CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-749

21-751

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

IND 4,041

Title: Trisodium calcium diethylenetriaminepentaacetate (Ca-DTPA).

Reviewer: Alfredo R. Sancho, Ph.D.
Submission Date: 24 May 1967
Final Review Date:

Assigned Date: 31 October 2001
Review Date: 05 June 2002
Revised Review Date: 02 December 2002

Dose: 1-gm per day of Ca-DTPA via bolus/infusion intravenous, aerosol inhalation

Proposed Indication: Chelating treatment of internal transuranium ion contaminants.
Sponsor: Oak Ridge Associated Universities, Oak Ridge, TN 37831.

EXECUTIVE SUMMARY

A radioprotectant is a substance, which if introduced immediately after or soon after a radiation exposure, attenuates or suppresses the symptoms caused by it and diminishes the risk of mortality. This submission, IND 4,041, is for the radioprotectant *trisodium calcium diethylenetriaminepentaacetate,* Ca-DTPA. This product comes in 1-gm ampules containing a clear, colorless, crystalline-free solution.

This product, Ca-DTPA, is a salt of diethylenetriaminepentaacetate, DTPA. It has been used as a chelating agent of plutonium and other transuranic elements such as ameridium, californium, and curium. [*Volf, 1978*] It is not approved for uranium or neptunium contamination treatment due to lack of efficacy. [*Bruenger et.al., 1991*] DTPA is also commonly used in lesser concentrations as a chelating vehicle in FDA-approved nuclear medicine studies. The efficacy of Ca-DTPA treatment for internal contamination with the actinides 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 effects 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.

Currently Oak Ridge Associated Universities (ORAU) manages IND 4,041 for the U.S. Department of Energy (DOE). This document is a summary of findings from the reviewed published literature and the proposed package insert for Ca-DTPA. The published literature reviewed for this document was provided in part by the sponsor and supplemented by literature searches by this reviewer via Medline search engine. The essential supporting articles are identified and listed in this document.

Based on the literature reviewed, Ca-DTPA is found to effectively reduce the toxicity of transuranium radio-element contaminants. No extensive and well-controlled human studies have been identified, but based on the reviewed literature it is known that Ca-DTPA has more side effects than Zn-DTPA. It is recommended that Ca-DTPA be co-administered with other radioprotectants such as Prussian blue to increase the efficacy of the overall treatment procedure. If Ca-DTPA is used to treat radio-element toxicity, it should be used only for one day or the initial day of treatment and without fractionating the 1 gm/day recommended dose. For long term therapy, Zn-DTPA should be used after the initial Ca-DTPA dose due to that Zn-DTPA shows less adverse effects.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the information and data submitted 24 May 1967. It is recommended that Ca-DTPA be co-administered with other radioprotectants (i.e., Prussian blue and KI) as a single one-day dose or be the initial dose of a long duration treatment plan for patients exposed to one or more known or unknown radio-elements. Although the dose and dosing regimen is not clearly established in the literature, these will be dependent on the amount and type of radio-element contamination. Detection and monitoring methods for early and effective identification and quantification of the radio-element

contaminants should also be in place so to aid in the dose and dosing regimen determination. In summary, the Clinical Pharmacology and Biopharmaceutics Division has completed the assessment of the current available data and information. The labeling changes as covered under the Labeling Recommendations section of this review (page 7) should be communicated to the sponsor.

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SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Diethylenetriaminepentaacetate, DTPA, belongs to the group of synthetic polycarboxylic acids which form stable complexes (metal chelates) with a large number of metal ions. Ca-DTPA chelates toxic metals by exchanging its cations for metals that form more stable complexes with the DTPA ligand. The metal-DTPA complexes are excreted in the urine. The chelating efficacy is greatest immediately or within an hour of exposure when the radio-element is circulating in or available to the tissue fluids and plasma.

Ca-DTPA can deplete the body of zinc (Zn) and manganese (Mn) with repeated dosing. The amount of Zn and Mn lost is determined by the amount of Ca-DTPA and the frequency of dosage. By depletion of these essential trace metals, Ca-DTPA can then interfere with necessary mitotic cellular processes. Over long Ca-DTPA treatment periods, depletion of Zn can result in transient inhibition of a metalloenzyme, d-aminolevulinic acid dehydrase (ALAD), in the blood, although without observable clinical effect which can be reversed by Zn replacement concomitant therapy. Ca-DTPA is the form of choice for initial patient management unless the patient has renal function problems. Within the first hour after radio-element exposure, Ca-DTPA is approximately 10 times more effective than Zn-DTPA for chelation of transuranics. Approximately, 24 hours after radio-element exposure, Zn-DTPA is as effective as Ca-DTPA.

