

"Medical Management of Radionuclide Internal Contamination"

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 **O R I S E**

OBJECTIVES

- Discuss the body's mechanisms for the internalization of radionuclides
- Discuss the procedures for treatment of internal contamination and methods for assessing the efficacy of that treatment

Internal contamination is the deposition of radioactive material inside the body

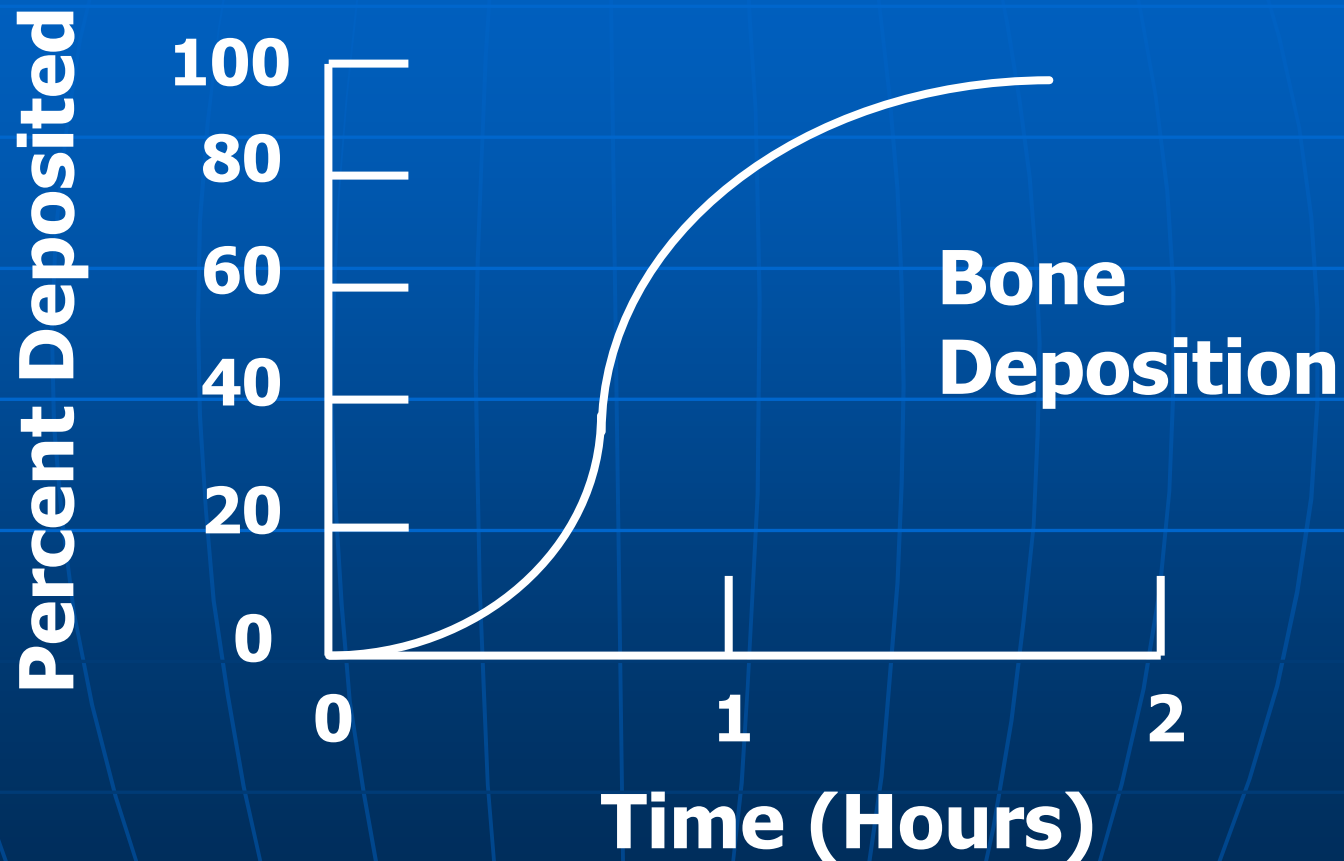
Other Terms

- Intake – merely crossing the 3-D confines of the human body
- Uptake – movement inside the body
- Incorporation – taken into the active metabolism of some cell, tissue or organ
- Decorporation – removal from the cell, tissue, organ or body

