

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-749

21-751

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

Ca- DTPA and Zn-DTPA

NDA 21-749, NDA 21-751

Drug: Generic: Pentetate calcium trisodium injection

Pentetate zinc trisodium injection

Chemical: Calciate (3-), [N, N-bis[2-bis(carbomethyl) amino]ethyl]glicinato(5-)-
trisodium

Trade: none

Pharmacological Category: Radioprotector

Routes of administration: IV, Nebulizer, —

How Supplied: Ampoules containing 1 g Ca-DTPA or Zn-DTPA

Proposed Dose: 1g IV or Nebulizer

Proposed Indication: _____

Sponsor: Hameln Pharmaceuticals GmbH

Manufacturer: Hameln Pharmaceuticals

Related INDs: 4,041 and 14,603

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EXECUTIVE SUMMARY

RECOMMENDATION:

- 1) Ca-DTPA and Zn-DTPA should be approved for the treatment of internal contamination with isotopes of transuranium elements of the actinide series. The dose of Ca-DTPA or Zn-DTPA should be 1 g IV. The same dose may be given by nebulizer or by intramuscular injection
- 2) A Phase 4 commitment should be obtained from the sponsor for systematic monitoring of the next 20 patients, treated with DTPA, for adverse events. Monitoring should consist of careful observation, vital signs, EKGs serum chemistries including zinc, and urinalysis at regular intervals for 72 hours after the initial injection, and for 4 hours after each subsequent injection

SUMMARY OF CLINICAL FINDINGS

^{239}Pu is the fissionable material in the majority of nuclear weapons. In the explosion of a crude nuclear device, in which much of the ^{239}Pu remains unfissioned, large numbers of individuals could be contaminated with this isotope. Exposure and internal contamination with ^{239}Pu , ^{241}Am and ^{242}Cm has occurred in weapons facilities and facilities for reprocessing nuclear fuel. One review article documents 485 such cases. These contamination incidents are isolated occurrences involving usually 1 and at most a few individuals. There were no incidents in which a large number of persons were contaminated and treated at the same time. The treatment has evolved with time so that all reported patients were not treated with the current recommended regimen. The literature on actinide decontamination consists of either case reports, each reporting on at most a handful of individuals, or review articles that summarize the results found in a large number of these published case reports. One prospective study in 6 volunteers, a pharmacokinetic study with 2 normal, uncontaminated human volunteers, four review articles and 10 case reports involving a total of 12 patients, provide the database for this review.

Safety

There are no adequate and well-controlled clinical studies of the use of Ca-DTPA or Zn-DTPA, in the treatment of actinide contamination. The type of rigorous safety monitoring characteristic of such studies was not seen in any of the published articles reviewed, or in the raw data we were able to obtain from REAC/TS. The conclusion, that the current treatment regimen of Ca-DTPA followed by Zn-DTPA, is safe, is based on both the absence of reports of serious adverse events attributable to DTPA therapy, in the clinical literature, and on pre-clinical data. The concerns about the safety of protracted therapy with Ca-DTPA come entirely from animal studies. While the review articles have described mild to moderate adverse events in a small number of patients, no serious toxicity has been reported in humans treated with Ca-DTPA or Zn-DTPA. Since DTPA has been used on hundreds of patients over the last 40 years, without any reports of serious adverse events, the safety of DTPA can be considered well established

Efficacy.

DTPA therapy has been the standard treatment for actinide contamination for almost 40 years and the combination of Ca-DTPA and Zn-DTPA has been in use since 1976. The current therapeutic regimen of 1 g Ca-DTPA immediately after contamination followed by subsequent daily doses of Zn-DTPA has evolved after many years of clinical experience. DTPA therapy has also been shown to be effective in numerous pre-clinical studies.

Although the principal toxicity of internalized transuranium isotopes is radiation carcinogenesis, an increase in cancer incidence, in contaminated humans, has not been demonstrated. A number of publications have used increased urinary excretion, or decreased total body burden, of the radioactive isotopes, as a surrogate variable to assess the efficacy of DTPA treatment. Ten case reports, one prospective study, one pharmacokinetic study and 4 review articles are discussed in this review. Eight of these case reports each reported on a single case and the highest number of cases described in any one report is 4. The treatment and the results are described in various amounts of detail. Of the 12 individuals described in the case reports, DTPA treatment was effective in increasing urinary output or in decreasing whole body

activity in 11. DTPA increased the activity excreted in the 24 hour urine collections by factors as high as 120. The exception was an adult male treated many years after contamination, when ^{241}Am was sequestered in the bone from which it is difficult to remove, who was only able to excrete a small fraction of his whole body activity. Incidentally, treatment was successful, in an adolescent male, who was contaminated and treated at the same time, possibly because of the bone growth and turnover in an adolescent whose epiphyses had not closed.

There is a possibility of publication bias, the tendency of authors to be more likely to publish case reports in cases where treatment is successful. The review articles do note that treatment is less successful when treatment is delayed and when the contaminant is in an insoluble chemical form. Nevertheless it is clear that DTPA therapy is very effective in treating some contaminated individuals and somewhat effective in the majority of cases.

INTRODUCTION

The transuranium elements have atomic numbers higher than that of Uranium. They do not exist in nature but are produced by neutron bombardment of Uranium in nuclear reactors. All isotopes of transuranium elements are radioactive and most are α emitters. These isotopes may be found in relatively small quantities in nuclear reactor cores and in spent nuclear fuel rods. ^{239}Pu is the fissile material in most nuclear weapons. In the sub-pharmaceutical quantities associated with human contamination, their toxicity is due entirely to their radioactivity. Alpha (α) particles are heavily ionizing charged particles with short track lengths known as High Linear Energy Transfer (High LRT) radiation, with a high relative biological effectiveness (RBE) when compared to photons (γ rays and x-rays). α particles are assigned a radiation-weighting factor of 20 by the International Commission on Radiation Protection (ICRP). At doses commonly encountered in man there is no acute radiation toxicity and the primary concern is increased cancer incidence years or even decades after exposure. Because of the short track length of the α particle, the organs where the isotopes are concentrated, would receive the highest doses of radiation. Since these isotopes eventually become sequestered in bone, a higher

incidence in primary bone cancers, such as osteogenic sarcomas, would be expected. Since such an increase in cancer incidence, with transuranium isotope contamination, could only be seen in a large population observed over a long period of time, it has not been documented in man. However radium is also an α emitter that is deposited in bone. Radium dial watch painters who ingested radium when licking the tips of their brushes were seen to have a high incidence of osteogenic sarcoma, years later. While an increased cancer incidence has been seen in animals exposed to high radiation doses from internalized ^{239}Pu and ^{241}Am , this increase in cancer incidence has not been documented in humans. However, Radium, which is also an α emitter deposited in bone, has been known to cause an increased incidence of osteogenic sarcoma in radium dial watch painters, who ingested radium when licking their brushes.

Of particular concern are the isotopes ^{239}Pu and ^{241}Am , which have relatively long half-lives and which are used in the production of nuclear weapons. ^{239}Pu and ^{241}Am are α particle emitters. Virtually all reported cases of human contamination with transuranium elements, have involved employees at nuclear facilities, accidentally contaminated with one or both of these isotopes. The route of internal contamination, in these cases, has been by inhalation and/or by wound contamination. Ingestion by eating contaminated food has not been reported.

The distribution of the contaminants in the body is determined by their physical and chemical properties. The chemical properties of all isotopes of the same element are the same so any statements concerning biodistribution and treatment of ^{239}Pu and ^{241}Am would apply to all isotopes of Plutonium or Americium. Other transuranium elements of the actinide series, Curium, Berkelium and Californium, have similar chemical properties to Plutonium and behave similarly in vivo. Inhaled particles of different sizes are deposited at different levels of the trachiabronchial tree. The rate at which deposited material is absorbed into the systemic circulation will depend on its solubility, which ranges from highly soluble (nitrate and citrate), to moderately soluble (chloride, oxalate and oxide) to insoluble (metal and dioxide). Plutonium and Americium that are absorbed into the systemic circulation are rapidly distributed throughout the extracellular fluid compartment and then taken up

by the liver and the bone. In the serum, ionized Plutonium is bound to transferrin and in the liver to ferritin and lipofuscin. Plutonium and Americium in the blood and interstitial fluid can be rapidly removed from the body by chelation therapy. The chelator-isotope complex is not protein bound, and is rapidly removed from the circulation by glomerular filtration. Once they are deposited in the liver and bone removal from the body will be slow, with the rate-limiting step being the re-mobilization of the isotope from the liver or bone parenchyma back into the interstitial fluid and the circulation. The kinetics of uptake from the circulation into the liver and bone are not well understood. The stability of the Plutonium-ferritin complex explains the slow release from the liver.

At the doses usually encountered, the principal toxicity of Plutonium and Americium is radiation-induced carcinogenesis and the clinical objective of treatment is to reduce the incidence of radiation induced cancer. The only effective treatment for contamination with radioactive isotopes is removal of those isotopes from the body. The more rapidly the radioactive material is removed, the lower the radiation absorbed dose (Gy) to the whole body and to individual organs will be. Since cancer risk is believed to increase linearly with increasing radiation absorbed dose, the rate of elimination of radioactivity from the body is usually accepted as a surrogate for the reduction in cancer incidence, in human studies. Treatment is considered effective if it increases the rate of elimination over what it would have been without treatment.

The initial treatment for wound contamination is surgical. The larger particles of radioactive material can be removed individually. Tissue contaminated with microscopic particles can be debrided. Wounds can be flushed with a solution containing chelators to help remove residual soluble material. Insoluble inhaled material can be flushed from the lungs with pulmonary lavage. These procedures should be performed as soon as possible after contamination, to minimize the activity absorbed into the systemic circulation. They are the only means of removing insoluble radioactive material, which is not absorbed.

Once transuranium isotopes have entered the systemic circulation, the objective of treatment is to increase the rate of excretion. Chelation with intravenous Ca-DTPA

or Zn-DTPA can increase the rate of urinary excretion by glomerular filtration, significantly reducing the effective serum half-life. Once the isotope has been sequestered in the liver and bone the rate-limiting step, in chelation therapy, will be the remobilization of the isotope from these organs into the systemic circulation and removal from the body will be slow. Since the fraction of the activity deposited in liver and bone increases with time, chelation treatment should be started as soon as possible after contamination to minimize the activity sequestered in these organs.

Nature of the NDA Submission

The database for this review consists of papers from the published literature and some primary data on patients treated by REAC/TS. The REAC/TS data was not collected in any systematic way and the amount and quality of the data varies significantly from patient to patient. The data on the majority of patients treated is inadequate for assessment of either efficacy or safety.

The clinical literature on DTPA treatment of internal actinide contamination consists of 10 retrospective case reports, reporting on between 1 and 4 patients each, 4 review articles, a single prospective study with 5 evaluable patients and a single human pharmacokinetic study in 2 uncontaminated human volunteers. Prospective clinical trials, in which humans would be deliberately contaminated with ^{239}Pu or ^{241}Am , would not be ethically acceptable. Only individuals who have been accidentally contaminated can be studied. In the single prospective study, 6 individuals who had been contaminated with clinically insignificant amounts of actinides were treated with DTPA with various treatment schedules.