Intestinal absorption of Ca-DTPA after oral administration is low, approximately 5%. [*Foreman, 1960*] The plasma half-life is 20-60 minutes. Almost the entire administered dose (~99%) is excreted in 12 hours, with only a small amount (~1%) bound to plasma proteins. DTPA undergoes minimal metabolic change in the body. Following intravenous administration, Ca-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of DTPA penetrates into erythrocytes or other tissues. 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 has not been observed. Although clearance of 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 inulin clearance. In stool samples tested with radioactively marled DTPA, on a very small amount of radioactivity (<3%) was detected.

Ca-DTPA is contraindicated for pediatrics, pregnant women, patients with the nephrotic syndrome, and patients with bone marrow depression. Ca-DTPA is ineffective for uranium or neptunium.

DTPA has been found to form unstable complexes with neptunium, which may increase bone deposition. [*Morin et.al., 1973*]

Toxicity apparently results from depletion of the Zn and Mn ions needed in the enzymatic steps leading to DNA synthesis that renews the epithelial cell in the intestinal epithelium. [*Gabard, 1974*] There is very limited pharmacokinetic information (human or animal) in the literature. [*Morgan, 1973; Stevens e.al., 1978; Stather et.al., 1983*]

PHARMACOKINETICS

There is a single pharmacokinetic study (plasma retention and urinary excretion) in human volunteers (n=2) in which ^{14}C-DTPA was administered intravenously and via inhalation. [*Stather et.al., 1983*] The intravenously administered dose was 750 kBq of ^{14}C-DTPA (diethylenetriaminepenta (2-^{14}C) acetic acid) in 5 g pyrogen-free water with 250 mg of non-radiolabeled Ca-DTPA. For inhalation, the dose was 2.3 MBq of ^{14}C-DTPA mixed with 455 mg of non-radiolabeled Ca-DTPA in 6 g of 10% ethanol. The 14C activity was determined by liquied scintillation counting to an accuracy of at least ±2%ID. The limit of detection of 14C was approximately 350 mBq (~0.5%ID).

In the intravenous data, the plasma retention up to 7 hours post administration could be expressed by the sum of three exponential components with average half-lives of 1.4 min, 14.5 min, and 94.4 min. The level of activity in the plasma was below the limit of detection by 24 hrs after injection and during the study, no detectable activity was exhaled in the breath or excreted in the feces. By the 24 hr time point, the cumulative urinary excretion of the radioactivity administered was more than 99%ID, a value similar to that reported in other studies. [*Stevens et.al., 1962*] Clearance of DTPA from the plasma in the first few hours is not reflective only of urinary excretion, but also indicative of a substantial DTPA transfer from the plasma into the extracellular fluid shortly after injection.

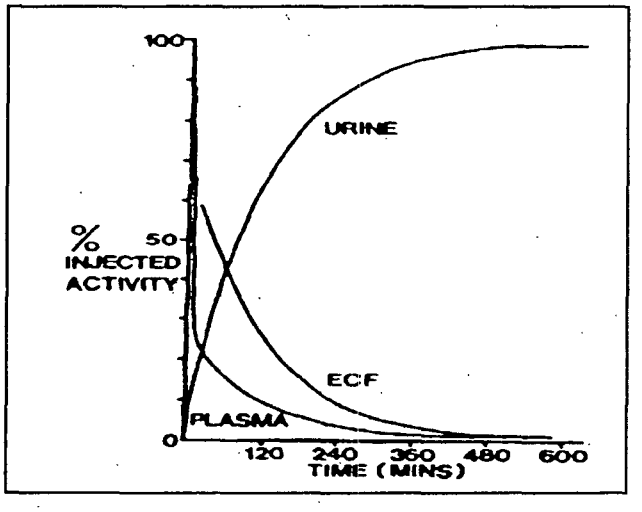

Figure 1. Levels of ^{14}C-DTPA in the body and cumulative excretion after intravenous administration calculated from averaged values for K1, K2, and K3. [*Stather et.al., 1983*]

The nebulising equipment used in this particular study [*Stather et.al., 1983*] retained most of the radioactivity to be administered. In one of the subjects, approximately 40% of the activity nebulised was inhaled in four separate inhalations. Of this, about 5% was exhaled during exposure, 2% was retained in the mouth, 24% was excreted in the feces, and 69% in the urine. Of the 40% inhaled, approximately only 25.7% enetered the plasma (estimated from the level of excretion in the urine). DTPA plasma concentrations remained relatively constant for between 10 min to 2 hr after exposure, subsequently falling with a half-life of about 140 minutes. These values are similar to those obtained from the second subject.

