Pharmacotherapy

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The deposition of radioactive materials in the body – or internal contamination – is a time-dependent phenomenon related to both the physical and chemical properties of the contaminant. Once internal contamination has occurred, the rate of radionuclide incorporation into target tissues can occur rapidly. Thus, time to treatment is critical. For treatment to be effective, it must be administered quickly in order to have the best chance at mitigating adverse health effects.

Clinicians will need to rely on the basic tools of diagnosis – history, physical examination, and a couple of confirmatory laboratory studies – to make a presumptive diagnosis of internal contamination. An exposure history can help identify the likelihood or potential for inhalation or ingestion of radionuclides following a radiation mass casualty event. These clues can help increase the clinician’s index of suspicion that internal contamination may have occurred. On physical examination, the presence of open wounds containing shrapnel should suggest the possibilities of internal contamination. Finally, a laboratory assessment can provide clues as to the likelihood of internal contamination. If present, measured levels of radioactivity in a victim’s urine are strongly suggestive of internal contamination.

Once internal contamination has occurred, a goal of treatment is to prevent incorporation of radionuclides in internal organs. Gastric lavage and catharsis are methods familiar to most physicians that can be used shortly after ingestion of a radionuclide to help facilitate rapid excretion from the body. Recommended treatment for cobalt 60, phosphorus 32, and radium 226, for example, includes the use of Gastric Lavage. In the case of Radium 226 ingestion, this should be accomplished using a 10% magnesium sulfate solution. Whether attempting gastric lavage on large numbers of patients is feasible or practical will be determined by the size of the event. An additional point I would like to make concerns the use of activated charcoal. Activated charcoal is widely available in most emergency departments for use as a GI decontaminant, and most clinicians are well acquainted with its use. Based on current information, however, the efficacy of activated charcoal may be limited. While there is no obvious downside to its use, it may not be a useful adjunct for gastrointestinal decontamination of radionuclides. The effects of radiation exposure, such as nausea and vomiting, should also be treated. Drugs to treat nausea, vomiting, and diarrhea should be used as necessary and fluid and electrolyte balance should be carefully monitored and aggressively treated.

Ultimately, treatment decisions may be based on a history that is only suggestive for exposure or on incomplete laboratory data. Nonetheless, for treatment to be most effective it should be initiated early following radiation exposure and clinicians may be required to make decisions about whom to treat in the absence of complete or compelling evidence. Some treatment modalities for internal contamination are currently available – the most sophisticated of which are directed at preventing incorporation or removing radioactive isotopes from the body.

I would now like to introduce the discussion of the pharmacotherapy of internal contamination and acute radiation illness. In the event of a radiological or nuclear event, four drugs are available for use from the Strategic National Stockpile. Three drugs: Potassium Iodide, Prussian Blue, and DTPA may
be used to treat internal contamination. The fourth, the granulocyte colony stimulating factor, filgrastim is used in the treatment of the hematopoietic syndrome. In a mass casualty situation, demand for these drugs may exceed initial supplies. Although some states already have stores of KI, the other drugs on this list will likely only be available in quantities sufficient to treat large numbers of casualties from the Strategic National Stockpile. A deliberate and careful use of these agents will necessitate an understanding and application of radiological mass casualty triage principles since not all individuals exposed to radiation or internally contaminated with radiation will be candidates for drug therapy. Pharmacotherapy may not be indicated in patients with low levels of exposure or internal contamination. Furthermore, assuming that resources will be limited following a radiation mass casualty event, it may be appropriate to withhold definitive care from those identified by triage criteria as having high levels of exposure and, consequently, a poor prognosis; such individuals should, however, receive adequate pain management, antiemetics, and antidiarrheals.