Each contamination accident involved one or at most a small number of individuals. The largest number of individuals contaminated in any one reported accident was 4. No single series containing a large number of patients has been published. The contaminants, the route of contamination, the amount of activity internalized, the time between contamination and treatment and the dose and treatment schedule used, have varied significantly from one patient to another. These accidents have occurred over a period of over 50 years during which the standard of care for treating transuranium contamination has progressed

significantly. In many of the reported cases the treatment and dosing schedule reported is no longer used. Before Zn-DTPA was introduced in 1976 patients were treated with Ca-DTPA alone. The current dosing schedule of 1g IV daily is a relatively recent innovation. The standard practice of starting treatment with Ca-DTPA and then switching to Zn-DTPA is also relatively recent.

There was no systematic monitoring for adverse events in any of the reported cases. EKGs, serum chemistries, vital sign monitoring, adverse event monitoring and urinalysis other than for radioactivity either were not performed or the results were not reported. Safety of DTPA treatment in humans can only be inferred from animal experiments and from the absence of reports of serious adverse events attributable to DTPA. Safety concerns about zinc depletion during protracted treatment with Ca-DTPA come entirely from pre-clinical studies. Other than asymptomatic microscopic hematuria, adverse events possibly attributable to protracted Ca-DTPA therapy have not been reported.

At FDA request, REAC/TS has provided case report forms on patients treated with DTPA for transuranium element (TU) contamination. Data was not collected in any systematic way and only minimal data was available for each patient. Of these 20 patients have been identified where urine samples were collected both before and after treatment, and can be compared to establish efficacy.

Because of the nature of the material reviewed, the standard format for NDA reviews is not applicable to this case. The material can best be coherently presented by discussing each publication separately and then presenting an overall summary of safety and efficacy. The publications from the clinical literature that have been reviewed are given in the table below

CLINICAL LITERATURE REVIEWED

Clinical Literature Database For This Review						
Number	First Author	Type of article	Number of Patients	Contaminant Isotopes	DTPA	Date
1	Volf	Review	60	²³⁹ Pu, ²⁴¹ Am, ²⁴² Cm	Ca, Zn	1978
2	Breitenstein	Case Report	1 (same patient in all 3 articles)	²⁴¹ Am	Ca, Zn	1989
3	Breitenstein	Case Report		²⁴¹ Am	Ca, Zn	1983
4	Kalkwarf	Case Report		²⁴¹ Am	Ca, Zn	1983
5	Norwood	Case Report	1	²³⁹ Pu	Ca	1962
6	Willis	Case Report	1	²³⁹ Pu, ²⁴¹ Am	Ca	1972
7	Brodsky	Case Report	1	²³⁹ Pu, ²⁴¹ Am	Ca	1968
8	Norwood	Prospective Study	6	²³⁹ Pu	Ca	1960
9	Cohen	Case Report	2	²⁴¹ Am	Ca	1976
10	Fasiska	Case Report	1	²⁴¹ Am	Ca	1971
11	Goans	Case Report	4	²³⁹ Pu	Ca, Zn	2001
12	Brodsky	Case Report	1	²⁴¹ Am	Ca	1979
13	Strather	Pharmacokinetic Study	2	none	Ca	1983
14	Norwood	Review	5	²³⁹ Pu	Ca	1962
15	Dolphin	Review	16	²³⁹ Pu, ²⁴¹ Am	Ca	1976
16	Breitenstein	Review	485	²³⁹ Pu, ²⁴¹ Am	Ca, Zn	1987

REVIEW OF THE LITERATURE**1) Treatment of Incorporated Transuranium Elements V Volf**

International Atomic Energy Agency Technical Report # 184 (1978)

Type of Study: Review (IAEA report)

Purpose: To provide a comprehensive review of the published clinical and pre-clinical literature on the treatment of internal contamination with isotopes of transuranium elements with DTPA and other chelators, as of the date of publication (1978)

Methods: This report reviews 344 pre-clinical and clinical articles in the literature, published between 1950 and 1976, on the treatment of internal contamination with radioactive isotopes of transuranium elements.

Preclinical Pharmacology-Toxicology Results In rats, absorption of DTPA from the gut is 3-5%, from the lungs 20 to 30% while intraperitoneal or intramuscular injections are rapidly and totally absorbed. The serum half-life in rats is 20 to 40 minutes. DTPA is excreted in the urine by glomerular filtration. Only 1-5% of the injected dose is eliminated in the feces. The initial volume of distribution is 25% of body weight indicating distribution in the extracellular water compartment. DTPA is hydrophylic and does not cross cell membranes

The acute LD50 of a single intraperitoneal injection of Ca-DTPA is 12mmol/kg in mice.

Reviewer's comment: Since the molecular weight of Ca-DTPA is 497, 12mmol/kg is about 400 times the standard daily human dose of 1g in a 70 kg man. Conversely, the 1g human dose in a 70-kg man corresponds to a dose of 30 μ mol/kg.

The LD50 in mice increased when the dose was given in multiple doses every second to fourth day. However if the dose was given in several doses per day in rats or beagle dogs, the toxicity increased and the LD50 decreased compared to single daily doses. The toxicity of Zn-DTPA does not depend on the treatment schedule. Histological changes have been seen, in the kidney and the intestines with high doses of Ca-DTPA. The LD50 also decreased when the dose was given by continuous infusion. In rats no deaths occurred after 4 daily intrathecal injections of

300 $\mu\text{mol/kg}$ (10 times the daily human dose). Ca-DTPA causes increased excretion of Zn and Mn, in miniature pigs and a corresponding transient decrease in serum levels of Zn and Mn. The decrease in serum Zn is not seen with Zn-DTPA. Histological changes have been seen, in the kidney and the intestines with high doses of Ca-DTPA. The toxicity of Ca-DTPA is believed to result from the depletion of zinc, a trace element used in the production of enzymes necessary for DNA synthesis.

Preclinical Efficacy Results: In the hamster, Plutonium nitrate was removed more rapidly from simulated puncture wounds with local intramuscular injections of Ca-DTPA than by intraperitoneal injection, demonstrating the importance of obtaining a high concentration of chelator at the contamination site. Similarly lung deposits of ^{239}Pu Citrate in rats can be reduced to 8%-10% of controls by inhaled aerosol, Ca-DTPA, whereas IV Ca-DTPA had little effect. Inhaled Ca-DTPA is less effective in removing ^{239}Pu -nitrate and is ineffective with ^{239}Pu -oxide. ^{241}Am nitrate is removed from the rat lung by inhaled or injected Ca-DTPA. 10 μmol inhaled Ca-DTPA is as effective as 100 μmol given by injection or 500 μmol given PO. Chelators were ineffective in removing insoluble ^{239}Pu -oxide from the lungs, however studies in baboons and beagle dogs have shown that 47% to 67% of the lung burden can be removed by repeated pulmonary lavage. Oral ion exchange resin (unspecified) can reduce the absorption of Pu-citrate or Pu nitrate from the GI tract

Transuranium elements that have entered the circulation from the lungs or wounds are in a soluble, chelatable state and can be treated with chelation therapy. For early treatment in rats, Ca-DTPA was more effective than Zn-DTPA in the removal of ^{239}Pu , ^{241}Am , ^{252}Cf and ^{242}Cm . Ca-DTPA was less effective in removal of ^{237}Np than of ^{239}Pu , since the Np-DTPA complex is unstable in vivo. When Ca-DTPA is given after ^{241}Am , in rats efficacy decreases with increasing time interval between ^{241}Am and DTPA injections but this effect can be compensated for by increasing the DTPA dose. Thus, in the rat, 30, 100 and 1000 $\mu\text{mol/kg}$ Ca DTPA were equally effective when given 1 min, 1 hour and 1 day after ^{241}Am , respectively. The differences in effectiveness of different chelators decrease with increasing time interval. When given immediately after contamination, a higher dose of Zn-DTPA

is needed to obtain the same effect as with Ca DTPA. However when given 4 days after contamination, the dose-effect curves for Ca-DTPA and Zn-DTPA for ^{239}Pu in rats, are identical. As ^{239}Pu is deposited in the liver and the skeleton, the fraction of the ^{239}Pu that is chelatable decreases with time. ^{239}Pu can be removed from the liver with a relatively short course of treatment, but removal of ^{239}Pu , once it has been deposited in the bones requires protracted therapy. In dogs, protracted treatment with Zn-DTPA can remove virtually all of the ^{241}Am in the liver and 80% of the ^{241}Am in the skeleton.

The Author states several conclusions from his review of the pre-clinical data:

- The effectiveness of a chelator depends on its concentration at the site of contamination. Irrigation of a contaminated wound, or injection at the wound site, with chelator, is more effective than giving the chelator by IV injection.
- With increasing time after contamination the isotopes become less available for removal due to deposition in the liver and bone. Prompt treatment is essential to achieve maximum effect
- The optimal dose is dependent on the route of administration. The doses given PO or by nebulizer should be higher than the IV dose, because of incomplete absorption.
- Prompt treatment with Ca-DTPA will decrease the amount of isotope deposited and retained in the skeleton.
- Even when treatment is started early, multiple doses of chelator will remove more isotope from the body than a single treatment
- The toxicity of Ca-DTPA is low for daily treatment but increases significantly if multiple daily doses are given.
- Zn-DTPA is 2.5 to 30 times less toxic than Ca-DTPA.
- Initial prompt treatment should be with Ca-DTPA, for maximum efficacy, but for prolonged treatment Zn DTPA should be used to minimize toxicity.
- Non-soluble deposits should be removed mechanically (i.e. by wound debridement).
- Care is necessary when extrapolating animal results to man.