ADVERSE EVENTS

When repeated dosing occurs, Ca-DTPA treatment lead to nausea, vomiting, diarrhea, chills, fever, pruritus, and muscle cramps within 24 hours of administration. Anosmia (loss of the sense of smell) may occur in long term therapy. Gray hair may appear due to the chelation of copper, an element that is essential for tyrosinase action in the formation of melanin. [*Lerner et.al., 1953; Yasunobu, 1959*]

DOSAGE

The sponsor recommends a dose of 1 gram of Ca-DTPA, either via intravenous (IV) bolus or infusion administration (undiluted or diluted with Ringers Lactate or normal saline) or via inhalation in a nebulizer (1:1 dilution with water or saline). In all methods of administration, the dose should NOT be fractionated. DTPA can also be given orally when immobilized on cellulose and administered in dough to reduce the gastrointestinal uptake of alkaline earth elements, such as ^{47}Ca, ^{85}Sr, or ^{226}Ra. [*Bulman et.al., 1983*]

The highest efficacy of Ca-DTPA occurs when given <1 hours post radio-element exposure. If given beyond the first hour after radio-element exposure, the efficacy of Ca-DTPA decreases until 24 hours post-exposure, when its efficacy is comparable to that of Zn-DTPA. Weekly treatments with Ca-DTPA did not reduce the risk of Zn and Mn depletion or diminish the risk of osteosarcoma induction as compared to daily Zn-DTPA treatment. [*Bruenger et.al., 1991*]

OVERDOSING

When administered to animals in high doses (>/= 2,000 umol/kg) the drug can produce severe lesions in the kidneys, intestinal mucosa, and liver. If not discontinued, death occured. A dog model in which Ca-DTPA was given at 5.8 umol/kg every 5 hours led to death by the forth day. In rats, continuos infusion at similar total doses per day, caused death in 8-14 days.

PEDIATRIC POPULATION

There are no studies conducted in pediatric population.

PREGNANCY AND LACTATION

Chelators such as DTPA do not significantly cross the placental barriers. Teratogenecity and fetal death have occurred in mice following daily injections of 720-2880 umol Ca-DTPA/kg given during gestation. Studies of two pregnant beagles given daily 30 umol/kg of Ca-DTPA starting at 15 days of gestation until end of pregnancy lead to severe brain defects in the fetuses. [*Taylor et.al., 1978; Mays et.al., 1979*]

DRUG-DRUG INTERACTIONS

No drug-drug interaction studies have been performed except for the orally co-administration of several treatment drugs, 15 gm calcium alginate, 2.5 gm Prussian blue, 0.015 gm Potassium iodide per 100 gm of food and 190 mg/kg IP of Ca-DTPA in a rat model. [*Kostial et.al., 1983*]

QUESTION BASED REVIEW

Are there any references to animal models that demonstrate Ca-DTPA efficacy?

There are several publications that support the use of Ca-DTPA as an antidote for transuranium element contamination. The following is an example of the supporting literature:

- In a study using a rat model, it was found that simultaneous administration of Calcium alginate, Prussian blue, Potassium iodide in 100 gm of food, and 190 mg/kg IP of Ca-DTPA reduced the retention of ^{85}Sr, ^{137}Cs, ^{131}I, and ^{141}Ce compared to the control (non-treated animals). [*Kostial et.al., 1983*] The following table summarizes the data in percent of injected dose (%ID ±SE) retention in whole-body at six-days post exposure between the non-treated versus the treated animals for each of the radio-elements used in the study:

Group	^{85}Sr	^{137}Cs	^{131}I	^{141}Ce
Control	63.3 ± 1.3 (n=12)	41.7 ± 0.8 (n=12)	16.4 ± 1.1 (n=12)	85.5 ± 1.3 (n=11)
Treated	61.1 ± 1.3 (n=12)	21.3 ± 0.4 (n=12)	1.8 ± 0.1 (n=11)	7.6 ± 0.3 (n=11)

Is there a set dose for Ca-DTPA?

The product comes in 1-gm ampules. Each ampule is considered a single daily dose. The dosing regimen will depend on the type and extent of radio-element contamination. Dosing regimen will vary in length from a single dose to several weeks. It is recommended that this product be given as a one-time dose or as the initial day single dose, in either case the dose should NOT be fractionated.

Is there a dose linearity response for Ca-DTPA?

There are no published studies on this matter.

What are the common adverse events documented with Ca-DTPA?