Common Routes of Entry

- Inhalation
- Ingestion
- Percutaneous or transdermal absorption through skin
- Injection or puncture

Uptake of Actinides is Remarkably Rapid

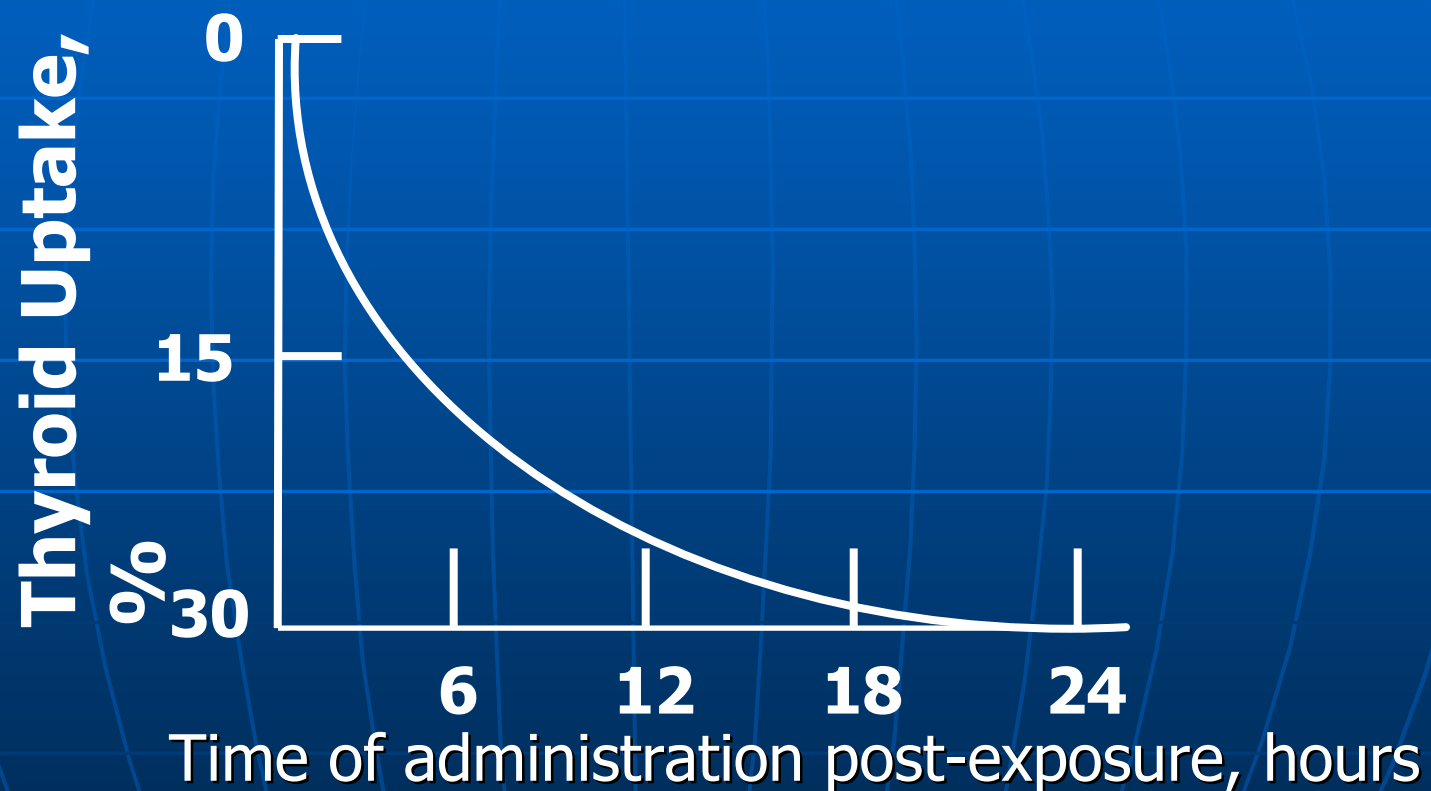


Prompt DTPA Treatment of ^{239}Pu Intake is Highly Effective

Retention (% of Uptake)

	Control	DTPA Treated
Liver	14.0	0.47
Skeleton	57.0	5.9

Prompt KI Treatment of ^{131}I Intake is Highly Effective



When to Treat?