Reviewer's Comment: The above results may imply that Ca-DTPA and Zn DTPA are equally effective after ^{241}Am or ^{239}Pu has been deposited in bone and liver, but Ca-DTPA is more effective than Zn-DTPA when the ^{241}Am or ^{239}Pu is still in the systemic circulation. For protracted treatment, Ca-DTPA is more toxic than Zn-DTPA because it depletes the body's store Zn. This is the rationale for treating patients with Ca-DTPA, for the first few daily treatments, and then switching to the less toxic Zn-DTPA. The optimal timing for the switch from Ca-DTPA to Zn-DTPA is unclear.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Results: The author has reviewed the clinical literature on patients treated for transuranium element decontamination. He has identified 54 papers, published between 1954 and 1974 describing the treatment of 70 patients. These cases are listed in table XVI of the reference. 60 of those patients were treated with DTPA, the majority with multiple doses. The other 10 patients (mostly the earliest cases) were treated with either EDTA or Zirconium malate or Zirconium citrate. 58 patients were contaminated with ^{239}Pu only. The other 12 patients were contaminated with ^{242}Cm , both ^{241}Am and ^{242}Cm , or both ^{241}Am and ^{239}Pu . The most common chemical form of the contaminant was ^{239}Pu nitrate but contamination with ^{239}Pu oxide, ^{239}Pu oxalate, ^{239}Pu metal, ^{241}Am oxide and ^{241}Am perchlorate also occurred. The estimated initial whole body activity ranged from 7 nCi (7×10^{-9} Ci) to 144,000 nCi. All of the patients were contaminated by either inhalation or wound contamination, and two patients had contamination from both inhalation and ingestion. For patients treated with Ca-DTPA, the individual doses ranged from 0.1 g to 5 g. The number of Ca-DTPA treatments ranged from 1 to 125 and the total doses of Ca-DTPA ranged from 0.55 g to 249 g. Although Ca-DTPA has been shown to be more toxic than Zn-DTPA, in preclinical studies, maximum total doses of Ca-DTPA in patients, have been 110 g IV, 80 g by inhalation and 249 g PO., but "No serious damage attributable to the toxic action of Ca-DTPA has been observed until now (1976) in man" For Zn-DTPA "no undesirable side effects were observed after injections of up to 3 g single doses".

For wound contamination, the primary treatment was surgery with local administration of DTPA used as an adjuvant. After flushing a wound with a solution of 0.1% Na_4DTPA , 4 times as much ^{239}Pu was recovered in the urine as in the flushing fluid, indicating that after flushing, some of the ^{239}Pu -DTPA complex enters the systemic circulation but is promptly removed from the body in the urine. Subcutaneous injection of DTPA in the region of the wound had a similar effect on urinary excretion. When both ^{239}Pu and ^{241}Am are incorporated, the effect of DTPA is greater for ^{241}Am than for ^{239}Pu . DTPA administration also increases the fecal excretion of ^{241}Am and ^{239}Pu , and the amount of activity removed in the feces can be as high as half the amount excreted in the urine. The effect of IV DTPA on

increased urinary and fecal excretion of ^{241}Am and ^{239}Pu persists for several days after injection. The effectiveness of DTPA decreases substantially with time after incorporation as the isotope becomes deposited in the liver and the bones.

The efficacy of DTPA can be quantified by assessing the rate of urinary excretion in terms of an "excretion enhancement factor" (EEF), defined as the ratio of the rate of urinary excretion after DTPA treatment to the rate of urinary excretion without treatment. If it can be assumed that the rate of urine production is relatively constant then the ratio of specific activities in the urine with and without treatment provide reasonable estimate of the excretion enhancement factor. Excretion enhancement factors are given for 28 of the patients treated with Ca-DTPA and/or Zn-DTPA and they range from 5 to 500. Excretion enhancement factors vary from patient to patient, vary over time for the same patient and vary with the chemical form of the contaminant, being lower for the less soluble chemical compounds..

Ca-DTPA has been shown to be superior to zirconium malate, zirconium citrate and Ca-EDTA in removing transuranium radionuclides in vivo and (by 1976) had become the agent of choice for decorporation of transuranium radionuclides in man. The commonly accepted standard human IV dose of Ca-DTPA is 1g, which would correspond to a dose of $30\ \mu\text{mol/kg}$ in a 70-kg man. Consequently when used in animal experiments, $30\ \mu\text{mol/kg}$ has often been referred to as the "human dose equivalent".

Only one case of lung lavage, using normal saline, was reported, in a patient contaminated by inhalation. The patient was also treated with IV Ca-DTPA. 59 nCi ^{239}Pu was removed by lavage compared to 71 nCi in the urine and 16 nCi in the feces.

For patients receiving multiple treatments the urinary concentration before each treatment period and the urinary concentration at the end of each treatment period can be followed separately giving different half-lives corresponding to treatment and non-treatment. In one case an under treatment half-life of 35 days and a non-treatment half-life of 75 days was found. In this same case, the EEF fell from 60 at 15 days post contamination to 20 at 150 days post contamination, demonstrating a decrease in the efficacy of chelation treatment with time. This decrease in efficacy

with time can be partially offset by increasing the dose or increasing the frequency of dosing, however giving more than one dose per day a of Ca-DTPA per day increases the toxicity.

When given 6 days after contamination, the EEF, in one case, for Ca-DTPA was 67 while for Zn-DTPA it was 35, indicating the greater efficacy of Ca-DTPA when given early. With a longer delay Ca-DTPA and Zn-DTPA were equally effective. In a case of incorporation of a large dose of ^{241}Am , treatment was started with a daily dose of 3 g Ca-DTPA. After the first week of treatment the dose was changed to 1 g./day Zn-DTPA.

In order to optimize therapy it is important to know:

- The time of exposure
- The radioactive isotopes involved
- The type of contamination (inhalation, wound, ingestion)
- The chemical forms of the contaminants and their chelatability
- The total activity incorporated
- The location of the activity in the body

Before treatment is started, urine and fecal samples, nasal swabs and sputum should be obtained for analysis, so that the magnitude of the radioactive contamination can be estimated. However because treatment is most efficacious when given early, treatment should not be unduly delayed by the need to obtain such samples.

Reviewer's comment: Whenever possible a urine sample should be taken before treatment so that urinary excretion before treatment can be compared to urinary excretion during treatment, in order to assess the efficacy of treatment. Doing so should only delay treatment by a few minutes.

- 2) **Lifetime Follow-up of the 1976 Americium Accident Victim** Breitenstein B., Palmer H Radiation Protection Dosimetry: 26 317-322 (1989)
- 3) **1976 Hanford Americium Exposure Incident: Medical Management and Chelation Therapy:** Breitenstein B. Health physics 45:855-866 (1983)
- 4) **1976 Hanford Americium Exposure Incident: Urinary excretion of Trace Metals During DTPA treatments** Kalkwarf D., Thomas V., Nielson ., Mauch M. Health Physics 45:937-947 (1983)

Reviewer's Comment: Since these three publications all describe the same incident concerning the same patient they are therefore reviewed together. This incident involved a single individual who was contaminated with a large quantity of ^{241}Am and who was therefore treated for a prolonged period of time.

Type of Study: Retrospective study of a single case of ^{241}Am contamination. These three articles explore different aspects of this case

Purpose: To investigate the clinical course of a single case of ^{241}Am contamination

Methods: Review of the medical records of a single case of ^{241}Am contamination.

The accident: In 1976, a 64 year old chemical technician was contaminated in the chemical explosion of a glove box ion exchange column, used for ^{241}Am recovery in the DOE Hanford Nuclear Reactor Facility. He was struck in the face and shoulder with nitric acid, glass beads, and metal glass and plastic debris all contaminated with ^{241}Am . Internal contamination resulted from wound contamination and inhalation. The initial contamination of the skin and subcutaneous tissues was estimated at 185 MBq (5 mCi). The patient had a history an aortic graft for an aneurysm in 1971 and an acute MI in 1974.

Reviewer's comment: *This may be the highest recorded level of human contamination with a single trans- uranium isotope.*

Treatment: The patient was immediately transferred to the DOE Emergency Decontamination Facility (EDF) in Richland, Washington where he received his first injection of 1g Ca-DTPA, two hours after the accident. Subsequently he was given 1g Ca-DTPA IV BID and Zn -sulfate 220 mg PO BID. The patient was switched to Zn-DTPA on the 6th day and the dose was increased to 1G q8h on the 8th day. This was the first patient treated with Zn-DTPA in the United States. On the 16th day treatment with Ca-DTPA and zinc sulfate oral supplement was resumed because the supply of Zn-DTPA had been exhausted. The patient continued at this dose until day 333 when the dose was reduced to 1 g three times per week.

Reviewer's Comment: *This experience indicates that Zn-DTPA 1 g IV OD can be given continuously, for a period of almost a year without any observed toxicity. Since it is noted that this was the first patient treated with Zn-DTPA, it follows that any patient previous to 1976 would have been treated with Ca-DTPA. This is useful to know since many of the older publications refer only to DTPA without specifying Ca or Zn.*

The DTPA dose was reduced to 1 g twice a week on day 623 and was discontinued on day 850 when the patient developed complaints of chest pain, syncope and a flu like illness, and was discontinued again on day 934. Radionuclide scanning, at regular intervals, showed a slow increase in liver ²⁴¹Am, so a decision to resume DTPA therapy on day 1254 (3.4 years). The increased liver contamination with ²⁴¹Am was believed to result from continued mobilization of isotope from slowly dissolving deposits remaining in the superficial tissues of the face and neck. He was given injections of 1g Zn-DTPA at approximately 2 week intervals. DTPA therapy was discontinued for good a on day 1540 (4.2 years)

Reviewer's Comment: There does not seem to be a pre-arranged treatment plan for this patient. Treatment was given empirically depending on the patient's response to treatment

In addition to the DTPA therapy described above, he was also initially decontaminated with a soap and water shower and removal of superficial foreign material from his face and back. X-ray guided surgical removal of more deeply imbedded foreign bodies began during the first week and over several months particles of metal, glass, cloth and plastic, up to 0.5 cm in diameter were removed. Treatment was performed, in a special inpatient-type facility, with 24-hour nursing care, set up especially for this one patient at the Emergency Decontamination Facility. In Nov. 1976, he was transferred to a trailer adjacent to EDF. He was discharged home in Jan. 1977 and continued on treatment as an outpatient.

His clinical course was complicated by a cataract (believed to be due to the trauma of the explosion, thrombocytopenia believed due to radiation of the bone marrow, thrombophlebitis and compromised coronary circulation. He died of progressive cardiac disease on August 17, 1987, 11 years after the accident.

Results

Efficacy: Detailed dosimetry data was obtained for this patient by scanning and by monitoring activity in the patient's feces and urine. These results are given in tables 1, 2, 3 and 4 below.

Time	Skin	Lungs	Bone	Liver
Day 0	185,000	-	-	-
Day 3	26,000	960	480	1400
Day 10	14,000	290	320	590
Day 60	5,500	74	250	150
1 year	13,00	74	230	150
2 years	740	55	220	ND**
3 years	480	ND**	300	3.7
4 years	310	ND**	280	9.3
5 years	196	ND**	280	9.6
6 years	220	ND**	290	18
7 years	190	ND**	-	17
8 years	140	ND**	350	18
9 years	120	ND**	350	20
10 years	110	ND**	350	19
11 years*	-	1.9	-	23

*Autopsy specimen ** Not Detectable - Not measured

Time	Skin	Lungs	Bone	Liver
@ 5.3 Years	8,000	1.3	5.5	1.6
@ 11 Years	10,300	1.5	14.4	3.8

Reviewer's Comment: The skin activities and doses in tables 1 and 2 are extremely high and are certainly more than enough to cause radiation necrosis. Presumably they apply only to small, localized areas of skin. Any necrotic areas of skin would have been debrided as part of the patient's continuing care. Because of the location of activity in the face, a more extensive debridement necessary to remove all activity in the skin and subcutaneous tissues could not be done without severely disfiguring the patient. In the time intervals when the patient was not receiving

DTPA, the activity a in the liver and bone increased due to transfer of activity from deposits in the skin and subcutaneous tissues. The doses to the liver and bone are below those associated with tissue necrosis, so the primary clinical concern would be radiation carcinogenesis.