Oak Ridge Institute for Science and Education (ORISE) provided the following table based on 1286 1-gm doses of Ca-DTPA given over 30-years:

Event	Ca-DTPA (1-gm dose)
Local: Severe pain at site of injection	10
Hypersensitivity: Urticaria	2
Cardiovascular: Blood pressure elevation during administration	0
Gastrointestinal: Nausea	2
Neurologic/Psychiatric:	
Headache	1
Numbness of fingers	1

Faintness and syncope	2
Respiratory:	2
Special Senses: Anosmia	1
Renal: Microscopic hematuria	5
TOTAL:	**24**

Are there examples of simultaneous multiple drug dosing?

The sponsor provides "*Combined Ca-DTPA/Ca-DTPA Therapy Guidelines*" as part of their proposed package insert. In the sponsor provided Guidelines, the initial treatment is with an un-fractionated 1-gm of Ca-DTPA, followed IF NEEDED by fractionated 1-gm Zn-DTPA doses daily for up to 5-days per week; after which, the patient should be re-evaluated. [*Breitenstein et. al., 1990*]

Based on the data and information obtained from the peer reviewed published literature, the oral co-administration of multiple therapeutic agents (Calcium alginate, Prussian blue, KI, and Ca-DTPA) can be used in humans without undesirable interactions for extended periods of treatment. [*Catsch et.al., 1979*]

Are there documented side-effects of Ca-DTPA in pregnant models?

Teratogenecity and fetal death have occurred in mice following daily injections of 720-2880 umol Ca-DTPA/kg given during gestation. Studies of two pregnant beagles given daily 30 umol/kg of Ca-DTPA starting at 15 days of gestation until end of pregnancy lead to severe brain defects in the fetuses. [*Taylor et.al., 1978; Mays et.al., 1979*] The sponsor proposed labeling states that this product has a Category D for use in pregnant patients.

From the database of reviewed published articles, which are identified as critical articles?

- Mays, C.W. Ca-DTPA safety in the mouse fetus. *Health Physics* 36(4): 526-529, 1979
- Taylor GN and Mays C.W. Fetal Injury Induced by Ca-DTPA in Dogs. Health Physics 35(6): 858-860, 1978
- Stevens W., Bruenger F.W., Atherton D.R., Buster D.S. and Howerton G. Retention and distribution of 241Am and 65Zn given as DTPA chelates in rats and of 14C-DTPA in rats and beagles. Rad Research 75: 397-409, 1978
- Stather J.W., Smith H., Bayley M.R., Birchall A., Bulman R.A., and Crawley F.E.H. The retention of C-14 DTPA in human volunteers after inhalation or injection. Health Physics 44:45-52, 1983
- Gabard B. The influence of DTPA on the Synthesis of DNA, RNA, and Proteins in the Regenerating Rat Liver. Biochem Pharmac 23:901, 1974
- Kostial K. and Kargacin B. Efficacy of a Composite Treatment for Mixed Fission Products in Rats. J Appl Toxicol 3(6): 291-296, 1983

- Kargacin B., Maljkovic T., Blanusa M., and Kostial K. The inlfuence of a composite treatment for internal contamination by several radionuclides on certain health parameters in rats. Arh. Hig. Rada. Toksikol. 36: 165-172, 1985
- Stevens E., Rosoff B., Weiner M., and Spencer H. Metabolism of the Chelating Agent Diethelenetriamine Pentaacetic Acid (14C-DTPA) in Man. Proc. Soc. Exptl. Biol. Med., 111: 235, 1962