- ALI (annual limit of intake) is that CEDE necessary to give 5 rem = 0.05 Sv
- For intake < 1 ALI, no treatment
- For $1 < \text{intake} < 5$ ALI, probably no treatment, with physician discretion
- For $5 < \text{intake} < 10$ ALI, consider treatment
- For intake > 10 ALI, treat with patient consent

The "University Seven"

- H-3
- C-14
- P-32
- Co-60
- I-125
- I-131
- Cf-252

The "Industrial Three"

➤ Ir-192

➤ Cs-137

➤ Co-60

The "Military Three"

➤ U-235

➤ Pu-239

➤ Am-241

General Health Physics Guidelines

- Attempt to determine the maximum credible accident – incident history/reconstruction
- Inhalation:
 - o Nasal swab taken within 1-2 hrs post-exposure can aid in nuclide identification and can approximate 5%-10% of intake.
 - o Prepare for whole-body and/or lung counting
- Wounds:
 - o Use of a wound probe helpful to ascertain maximum credible accident
 - o Surgical debridement sometimes helpful if decontamination efforts are unsuccessful

Immediate Diagnosis

- Incident history/reconstruction with health physics input are absolutely essential
- Wound surveys
- Facial surveys
- Nasal swipes
- Nasal blows
- Sputum
- Spot urine – check for gammas

Methods for Assessing Intakes

- Whole Body Counting:
 - o Feasible for nuclides that emit penetrating x or gamma rays
 - o Useful also for nuclides emitting energetic beta particles - can be detected by their bremsstrahlung radiation
- Bioassay:
 - o Urine - most widely used
 - o Feces
 - o Excised material from wounds
- Chromosome aberration analysis

Bioassay

- Slow
- Must have total collection of both urine and feces
- May overestimate uptake by factor of 3-5
- Specimen may get contaminated

Whole Body Counting Difficult When Actinides Involved

- Residual skin contamination
- Calibration of phantoms difficult
- Lung distribution varies with time
- Variable thickness of chest wall

Clearance Time - Nasopharynx

Time to Swallowing

Anterior Nares

Approx. 60 min.

Nasopharynx

10 min.

[10 mm/min.]