Time	Urine	Feces
Day 0	4800	0
Day 3	5000	4700
Day 10	22,000	6800
Day 60	31,000	7000
1 year	33,000	7000
2 years	34,000	7000
3 years	34,000	7000
4 years	34,000	7000
5 years	34,000	7000

Reviewer's comment: The total excreted activity is less than the initial total activity in the skin, since much of that activity was removed surgically. The DTPA treatment removed activity from the liver, and, to a lesser extent, from the bone. It also reduced the amount a of activity transferred from deposits in the skin to the liver and bone. It is interesting to note that 70 % of the total activity excreted was excreted in the first 10 days, 92% in the first 60 days and 97.5% in the first year

Time	Urine	Feces
6 years	5.4	1.4
7 years	5.4	1.4
8 years	9.5	-
9 years	4.1	0.30
10 years	4.8	0.036
Total, Years 6-10	29.2	3.1

Reviewer's comment: The total activity excreted in years 6 through 10 is about 0.1% of the activity excreted in the first 10 days.

Safety: Since trace element depletion is a known safety concern with Ca-DTPA treatment, Serum trace elements were monitored. 568 samples of the patients' urine were analyzed for 24 elements and compared to urine samples from 14 normal healthy volunteers. The only element which had a higher than normal concentration in the patient's urine was zinc. An analysis of eight 24-hour urine collections from this patient showed that each gram of Na₃-Ca-DTPA lead to the urinary excretion of an average additional 18 mg of zinc in 24 hours. However, since there is 132 mg of zinc in each gram of Na₃-Zn-DTPA, this should more than compensate for the loss. Similarly if given with each 1g dose of Na₃-Ca-DTPA, the 89 mg of zinc in a zinc sulfate capsule should also be more than enough to compensate. In fact, the patient's serum Zn was higher than normal. While the normal range is 0.04 to 1 mg/l, and the normal volunteers range was 0.1 to 1 mg/l, the patient's range while under treatment was 0.1 to 450 mg/l.

Reviewer's Comment: There is no information presented on the timing of the blood sampling for zinc and the time of dosing with Zn-DTPA. It is possible that the serum zinc levels vary greatly between treatments with the highest values (450 mg/l) occurring right after injection. There is no discussion of any possible toxicity that may be caused by elevated values of serum zinc. If in fact the toxicity of Ca-DTPA results only from the depletion of serum zinc then theoretically, Ca-DTPA with oral zinc supplementation should be as safe Zn-DTPA treatment. Unfortunately, there is no data to support this hypothesis.

Author's Conclusions:

- 1) The only clinical effects of the radiation observed were depressed peripheral blood counts of neutrophils, platelets, and lymphocytes.
- 2) Prompt intensive chelation therapy proved effective. Without such therapy additional radiation toxicity may have occurred.
- 3) Although a total of 583 g of Zn-DTPA was administered between 1976 and 1980, no toxicity attributable to DTPA were observed

- 4) Accurate measurements of internal contamination of specific organs was consistent with the transfer of isotope from deposits in the face and lung to the liver and bone over time.

Reviewer's Assessment

Efficacy Unfortunately a pre-treatment urine sample was not obtained from this patient, so a direct comparison of activity excreted in the urine before treatment and during treatment can not be made. However, after 4 years of treatment, a total of 34 MBq had been excreted in the urine and 7 MBq in the feces. This should be compared to the residual activity at 4 years of 0.31 MBq in the skin, 0.28 MBq in the skeleton, 0.0093 MBq in the liver and undetectable activity in the lungs. The fact that the cumulative activity excreted in the urine greatly exceeded the residual activity in the liver and bone does indicate that the primary clinical objective was achieved. In contrast, in pre-clinical studies untreated animals retained 90% of injected activity in the bone and liver and only 10% was excreted in the

Safety: There appears to have been no systematic monitoring for adverse events, but there was no reported toxicity associated with either Ca-DTPA or Zn-DTPA treatment. Treatment with Ca-DTPA was seen to increase excretion of zinc in the urine. Each gram of Na₃-Ca-DTPA lead to the urinary excretion of an average additional 18 mg of zinc in 24 hours. However, since there is 132 mg of zinc in each gram of Na₃-Zn-DTPA, this should more than compensate for the loss. Similarly if given with each 1g dose of Na₃-Ca-DTPA, the 89 mg of zinc in a zinc sulfate capsule should also be more than enough to compensate. Thus, although the current standard of care is to treat with an initial dose of Ca-DTPA and then switch to Zn-DTPA for subsequent daily treatments, theoretically, protracted treatment with Ca-DTPA and oral zinc supplements, should be equally safe. Monitoring of serum zinc showed that with the switch from Ca-DTPA to Zn-DTPA there was no depletion of serum zinc during DTPA treatment for this patient. There was no systematic motoring for adverse events in this patient and no adverse events, attributed to DTPA treatment were reported in any of the three articles

5) Long Term Administration of DTPA for Plutonium Elimination Norwood W. Journal of Occupational Medicine 4:130-132 (1962)

Type of Study: Retrospective study of a single case of ^{239}Pu contamination.

Purpose: To investigate the clinical course of a single case of ^{239}Pu contamination

Methods: Review of the medical records of a single case of ^{239}Pu contamination.

The Accident: A worker at the Hanford Atomic Products Operation was internally contaminated with $0.4\mu\text{Ci } ^{239}\text{Pu}$, by inhalation, in 1956. This dose is 10 times the allowable internal contamination in humans. This estimate is based on urinary excretion and thus does not include any insoluble ^{239}Pu retained in the lungs.

Treatment: The patient was treated with 1.6 to 2 g $\text{Na}_3\text{-Ca DTPA}$ per week beginning 30 months after contamination. Treatment was continued for 103 weeks with interruptions.

Results

Efficacy: The effectiveness was assessed in terms of a "Treatment Effectiveness Factor". This factor was the ratio of the average daily activity excreted in the urine (or the feces) during treatment, to the average daily activity excreted before treatment. The urinary treatment enhancement factor was 55 for the first week of treatment, declining to 10 at the 50th week. After treatment was discontinued for 41 weeks (weeks 51-92) it rose to 45 when 3 g $\text{Na}_3\text{-Ca DTPA}$ were given.

Safety: No adverse events attributable to DTPA are mentioned.

Reviewer's Comment: The treatment is not described in detail. In particular, it is not stated whether the weekly dose of DTPA was given in a single dose or in divided doses. Although this is not explicitly stated the dose was probably administered IV.

Reviewer's Assessment

Efficacy

Treatment with 1.6 to 2 g $\text{Na}_3\text{-Ca DTPA}$ per week was seen to increase urinary excretion of ^{239}Pu , by up to a factor of 55 compared to pre-treatment. Efficacy

slowly declined as treatment continues but rose to initial levels after a long interval without treatment.

Safety: There is no mention of adverse events attributable to DTPA treatment

6) Plutonium-Americium Contamination of a Dry Box Involving Hand Amputation Willis C in Health Physics Operational Monitoring, Willis C, Handloserr J Eds. Gordon and Breach New York, 1972.

Type of study: Retrospective case report

Purpose: Report of a case of a single contaminated individual.

Methods: The medical records of a contaminated individual are reviewed

The accident: A worker's hand was amputated, by a milling machine, in a glove box, containing ^{241}Am and ^{239}Pu . The hand fell into the glove box and was recovered. Most of the contamination was believed to be limited to the skin surface of the hand and the stump. Eight hours later, the hand was reattached. Because of the development of gangrene, the hand had to be re-amputated (above the line of re-attachment) two days later.

Treatment: Both the hand and the stump were cleaned and debrided. Before the hand was surgically re-attached, it was perfused with a Ca-DTPA- saline solution. In addition the patient received 1 g Ca-DTPA IV immediately before the surgery.

Efficacy: The initial contamination was estimated to be 100 μCi on the hand and 5 μCi on the stump. Immediately before surgery the activity was 4 μCi on the hand and 4 μCi on the stump. After re-amputation, 4 μCi on the amputated hand and 0.009 μCi on the new stump. After the first 2 days, no detectable Pu was found in the urine.

Safety: No adverse events attributable to DTPA are mentioned

Author's conclusion: "Either no contamination had entered the system or whatever amount entered was immediately removed by the DTPA.

Reviewer's assessment:

Efficacy: If it can be assumed that some ^{239}Pu or ^{241}Am would have entered the systemic circulation, either at the time of the initial accident or at the time of

surgery, this case would offer additional evidence of Ca-DTPA to remove these isotopes from the systemic circulation if given early.

Safety: There is no mention of any toxicity attributable to DTPA.

7) The Measurement and Management of Insoluble Plutonium-Amercium

Inhalation in Man Brodsky A Sayeg J Wald N Wechsler R Caldwell R in

Proceedings of the First International congress of radiation Protection Synder W Ed
Pergamon Press New York 1968

Type of study: Retrospective case report

Purpose: The primary purpose of this article is to discuss methods of measuring ^{239}Pu and ^{241}Am internal contamination in humans, but in the process a single case of ^{239}Pu and ^{241}Am contamination is reviewed

Methods: Dosimetry data on a single contaminated individual are reviewed

The accident: On 1/17/1976 an explosion occurred in a glove box containing ^{241}Am and ^{239}Pu , when the glove box operator attempted to light a propane torch inside the glove box. The explosion blew out the gloves and knocked the operator down. Air samples taken after the accident found an activity of $1.1 \times 10^{-7} \mu\text{Ci/cc}$ and the operator was contaminated by inhalation. From whole body counts obtained 18 hours after the accident, the lung burden was estimated to be as high as $0.4 \mu\text{Ci}$.

Treatment: The patient was given 3 daily 1g doses of DTPA, IV on days 5, 6 and 7 after the accident.

