

July 12, 1994

Ca-DTPA (Trisodium calcium diethylenetriaminepentaacetate)

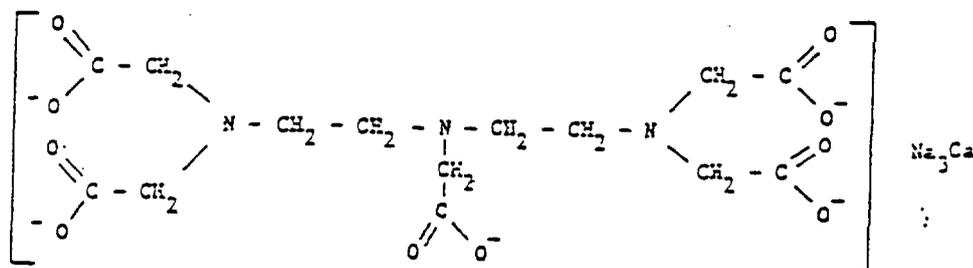
INFORMATIONAL MATERIAL

PACKAGE INSERT*

REPOSITORY Oak Ridge Institute for Science & Education
 COLLECTION Medical Science Division Forms
 BOX No. _____
 FOLDER ORAU 30035

Note: Some vials may be labeled as "Calcium chel 330." This is the same drug.

Structural formula



DESCRIPTION

IND 4041. Trisodium calcium diethylenetriaminepentaacetate (Ca-DTPA), is a calcium salt of DTPA. It has been used in the U.S. as a chelating agent for plutonium and some other various transuranic elements such as americium, californium, and curium. DTPA is also commonly used in lesser concentrations as a chelating vehicle radioisotopic in FDA-approved nuclear medicine studies.

The Ca-DTPA is distributed by Oak Ridge Associated Universities (ORAU) under contract with the U.S. Department of Energy (DOE), Contract No. DE-AC05-76OR00033. ORAU manages the FDA Investigational New Drug (IND) authorizations for Ca-DTPA and the analogous Zn-DTPA for (DOE). A review of the use of DTPA drugs (Ca-DTPA and Zn-DTPA) in decorporation therapy in the United States from 1958 through 1987 has been published.¹

CLINICAL PHARMACOLOGY

DTPA belongs to the group of synthetic polyamino polycarboxylic acids which form stable complexes (metal chelates) with a large number of metal ions. When releasing a metal such as calcium, it binds to another metal of greater binding power and carries it to the kidneys where it is then excreted in the urine.

The plasma half-life of DTPA is 20-60 minutes. Almost the entire administered dose is excreted in 12 hours, with only a small amount bound to plasma proteins, having a half-life of >20 hours. DTPA undergoes only a minimal amount of metabolic change in the body. Only a very minor release of acetate groups has been demonstrated and splitting of ethylene groups has not been detected. Following intravenous administration Ca-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of DTPA penetrates into erythrocytes or other tissue. No accumulation of DTPA in specific organs has been observed. There is little or no binding of the chelate by the renal parenchyma, and it is promptly cleared from the body by glomerular filtration. Tubular excretion was not observed. Although the chelate gives useful information on the glomerular filtration rate, the variable percent which is protein bound leads to a measured clearance rate which is lower than that determined by inulin clearance. In stool samples tested with radioactively marked chelating agents, only a very small amount of radioactivity (<3%) was detected.

Ca-DTPA can deplete the body of zinc and to a lesser extent manganese with repeated dosing. The amount of zinc lost is determined by the amount of DTPA and the frequency of dosage. From depletion of these essential trace metals, Ca-DTPA can then interfere with necessary mitotic cellular processes. Over longer time periods, depletion of zinc due to Ca-DTPA therapy has resulted in transient inhibition of a metalloenzyme, B-aminolevulinic acid dehydratase (ALAD), in the blood, although without observable clinical effect. Clinical zinc depletion appears to be avoidable by giving zinc replacement concomitantly.

Ca-DTPA is approximately 10 times more effective than Zn-DTPA for initial chelation of transuranics; therefore, Ca-DTPA should be used whenever larger body burdens of transuranics are involved. Ca-DTPA is the form of choice for initial patient management unless contraindicated. After approximately 24 hours, however, Zn-DTPA is for all practical purposes as effective as Ca-DTPA, since the inefficiency of both agents is about the same. This comparable efficacy, coupled with its lesser toxicity, makes Zn-DTPA the preferred

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*Reviewed and approved by the ORAU/ORNL Committee on Human Studies, June 6, 1991.

agent for protracted therapy.

INDICATIONS AND USAGE

Ca-DTPA and Zn-DTPA effectively chelate several transuranium ions (plutonium, americium, berkelium, curium, and californium). Their clinical use has been primarily for treatment of internal contamination with plutonium and americium. One patient contaminated with in excess of 1 mCi of americium had 99% of the total body burden removed with prolonged therapy over 4 years with a combination of Ca-DTPA/Zn-DTPA therapy.⁶

The efficacy of Ca-DTPA and/or Zn-DTPA treatment for plutonium incorporations is good for soluble salts, such as the nitrate or chloride, but is essentially nil for highly insoluble compounds, such as the high-fired oxide. The same characteristics are noted experimentally when a soluble (monomeric) form of plutonium is administered that gradually converts to less soluble (polymeric) forms as it is distributed and deposited in various tissues in the body. Thus, chelation is highly dependent not only on the metal itself, but also on the chemical and physical characteristics of the compound at the time of DTPA administration.