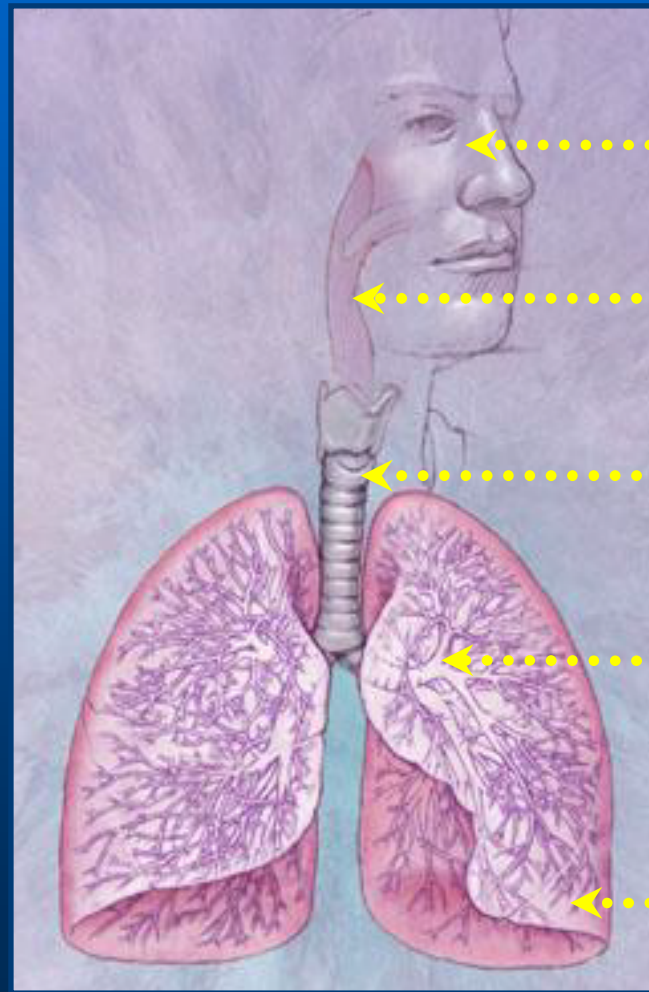
Clearance Time of Respiratory Tract

	Time
Trachea	0.1 hours
Bronchi	1 hours
Bronchioles	4 hours
Terminal Bronchioles	10 hours
Alveoli	100 Days +

Inhalation Pathway

- Size of the aerosol particles determine region of the respiratory tract where most are deposited
- Fate of inhaled particles is dependent on their physico-chemical properties
- Highly insoluble particles remain in the lung for long periods of time
 - o A small fraction will be transported to the tracheo-bronchial lymph nodes by pulmonary macrophages
 - o Some are cleared through the airways, swallowed, and excreted in the feces

Particle Size Distribution in the Respiratory Tree



Mass Median Diameter
[microns]

18-20

15-18

7-12

4-6
(bronchioles)

1-5
(alveoli)

Clearance Time of Gastrointestinal Tract

Occupancy Time
[hours]

Stomach	6
Small Intestine	14
Upper Large Intestine	18
Lower Large Intestine	22

Absorption of Ingested Radionuclides

Group	Radioactive Elements of	% Absorbed
Alkali Metals	Na, K, Rb, Cs	High ~90
Group VIII Metals	Fe	10
	Co	30-90
	Ru	3

Absorption of Ingested Radionuclides

Group	Radioactive Elements of	% Absorbed
Lanthanides	Ce, Pm, Eu, Tb	<0.1
Actinides	Th, U, Np, Pu	<0.1

The SC 4-1 document will provide many hypothetical case examples of diagnostic and operational guidelines for care of patients ,such as follows:

- A chemist at a Pu processing facility is involved in a loss of containment accident involving Pu-239 oxide
- His nasal swabs read approximately 1,000 dpm total alpha bilaterally (500 dpm each nostril)
- Total nasal =5% of deep deposition (LLNL, ICRP 30 methodology)
- Estimated deep lung deposition is therefore approximately 20,000 dpm = 333 Bq

Magnitude of the Problem

- $1 \text{ Ci} = 37 \times 10^9 \text{ Bq}$ (37 GBq); $1 \text{ nCi} = 37 \text{ Bq}$
- Estimated lung deposition = 333 Bq
- ALI for Pu-239 is $6 \times 10^{-4} \text{ MBq} = 600 \text{ Bq}$ (EPA FGR #11)
- So, estimated deposition is approximately 0.5 ALI

Treatment Methods

- Minimize intake
- Reduce and/or inhibit absorption
- Block uptake
- Use isotopic dilution
- Promote excretion
- Alter chemistry of the substance
- Displace isotope from receptors
- Chelate

Displace

- Use calcium to compete with radio-strontium
- Use stable iodide to compete with radio-technetium

Chelate

- DTPA – Diethylenetriaminepentaacetic Acid
- EDTA – Versene
- BAL – Dimercaprol
- DFOA – Deferoxamine
- PCA - Penicillamine

Reduction of Absorption From Gastrointestinal Tract

- Antacid
- Precipitation into insoluble salt
- Catharsis

*Prussian Blue is Highly Effective in Rx of Radio-Cesium or Thallium Uptake**

- Binds ions in gut
- Reduces biological half-life to one third of untreated value
- Not absorbed
- Reduces recycling (enterohepatic circulation)