Efficacy: 24 hour urine and fecal collections were obtained starting on the second day after contamination. Decays per minute (dpm) of both ^{239}Pu , and ^{241}Am were obtained. Estimates of the lung burden from scanning were $0.4 \mu\text{Ci}$ at 18 hours $7 \times 10^{-3} \mu\text{Ci}$ on day 4, $4 \times 10^{-3} \mu\text{Ci}$ on day 11, $6 \times 10^{-4} \mu\text{Ci}$ on day 28 and $4 \times 10^{-4} \mu\text{Ci}$ on day 57 Results for urine and fecal measurements are given in table 5 below

Table 5 Decays Per Minute in 24 Hour Urine and Feces		
Date	Urine (dpm)	Feces (dpm)

	²³⁹ Pu,	²⁴¹ Am	²³⁹ Pu,	²⁴¹ Am
1/18	0.3	0.5		
1/20	1.33	0.6		
1/19			57	36,300
1/21	0.29	No sample	1.9	8.8
1/22 After 1st DTPA dose	2.6	4.4	0.8	2.8
1/23 After 2nd DTPA dose	1.55	31.4	2.1	16.9
1/24 After 3rd DTPA dose	2.37	28.5	2.2	15.3
1/25	1.92	36.7		
1/26	2.6	4.4	2.3	26.6
1/27	2.2	25.4		18.6
1/28	1.29	17.6		
1/29	0.94	10.1		15.1
1/30	0.8	17.4		11.3

Reviewer's comment: *The very high fecal excretion on 1/19 may represent activity in the lungs that was coughed up and swallowed and rapidly excreted in the feces. This was the first bowel movement after the accident. Since the estimate of lung activity dropped from 0.4 μ Ci at 18 hours to 7 x 10⁻³ μ Ci on day 4 the activity in the first fecal sample represents about 90% of the activity originally deposited in the lung.*

Safety: This paper is primarily concerned with radiation measurement. No adverse events attributable to DTPA are mentioned. Safety concerns are not discussed

Author's conclusion: "Urine excretion rates, originally less than 0.4 dpm/24 hr. increased 50 to 100 times on day 5-8 suggesting the efficacy of DTPA in removing ²⁴¹Am from the lung

Reviewer's Assessment:

Efficacy: It is instructive that in this case about 90 % of the original lung activity was removed in the first fecal sample, probably after being coughed up and

swallowed. When insoluble forms of transuranium elements are inhaled, encouraging or inducing coughing, immediately after the incident, may be the most effective method of removing most of this material. The efficacy of DTPA is shown in the increase of urinary excretion of both ^{239}Pu and ^{241}Am , on the days when DTPA was given. The increase was more dramatic for ^{241}Am than for ^{239}Pu . The effect of treatment is also seen in the reduction of the lung activity from $0.4\mu\text{Ci}$ at 18 hours to $4 \times 10^{-4} \mu\text{Ci}$ on day 57.

Safety: The safety of DTPA therapy is not discussed in this paper. There is no mention of adverse events attributable to DTPA.

8) DTPA-Effectiveness in Removing Internally Deposited Plutonium From Humans Norwood W Journal of Occupational medicine 2: 371-376 (1960)

Type of study: Dose ranging crossover study on the safety and effectiveness of Ca-DTPA treatment for ^{239}Pu

Reviewer's Comment: This is the only prospective study of DTPA therapy that we have found in the literature. It can be called a dose ranging crossover study since both the dose and dosing schedule and the individual dose are varied for individual patients and between patients, and since pre treatment urinary excretion is compared to post treatment urinary excretion each patient serves as his own control. There are only 5 evaluable patients in this study

Purpose: To study the efficacy and safety of Ca-DTPA treatment of ^{239}Pu contamination in man.

Methods: Six individuals who had been contaminated with ^{239}Pu volunteered for this study. In all cases the amount of ^{239}Pu contamination was small and was believed to have no clinical significance. At this level of contamination, these patients would not have been treated for therapeutic reasons. In 5 of the 6 cases the contamination was estimated to be less than the maximum permissible deposit of $0.04 \mu\text{Ci}$. In the 6th case it was several times the maximum permissible deposit. 5 patients had become contaminated between 2.5 and 8 years prior to DTPA

treatment. Two of these patients had been previously treated with EDTA. The 6th patient began treatment 3 hours after contamination but irregular absorption has prevented accurate analysis of this case

Treatment: Various treatment schedules were used, on different patients and on the same patient at different times. Individual IV doses of Ca-DTPA ranged from 0.1 g to 2 g. Frequency of treatment ranged from twice per day to three times per week. 24-hour urine collections were obtained before treatment and several times during and after treatment for each individual. The activity was measured in each 24-hour urine sample. Feces was also collected and activity was measured.

Results:

Efficacy: Data is available for 5 of the 6 patients. In all 5 cases the activity in the 24-hour urine collections was much higher during treatment than before treatment. The activity in the pre treatment collections ranged from 0.12 decays per minute (DPM) to 7.25 DPM. The activities in the collections taken during treatment ranged from 5 DPM to 742 DPM. The ratio of the two (Volf's excretion enhancement factor) ranged from 42 to 120. In the two patients treated previously with EDTA, the enhancement factors had been 6 and 10 for EDTA treatment. Excretion was also greater in the feces during treatment but the enhancement factors were smaller, ranging from 2 to 8. The results are given in table 6

Table 6 Treatment and Results for the 5 Evaluable Patients						
Dose (g)	Doses/day	Days/wk.	Mean dose for 5 doses/wk	Average 24 hr Urinary excretion (decays per minute)		
				Before treatment	After treatment	Ratio
Patient # 1 2.5 years post contamination						
0.1-0.4	2	5	0.2-0.8	7.25	742	102
0.4	2	3	0.48	7.25	481	67
0.5	2	3	.9	7.25	495	68
Patient # 2 2.5 years post contamination						
0.1-0.2	2	5	0.34	2.07	1.02	49
Patient # 3 4 years post contamination						
0.8	1	3	0.48	0.12	9.1	76
0.4	2	5	0.8	0.12	10.3	86
1.6	1	5	1.6	0.12	8.7	72
1.6	1	2	0.63	0.12	5.0	42
Patient #4 7 years post contamination						
0.2	One dose only	-	-	0.44	20	45
Patient # 5 8 years post contamination						
0.4-1.2	1	5	0.95	0.15	18	120
1.2-2.0	1	5	1.6	0.15	14	93

Reviewer's Comment: It is unclear how an optimal dose and treatment schedule can be determined from this data. There were only 5 evaluable patients. All patients did not receive the same treatment schedules. Both the dose and the schedule were varied in an unsystematic way. Different patients had different amounts of contamination and different time intervals from contamination to treatment. Looking at individual patients, such as patient #5 it would appear that an average daily dose of 1.6 g carries no advantage over 0.95 g for 5 days per week treatment,

but general conclusions can not be made from a single patient's data. The conclusion that can be drawn is that every schedule used increased the urinary excretion of ^{239}Pu

Safety: No adverse events attributed to DTPA treatment were mentioned. CBC and serum chemistries were normal, but trace elements such as zinc were not measured. With one exception, urinalyses were also normal. After 5 days of twice daily treatment at doses of 0.1-0.4 g. patient #1 developed asymptomatic microscopic hematuria with 30 RBCs per HPF. Treatment was stopped and the urine on subsequent days was normal. Treatment was resumed after 8 weeks but no other urine abnormalities were seen.

Reviewer's comment: this single adverse event may indicate the toxicity that can occur when multiple treatments per day are given. With the current standard of care, no more than one dose per day of DTPA is given.

Author's conclusions

- 1) Animal studies have shown DTPA to be the most effective agent for removal of internally deposited plutonium
- 2) DTPA has been shown to be about as effective in treating a small series of humans as previous work by others has shown it to be in removing deposited plutonium from rats.
- 3) The rate of elimination in the urine increased by a factor ranging from 45 to 120 which is much better than any agent previously used
- 4) 1 g DTPA given once per day was more effective than when given on alternate days or every third day
- 5) Not much is gained by giving doses larger than 1 g per day

Reviewer's assessment: Although this is a prospective study, it would not be considered to be well designed by today's standards. There was no single dosing

schedule for all patients. There was no systematic monitoring for adverse events. There were only 5 patients with analyzable data. Nevertheless this study presents conclusive evidence for the effectiveness of DTPA in these patients. The urinary excretion of plutonium was increased by DTPA treatment at least a factor of 42 in all patients. DTPA was seen to be more effective than EDTA in those patients previously treated with EDTA. Fecal excretion also increased in all patients. The occurrence of microscopic hematuria, in one patient, indicates that multiple doses of Ca-DTPA may have renal toxicity

9) Enhancement of ^{241}Am Excretion by Intravenous administration of $\text{Na}_3\text{Ca-DTPA}$ in Man and Baboon Cohen N Guilmette R LoSasso T in Seminar on Diagnosis and Treatment of incorporated radionuclides International Atomic Energy agency, Vienna (1976)

Reviewer's Comment This paper discusses two studies, a retrospective analysis of two cases of human ^{241}Am contamination and a prospective study of the treatment of ^{241}Am contamination in non human primates (adult and juvenile baboons) Direct comparisons are made between the human and animal data.

Human Study

Type of study: Retrospective case report

Purpose: Report of a case of two individuals contaminated with ^{241}Am .

Methods: The medical records of the two contaminated individuals are reviewed:

The Accident: Two individuals, a father and his young son, were internally contaminated with ^{241}Am , over a period of several years, while working in a home workshop. The son was 4 years old at the time of initial exposure. Chelation therapy was administered 12 years after the initial exposure, when the contamination was discovered. The patients underwent three courses of treatment with Ca-DTPA, in 1970, 1973, and 1975

Reviewer's comment: The nature and magnitude of the source of contamination in the "home workshop", and the way the workshop became contaminated, are not discussed in this article. The most likely explanation is that someone who was occupationally exposed accidentally brought the ^{241}Am into the workshop on contaminated clothing. The ability to study ^{241}Am contamination in a pediatric patient is unique, since all other reported cases involved occupational exposure.

Treatment: The patients underwent three courses of treatment with Ca-DTPA, in 1970, 1973, and 1975. The data presented in this paper come from the last course of treatment only. Treatment consisted of four weekly IV injections of Ca-DTPA. The dose was 23.3 $\mu\text{mol/kg}$ in the adult patient and 41.8 $\mu\text{mol/kg}$ in the adolescent patient.

Reviewer's Comment: 23.3 $\mu\text{mol/kg}$ would represent about 800 mg in a 70 kg man, which is close to the currently accepted single human IV dose of 1g. It is not clear why a higher dose (on a per kilogram basis) was given to the adolescent than to the adult)

The total body burden as well as the activity in the skull, liver and lungs were determined by counting the ^{241}Am 56.9 keV γ using a NaI scintillation detector.

Results

Efficacy

Chelation therapy was started 12 years after the initial exposure when most of the internalized ^{241}Am would be expected to be in the skeleton. The total body activity, in the two individuals was determined before the last course of treatment was started, and again when that course of treatment was completed. The results are given in table 7

Table 7 Whole Body Activity in the Adult Male and the Adolescent Male		
	Adult	Adolescent
Activity before treatment	69.6 nCi	20.1 nCi
Activity after treatment	67.2 nCi	12.7 nCi
Difference (activity excreted)	2.4 nCi	7.4 nCi
Activity excreted as percent of whole body activity before treatment	3.4%	36.8%

Before treatment, external in vivo measurements showed that activity was concentrated in the liver and bone with 75% to 85% of the activity in the skeleton. However, in the adolescent there would still be considerable bone growth and bone remodeling, making the ^{241}Am in the bone more accessible to chelation. In fact, as table 6 shows, as a percentage of the total body activity, DTPA is ten times as effective in removing ^{241}Am in the adolescent than in the adult. The amount of activity removed from the adult 3.4% is small and has little clinical significance, demonstrating the lack of effectiveness of DTPA treatment of long standing contamination with ^{241}Am .