LABELING RECOMMENDATIONS

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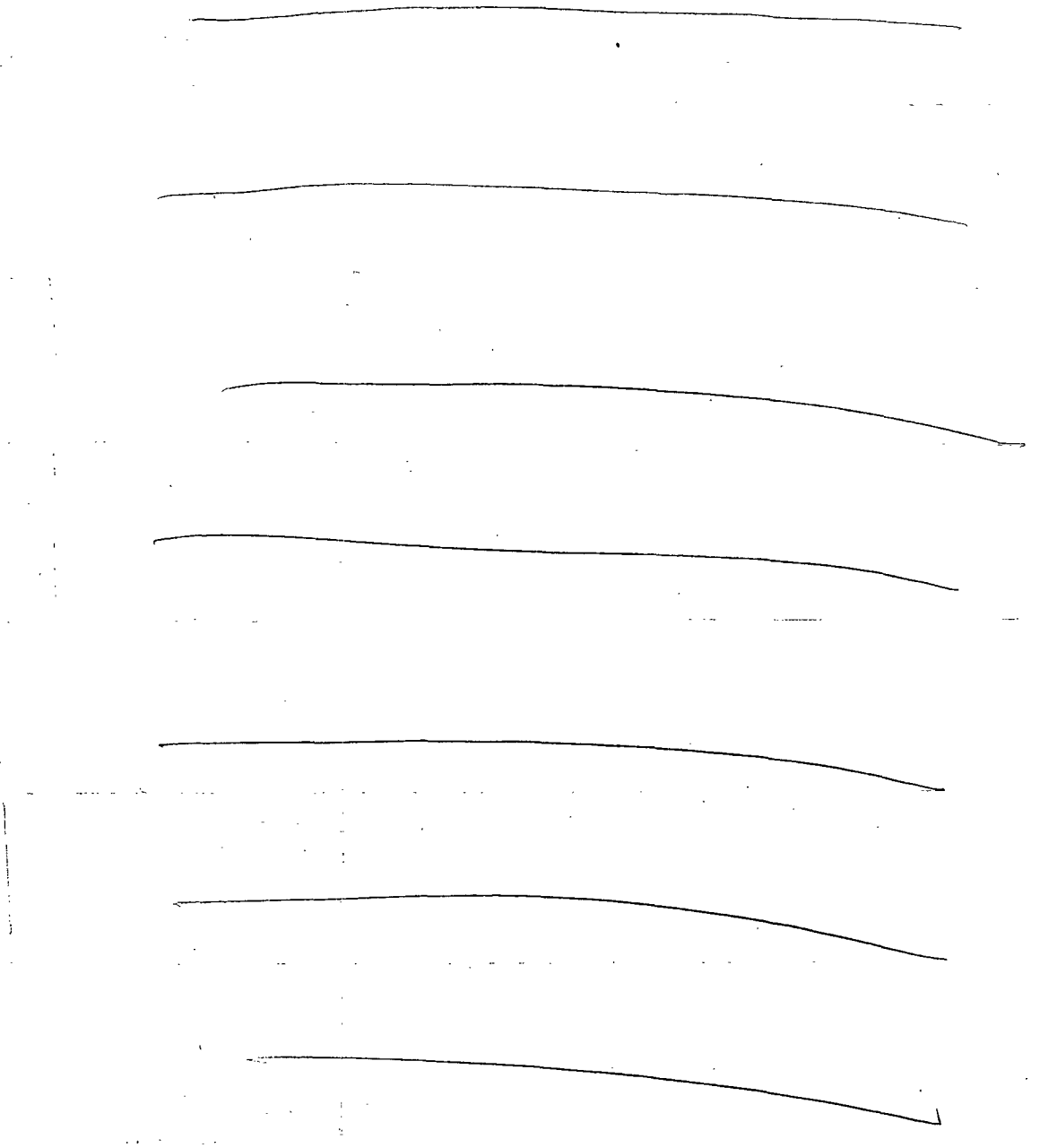

CONCLUSIONS

- The **effectiveness of Ca-DTPA in the treatment of transuranium radio-element contamination is established** in several peer reviewed published articles. [*Bruenger et. al., 1991; Breitenstein, 1983*]
- **Ca-DTPA human and animal pharmacokinetic data and information is limited.**

- **Zn-DTPA as compared to Ca-DTPA is more desirable due to the flexibility of giving multiple doses as well as being less toxic than Ca-DTPA.** Usage of Zn-DTPA would allow for steady state concentrations of the chelator DTPA in the plasma, interstitial fluid, and intracellular fluid, which would lead to better scavenging of radio-element contaminants.
- There is **no standardized pattern for treating patients** with Ca-DTPA. Therapy and treatment must be specifically tailored for individual patients under unique conditions. It is recommended that Ca-DTPA be given only as the initial day IV dose of a long duration treatment with Zn-DTPA or as a single-time dose treatment.
- There are **no studies on overdose** of Ca-DTPA have been conducted in humans.
- There are **no well-controlled studies in children** were found in the reviewed literature.
- **No studies in pregnant women, or breast-feeding patients** have been conducted. Based on results from a pregnant-mice model, Zn-DTPA is preferred over Ca-DTPA to treat a pregnant female with internal transuranic contamination. Ca-DTPA administered during gestation in rat and dog models, led to fetal death or malformations.
- **Pertaining renally impaired and/or compromised liver function patients,** no data was available nor well controlled studies have been conducted. The main route of elimination is via the renal system. Renal function of patients should be normal and should proteinuria, hematuria or other anomalies occur during treatment, Ca-DTPA administration should stop. Ca-DTPA treatment is contraindicated where there is known pre-existing serious kidney disease or depressed myelopoietic function, e.g. leukopenia or thrombocytopenia.