Potassium iodide – or KI – is an orally administered radioactive iodine blocking agent. KI is available as a variety of preparations, including an FDA-approved solution – for administration to children. KI acts by blocking the incorporation of radioactive iodine into the thyroid gland by competing with the radioisotope for uptake binding sites. This agent should be administered as quickly as possible following a radiation mass casualty event in which there is a high likelihood of exposure to radioactive iodine. Radiation mass casualty events in which the release of radioactive iodine is most likely include: Nuclear power plant incidents – for example, significant levels of radioactive iodine were released following the Chernobyl nuclear power plant explosion in 1986. Also, the detonation of an improvised nuclear device or a nuclear bomb could serve as sources of radioactive iodine. So-called “dirty bombs” – more formally referred to as radiation dispersal devices or RDDs – in which a conventional explosive is laced with radioactive activity – represent an unlikely source of exposure to radioactive iodine. Therefore – victims of a “dirty bomb” attack – are unlikely to need treatment with KI. As I said earlier, KI must be administered within hours following a radiological mass casualty event. As seen in the graph on this slide, the effectiveness of KI is highly time-dependent. Taken as early as 24 hours in advance of an exposure to radioactive iodine, KI can provide near total blockade of radioactive iodine uptake. As soon as exposure has occurred, however, the effectiveness of this drug falls rapidly. At 2 hours post-exposure, KI is 80% effective in blocking radioactive iodine uptake, At 8 hours, it is 40% effective, and By 24 hours, KI provides little effective blockade and radioactive iodine has been incorporated into the thyroid gland. The populations most sensitive to the effects of radioactive iodine exposure – cancer of the thyroid – are among the youngest. During the years following the Chernobyl nuclear power plant disaster, it was discovered that children developed cancer of the thyroid at rates much greater than adults having similar levels of exposure. Thus, according to current treatment recommendations, the threshold for initiating treatment with KI in children and in pregnant mothers after a radiation mass casualty event is lower than it is for non-pregnant adults. Additional guidance concerning the administration of KI – including dosages and dosing schedules – is available from the US Food and Drug Administration and may be found on their website.

The next drug I will discuss is Prussian Blue or Ferric hexacyanoferrate. In January, 2003, the Food and Drug Administration determined that Prussian blue had been shown to be safe and effective in treating people exposed to radioactive elements such as Cesium 137 and also to thallium. Once absorbed into the body, cesium and thallium are removed by the liver, passed into the intestine and then re-absorbed into the bloodstream from the intestinal lumen – a process known as entero-hepatic circulation. Prussian Blue, an orally administered decorporation agent acts by adsorbing radioactive cesium and thallium within the gastrointestinal tract and promoting the excretion of these isotopes into the stool. Prussian blue does not, however, treat the complications of radiation exposure – supportive care will undoubtedly be required. This means the use of antibiotics, antiemetics, nutritional support, intravenous fluids, and irradiated blood products and platelet transfusions as necessary. Administration of Prussian Blue is indicated when internal contamination with radioactive cesium occurs at doses in excess of 10 times the annual limit of intake. The decision to treat therefore requires an assessment of the patient by a qualified health physicist who will determine the amount of internal contamination. The
health physicist is also needed to help monitor the patient’s course since current recommendations are that Prussian Blue should be discontinued once the total body burden is estimated to be less than 1 annual limit of intake. Treatment is not generally recommended for persons who are internally contaminated with a dose less than 1 annual limit of intake and the need for treatment of internal contamination between 1 and 10 times the annual limit of intake remains controversial. Ideally, treatment with Prussian Blue should begin as soon as possible. Even when treatment cannot be started right away, treatment with Prussian Blue is effective and should not be withheld – it should be administered as soon as it becomes available. Additional sources of guidance for Prussian Blue administration are included here.