***Complete package information available at
www.ornl.gov/reacts/resources.htm**

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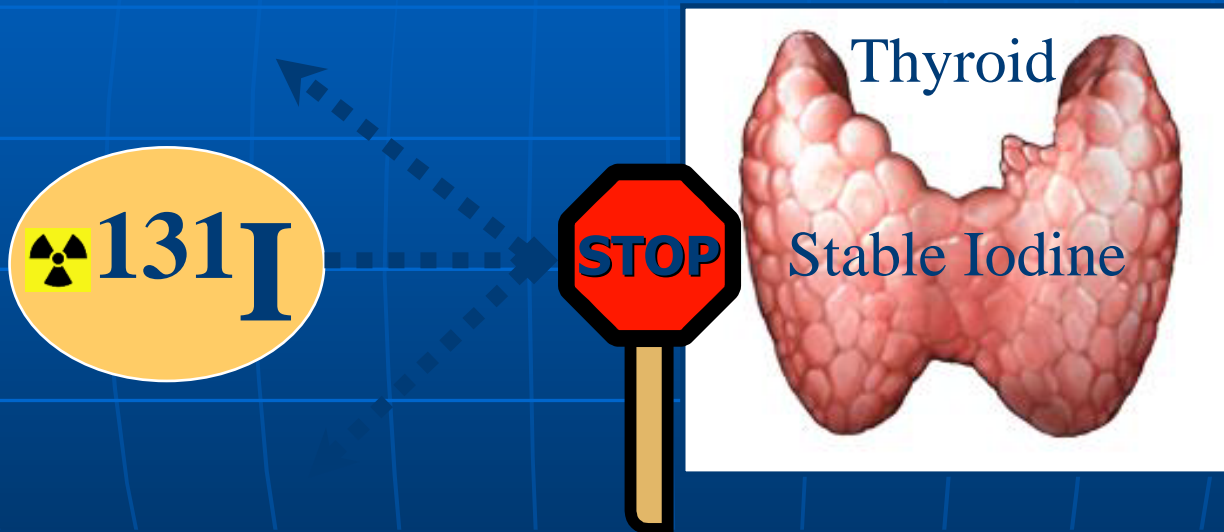
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Cesium

- ^{137}Cs (physical half-life, 30 years; biological half-life 109 days) is the dominant radioisotope in *aged* fission products
- Distributes in body fluids similarly to potassium
- One gram orally three times daily x 3 weeks reduces the biological half-life to about 1/3 of the normal value (low ALI). For higher intake, titrate upward

Saturate the Critical Organ with the Stable Isotope



Nuclear Incidents

- In the immediate vicinity of a nuclear accident (the near field), exposure could begin immediately if the released plume is at a low level. Main route of exposure is inhalation. Potentially larger thyroid doses might be expected from radioiodine.
- Further away from the site of the accident (the far field), the main route of exposure to radioiodine would be ingestion of contaminated food and drink, particularly milk. Exposure by these routes could last longer, cover a larger area, and affect a larger population than exposure in the near field.

Iodine

- The dominant initial internal contaminant after a reactor accident, nuclear weapons test, or any incident involving *fresh* fission products is likely to be ^{131}I .
- Thyroid is generally blocked by dilution; 130 mg KI tablet stat and one tablet daily x 7-14 days.
- 5 or 6 drops of SSKI, Saturated Solution of Potassium Iodide (1 g/ml) is another convenient way to administer stable iodide.
- Potassium perchlorate (200 mg) may be used in patients with iodine sensitivity.

Dose of Stable I to Exposed Groups

- Consider a basic tablet giving 50 mg of I
- Adults: two tablets
- Children and adolescents: one tablet.
- Infants: 1/2 tablet
- Neonates: 1/4-1/2 tablet crushed up in jam or a drink
- Timing: ASAP. In a situation with continuing exposure, stable I may be 50% effective even 5 hours after exposure to radioiodine.

Rubery and Smales. *Iodine Prophylaxis Following Nuclear Accidents.* 1988.