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Concurrence:

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Cc: HFD-160 14,603 IND (1x); DIV.FILE (1x); STEWART (1X); SANCHO (1X); CHOI (1X)
HFD-870 JHUNT (1x); MALINOWSKI (1x)

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- Kargacin B., Maljkovic T., Blanusa M., and Kostial K. The inlfuence of a composite treatment for internal contamination by several radionuclides on certain health parameters in rats. Arh. Hig. Rada. Toksikol. 36: 165-172, 1985

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/s/

Patricia Stewart
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CSO
Review originally signed by Alfredo Sancho, Ph.D. on 12/2/02

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

IND 14,603

Title: Trisodium zinc diethylenetriaminepentaacetate (Zn-DTPA).

Reviewer: Alfredo R. Sancho, Ph.D.
Submission Date: 24 July 1978
Final Review Date:

Assigned Date: 31 October 2001
Review Date: 05 June 2002
Revised Review Date: 26 November 2002

Dose: 1-gm per day of Zn-DTPA via bolus/infusion intravenous or aerosol inhalation
Proposed Indication: Chelating treatment of internal transuranium ion contaminants.
Sponsor: Oak Ridge Associated Universities, Oak Ridge, TN 37831.

EXECUTIVE SUMMARY

A radioprotectant is a substance, which if introduced immediately after or soon after a radiation exposure, attenuates or suppresses the symptoms caused by it and diminishes the risk of mortality. This submission, IND 14,603, is for the radioprotectant *trisodium zinc diethylenetriaminepentaacetate,* Zn-DTPA. This product comes in 1-gm ampules containing a clear, colorless, crystalline-free solution.

This product, Zn-DTPA, is a salt of diethylenetriaminepentaacetate, DTPA. It has been used as a chelating agent of plutonium and other transuranic elements such as ameridium, californium, and curium. [*Volf, 1978*] It is not approved for uranium or neptunium contamination treatment. DTPA is also commonly used in lesser concentrations as a chelating vehicle in FDA-approved nuclear medicine studies. The efficacy of Zn-DTPA treatment for internal contamination with the actinides 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 effects 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.

Currently Oak Ridge Associated Universities (ORAU) manages IND 14,603 for the U.S. Department of Energy (DOE). This document is a summary of findings from the reviewed published literature and the proposed package insert for Zn-DTPA. The published literature reviewed for this document was provided in part by the sponsor and supplemented by literature searches by this reviewer via Medline search engine. The essential supporting articles are identified and listed in this document.

Based on the literature reviewed, Zn-DTPA is found to effectively reduce the toxicity of transuranium radio-element contaminants. Although no extensive and well-controlled human studies have been conducted, Zn-DTPA has fewer side effects than Ca-DTPA. It is recommended that Zn-DTPA be co-administered with other radioprotectants such as Prussian blue to increase the efficacy of the overall treatment procedure.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the information and data submitted 24 July 1978. It is recommended that the oral long-term co-administration of Zn-DTPA with other radioprotectants (i.e., Prussian blue, KI, and calcium alginate) be the standard procedure for patients exposed to one or more known or unknown radio-elements. Although the dose and dosing regimen is not clearly established in the literature, these are dependent on the amount and type of radio-element contamination. Detection and monitoring methods for early and effective identification and quantification of the radio-element contaminants should also be in place so to aid in the dose and dosing regimen determination. In summary, the Clinical Pharmacology and Biopharmaceutics Division has completed the assessment of the current available data and information. The labeling changes as covered under the Labeling Recommendations section of this review (page 6) should be communicated to the sponsor.

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Intestinal absorption of Zn-DTPA after oral administration is low, approximately 5%. [*Foreman, 1960*] The plasma half-life is 20-60 minutes. Almost the entire administered dose (~99%) is excreted in 12 hours, with only a small amount (~1%) bound to plasma proteins. DTPA undergoes minimal metabolic change in the body. Following intravenous administration, Zn-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of DTPA penetrates into erythrocytes or other tissues. 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 has not been observed. Although clearance of 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 inulin clearance. In stool samples tested with radioactively marked DTPA, on a very small amount of radioactivity (<3%) was detected.

In a long-term treatment regimen (>3 years) 24 elements were assayed, including the trace metals recognized as essential for human good health. Zinc was found to be the only metal excreted more rapidly than normal. [*Morin et. al., 1973*] There is limited experience with human therapy which showed that prolonged oral chelation treatment significantly enhanced ^{239}Pu excretion from the body. [*Lagerquist et.al., 1967*]

PHARMACOKINETICS

There is a single pharmacokinetic study (plasma retention and urinary excretion) in human volunteers (n=2) in which ^{14}C-DTPA was administered intravenously and via inhalation. [*Stather et.al., 1983*] The intravenously administered dose was 750 kBq of ^{14}C-DTPA (diethylenetriaminepenta (2-^{14}C) acetic acid) in 5 g pyrogen-free water with 250 mg of non-radiolabeled Ca-DTPA. For inhalation, the dose was 2.3 MBq of ^{14}C-DTPA mixed with 455 mg of non-radiolabeled Ca-DTPA in 6 g of 10% ethanol. The ^{14}C activity was determined by liquid scintillation counting to an accuracy of at least ±2%ID. The limit of detection of ^{14}C was approximately 350 mBq (~0.5%ID).