Calcium and zinc DTPA – diethylenetriaminepentaacetate – are chelating agents that effectively bind the transuranic, radioactive elements plutonium, americium, and curium. DTPA acts by exchanging cations for these specific radioisotopes which, in turn, form stable, water-soluble complexes with the DTPA ligand. The radioisotope-DTPA complex is then excreted in the urine. Although DTPA is an effective chelator for some transuranic radioisotopes it is important to remember that internal contamination with uranium and neptunium should not be treated with DTPA. It is believed that DTPA forms unstable complexes with uranium and neptunium that may result in increased deposition of these radioisotopes into bones. Current recommendations for treating uranium call for alkalinizing the urine with bicarbonate in order to promote renal excretion. As with the other agents we have been discussing, the effectiveness of DTPA administration – particularly calcium DTPA – is time-dependent. When administered within the first 6 hours of exposure, calcium DTPA is maximally effective as a chelating agent, even exceeding the binding of zinc DTPA by as much as 10x. By 24 hours post-exposure, however, calcium and zinc DTPA have approximately equal efficacy. In addition, over time, calcium DTPA is associated with more complications than is zinc DTPA. Because zinc DTPA does not deplete zinc and magnesium from the body like calcium DTPA does, it has a better safety profile over the long term. Therefore, current guidance recommends initiating chelation with calcium DTPA in the first 24 hours and then suspending its use – to be followed by zinc DTPA. The use of zinc DTPA is also preferable to calcium DTPA among children, pregnant women, in people with serious kidney disease, and in those who have a suppressed bone marrow. Clinicians should remember to check a patient’s renal function prior to each administration of the drug since it is known itself to be toxic to the kidneys. The use of DTPA should be discontinued if proteinuria, hematuria, or renal casts develop during its use. Further guidance concerning the use, contraindications, and adverse side effects associated with the use of DTPA may be found at these web sites.

The last agent I would like to discuss differs somewhat from the previous three in that it is neither a blocking agent nor is it a drug that promotes decorporation after internal contamination. Instead, this drug is used to treat one of the more serious adverse effects of acute radiation syndrome: bone marrow suppression. Drugs of this class are known as colony stimulating factors. In fact, colony stimulating factors occur naturally within the body where they act to induce hematopoietic progenitor cells of the bone marrow to proliferate and differentiate into specific mature blood cell types. One drug of this class – filgrastim – has been genetically engineered to stimulate the proliferation and maturation of granulocytes. Filgrastim specifically activates the neutrophil progenitor cells and its effect on stimulating the proliferation of other hematopoietic precursor cells – other than neutrophils – is minimal. Filgrastim has been used now for several years with FDA approval, and with good effect, in the treatment of cancer patients receiving myelosuppressive therapies. Although filgrastim has not been approved by the FDA for the treatment of bone marrow suppression following acute radiation exposure, studies involving irradiated animals receiving colony stimulating factors in the first 24 hours post-exposure indicate improved rates of survival compared to untreated controls. In addition, these drugs have been used with some success in victims of unintentional radiological exposures, such as have occurred in workplace settings.

Following a radiation mass casualty event, it is anticipated that filgrastim would be administered to victims suffering from bone marrow suppression secondary to acute radiation syndrome. Administration
of colony stimulating factors is recommended for any adult having whole body or significant partial-body radiation exposures resulting in a moderate to severe Acute Radiation Syndrome prodrome. Short-term therapy with colony stimulating factors is appropriate when exposure doses following a radiological or nuclear incident are relatively low. For victims with high exposure doses, a more prolonged course of therapy may be appropriate. The use of these drugs may be discontinued when the absolute neutrophil count has rebounded to 1000 cells per microliter or greater. Since victims of combined injury have an overall worse prognosis, it may be appropriate in a mass casualty situation to withhold use of filgrastim in favor of children and adults with atraumatic irradiation. Overall the safety profile of the colony stimulating factors is largely good but they are not without potential adverse side effects. Allergic reactions have been reported in less than 1 in 4000 patients and the reactions all respond well to conventional therapies such as antihistamines and steroids. Less commonly there have been reports of fatal and non-fatal splenic rupture in patients receiving colony stimulating factors – patients receiving these drugs must be cautioned about reporting immediately any abdominal pain, left upper quadrant pain, or any left shoulder pain. Finally, in patients with sickle cell disease, the colony stimulating factors have induced severe sickle cell crises requiring hospitalization, IV hydration and aggressive pain management. Additional guidance information concerning the appropriate use of colony stimulating factors and filgrastim may be found at the web sites listed here. Oncology specialists in your own institution may also be able to provide you with information and answers to questions concerning the use of these drugs.