CONTRAINDICATIONS

Ca-DTPA is contraindicated for minors, pregnant women, nephrotics, and persons with bone marrow depression. (Such patients may be treated with Zn-DTPA).

Ca-DTPA is not approved under the current IND as a chelator for uranium or neptunium. Incorporation of uranium, an actinide, is not to be treated with DTPA because of the risk of renal damage from the excretion of uranium.² DTPA appears to form an unstable complex with neptunium, which actually can contribute to increased bone deposition of this actinide.³

WARNINGS AND PRECAUTIONS

- 1) Ca-DTPA treatment is contraindicated where there is known pre-existing serious kidney disease or depressed myelopoietic function (e.g., pathologic leukopenia or thrombocytopenia).
- 2) Kidney function should be normal. Urinalysis should be normal prior to each use. If proteinuria, blood or casts are present, discontinue drug administrations.
- 3) Fractionation of the recommended 1 g dose (several smaller doses per day) is contraindicated.
- 4) Check blood pressure during infusion.
- 5) Discontinue drug if diarrhea occurs.

Pregnancy Category D

Teratogenicity and fetal death have occurred in mice following five daily injections of 720-2880 μmol Ca-DTPA/kg given throughout the entire gestation. However daily doses of 360 μmol Ca-DTPA/kg in mice, about 10 times the daily human dose, produced no harmful effects.

Studies of 2 pregnant beagles given daily injections of Ca-DTPA at 30 $\mu\text{mol}/\text{kg}$, a daily dose comparable to 1 g in a 70 kg man, starting at 15 days of gestation until the end of pregnancy, have shown severe effects (especially brain damage in the fetuses).⁷

On the basis of these results and the lesser daily intake of zinc by humans compared to rats and mice, it has been postulated that some toxic effects on the human fetus might occur at the recommended daily dose levels of about 30 μmol Ca-DTPA/kg. In the same experiments Zn-DTPA did not give similar toxicity. Zn-DTPA is preferred and should be used if available to treat a pregnant female with internal transuranic contamination, although it is doubtful that a single or even several well-spaced doses of Ca-DTPA would be harmful to the pregnant female or fetus, especially if prophylactic zinc is given.

ADVERSE REACTIONS

No serious toxicity in man has been reported as a result of over 600 Ca-DTPA administrations in recommended doses. When given repeatedly, with short intervals for recovery, Ca-DTPA treatment in man may cause nausea, vomiting, diarrhea, chills, fever, pruritus, and muscle cramps in the first 24 hours. Anosmia (loss of the sense of smell) was observed in one individual after 123 g of Ca-DTPA over twenty-seven months of therapy and possibly could have been related to zinc depletion. After 100 days of no further DTPA administration, the patient's sense of smell began to return.

OVERDOSAGE

Studies in animals indicate that the toxicity of Ca-DTPA depends on the total dose and the dose schedule. When administered to animals in high doses ($\geq 2000 \mu\text{mol/kg}$ - clinical dose range is $10\text{-}30 \mu\text{mol/kg}$), it can produce severe lesions of the kidneys, intestinal mucosa, and liver, and can even be lethal. Increased toxicity from fractionated dose schedules has been demonstrated in dog experiments in which injections at human dose levels, $5.8 \mu\text{mol/kg}$ of Ca-DTPA given every 5 hours were fatal as early as four days after the onset of treatment. The most significant injury occurs in the intestinal epithelium. In rats, continuous infusion of similar total doses per day caused death in 8-14 days, but the same dose given as a single daily injection failed to elicit this response. Toxicity in these cases apparently resulted from depletion of the Zn and Mn ions needed in the enzymatic steps leading to DNA synthesis that renews the epithelial cells in the intestinal epithelium. No untoward effects in rats were noted with doses of $100 \mu\text{mol}$ Ca-DTPA given twice weekly and apparently there was no influence on Zn or Mn concentrations over a 44-week period.

In one patient, long-term, low-dose Ca-DTPA administration, 1 g per week, showed no adverse effects after one month of such administration.⁶ Urinary zinc excretion studies suggest that the zinc supply is quickly replenished under this treatment regimen and that any partial depletion of the zinc stores, if it occurs at all, would be transient.

DOSAGE AND ADMINISTRATION

Each dose of Ca-DTPA should be 1 g (4.0 ml). Doses should not be fractionated. The route of administration may be either intravenous injection of the undiluted solution over a period of 3-4 minutes, intravenous infusion (250 ml D5W or normal saline), or inhalation in a nebulizer (1:1 dilution with water or saline). Intravenous administration should not be protracted over more than 2 hours.