24-hour urine collections were obtained and assayed for zinc. After each DTPA treatment, zinc excretion increased from ten to sixty fold over baseline. A corresponding decrease in the serum level of the zinc dependent enzyme ALAD (an enzyme involved in the production of hemoglobin) was seen.

Animal Study:

Type of study Pre-clinical study

Purpose: To study the safety and efficacy of Ca-DTPA treatment of ^{241}Am contamination in baboons and to compare the results to the data on the two human patients discussed above.

Methods: Six adult and two juvenile female baboons (females were chosen for the simplicity of catheterization to obtain urine samples) were each injected with 0.2 μCi ^{241}Am citrate. Treatment consisted of IV infusion of 28.7 $\mu\text{mol/kg}$ Ca-DTPA. 10-12 treatments were given in 1 month. Treatments were given, to different animals, at different times after contamination. Control animals received a saline

infusion at the same rate. Activity in the whole body, liver, and skull were determined by γ counting. Activity was measured in blood urine and feces samples. Urine zinc concentration was also determined. Tissue was obtained from biopsies of the liver and skull at sacrifice. Activity in the whole skeleton was calculated assuming that the skull contained 12% of the skeletal activity.

Results,

Efficacy

Three different adult animals were treated at 1 day, 1.5 months and 13 months after ^{241}Am injection, respectively. Treatment consisted of 10 to 12 injections, of 28.7 $\mu\text{mol/kg}$ Ca-DTPA each, given in a period of one month. Total body burden and distribution of ^{241}Am was determined at the start of treatment. The total amount of ^{241}Am excreted in the urine and feces, as a percentage of the total body burden was determined at the end of treatment. Results are given in table 8.

	Animal B-164	Animal B-520	Animal B-460
Time from injection to treatment.	1 day	1.5 mo.	13 mo.
% ^{241}Am in soft tissue at start	60%	21%	5%
% ^{241}Am in skeleton at start	40%	79%	95%
% of body burden excreted in urine	36.6%	11.2%	7.8%
% of body burden excreted in feces	11.4%	3.9%	0.05%
Total % of body burden excreted	48%	15.1%	7.9%

It should be clear from table 1 that internalized ^{241}Am is initially found mainly in the soft tissue (including the liver). With the passage of time the ^{241}Am becomes more and more concentrated in the bone. Thus at 1 day after injection, 60% of the ^{241}Am is in the soft tissue, and 40 % in the bone.

Reviewer's Comment: The fact that, in primates, at one day 40% of the activity is already in the bone and largely unavailable to chelation, illustrates the need for immediate treatment. DTPA treatment should be given as soon as possible after

contamination. Delay of even 1 day could significantly reduce the efficacy of treatment.

By 134 months, 95% of the activity is in the bone and only 5 % is in the soft tissue. It is clear that treatment is more effective when given early. When treatment was given 1 day after injection, it resulted in the excretion of 48% of the total body ^{241}Am in the urine and feces. When the same treatment was given 13 months after injection, only 8% was excreted. The most likely explanation is that ^{241}Am is more difficult to remove from the skeleton than from soft tissues.

Comparison was also made between juvenile and adult animals, and between treated animals and controls. Four animals were used, 2 adults and two juveniles. There was one of each in the treatment arm and in the control arm. Therapy consisted of 10-12 injections given in a 1-month period, beginning 1.5-1.6 months after ^{241}Am injection, when about 80% of the activity is concentrated in the bone (table 6). The percent of the body burden excreted in the urine and in the feces during the treatment month were determined. The results are given in table 9

Table 9 ^{241}Am Excretion in Treated Baboons and in Control animals				
Animal	Treatment group	Percent of whole body activity excreted		
		Urine	Feces	Total
Juveniles				
B-400	DTPA treatment	28.7%	5.1%	33.8%
B-406	Control	0.7%	3.5%	4.2%
Adults				
B-520	DTPA treatment	12.0%	9.3%	20.3%
B-352	Control	0.8%	5.4%	6.2%

This table demonstrates the efficacy of DTPA treatment. Treatment increased the amount of ^{241}Am removed from the body by a factor of 8 in the juvenile baboon and by a factor of 3 in the adult. The reason for the increased efficacy in the juvenile is believed to be the large amount of bone growth and bone remodeling seen in the juvenile animal. Comparing table 9 to table 6, the same increase in treatment efficacy in the juvenile subject is seen. However since in the human subjects,

treatment was given years after contamination, only a small fraction of the whole body activity could be removed from the bone.

Author's conclusions:

- 1) The efficacy of DTPA therapy depends on the site of deposition of ^{241}Am in the body
- 2) DTPA increases the excretion of ^{241}Am in both the urine and the feces in both man and baboon. ^{241}Am in the urine comes primarily from the skeleton, while ^{241}Am in the feces comes primarily from the liver
- 3) In both man and baboons, after ^{241}Am has been deposited in the skeleton, DTPA therapy is more effective in juveniles than in adults.
- 4) Treatment with Ca-DTPA causes increased excretion of zinc in the urine and decreased activity in zinc dependent metalloenzymes such as ALAD

Reviewer's Assessment:

Efficacy This paper is unique in two respects. First it describes the decontamination of an individual who was contaminated as a child. Since transuranium element contamination is almost always occupational, contamination of children has been extremely rare. However, a significant number of children would be expected to be exposed in either a nuclear reactor accident or a "dirty bomb" terrorist attack. Secondly this paper directly compares data from a prospective controlled study in non-human primates with retrospective human data. Controlled studies of radioactivity decontamination can not, of course be ethically performed in humans. The animal experiments seem to have been deliberately designed to mimic the two human cases. The human data shows a much greater effectiveness of DTPA treatment in the adolescent compared to the adult when the ^{241}Am has been deposited in bone. This greater efficacy in the juvenile is confirmed in the baboon experiments. The human data also demonstrates an increased excretion of zinc with DTPA therapy. The controlled experiment in baboons, demonstrates directly the increased excretion in the treated animals compared to controls.

Safety: The toxicity of CA-DTPA appears to be associated with the increased urinary excretion of zinc and the consequent decrease in activity of zinc containing metalloenzymes such as ALAD.

10) **Urinary Excretion of ^{241}Am Under DTPA Therapy** Fasiska B Bohning D Brodsky A Horm J. Health Physics 21:523-529 (1971)

Type of Study: Retrospective study of a single case of ^{241}Am contamination

Purpose: The primary purpose is to develop a mathematical model to describe ^{241}Am excretion in a patient receiving DTPA therapy

Methods: Review of the medical records of a single case of ^{241}Am contamination.

The Accident: The patient inhaled $1.8 \mu\text{Ci } ^{241}\text{Am}$ oxide. The isotope eventually contaminated various body organs including both lungs and bones. The details of the accident and demographic information on the patient are not given in this article.

Treatment: The patient was treated over a period of 3 years. Various treatment schedules were tried. From Sept. 1967 to Dec 18, 1968, the patient received IV injections of 1g Ca-DTPA weekly. There was then a two-week interval of no treatment. From Jan 3, 1969 to April 1969 the patient received 0.5 g twice weekly and 0.5 g once weekly from April 1969 to Dec 1969

Reviewer's comment. Although not explicitly stated in the paper, since Zn-DTPA was first used in the US in 1976, it can be assumed that Ca-DTPA was used in this case. The low dose (1 g/wk compared to today's standard dose of 1 g/day) could be explained as a strategy for avoiding the toxicity of Ca-DTPA

Results

Efficacy: 24 hour urine was collected daily and activity was determined. Daily ^{241}Am excretion in μCi were obtained. The data is presented graphically. The graphs show distinct peaks in urinary activity excreted, after each treatment with a rapid falloff in excretion between treatments

Safety: No adverse events attributable to DTPA therapy are mentioned

Authors conclusion: Weekly 1 g DTPA treatments continue to be effective for a period of almost 3 years. Weekly 0.5 g DTPA treatments are less effective.

Reviewer's Assessment:

Efficacy Although little information about this patient is given, efficacy, over a 3 year period, is demonstrated by distinct peaks in the ^{241}Am urinary excretion, corresponding to each weekly DTPA treatment. Since the data is presented in graphs rather than tables, this, efficacy is difficult to quantify.

Safety: This paper appears to demonstrate that treatment with Ca-DTPA for protracted periods, at a dose of 1g/day, is tolerable. However there is no discussion of safety monitoring and only 1 patient was studied. Excretion of zinc was not assessed.

11) Update on the Treatment of Internal Contamination Goans R in the Medical Basis for Radiation Preparedness Ricks R, Berger M, O'Hara F Eds. Proceedings of the Fourth International Reacts Conference, Orlando, FL, 2001

Type of Study: Case Report of 4 patients contaminated with ^{239}Pu

Purpose: The Purpose of this article is to discuss the current standard of care for patients contaminated with radioactive a isotopes. As an Illustration, a case of 4 individuals contaminated with ^{238}Pu is discussed

Methods: Review of the medical records of 4 individuals contaminated with ^{239}Pu . In a glove-box accident.

The Accident: On March 13, 2000 four employees of a national laboratory inhaled ^{239}Pu oxide when containment was lost in a glove-box due to "worker induced mechanical vibration". Nasal swabs were positive on four workers with readings ranging from 1,250 to 170,000 α decays per minute.

Treatment: All four patients received an initial dose of Ca-DTPA on the day of contamination. A total of 99 doses of DTPA were given to the four patients over a period of three months. This was the third highest number of DTPA doses given in a single incident.

Results

Efficacy: “In the first two months after the accident, urinary excretion of ^{238}Pu was approximately linear with time, indicating a medically significant response to DTPA therapy”

Reviewer’s comment: The meaning of the author’s statement, above is not clear to this reviewer. What is clear is that the author believes that efficacy was demonstrated

Safety: “No adverse reactions were noted in the first two months after the incident”

Current Standard of Care. The principal purpose of this article is to state the current standard of care for radioisotope internal contamination. Individual cases are discussed only to provide illustrations. In regard to DTPA therapy for actinide contamination the author states, without providing supporting data, the current treatment practices at REAC/TS:

- Ca-DTPA is approximately 10 times as effective as Zn-DTPA for initial therapy
- Approximately 24 hours after exposure, Zn-DTPA becomes as effective as Ca-DTPA. Zn-DTPA is therefore preferred for protracted therapy
- Each dose of Ca-DTPA or Zn-DTPA should be 1g and should not be fractionated
- DTPA should be given by slow IV push, by continuous IV infusion over a period of not more than 2 hours, or by inhalation in a nebulizer with 1:1 dilution of water and saline
- The chelating efficiency is greatest during the first hour after exposure when the radionuclide is in the systemic circulation or the interstitial fluid.

Reviewer’s assessment:

Efficacy

The presentation of these cases in this article is very brief. A specific comparison between pre-therapy excretion and post therapy excretion is not made.

