a liquid such as low fat milk.

Potassium phosphate: This drug would be used to block uptake of radioactive phosphate. K-Phos^{R} Neutral contains 250 mg phosphorus per tablet. Usual adult dose is 1-2 tabs p.o. qid, with full glass of water each time, with meals and at bedtime. Pediatric patients over 4y, 1 tab qid. Contraindicated in hyperphosphatemia, renal insufficiency, and infected phosphate stones.

Propylthiouracil: This drug is useful to decrease the thyroid's retention of radioiodine,

and may be considered if it is too late for KI to be effective. The adult dose is 50 mg tabs, 2 p.o. tid x 8 days.

Prussian blue: This oral ion-exchange drug is indicated for decorporation of cesium, thallium, and rubidium, and has been shown to be highly effective for Cs-137 contamination. It is benign, with the exception of occasional constipation. Stool turns blue. Usual dose starts at 0.5 g capsule, 2 caps p.o. tid for up to 3 weeks or longer as required. Doses up to 10-12 g/day for significantly contaminated adults may be used.

Sodium alginate: A derivative of kelp used in the manufacture of ice cream. Oral alginates efficiently bind strontium in the gastrointestinal tract, and prevent its absorption. The dose is 10 gm powder in a 30 cc vial, add water and drink.

Sodium bicarbonate: Used to alkalinize the urine after uranium intake, which protects the kidneys from uranium deposition. Oral or intravenous, take as needed to maintain alkaline urine. The intravenous formulation is 8.9%, 100 or 200 cc vials.

Sodium phosphate: See potassium phosphate. Also used for radioactive phosphate decorporation.

Zn-DTPA: See Ca-DTPA.

Allowable Levels of Intake (ALI's) for Selected Radionuclides

These are the yearly legal limits for radiation workers, who may experience such intakes *every year*. Internally contaminated individuals with less than one ALI would not ordinarily be candidates for decorporation therapy, as their effective dose is not significant enough to merit concern. The ALI limits differ for ingestion and inhalation routes because of biodistribution and kinetic differences leading to different effective radiation doses. One ALI gives an effective dose of about 5 rem, the annual limit of radiation dose permitted for a radiation worker. Compounds may be represented as D, W, and Y signifying body retention times in Days, Weeks, or Years. If there is no such representation, the ALI is for all compounds.

	Ingestion (µCi)	Inhalation (µCi)
Americium-241:	8E-1	6E-3
Cesium-137:	1E+2	2E+2
Cobalt-60:	W: 5E+2 Y: 2E+2	W: 2E+2 Y: 3E+1
Iodine-125:	4E+1	6E+1

Iodine-131:	3E+1	5E+1
Iridium-192:	9E+2	D: 3E+2 W: 4E+2 Y: 2E+2
Palladium-103:	6E+3	D: 6E+3 W: 4E+3 Y: 4E+3
Phosphorus-32:	6E+2	D: 9E+2 W: 4E+2
Plutonium-239:	8E-1	W: 6E-3 Y: 2E-2
Radium-226:	2E+0	6E-1
Strontium-90:	3E+1	D: 2E+1 Y: 4E+0
Tritium (hydrogen-3):	8E+4	8E+4
Uranium-233:	1E+1	D: 1E+0 W: 7E-1 Y: 4E-2
Uranium-234:	1E+1	D: 1E+0 W: 7E-1 Y: 4E-2
Uranium-235:	1E+1	D: 1E+0 W: 8E-1 Y: 4E-2
Yttrium-90:	4E+2	W: 7E+2 Y: 6E+2

References

1. Most of the material contained herein comes from NCRP Report No. 65, Management of Persons Accidentally Contaminated with Radionuclides, April 15, 1980. This publication may be ordered on line at www.ncrp.com for $50.00.

2. The ALI's come from 10 CFR Part 20, the regulations of the Nuclear Regulatory Commission.

3. Information on Ca-DTPA, Zn-DTPA, and Prussian blue came from the REAC/TS web site, http://www.orau.gov/reacts/.

4. Medical Management of Radiological Casualties, 2nd Edition, Military Medical Operations, AFRRI, Bethesda, MD, April, 2003.

5. Physician's Desk Reference for material on oral calcium supplements and potassium phosphate.