Clinical experience has shown that aerosol inhalation of Ca-DTPA is more effective than intramuscular injection, apparently because diffusion to the body from the lung is slower than from muscle, and results in a longer lasting plasma level. The same relationship exists when comparing the effectiveness of aerosol inhalation of Ca-DTPA to intravenous injection.

Ca-DTPA may be administered undiluted by intramuscular injection when intravenous administration is not practical, although significant pain at the injection site has resulted when this route is used. Addition of 1-2% procaine to the undiluted Ca-DTPA prior to intramuscular injection has proven to be helpful.

The chelating efficacy is greatest immediately or within one hour of exposure, when the radionuclide is circulating in or available to the tissue fluids and plasma. However, a post-exposure interval > 1 hour does not preclude the administration and effective action of Ca-DTPA.

Combined Ca-DTPA/Zn-DTPA Therapy Guidelines

It must be noted that this is a general guide for DTPA therapy and that treatment must be specifically tailored for individual patients. Ca-DTPA and Zn-DTPA generally can be thought of as two components of transuranic decorporation therapy. If there is any contraindication to the use of Ca-DTPA, the same dose of Zn-DTPA may be substituted.

A. On assurance that a credible incident has occurred and the exposed person(s) at risk had in all likelihood received internal transuranic contamination:

1. Obtain signature on informed consent form for DTPA therapy (which should cover both Ca and Zn forms).
2. Obtain base-line blood and urine samples (CBC with differential, BUN, serum creatinine, urinalysis and urine radioassay).
3. Administer 1 g (4.0 ml of 0.5 M) Ca-DTPA by the most appropriate route for the particular case.
4. Begin collection of ALL urine and fecal samples for bioassay. Whole body and chest counting should be performed. Blood assays are done if the initial urinalysis was positive for transuranic contamination.
5. If long-term use of Ca-DTPA is contemplated, one should consider the use of supplemental zinc therapy (one 220-mg zinc sulfate tablet daily delivers 50 mg zinc).
6. Repeat doses of 1 g Zn-DTPA daily for up to 5 days if the radioassay data or history indicate the need for additional chelation. Keep in mind that the majority of patients in the past have received only one dose of DTPA.
7. Although no significant side effects of DTPA at the recommended dosage level are known and there are no known contraindications to its use, urinalysis and complete blood counts should be done on the day following each treatment with DTPA, and the patient's pulse and blood pressure also should be monitored to determine any effect of the drug. Bioassay results and any side

effects should be noted and recorded on the standard treatment form and reported to ORAU for the annual DTPA usage survey.

8. Additional tests may be ordered at the discretion of the investigator.

B. Before, during and after chelation therapy, pertinent measurements for radioactivity should be made to determine the efficacy of treatment. By the fifth day, evaluate bioassay data for body-burden estimation and decide whether further chelation is necessary. IF SO, a Zn-DTPA treatment regimen should be implemented.

1. Begin therapy regime by administration of Zn-DTPA on a two-dose per week basis, 1 g Zn-DTPA doses, until such time as excretion rate of transuranic is not increased by Zn-DTPA administration.

2. Wait four to six months, re-establish base-line urinary excretion-rate value and give a 1 g Zn-DTPA dose by an appropriate route. Obtain bioassay of urinary excretion to determine whether the Zn-DTPA increased excretion of the contaminant. IF SO,

3. Begin a second course of Zn-DTPA treatment on a two dose per week basis as in (1) above.

C. If bioassay data indicates that contamination was not in excess of minimally detectable amounts, then further therapy is not recommended.

D. When patient is released from further therapy, he should be followed at the routine intervals established by occupational practice. A urinalysis is recommended at these examinations.

E. It is recommended that at the time of an employment termination, the physician should ascertain at the physical examination the person's plans so he can forward the history to an M.D. of the patient's choice. In addition, the M.D. should offer the person the opportunity to be followed medically by the DOE follow-up system. This should be done in order to ensure continuity of patient care and assist if the person again should again become contaminated and require therapy at another plant. site.

Patients who have received extensive chronic incorporation of transuranics require unusual therapy and will be treated largely according to the discretion of the investigator. In the past, treatment has not exceeded three 1 g doses during any 24-hour period. Doses should be administered by the route considered most appropriate for the particular case.

HOW SUPPLIED

Each ampule provided contains 1 g Ca-DTPA, 0.5 M in 4.0 ml (25%) water. The solution should be clear, colorless, and free of crystalline or other material. The ampules should be stored in a cool place and away from sunlight.

As a part of the management of the IND for Ca-DTPA, chemists at Oak Ridge Associated Universities carry out annual analytical tests on randomly selected ampules of the drug. There is no indication that deterioration, pyrogenicity, or loss of sterility occur when the ampules are stored at room temperature. However, if any problem of this nature should be observed, all co-investigators would, of course, be notified immediately. Likewise, any signs of deterioration (discoloration or cloudiness) of the solution or reaction on the part of the patient should be reported at once to one of the persons listed below.