In the intravenous data, the plasma retention up to 7 hours post administration could be expressed by the sum of three exponential components with average half-lives of 1.4 min, 14.5 min, and 94.4 min. The level of activity in the plasma was below the limit of detection by 24 hrs after injection and during

the study, no detectable activity was exhaled in the breath or excreted in the feces. By the 24 hr time point, the cumulative urinary excretion of the radioactivity administered was more than 99%ID, a value similar to that reported in other studies. [*Stevens et.al., 1962*] Clearance of DTPA from the plasma in the first few hours is not reflective only of urinary excretion, but also indicative of a substantial DTPA transfer from the plasma into the extracellular fluid shortly after injection.

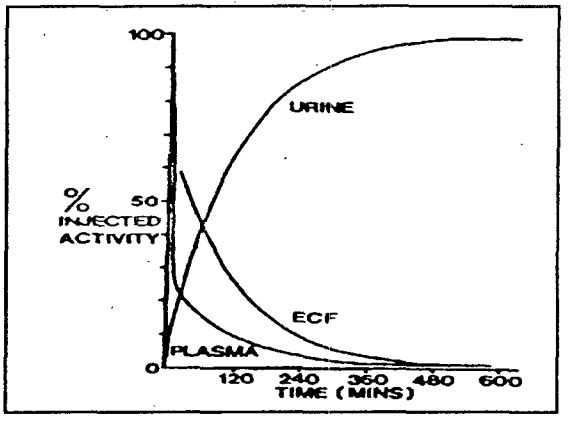

Figure 1. Levels of ^{14}C-DTPA in the body and cumulative excretion after intravenous administration calculated from averaged values for K1, K2, and K3. [*Stather et.al., 1983*]

The nebulising equipment used in this particular study [*Stather et.al., 1983*] retained most of the radioactivity to be administered. In one of the subjects, approximately 40% of the activity nebulised was inhaled in four separate inhalations. Of this, about 5% was exhaled during exposure, 2% was retained in the mouth, 24% was excreted in the feces, and 69% in the urine. Of the 40% inhaled, approximately only 25.7% entered the plasma (estimated from the level of excretion in the urine). DTPA plasma concentrations remained relatively constant for between 10 min to 2 hr after exposure, subsequently falling with a half-life of about 140 minutes. These values are similar to those obtained from the second subject.

DOSAGE

The sponsor recommends a dose of 1 gram of Zn-DTPA; either via intravenous bolus or infusion administration (undiluted or diluted with Ringers Lactate or normal saline) or via inhalation in a nebulizer (1:1 dilution with water or saline).

DTPA can also be given orally when immobilized on cellulose and administered in dough to reduce the gastrointestinal uptake of alkaline earth elements, such as ^{47}Ca, ^{85}Sr, or ^{226}Ra. [*Bulman et.al., 1983*] Another mode of oral administration is Zn-DTPA diluted in drinking water when treating ^{239}Pu contamination in a rat model. [*Taylor et.al., 1980*]

OVERDOSING

Zn-DTPA is found to be approximately 30 times less toxic than Ca-DTPA in mice when given daily at high doses. Acutely lethal doses of Zn-DTPA are estimated at >20 mmol/kg or 10 g/kg in adult mice. In animal and human studies, there was no observed decrease in Zn or Mn in the liver, small intestine, or in the kidneys. [*Mays et.al. 1979*]

PEDIATRIC POPULATION

There were no studies conducted in pediatric population in the reviewed literature.

PREGNANCY AND LACTATION

Chelators do not significantly cross the placental barriers. There have been several studies indicating the lack of teratogenic effect by Zn-DTPA at doses up to several times the human intravenous dose of 0.0287 mmol/kg.

DRUG-DRUG INTERACTIONS

No drug-drug interaction studies have been performed except for the orally co-administration of several treatment drugs, 15 gm calcium alginate, 2.5 gm Prussian blue, 0.015 gm Potassium iodide, 3.3 mmol Zn-DTPA per 100 gm of food in a rat model. [*Kargacin et.al., 1985*]

QUESTION BASED REVIEW

Are there any references to animal models that demonstrate Zn-DTPA efficacy?