FDA Recommendations for Potassium Iodide

Group	Daily Dose [mg]
Infants <1 month	16
Children 1 month – 3 years	32
Children and teenagers 3 – 18 years	65
Adults (including pregnant and lactating women and adolescents over 150 pounds)	130

Daily dosing should continue until the risk of exposure has passed and/or until other measures (evacuation, sheltering, control of the food and milk supply) have been successfully implemented

Exposed Population Groups

- Pregnant women
 - o First trimester - In the near field, stable I will protect mother; no fetal action necessary. In the far field, maternal protection may be effected by controls on food.
 - o Second trimester - Fetal thyroid begins to function around the 12th week of gestation. Stable I should be given for subjects in both near and far fields to protect maternal and fetal thyroids.
 - o Third trimester - Same as 2nd trimester.
- Conclusions: Stable I to all pregnant women in near field for all trimesters; stable I to 2nd and 3rd trimester women in the far field. (Rubery and Smales, 1988).

Tritium - ^3H

- Follows pathway of water in the body
- Penetrates skin, lungs, and GI tract, either as tritiated water (HTO) or in the gaseous form
- Single exposures are treated by forcing fluids
- This has the dual value of diluting the tritium and increasing excretion
- Biological half-life - 10 days
- Forcing fluids to tolerance (3-4 L/d) will reduce the biological half-life to 1/3 to 1/2 of the normal value

Isotopically Dilute



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NCRP 65 Rule of Thumb

- 1 $\mu\text{Ci/L}$ of urine equates to 10 mrem whole body dose (conservative)
- Five teens steal a H-3 exit sign and open it in an enclosed basement bedroom
- Highest urine activity is approximately 5.8 $\mu\text{Ci/L}$
- Maximum estimate of CEDE is 58 mrem

Strontium (Sr-90)

- Strontium-90 (Sr-90) is a by-product of the nuclear fission process, as found in nuclear power reactors or nuclear weapons
- Sr-90 could be used by terrorists to create a radiological dispersal device (RDD or “dirty bomb”)
- It could also be released as the result of a catastrophic event at a nuclear power plant
- Medical countermeasures include aluminum phosphate, aluminum hydroxide, barium sulfate, IV calcium gluconate, sodium alginate

Actinides

- Plutonium, Americium, Curium, and Californium
- All have long biological half-lives
- Inhalation is approximately 75% of industrial exposures
- If the compound is soluble (nitrate, citrate, fluoride), compound is ultimately translocated from the lungs to ultimate disposition sites (bone and liver)
- Ca-DTPA and Zn-DTPA chelation therapy is the treatment of choice

DTPA

- Trisodium calcium diethylenetriaminepentaacetate (Ca-DTPA)
- Chelating agent for transuranic elements
- Ca-DTPA is approximately 10 times more effective than Zn-DTPA for initial chelation of transuranics
- It is the treatment of choice for initial patient management
- Must be given as soon as possible after accident
- After 24 hours, Ca-DTPA and Zn-DTPA are essentially equally effective
- Repeated dosing of Ca-DTPA can deplete the body of zinc and manganese

Clinical Pharmacology of DTPA

- DTPA belongs to the group of synthetic polyamino polycarboxylic acids which form stable complexes (metal chelates) with a large number of metal ions

- DTPA
 - o exchanges calcium (zinc) for another metal of greater binding power
 - o Chemical complex then excreted by the kidneys
 - o The plasma half-life of DTPA is 20-60 minutes.
 - o DTPA undergoes only a minimal amount of metabolic change

Clinical Pharmacology of DTPA

➤ DTPA

- o No accumulation of DTPA in specific organs has been observed
- o promptly cleared from the body by glomerular filtration
- o Ca-DTPA can deplete the body of zinc and, to a lesser extent, manganese with repeated dosing
- o Ca-DTPA is approximately 10 times more effective than Zn-DTPA for initial chelation of transuranics