The Food and Drug Administration (FDA) requires that the Sponsor and Manager(s) of the IND be in a position to account for all ampules sent to investigator-physicians. Please, therefore, set up an accounting system on the supplies of Ca-DTPA and be prepared to report your experience annually, including observations on the safety and efficacy of the Ca-DTPA used according to the protocols you submitted with your original request for Ca-DTPA. The Manager(s) of the Ca-DTPA IND will contact you in June each year to obtain your report which will be incorporated into ORAU's summary report to the FDA for the 12-month period.

Questions regarding the use of Ca-DTPA may be referred to one of the following personnel at the Medical Sciences Division of Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831-0117:

Robert C. Ricks, Ph.D.
IND Co-manager
(615) 576-3131

Shirley A. Fry, M.B., B.Ch., M.P.H.
(615) 576-3480

W. W. Burr, M.D., Ph.D.
(615) 576-5262

Dale E. Minner, M.D., F.A.C.O.M.
(615) 576-2124

or

A. Seaton Garrett, M.D., F.A.C.O.M.
Oak Ridge National Laboratory
(615) 576-7431

REFERENCES:

- ¹ Breitenstein, B.D., Jr., Fry, S.A. and Lushbaugh, C.C. "DTPA therapy: The U.S. Experience 1958-1987" in: *The Medical Basis of Radiation Accidents Preparedness*, 2nd ed., Ricks, R. and Fry, S.A. eds., Elsevier Science Publishing Co., Inc., pp. 397-406, 1990.
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- ³ Morin, M., Nenot, J.C., Lafuma, J., "The behaviour of 237-Np in the rat. *Health Physics*. 24 (1973) 311.
- ⁴ NCRP publication #65, *The Management of Persons Accidentally Contaminated with Radionuclides*, NCRP, pp. 122-123, pp. 146-152, 1980.
- ⁵ IAEA publication #47, *Manual on Early Medical Treatment of Possible Radiation Injury*, IAEA, pp. 15-31, 1978.
- ⁶ "1976 Hanford Americium Exposure Incident", *Health Physics*, October 1983, V.45, No.4, special issue. Pergamon Press.
- ⁷ Taylor G.N., Mays C. W., Fetal injury induced by Ca-DTPA in dogs. *Health Physics*, 35:858-860.

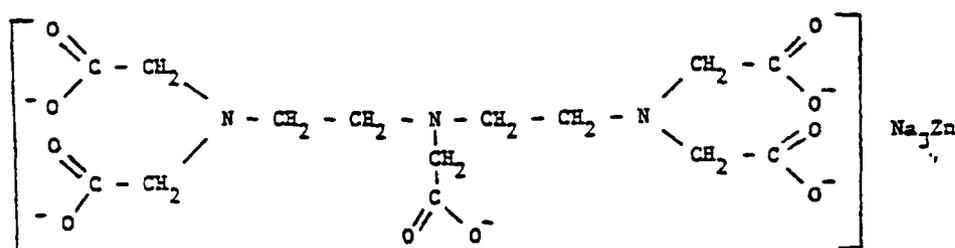
July 12, 1994

Zn-DTPA (Trisodium zinc diethylenetriaminepentaacetate)

INFORMATIONAL MATERIAL

PACKAGE INSERT*

Structural formula



DESCRIPTION

IND 14603, Trisodium zinc diethylenetriaminepentaacetate (Zn-DTPA), is a zinc salt of DTPA. It has been used in the U.S. as a chelating agent for plutonium and some other various transuranic elements such as americium, californium, and curium. DTPA is also commonly used in lesser concentrations as a chelating vehicle radioisotopic in FDA-approved nuclear medicine studies.

The Zn-DTPA is distributed by Oak Ridge Associated Universities (ORAU) under contract with the U.S. Department of Energy (DOE), Contract No. DE-AC05-76OR00033. ORAU manages the FDA Investigational New Drug (IND) authorizations for Zn-DTPA and the analogous Ca-DTPA for DOE. A review of the use of DTPA drugs (Zn-DTPA and Ca-DTPA) in decorporation therapy in the United States from 1958 through 1987 has been published.¹

CLINICAL PHARMACOLOGY

DTPA belongs to the group of synthetic polyamino polycarboxylic acids which form stable complexes (metal chelates) with a large number of metal ions. Zn-DTPA functions to remove toxic metals by exchanging its cations for metals that form more stable complexes with the DTPA ligand. The complex next moves to the kidneys where it is then excreted in the urine.

The plasma half-life of DTPA is 20-60 minutes. Almost the entire administered dose is excreted in 12 hours, with only a small amount bound to plasma proteins, having a half-life of >20 hours. DTPA undergoes only a minimal amount of metabolic change in the body. Only a very minor release of acetate groups has been demonstrated and splitting of ethylene groups has not been detected. Following intravenous administration Zn-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of DTPA penetrates into erythrocytes or other tissue. No accumulation of DTPA in specific organs has been observed. There is little or no binding of the chelate by the renal parenchyma, and it is promptly cleared from the body by glomerular filtration. There is little difference in the glomerular filtration rates for these ligands from changing the cations from Ca to Zn. Tubular excretion was not observed. Although the chelate gives useful information on the glomerular filtration rate, the variable percent which is protein bound leads to a measured clearance rate which is lower than that determined by inulin clearance. In stool samples tested with radioactively marked chelating agents, only a very small amount of radioactivity (<3%) was detected.