In most cases – in order to maximize efficacy available pharmacotherapy for the treatment of internal contamination and acute radiation exposure should occur in a timely fashion.

Some drugs may have limited or no efficacy when administered too long after a radiation exposure. This means that clinicians may need to begin some treatments in the absence of a definitive diagnosis. Treatment should be appropriate to the exposure. For example, administering KI to a population exposed to a “dirty bomb” detonation may not be appropriate and use of DTPA to treat internal contamination with uranium is contraindicated. Guidance concerning the use of these agents – many of which may be novel to you – is available from the US Food and Drug Administration and from the Centers for Disease Control and Prevention.

To conclude, I would like to quote a recent article published in the Annals of Internal Medicine, entitled “Medical Management of the Acute Radiation Syndrome: Recommendations of the Strategic National Stockpile Radiation Working Group”. This paragraph succinctly summarizes some of the most important points I have tried to make in this series of lectures. I highly recommend this reference to any of you who may be looking for additional, in-depth information on the topics I have discussed.

“Barriers to the provision of optimal care [in a radiation mass casualty event] include limitations of resources, loss of infrastructure, a high volume of victims, and presence of combined injury. Allocation of potentially limited resources should be determined by the number of victims and their long-term prognosis. Estimation of individual radiation dose is recommended for determining survivability of patients in a range of doses that indicate predisposition to the acute radiation syndrome. Treatment recommendations are based on this dose range, which becomes increasingly narrower as the number of casualties increases and with the occurrence of combined injuries.”
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1. **Internal Contamination**
   a. Time-dependent phenomenon
   b. Related to physical properties of isotope
   c. Incorporation can occur rapidly

2. **Internal Contamination: Diagnosis**
   a. Exposure history
   b. Physical exam
   c. Laboratory studies
      - Complete blood count
      - Urinalysis

3. **Treatment for Internal Contamination**
   a. Gastric lavage and catharsis
      - Recommended treatment for cobalt 60, phosphorus 32, and radium 226
      - Radium 226 ingestion – 10% magnesium sulfate solution
   b. Activated charcoal
      - May have limited or no significant efficacy in radionuclide GI decontamination
   c. As necessary
      - Anti-emetics
      - Anti-diarrheals
      - Replace fluids and electrolytes
   d. Decisions may have to be based on:
      - History only suggestive of exposure
      - Incomplete laboratory data
   e. Treatment modalities:
      - Prevent incorporation
      - Remove radioactive isotopes
   f. Pharmacotherapy
      - Potassium Iodide or KI
      - Prussian Blue
      - Diethylenetriaminepentaacetate (DTPA)
      - Granulocyte colony stimulating factor, filgrastim
   g. Mass Casualty Implications
      - Demand for drugs may exceed initial supplies
      - Quantities - Strategic National Stockpile
      - Not all individuals exposed will be candidates for drug therapy
4. Potassium Iodide

a. IOSAT™; ThyroSafe™; Thyro-Block™
b. ThyroShield™ solution for children
c. Orally administered radioactive iodine blocking agent
d. Prevents radioactive iodine uptake in thyroid gland by competing for binding sites
e. Radioactive iodine release scenarios
   - Nuclear power plant incident
   - Detonation of improvised nuclear device
   - “Dirty bomb” is unlikely source
f. Blockade of radioactive iodine uptake is time-dependent
   - KI is 80% effective at 2 hours post-exposure; 40% effective at 8 hours


Thyroid of fetus and young children more sensitive to carcinogenic effects of radioiodine
   - Radioiodine uptake inversely proportional to thyroid size
h. Administration guidance available from US Food and Drug Administration (FDA)