Safety: No adverse events related to DTPA therapy are discussed.

REAC/TS Standard of Care. These treatment principles have been arrived at after years of experience of treating internal contamination with transuranium elements. These treatment principles are consistent with the data in the published literature.

12) The Removal of ^{241}Am from Humans by DTPA (abstract) Brodsky A Wald N Horm I and Varzaly B Health Physics 17:379 (1979)

Type of study: Case report

Purpose: To describe the results of DTPA treatment in a patient contaminated with ^{241}Am

Methods: Review of the medical records of an individual contaminated with ^{241}Am .

The Accident: An employee was contaminated with $2\mu\text{Ci } ^{241}\text{Am}$ through chronic exposure to ^{241}Am oxides over several years.

Treatment: The Patient received 1g DTPA weekly from Sept. 1967 to Dec.1968. Treatment was stopped on Dec. 16 1968. Two weeks later the patient was started on 0.5 g DTPA twice per week

Reviewer's Comment: Comparing treatment chronologies, it appears that this patient may be the same patient described in Publication number 10 above.

Results

Efficacy: When treatment was stopped on Dec. 16 1968, more than half of the body burden had been removed from the liver and lung, but approximately $1\mu\text{Ci } ^{241}\text{Am}$ remained in the skeleton. After treatment was stopped, urinary excretion of ^{241}Am dropped to negligible levels in two weeks.

Safety: There is no discussion of toxicity or of adverse events

Reviewer's Assessment: There is very little detail about this case contained in this brief abstract. However several points can be made:

- 1) DTPA treatment is more effective in removing ^{241}Am from the liver and lungs than from the bone
- 2) When DTPA treatment is stopped, urinary excretion slowly decreases to very low values
- 3) Since no serious or severe adverse events are mentioned, it is likely that none occurred.

13) The retention of ^{14}C -DTPA in Human Volunteers After Inhalation or Intravenous Injection Stather J Smith H Bailey M Bulman R Crawley F Health Physics 44:45-52 (1983)

Type of study: Prospective Human Pharmacokinetic Study

Purpose: To study the Pharmacokinetics of DTPA in humans

Methods: ^{14}C labeled Ca-DTPA (^{14}C -DTPA) obtained from Amersham

International was administered twice by injection and twice by inhalation to two normal male human volunteers. The injection consisted of 750 kBq ^{14}C -DTPA and 250 mg cold Ca-DTPA in 5ml pyrogen free water. For inhalation 2.3 MBq ^{14}C -DTPA and 455 mg Ca-DTPA in 6ml 10% ethanol. Blood samples were taken at regular intervals for 24 hours and urine samples were collected for 1 week

Results: For the injection, in both subjects, the plasma level of activity was below the level of detection in 24 hours. However small amounts of DTPA continued to be excreted in the urine, 0.1 % of the injected activity on the third day and 0.02% on the seventh day. All of the activity was eventually excreted in the urine. There was no detectable activity in the breath or the feces. The data could be fit with a three compartment model, with plasma, extracellular water and urine compartments. The average half lives for transfer from plasma to extracellular water, from extracellular water to plasma and from plasma to urine are T_1 , T_2 and T_3 respectively. The mean values for these half-lives are 2.5 min., 6.3 min. and 18.7 min. respectively. The plasma clearance half-life for inulin in man is 17 min., which is close to the 18.7 min. half-life for DTPA, supporting the view that DTPA is excreted into the urine

primarily by glomerular filtration. For inhalation, 5% of the inhaled activity was exhaled, 2% remained in the mouth, 24% was excreted in the feces and 69 % in the urine. Urinary excretion can be fit with a 4 compartment model by adding the lung as a 4th compartment to the 3 component model used for injection. The average half-life for transfer from lung to plasma is 74.5 minutes.

Author's Conclusion: The very small amount of DTPA still present several days after injection could explain the persistent elevation of ^{239}Pu and ^{241}Am excretion, in treated patients. Because of the long half-life for DTPA transfer from the lungs to the plasma, inhaled DTPA would theoretically be more effective than injected DTPA since a high concentration of DTPA in the plasma would be maintained for a longer period of time.

Reviewer's Assessment: This human Pharmacokinetic information is useful in evaluating treatment schedules. The rapid falloff in serum concentration of DTPA after injection, would tend to justify the schedule of once daily injections compared to once or twice per week schedules that have been used in the past. When weekly or twice weekly dosing schedules are used, a substantial decrease in urinary excretion of Pu and Am is seen between doses. The rapid falloff in serum concentration would make it likely that any *acute* toxicity of DTPA would occur in the first few hours after injection. Careful monitoring of vital signs, EKG and serum electrolytes, during that time period would be useful in ruling out any physiological changes that might cause clinically significant toxicity in a small number of patients. Unfortunately, the results of such monitoring have not been reported in the clinical literature. The slow uptake, of DTPA, from the lungs into the serum implies that with inhalation, a lower peak serum concentration but a longer duration of high concentration would be achieved with inhalation than with injection. Theoretically, inhalation therapy would be more effective than injection, although there is no clinical data that would confirm that hypothesis. Inhalation therapy with a nebulizer has, of course, another advantage in that it can be self-administered, while IV injection requires the participation of skilled medical personnel. Nebulizers could thus be pre-distributed to people thought to be particularly at risk, such as people living in very close proximity to nuclear reactors.

14) Therapeutic removal of Plutonium in Humans Norwood W Health Physics
8; 747-750 (1962)

Type of study: Review

Purpose: The purpose of this paper is to discuss the state of the art for treatment of plutonium contamination in humans, at the time of publication (1962) The cases of five Hanford employees contaminated with ^{239}Pu are briefly discussed.

Methods Review of the records of five Hanford employees contaminated with small amounts of ^{239}Pu . Information on the types of accident, the about of activity ingested and demographic information about the individual patients is not given.

Treatment : Patients were treated with different treatment schedules with daily doses of DTPA ranging from 0.1 g to 2.0 g

Author's conclusions:

- 1) There was no difference in efficacy between doses of 0.9 g /day and 1.6g/day DTPA treatment
- 2) 1 g DTPA, IV, by slow drip, three times per week on alternate days, for three weeks has proven effective
- 3) DTPA should be given as soon as possible after an accident, preferably within four hours
- 4) No toxicity was seen except for "mild reversible kidney irritation" in one individual who was treated for several months.

Reviewer's comment: The "mild reversible kidney irritation" referred to may be mild transient microscopic hematuria which is known to occur in animals and patients receiving long term treatment with Ca-DTPA. Today it is the standard of care to switch to Zn-DTPA after the first few treatments, so this type of toxicity should not occur.

- 5) Oral DTPA is only 10% as effective as IV DTPA

Reviewer's Assessment: The general conclusions are consistent with the results of other clinical publications

15) Review of Some Problems and Recent Research Work Associated with the Use of Chelating Agents for Removal of radionuclides in Humans. Dolphin G in Seminar on the Diagnosis and Treatment of Incorporated Radionuclides, International Atomic Energy Agency, Vienna (1976)

Type of Study: Review

Purpose: To review clinical and preclinical data on the treatment ^{239}Pu and ^{241}Am internal contamination

Methods: 16 Cases of contamination with ^{239}Pu or ^{241}Am are discussed They are listed in table 10

Treatment: Treatments and results are given in Table 9. The route of entry, time of first treatment after exposure, number of doses and total dose of Ca-DTPA are given. The results of treatment are stated by the author in one or two sentences. If either a substantial fraction of the total body activity is eliminated or the rate of urinary excretion is substantially increased the treatment is characterized as effective. Otherwise the effect of treatment is considered minimal

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patient	Route of entry	²³⁹ P or ²⁴¹ Am compound	Time of first dose	Number of doses	Total DTPA (g)	Efficacy
1	wound	Pu Oxalate	40 min	41	12.75	effective
2	wound	Pu Oxide	690 min	4	0.55	minimal
3	wound	Pu Nitrate	30 min	8	3.9	effective
4	wound	Pu Oxide	70 min	11	4.25	effective
5	inhalation	Pu Oxide	Few hours	1	0.25	minimal
6	inhalation	Pu Oxide	Few hours	1	0.25	minimal
7	inhalation	Pu Oxide	Few hours	1	0.25	minimal
8	inhalation	Pu Nitrate	4 days	3	2.25	effective
9	inhalation	Pu Nitrate	16 days	2	1.5	effective
10	wound	Pu metal	1 day	81	81	effective
11	Wound & inhalation	Pu Nitrate Pu chloride	1 hr	11	11	minimal
12	wound	Pu metal	1 hr	9	9	effective
13	wound	Pu Nitrate	1 day	108	108	effective
14	inhalation	Am Oxide	?	150	150	effective
15	inhalation	Am Oxide Cm Oxide	Few hours	15	15	minimal
16	inhalation	Cm (soluble)	150 min	5	5	minimal

In the one case discussed in detail, the patient's right hand was contaminated with 14 μCi ²³⁹Pu which was reduced to 1.5 μCi by surgical excision 14 days after contamination. In the 14 days between contamination and surgery, the patient was treated with daily doses of Ca DTPA to divert into the urine, any plutonium entering the circulation from the wound. After surgery treatment was continued with larger intervals between treatment. Daily urinary excretion was determined during treatment and in the longer intervals between treatments. The excretion ratio ranged from 60 during the initial period of treatment to 20 at 150 days indicating that plutonium is becoming less available to chelation with increasing time.

Author's Conclusions:

- 1) Treatment of wound contamination appears to be more successful than treating inhalation and treatment of soluble nitrates and oxalates is more successful than treatment of insoluble oxides.
- 2) The effect of DTPA, on urinary excretion of plutonium lasts for several days even though DTPA is excreted in a few hours
- 3) DTPA is most effective during the initial transfer phase of plutonium so that DTPA should be given as soon as possible after contamination. This can be done most easily with a nebulizer which does not require trained medical personnel. Since the uptake from the lungs to the circulation is slow, a high serum concentration of DTPA would be maintained for a longer time.
- 4) No significant side effects have been reported in any of these cases.

Reviewer's Assessment

Efficacy: Table 10 demonstrates that treatment with DTPA is not always successful. In particular DTPA treatment is less likely to be effective in cases of inhalation of insoluble chemical compounds of plutonium, such as oxides. The individual case reports found in the literature may give a distorted picture due to publication bias. Authors may be more likely to submit a case report for publication when treatment is successful than when it is not.

Safety: There is no mention of safety monitoring. However it is explicitly stated that there were no reports of significant side effects

16) DTPA Therapy: The U.S. Experience 1958-1987 Breitenstein B Fry S

Lushbaugh C in The Medical Basis for Radiation Accident Preparedness, Ricks R Fry S Eds. Elsevier Science Publishing Co (1987)

Type of study: Review

Purpose: To Review the development of DTPA therapy for transuranium element contamination, from 1958 to 1987

Methods Review of clinical literature on DTPA therapy

Results: From 1958 to 1987, a total of 485 patients receiving a total of 3077 individual doses of Ca-DTPA or Zn-DTPA, for transuranium element

decontamination were recorded in the Oak Ridge Associated Universities DTPA register. 460 patients had been involved in a single contamination incident while 25 were contaminated from 2 to 5 times. ^{239}Pu was the most common contaminant and exposure was by inhalation in 70% of cases. 258 patients received a single dose of DTPA and 208 received multiple doses. The largest number of doses given to a single patient was 589. 50% of the 3077 doses were given IV and 25 % by aerosol inhalation. Of the remaining 25% the route of administration was not recorded.