One patient with chronic Ca/Zn-DTPA administration for over 3 years was assayed for 24 elements including almost all of the trace metals recognized as essential for good health. Zinc was found to be the only metal excreted more rapidly than normal.⁹ The 132 mg of zinc contained in 1 g of Zn-DTPA should more than compensate for the loss of 18 mg of zinc that was found to be associated with the injection of 1 g of DTPA salt.

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INDICATIONS AND USAGE

Ca-DTPA and Zn-DTPA effectively chelate several transuranium ions (plutonium, americium, berkelium, curium, and californium). Their clinical use has been primarily for treatment of internal contamination with plutonium and americium. One patient contaminated with in excess of 1 mCi of americium had 99% of the total body burden removed with prolonged therapy over 4 years with a combination of Ca-DTPA/Zn-DTPA therapy.⁹

The efficacy of Ca-DTPA and/or Zn-DTPA treatment for plutonium incorporations is good for soluble salts, such as the nitrate or chloride, but is essentially nil for highly insoluble compounds, such as the high-fired oxide. The same characteristics are noted experimentally when a soluble (monomeric) form of plutonium is administered that gradually converts to less soluble (polymeric) forms as it is distributed and deposited in various tissues in the body. Thus, chelation is highly dependent not only on the metal itself, but also on the chemical and physical characteristics of the compound at the time of DTPA administration.

Zn-DTPA is initially 10 times less effective than Ca-DTPA for initial chelation of transuranics; therefore, Ca-DTPA should be used whenever larger body burdens of transuranics are involved. Ca-DTPA is the form of choice for initial patient management unless contraindicated. After approximately 24 hours, however, Zn-DTPA is for all practical purposes as effective as Ca-DTPA, since the efficiency of both agents is about the same. This comparable efficacy, coupled with its lesser toxicity, makes Zn-DTPA the preferred agent for protracted therapy.

CONTRAINDICATIONS

Zn-DTPA is not approved under the current IND as a chelator for uranium or neptunium. Incorporation of uranium, an actinide, is not to be treated with DTPA because of the risk of renal damage from the excretion of uranium.² DTPA appears to form an unstable complex with neptunium, which actually can contribute to increased bone deposition of this actinide.³

WARNINGS AND PRECAUTIONS

- 1) Fractionation of the recommended 1 g dose (several smaller doses per day) is not recommended, although Zn-DTPA does not appear to have the increased toxicity of Ca-DTPA (associated with fractionated treatment).
- 2) Check blood pressure during infusion.
- 3) Discontinue drug if diarrhea occurs.

Usage in Pregnancy - Pregnancy Category C -

The chelates do not significantly cross placental barriers and the observed effects on rodent fetuses are probably mediated through the dam.

There have been several studies indicating the lack of teratological effect by Zn-DTPA at doses up to several times the human intravenous dose, 0.0287 mmol/kg.

In the same experiments as Ca-DTPA, Zn-DTPA did not give similar toxicity during pregnancy. In pregnant mice given a daily dose of 11.5 mmol/kg (400 times the human dose), the only fetal effect observed was a slight reduction in the average birth weight.⁸ Zn-DTPA is preferred over Ca-DTPA and should be used if available to treat a pregnant female with internal transuranic contamination. There are no adequate and well-controlled studies of Zn-DTPA in pregnant women. The potential benefits of transuranic decorporation must be weighed against the risk to the fetus.

ADVERSE REACTIONS

No serious toxicity in man has been reported as a result of over 1000 doses of Zn-DTPA administrations in recommended doses. When given repeatedly, with short intervals for recovery, Zn-DTPA treatment in man may cause nausea, vomiting, diarrhea, chills, fever, pruritus, and muscle cramps in the first 24 hours.

In one patient, long-term, low-dose combination Ca/Zn-DTPA administration was begun using six different schedules of: 1g Ca-DTPA/24h, 1g Ca-DTPA/12h, 1g Zn-DTPA/12h, 1g Zn-DTPA/8h, 1g Zn-DTPA/12h, 0.5g Zn-DTPA/12h, 1g Zn-DTPA/24h and 1g Zn-DTPA three times a week. After 934 days of such administration, there were no adverse effects known.⁹

OVERDOSAGE

Zn-DTPA is some 30 times less toxic than Ca-DTPA to mice when given daily at high doses. Acutely lethal doses of Zn-DTPA are estimated at >20 mmol/kg or 10g/kg in the adult male mouse.¹⁰

In rats, there was no decrease in concentration observed of the trace elements Zn or Mn in liver, small intestine, or kidneys in contrast to Ca-DTPA.¹²

DOSAGE AND ADMINISTRATION

Each dose of Zn-DTPA should be 1 g (4.0 ml). The route of administration may be either intravenous injection of the undiluted solution over a period of 3-4 minutes, intravenous infusion (250 ml D5W or normal saline), or inhalation in a nebulizer (1:1 dilution with water or saline). Intravenous administration should not be protracted over more than 2 hours.