DTPA Dosing Schedules

- Dosage of Ca-DTPA and Zn-DTPA is 1 gm IV or inhalation in a nebulizer (1:1 dilution with water or saline)
- Very safe drug with no significant adverse reactions noted during 25 years of usage
- Initially: 1 gm Ca-DTPA; repeat 1 gm Zn-DTPA daily up to five days if bioassay results indicate need for additional chelation
- Ca-DTPA - Pregnancy category D; Zn-DTPA - Pregnancy category C
- DTPA + DFOA may be a better combination

DTPA - Relative Contraindications

- Pregnancy - Use first dose as Zn-DTPA instead of Ca-DTPA
- Diabetic on Insulin - Use Zn-DTPA and monitor glucose levels
- Depressed myelopoietic function - clinical judgment
- Impaired renal function - clinical judgment
- Children - no data available

*How to Administer DTPA**

- IV injection of DTPA (1 gm/4ml) with 6 ml saline over 5-10 minutes
- IV Piggyback (1 gm DTPA in 100ml saline) over 20 minutes
- Aerosol: 1 gram undiluted via hand-held nebulizer; inhalation takes 10-15 minutes
- IM injection (painful)
- Under 18 YOA, use zinc-DTPA
- Monitor magnesium and other electrolytes routinely

*Complete package information available at
www.ornl.gov/reacts/resources.htm

Uranium

- Solubility classes:
 - UF_6 (uranium hexafluoride): Class D (days)
 - $\text{UO}_2(\text{NO}_3)_2$ - Uranyl nitrate: Class D
 - UO_2 - Uranium dioxide: Class W,Y (weeks, years)
 - UO_2 - High-fired Uranium dioxide: Class Y
- Inhalation is usual occupational exposure
- Overall biological half-life of 15 days
- 85% of retained U resides in bone
- Kidney toxicity is the basis of occupational exposure limits

Uranium

- In acidic urine, uranyl ion complex with tubule surface proteins
- Some of the bound UO_2^{2+} is retained in the kidney
- Kidney is the first organ to show chemical damage in the form of nephritis and proteinuria
- Oral doses or infusions of sodium bicarbonate are the US treatment of choice and should be dosed to keep the urine alkaline by frequent urine pH checks

Recent Clinical Research I - Uranium

- Henge-Napoli have evaluated the efficacy of ethane-1-hydroxy-1,1 bisphosphonate (EHBP, Etidronate, Didronel®) in experiments to obtain compounds that will reduce the fixation of uranium in its main target organs of bone and kidney
-
- One injection of EHBP (50-100 micromol/kg), given acutely after uranium inhalation in animals, reduced uranium deposition in the renal system by a factor of five, and still a factor of two when given 30 minutes post-exposure

Recent Clinical Research II - Uranium

- In another series of animal experiments, Destombes, *et al*, compared the carbonic anhydrase inhibitor, acetazolamide (Diamox®), with bicarbonate in the treatment of internal contamination with uranium
- Acetazolamide is three times more effective than bicarbonate in reducing the renal content of uranium, but has no effect on skeletal content

Uranium

Urine Alkalinization:

- Sodium bicarbonate
- IV dosage: 1 mEq/kg/day IV with 10-20 mEq KCl to maintain urine at pH >7.5
- Oral dosage: from the 1979 NCRP 65 but probably not to be recommended in 2009.
- *Adults*: Initially, 1-10 mEq/kg/day or 4 g PO then 1-2 g every 4 hours. Titrate dosage based on urinary pH.
Children: 1-10 mEq/kg/day (84-840 mg/kg/day) PO, given in divided doses every 4-6 hours. Titrate dosage based on urinary pH.
- May need renal dialysis until renal recovery from injury.

Good References

- NCRP 65: *Management of Persons Accidentally Contaminated with Radionuclides* (April, 1980) - but ,NCRP SC 4-1 is updating and expanding NCRP 65 to be reissued as NCRP 161 in 2009 .
- EPA Federal Guidance Report #11: *Limiting Values of Radionuclide Intake and Air Concentration and Dose Conversion Factors for Inhalation, Submersion and Ingestion* (EPA-520/1-88-020, Sept., 1988)

Thank You for Your Attention!

Questions?

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