5. Additional guidance on KI


6. Prussian Blue

a. Ferric (III) hexacyanoferrate (II) (Radiogardase®)

b. Orally administered decorporation agent (capsules)

c. Promotes fecal excretion of radioactive cesium and thallium

d. Binds isotopes in gastrointestinal tract via ion-exchange, adsorption, and mechanical trapping; limits entero-hepatic recirculation

e. Does not treat complications of radiation exposure
   - Need concomitant supportive care
     - antibiotics
     - antiemetics
     - nutritional support
     - IV fluids
     - irradiated blood products/filtered transfusions

f. Recommended for internal contamination ≥ 10 times the annual limit of intake

g. Requires a Health Physicist to assess

h. Treat until body burden ≤ 1 annual limit of intake

i. Initiate treatment as soon as possible

j. Treat for minimum of 30 days
   - Duration based on level of contamination
7. Additional guidance on Prussian Blue

http://www.fda.gov/cder/drug/infopage/prussian_blue/default.htm
http://www.bt.cdc.gov/radiation/prussianblue.asp
http://www.orau.gov/reacts/prussian.htm

8. DTPA - Diethyleneetriaminepentacacetate

- Calcium (Ca) and zinc (Zn) salts
- Intravenous chelating agents for plutonium, americium, curium
- DO NOT USE for uranium, neptunium
- Ca-DTPA
  - Within 6 hours of exposure is most effective
  - Initially 10x more effective than Zn-DTPA
  - At 24 hours post-exposure Zn-DTPA and Ca-DTPA have equal efficacy
  - With chronic use, Ca-DTPA causes depletion of zinc and magnesium
  - Use Ca-DTPA during first 24 hours, then replace with Zn-DTPA
- Ca-DTPA contraindications
  - Minors, pregnant women, serious kidney disease, bone marrow suppression
  - Check renal function prior to each administration
  - Discontinue if
    - proteinuria
    - hematuria
    - casts

9. Additional Guidance on DTPA

http://www.fda.gov/cder/drug/infopage/dtpa/default.htm
http://www.orau.gov/reacts/calcium.htm
http://www.orau.gov/reacts/zinc.htm
http://www.bt.cdc.gov/radiation/dtpa.asp
10. Filgrastim - Colony Stimulating Factors (CSF)

a. Endogenous glycoproteins
b. Induce hematopoietic progenitor cells of bone marrow to proliferate and differentiate into specific mature blood cell types
c. Filgrastim [Granulocyte-CSF (G-CSF)]
   - Genetically engineered protein
   - Daily IV or IM administration
   - Minimal effect on hematopoietic cell types other than neutrophil progenitors
d. FDA-approved for treatment of neutropenia resulting from myelosuppressive cancer therapy
e. Not approved for treatment of ARS
f. Recommended for adults with moderate to severe ARS
g. Discontinue use when absolute neutrophil count rebounds to 1,000 cells per μL
h. Has been used as investigational drug for persons with unintentional radiological exposures
i. Side effects
   - Allergic reactions (< 1 in 4,000 patients)
     - Good response to antihistamines, steroids, bronchodilators and/or epinephrine
     - ~50% have recurrence on re-exposure
   - Fatal and non-fatal splenic rupture
   - Severe sickle cell crises in patients with sickle cell disease

11. Additional Guidance on Filgrastim

http://www.bt.cdc.gov/radiation/neupogenfacts.asp
12. SUMMARY

a. Pharmacotherapy must be administered quickly after exposure
b. May need to begin treatment in the absence of a definitive diagnosis
c. Match the treatment to the exposure
d. Guidance is available from the FDA and CDC concerning appropriate administration

From “Medical Management of the Acute Radiation Syndrome: Recommendations of the Strategic National Stockpile Radiation Working Group”
http://www.annals.org/cgi/reprint/140/12/1037.pdf

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Allocation of potentially limited resources should be determined by the number of victims and their long-term prognosis.

Estimation of individual radiation dose is recommended for determining survivability of patients in a range of doses that indicate predisposition to the acute radiation syndrome.

Treatment recommendations are based on this dose range, which becomes increasingly narrower as the number of casualties increases and with the occurrence of combined injuries.”

Source: “Radiological and Nuclear Terrorism: Medical Response to Mass Casualties,” a self-study training program for clinicians, developed by the Centers for Disease Control and Prevention, 2006.

For copies of this product, email cdcinfo@cdc.gov.

To learn more about responding to a radiological incident, visit http://www.bt.cdc.gov/radiation