Clinical experience has shown that aerosol inhalation of Zn-DTPA is more effective than intramuscular injection, apparently because diffusion to the body from the lung is slower than from muscle, and results in a longer lasting plasma level. The same relationship exists when comparing the effectiveness of aerosol inhalation of Zn-DTPA to intravenous injection.

Zn-DTPA may be administered undiluted by intramuscular injection when intravenous administration is not practical, although significant pain at the injection site has resulted when this route is used. Addition of 1-2% procaine to the undiluted Zn-DTPA prior to intramuscular injection has proven to be helpful.

The chelating efficacy is greatest immediately or within one hour of exposure, when the radionuclide is circulating in or available to the tissue fluids and plasma. However, a post-exposure interval > 1 hour does not preclude the administration and effective action of Zn-DTPA.

Combined Ca-DTPA/Zn-DTPA Therapy Guidelines

It must be noted that this is a general guide for DTPA therapy and that treatment must be specifically tailored for individual patients. Ca-DTPA and Zn-DTPA generally can be thought of as two components of transuranic decorporation therapy. If there is any contraindication to the use of Ca-DTPA, the same dose of Zn-DTPA may be substituted.

A. On assurance that a credible incident has occurred and the exposed person(s) at risk had in all likelihood received internal transuranic contamination:

1. Obtain signature on informed consent form for DTPA therapy (which should cover both Ca and Zn forms).
2. Obtain base-line blood and urine samples (CBC with differential, BUN, serum creatinine, urinalysis and urine radioassay).
3. Administer 1 g (4.0 ml of 0.5 M) Ca-DTPA by the most appropriate route for the particular case.
4. Begin collection of ALL urine and fecal samples for bioassay. Whole body and chest counting should be performed. Blood assays are done if the initial urinalysis was positive for transuranic contamination.
5. If long-term use of Ca-DTPA is contemplated, one should consider the use of supplemental zinc therapy (one 220-mg zinc sulfate tablet daily delivers 50 mg zinc).
6. Repeat doses of 1 g Zn-DTPA daily for up to 5 days if the radioassay data or history indicate the need for additional chelation. Keep in mind that the majority of patients in the past have received only one dose of DTPA.
7. Although no significant side effects of DTPA at the recommended dosage level are known and there are no known contraindications to its use, urinalysis and complete blood counts should be done on the day following each treatment with DTPA, and the patient's pulse and blood pressure also should be monitored to determine any effect of the drug. Bioassay results and any side effects should be noted and recorded on the standard treatment form and reported to ORAU for the annual DTPA usage survey.
8. Additional tests may be ordered at the discretion of the investigator.

B. Before, during and after chelation therapy, pertinent measurements for radioactivity should be made to determine the efficacy of treatment. By the fifth day, evaluate bioassay data for body-burden estimation and decide whether further chelation is necessary. If SO, a Zn-DTPA treatment regimen should be implemented.

1. Begin therapy regime by administration of Zn-DTPA on a two-dose per week basis, 1 g Zn-DTPA doses, until such time as excretion rate of transuranic is not increased by Zn-DTPA administration.

2. Wait four to six months, re-establish base-line urinary excretion-rate value and give a 1 g Zn-DTPA dose by an appropriate route. Obtain bioassay of urinary excretion to determine whether the Zn-DTPA increased excretion of the contaminant. IF SO,

3. Begin a second course of Zn-DTPA treatment on a two dose per week basis as in (1) above.

C. If bioassay data indicates that contamination was not in excess of minimally detectable amounts, then further therapy is not recommended.

D. When patient is released from further therapy, he should be followed at the routine intervals established by occupational practice. A urinalysis is recommended at these examinations.

E. It is recommended that at the time of an employment termination, the physician should ascertain at the physical examination the person's plans so he can forward the history to an M.D. of the patient's choice. In addition, the M.D. should offer the person the opportunity to be followed medically by the DOE follow-up system. This should be done in order to ensure continuity of patient care and assist if the person again should again become contaminated and require therapy at another plant site.

Patients who have received extensive chronic incorporation of transuranics require unusual therapy and will be treated largely according to the discretion of the investigator. In the past, treatment has not exceeded three 1 g doses during any 24-hour period. Doses should be administered by the route considered most appropriate for the particular case.

HOW SUPPLIED

Each ampule provided contains 1.1 g Zn-DTPA, 0.5 M in 4.40 ml (25%) sterile water. The solution should be clear, colorless, and free of crystalline or other material. The ampules should be stored in a cool place and away from sunlight.

As a part of the management of the IND for Ca-DTPA, chemists at Oak Ridge Associated Universities carry out annual analytical tests on randomly selected ampules of the drug. There is no indication that deterioration, pyrogenicity, or loss of sterility occur when the ampules are stored at room temperature. However, if any problem of this nature should be observed, all co-investigators would, of course, be notified immediately. Likewise, any signs of deterioration (discoloration or cloudiness) of the solution or reaction on the part of the patient should be reported at once to one of the persons listed below.