Efficacy: No specific efficacy data is presented

Safety: Minor transient side effects such as diarrhea, nausea, allergic rashes, and pain at the site of intramuscular injection have been reported in 12 patients (2.5%) No serious or long term sequelae have been reported.

Reviewer's comment: A 2.5% incidence of non-serious adverse events is smaller than what one usually sees in the placebo group in a typical Phase 3 controlled clinical trial.

Authors Conclusion: "DTPA has proven to be an effective and safe chelating agent for the treatment of plutonium and americium internal deposition".

Reviewer's Assessment: The 485 patients mentioned in this review would have provided an excellent clinical data base for DTPA if the relevant safety and efficacy data had been available for all of them.

CONCLUSIONS:**SAFETY**

The safety of DTPA treatment is established by the fact that, although Ca-DTPA has been used for the treatment of actinide internal contamination since 1958 and Zn-DTPA has been used since 1976 with hundreds of patients having been treated, there are no published reports of serious adverse events in humans attributable to either Ca-DTPA or Zn-DTPA. Only mild to moderate side effects such as nausea, diarrhea, allergic rashes and asymptomatic microscopic hematuria have been reported in a small number of patients.

The toxicity of protracted therapy with Ca-DTPA, due to the depletion of body stores of zinc, is known only from animal experiments. Before 1976 Ca-DTPA alone was the treatment of choice for actinide contamination, yet no serious toxicity was reported.

There is no discussion in the literature of systematic adverse event monitoring during DTPA treatment. If EKGs, serum chemistries, routine urinalysis, and monitoring of vital signs, have been obtained before and after DTPA treatment, the results have not been reported. Case report forms, obtained from REAC/TS did not contain data from such monitoring. A Phase 4 commitment, from the sponsor, to carefully monitor future patients on the day of treatment should be obtained.

The toxicity profile of DTPA has been investigated in animal studies, which have demonstrated the toxicity of protracted therapy, and of multiple doses per day with Ca-DTPA. However Volf (ref.1) states " Although maximum total doses of Ca-DTPA have been 110 g IV, 80 g by inhalation and 249 g PO, no serious damage attributable to Ca-DTPA has been observed in man" Nevertheless, the current practice of treating with a single dose of Ca-DTPA followed by subsequent daily doses of Zn-DTPA, avoids even the theoretical risk of protracted Ca-DTPA therapy.

EFFICACY:

Although the principal toxicity of transuranium element incorporation is believed to be an increase in the incidence of primary bone tumors, this increased incidence

has not been documented in man. Thus the clinical benefit of DTPA treatment, a decrease in the increased cancer incidence, can not be directly assessed in clinical studies. An increase in cancer incidence with ^{239}Pu incorporation has been observed in rats, and a decrease in that incidence with DTPA treatment, associated with increasing ^{239}Pu excretion has also been observed. Based on this animal data, an increase in the rate of urinary and/or fecal excretion of ^{239}Pu or ^{241}Am would be an appropriate surrogate endpoint, and a significant decrease in the total body activity would also be an appropriate endpoint. In the absence of data on radiation induced cancer incidence in humans, increased urinary excretion of ^{239}Pu or ^{241}Am , or decreased whole body activity, have been used as a surrogate endpoint, for decreased cancer incidence, in most of the published clinical studies of DTPA therapy.

As in any review of clinical literature, there is a concern about publication bias. Researchers are more likely to submit case reports for publication in cases when treatment has been effective than in a cases where treatment has failed. Thus a review of the literature can demonstrate that a treatment is effective in *some* patients. It can not be used to demonstrate that treatment will be effective in all patients. It can not provide a reliable estimate of the percent of patients for which treatment will be effective

A search of the clinical literature on DTPA treatment has yielded 16 publications including 4 review articles, one report of a prospective clinical study in 6 volunteers (5 of whom were evaluable) who had been accidentally contaminated with minute quantities of ^{239}Pu , one report of a human pharmacokinetic study involving 2 normal, uncontaminated human volunteers and 10 case reports describing a total of 12 patients treated with Ca-DTPA and/or Zn-DETPA for accidental internal contamination with transuranium elements.. In all reported cases contamination occurred by wound contamination, inhalation or both. There were no reported cases of contamination by ingestion of contaminated food. Of the 12 patients described in the case reports, 5 were contaminated with ^{239}Pu , 5 were contaminated with ^{241}Am and 2 were contaminated with both ^{239}Pu and ^{241}Am . Seven patients were treated with Ca-DTPA alone and five patients were treated with both Ca DTPA and Zn-DTPA.

In the single prospective clinical study there were 5 evaluable subjects who had been accidentally contaminated with minute amounts of ^{239}Pu . These subjects were treated with Ca-DTPA using various doses and treatment schedules. The efficacy endpoint was the EEF. This EEF was large in all patients ranging from 42 to 120. Two of the subjects had previously been treated with EDTA where the EEF had been 6 and 10 respectively.

In the single pharmacokinetic study in 2 normal volunteers, ^{14}C labeled Ca-DTPA, given IV, was eliminated in the urine with a serum half life of 19 min. By 24 hours it was undetectable in the serum but small amounts continued to be detected in the urine, 0.1% of the injected dose on the third day. This small amount of excreted chelator may be responsible for the continued elevated excretion of ^{239}Pu and ^{241}Am for several days after DTPA injection.

One patient heavily contaminated with ^{241}Am , by wound and inhalation, was treated over a period of four years with both Ca-DTPA and Zn-DTPA. At the end of 4 years the total activity excreted was 34 MBq in the urine and 7 MBq in the feces. The residual activity in the patient's body at 4 years was 0.31 MBq in the skin, 0.28 MBq in the skeleton, 0.009 MBq in the liver and activity below the threshold of detection in the lungs. The total activity excreted in the feces and urine was 70 times as great as the total activity retained in the body. Although we do not know what percentage of the internalized activity would have been excreted, if the patient had not been treated, some preclinical studies have shown that up to 90% of the activity absorbed into the general circulation will be retained in the liver and bone with less than 10% excreted. Although 31 MBq had been excreted during the first 4 years while the patient was under treatment, only 0.032 MBq excreted during years 6 through 10 when the patient was not under treatment.

In another case an adult and an adolescent who had been chronically exposed to ^{241}Am began treatment years after the start of exposure when most retained activity was in the bone. Both patients received three courses of treatment with Ca-DTPA. In the adult, at the end of treatment, whole body activity had been reduced from 69.6 nCi to 67.2 nCi or by 3.4%. In the adolescent, whole body activity was reduced from 20.1 nCi to 12.7 nCi or by 36.8%. Similar age dependence was seen in studies

with adult and juvenile baboons. These results indicate that actinides are more readily removed from the skeletons of children and adolescents where bone growth and bone remodeling are still occurring.

In the review article by Volf, EEFs are available for 28 patients and these ranged from 5 to 500. EEFs vary from patient to patient and are lower for less soluble compounds of ^{239}Pu and ^{241}Am . This variability is also seen in the review by Dolphin, in which a clinically significant effect of treatment was seen in only 9 of the 15 patients discussed. In fact, all of the individual case reports demonstrated either a large increase in urinary excretion of ^{239}Pu or ^{241}Am , or a significant decrease in whole body activity or both.

In summary, from results published in the clinical literature several general conclusions can be made

- Initial treatment with Ca-DTPA followed by protracted treatment with Zn-DTPA is a safe and effective treatment for actinide contamination.
- The IV dose of Ca-DTPA or Zn-DTPA should be 1g and should not be fractionated
- No more than 1 dose of Ca-DTPA or Zn-DTPA should be given in any 1-hour period.
- The first treatment should be with Ca-DTPA. If additional treatment is necessary, daily doses of Zn-DTPA should be given on subsequent days
- In the cases of human contamination with actinides reported in the literature, the activity incorporated has been too low to induce any of the acute radiation syndromes. The principal clinical concern is therefore radiation induced carcinogenesis
- While there is no direct evidence that DTPA treatment reduces the incidence of radiation induced cancers, enhanced urinary excretion and decreased whole body activity are appropriate surrogate variables.
- Although animal studies raise safety concerns about protracted treatment with Ca-DTPA, there have been no serious adverse events reported in man with any form of DTPA therapy.

- Treatment is most effective if given as soon as possible after contamination. Once actinides have been sequestered in liver and bone treatment is less effective.
- Delayed treatment is more effective in juveniles than in adults
- The effectiveness of treatment is highly variable from patient to patient depending on the time interval between contamination and therapy, the route of contamination, the chemical form of the contaminant (soluble or insoluble) and the age of the contaminated individual.

RECOMMENDATION:

- 3) Ca-DTPA and Zn-DTPA should be approved for the treatment of internal contamination with isotopes of transuranium elements of the actinide series
- 4) A Phase 4 commitment should be obtained from the sponsor for systematic monitoring of the next 20 patients, for adverse events. Monitoring should consist of careful observation, vital signs, EKGs serum chemistries including zinc, and urinalysis at regular intervals for 4 hours after each injection.

APPENDIX

GLOSSERY OF TERMS AND UNITS

RADIATION ABSORBED DOSE:

Energy deposited in tissue per unit mass of tissue

Units: Gray (Gy): $1\text{Gy} = 1\text{ Joule per kilogram (J/kg)}$

Rad: $1\text{ Gy} = 100\text{ Rad}$

The unit of radiation absorbed dose used in this review is Gy

Clinical and biological effects in any organ are determined by the radiation absorbed dose to that organ

ACTIVITY:

Radioactive decays per unit time

Units: Becquerel (Bq) $1\text{ Bq} = 1\text{ decay per second}$

Megabecquerel (MBq) $1\text{ MBq} = 10^6\text{ Bq}$

$1\text{ MBq} = 10^6\text{ decays per second}$

Curie (Ci) $1\text{ Ci} = 3.7 \times 10^{10}\text{ decays per second}$

Milicurie (mCi) $1\text{ mCi} = 3.7 \times 10^7\text{ decays per second}$

$1\text{ mCi} = 37\text{ MBq}$

HALF-LIFE ($t_{1/2}$)

The time it takes for activity to decay to $\frac{1}{2}$ of its initial value

EEF Excretion Enhancement Factor. The ratio of the rate of urinary excretion of a radioactive isotope during treatment to the rate of urinary excretion before treatment. Ideally the EEF should be determined by comparing the activity in 24 hour urine collections. If 24 hour urine collections are not available the EEF can be estimated by comparing urine concentrations.

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