The Food and Drug Administration (FDA) requires that the Sponsor and Manager(s) of the IND be in a position to account for all ampules sent to investigator-physicians. Please, therefore, set up an accounting system on the supplies of Zn-DTPA and be prepared to report your experience annually, including observations on the safety and efficacy of the Zn-DTPA used according to the protocols you submitted with your original request for Zn-DTPA. The Manager(s) of the Zn-DTPA IND will contact you in June each year to obtain your report which will be incorporated into ORAU's summary report to the FDA for the 12-month period.

Questions regarding the use of Zn-DTPA may be referred to one of the following personnel at the Medical Sciences Division of Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831-0117:

Robert C. Ricks, Ph.D.
IND Co-manager
(615) 576-3131

Shirley A. Fry, M.B., B.Ch., M.P.H.
(615) 576-3480

W. W. Burr, M.D., Ph.D.
(615) 576-5262

Dale E. Minner, M.D., F.A.C.O.M.
(615) 576-2124

or

A. Seaton Garrett, M.D., F.A.C.O.M.
Oak Ridge National Laboratory
(615) 576-7431

REFERENCES:

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- ⁴ NCRP publication #65, *The Management of Persons Accidentally Contaminated with Radionuclides.*, NCRP, 122-123, 146-152, 1980.
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- ⁷ Taylor GN, Mays CW, Fetal injury induced by Ca-DTPA in dogs. *Health Physics*, 35:858-860.
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**Consent for CHELATION THERAPY using Ca-DTPA and/or Zn-DTPA,
an FDA Investigational Drug**

INSTITUTION: _____ DATE/TIME: _____

I have been involved in an incident in which I may have been exposed to radioactive material and may have been internally contaminated. My participation in DTPA chelation therapy is voluntary, and I may stop at any time.

I, _____, (Patient) authorize Dr. _____ (Physician) and his/her staff to administer chelation therapy utilizing the drug(s) Calcium trisodium diethylenetriaminepentaacetate (Ca-DTPA) and/or Zinc trisodium diethylenetriaminepentaacetate (Zn-DTPA) in an attempt to (1) determine if a medically significant amount of radionuclide is in my body, and (2) to enhance the removal of these radionuclides if a medically significant amount is found. I know that DTPA is recommended as the preferred drug for radionuclide removal by national and international radiation protection councils.

I am aware that there is no other approved treatment for removing transuranic radionuclides from my body. My alternatives are, therefore, (1) DTPA treatment or (2) no treatment.

I understand that chelation therapy in general has become a part of widely accepted medical practice in removing heavy metal contamination from humans. I am aware that DTPA has been used medically since 1958 but is not available for general use as a chelator, although it is available for general use for other medical purposes. DTPA remains on investigational drug status to help ensure accurate reporting of possible contamination accidents and to record any side effects.

Dr. _____ (Physician) and his/her staff have described the potential risks and benefits of chelation therapy with DTPA and have described what the drug does, which is, in my own words, to:

I understand that if a large amount of contamination is found, treatment may require repeated doses of this drug several times a week for up to several months. The human experience with Ca-DTPA is limited; however, there are no known significant risks from a single dose of Ca-DTPA or Zn-DTPA. I have been told that there have been no known immediate risks in taking Zn-DTPA with daily doses of up to 2 grams.

I have been told that long-term therapy with Ca-DTPA may deplete the body of zinc and some zinc-dependent enzymes. Therefore, its use is avoided in the case of pregnancy, certain kidney disease, and if full growth is not completed. I will advise you if any of the above conditions exist. The drug may be injected, and injection of any drug can cause potential complications of bleeding and infection. Questions regarding current DTPA research or complications regarding its use may be directed to the Radiation Emergency Assistance Center/Training Site (REAC/TS) through the operator at Methodist Medical Center, Oak Ridge, Tennessee, (615) 481-1000.

I give permission for general information relating to my case to be used in professional medical literature, in the interest of increasing medical knowledge. I understand that confidentiality of my identity will be maintained, and I shall not be identified in any way. I know that FDA has the right to review my medical records pertaining to DTPA treatment.

I am aware that further follow-up visits with my physician will be necessary.

Patient: _____ Date/Time: _____

Relative acting
for patient: _____ Physician: _____

Relationship: _____ Witness: _____

(This form has been approved for use by physicians by the ORAU/ORNL Committee on Human Studies, Oak Ridge, Tennessee)

1080510

(This form has been approved for use of noninstitutional physicians by the ORAU/ORNL Committee on Human Studies, Oak Ridge, Tennessee and DOE Biomedical Research Division of Safety, Standards, and Compliance.)

INFORMED CONSENT FORM
FOR USE OF CA-DTPA, AN INVESTIGATIONAL DRUG

NAME: _____ AGE: _____ DATE: _____ TIME: _____ AM/PM

I _____, hereby request and authorize
_____ M.D. to give to _____
(myself)

the drug trisodium calcium diethylenetriaminepentaacetate (CA-DTPA) in an attempt to enhance the removal of _____ from my body. I understand that I have been involved in an incident where I was exposed to radioactive _____ and may have been contaminated, to some degree, by this exposure. The above-named physician has consulted with me concerning this condition and has advised me that one method of treatment is the use of the drug CA-DTPA. I understand that I may require repeated doses of this drug several times a week and may need to get additional treatments with a drug called Zn-DTPA, depending on the level of contamination that I have experienced, should I decide to accept this method of treatment.

I understand that CA-DTPA is an investigational drug and not available for general use. The term "investigational drug" means that the drug, CA-DTPA, is undergoing investigation, under FDA control, to determine its effect on humans. It has been explained to me that this compound has the property to bind with some heavy metals, including iron, lead, plutonium, americium, and the other heavy metals within the body and helps the body to excrete them. I have been told that CA-DTPA especially when given in high doses for prolonged periods of time tends to remove zinc from the body. For this reason treatment is switched from CA-DTPA to Zn-DTPA if prolonged treatment is necessary. I understand that all risks may not be known and that unforeseen results may occur. On the other hand, it has been explained to me that the risk of developing adverse late effects from actinide incorporation is decreased with CA-DTPA followed by Zn-DTPA therapy, and I realize that this treatment is offered to me only after careful deliberation by Dr. _____ and colleagues.

I am consenting to its use for the study and treatment of my condition with the understanding that the results of this treatment may not necessarily be of benefit to me. The use of CA-DTPA in the treatment of internal radionuclide contamination is part of a national research program. I do not object if any information relating to my case is used in professional journals or medical books, or for any other purpose in the interest of medical education, knowledge, or research; provided, however, that it is specifically understood that in any such publication or use I shall not be identified in any way. I further agree that I will participate in whatever follow-up studies are deemed appropriate by my physician at whatever intervals are found suitable by the investigators. I am reserving the right to withdraw my permission at any time without prejudicing my further medical care. Dr. _____ has also offered to answer any additional questions.

Signed: _____
(patient)

Witness: _____

The foregoing consent was read, discussed, and signed in my presence, and in my opinion the person so signing did so freely and with full knowledge and understanding.

Witness: _____

Date: _____

Addendum:

Dr. _____ has explained to me the possible effects to fetus that may occur from prolonged treatment with Ca-DTPA.

Signed: _____
(patient)

Witness: _____

(This form has been approved for use of noninstitutional physicians by the ORAU/ORNL Committee on Human Studies, Oak Ridge, Tennessee, and DOE Biomedical Research Division of Safety, Standards, and Compliance.)

INFORMED CONSENT FORM
FOR USE OF ZN-DTPA, AN INVESTIGATIONAL DRUG

NAME: _____ AGE: _____ DATE: _____ TIME: _____ AM/PM

I _____, hereby request and authorize _____ M.D.

to give to _____ (myself) the drug trisodium zinc diethylenetriaminepentaacetate

(Zn-DTPA) in an attempt to enhance the removal of _____ from my body.

I understand that I have been involved in an incident where I was exposed to radioactive _____ and may have been contaminated, to some degree, by this exposure. The above named physician has consulted with me concerning this condition and has advised me that one method of treatment is the use of the drug Zn-DTPA. I understand that I may require repeated doses of this drug several times a week for up to several months depending on the level of contamination that I have experienced, should I decide to accept this method of treatment.

I understand that Zn-DTPA is an investigational drug and not available for general use. The term "investigational drug" means that the drug, Zn-DTPA, is undergoing investigation, under FDA control, to determine its effects on man. It has been explained to me that this compound has the property to bind with some heavy metals, including iron, lead, plutonium, americium, and the other heavy metals within the body and helps the body to excrete them. There are no known risks at this time in taking Zn-DTPA with daily doses of up to 2 grams. However, I understand that all risks may not be known. I have been fully informed of the possible consequences and understand that unforeseen results may occur. The alternative methods of treatment such as waiting for spontaneous excretion have been explained to me, and I realize that this drug (Zn-DTPA) is offered to me only after careful deliberation of Dr. _____ and his colleagues.

I am consenting to its use for the study and treatment of my condition with the understanding that the results of this treatment may not necessarily be of benefit to me. The use of Zn-DTPA in the treatment of internal radionuclide contamination is part of a national research program. I do not object if any information relating to my case is used in professional journals or medical books, or for any other purpose in the interest of medical education, knowledge, or research; provided, however, that it is specifically understood that in any such publication or use I shall not be identified in any way. I further agree that I will participate in whatever follow-up studies are deemed appropriate by my physician at whatever intervals are found suitable by the investigators. I am reserving the right to withdraw my permission at any time without prejudicing my further medical care.

Dr. _____ has also offered to answer any additional questions about this drug and possible delayed effects.

Signed: _____ (patient)

Witness: _____

The foregoing consent was read, discussed, and signed in my presence, and in my opinion the person so signing did so freely and with full knowledge and understanding.

Witness: _____

Date: _____