There are several publications that support the use of Zn-DTPA as an antidote for transuranium element contamination. The following are examples of the supporting literature:

- In a study using a rat model, it was found that simultaneous administration of Calcium alginate, Prussian blue, Potassium iodide, and Zn-DTPA reduced the retention of ^{85}Sr, about 9 time, ^{137}Cs about 40 times, ^{131}I about 12 times whole body and 70 time in the thyroid as compared to the control (non-treated animals). [*Kargacin et.al., 1985*] The following table summarizes the data in percent of injected dose (%ID ±SE) retention in whole-body at six-days post exposure between the non-treated versus the treated animals for each of the radio-elements used in the study:

Group	^{85}Sr	^{137}Cs	^{131}I	^{141}Ce
Control	14.16 ±0.79 (n=10)	41.47 ±1.00 (n=10)	16.63 ±1.48 (n=9)	86.28 ± 0.72 (n=9)
Treated	1.57 ±0.10 (n=12)	1.12 ±0.28 (n=12)	1.44 ± 0.007 (n=11)	60.41 ± 2.50 (n=7)

Is there a set dose for Zn-DTPA?

The product comes in 1-gm ampules. Each ampule is considered a single daily dose. The dosing regimen will depend on the type and extent of radio-element contamination. Dosing regimen will vary in length from a single dose to several weeks.

What are the common adverse events documented with Zn-DTPA?

Oak Ridge Institute for Science and Education (ORISE) provided the following table based on 1286 1-gm doses of Zn-DTPA given over 30-years:

Event	Zn-DTPA (1-gm dose)
Local: Severe pain at site of injection	1
Hypersensitivity: Urticaria	0
Cardiovascular: Blood pressure elevation during administration	7
Gastrointestinal: Nausea	0
Neurologic/Psychiatric:	
Headache	4
Numbness of fingers	0
Faintness and syncope	2
Respiratory:	0
Special Senses: Anosmia	0
Renal: Microscopic hematuria	0
TOTAL:	**14**

Are there examples of simultaneous multiple drug dosing?

The sponsor provides "*Combined Ca-DTPA/Zn-DTPA Therapy Guidelines*" as part of their proposed package insert. In the sponsor provided Guidelines, the initial treatment is with 1-gm of Ca-DTPA, followed IF NEEDED by 1-g Zn-DTPA doses daily for up to 5-days per week; after which, the patient should be re-evaluated. [*Breitenstein et. al., 1990*]

Based on the data and information obtained from the peer reviewed published literature, the oral co-administration of multiple therapeutic agents (Calcium alginate, Prussian blue, KI, and Zn-DTPA) can be used in humans without undesirable interactions for extended periods of treatment. [*Catsch et.al., 1979*]

Are there documented side-effects of Zn-DTPA in pregnant models?

This product, Zn-DTPA, has not shown toxicity during pregnancy, as has Ca-DTPA. 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. It is recommended that continuos sampling of the patient's blood, urine, and feces for radio-element contaminants until no traces of the radio-element contaminant are found in any of the body fluids sampled.

Is there a dose linearity response for Zn-DTPA?

In a study using rats (n=40) exposed to ^{137}Cs it was demonstrated that there is dose linearity from 1 to 50 mg/day, but little improvement between 50 to 100 mg/day [*Nigrovic V. et.al., 1965*].

Dosing	Body weight (gm)	% ID (range)	% of Control
Control – 0 mg/day	219	58.1 (63.3 – 53.4)	100
1 mg/day	215	9.42 (13.2 – 6.72)	16
10 mg/day	203	1.17 (1.64 – 0.84)	2
50 mg/day	186	0.57 (0.80 – 0.41)	1
100 mg/day	188	0.52 (0.73 – 0.37)	0.9

From the database of reviewed published articles, which are identified as critical articles?

- Mays, C.W. Zn-DTPA safety in the mouse fetus. *Health Physics* 36: 526-529, 1979
- Breitenstein B.D., Fry S.A., Lushbaugh C.C. "DTPA therapy: The US experience 1958-1987." in *The Medical Basis of Radiation Accident Preparedness*, 2nd Ed. Ricks R and Fry SA editors, Elsevier Science Publishing Co. Inc. pp. 397-406, 1990
- Volf V. Treatment of Incorporated Transuranium Elements. Technical Reports Series No. 184, IAEA, Vienna
- Kargacin B., Kostial K. Reduction of 85Sr, 137Cs, 131I and 141Ce retention in rats by simultaneous oral administration of Calcium alginate, Ferrihexacyanoferrate(II), KI and Zn-DTPA. Health Physics, 49(5): 859-864, 1985.
- Bulman R.A., Vanderborght O., Van Puymbroeck S. Reduction in the gastrointestinal uptake of alkaline earth radionuclides by DTPA immobilized on cellulose. Health Physics, 44: 428-430, 1983
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LABELING RECOMMENDATIONS

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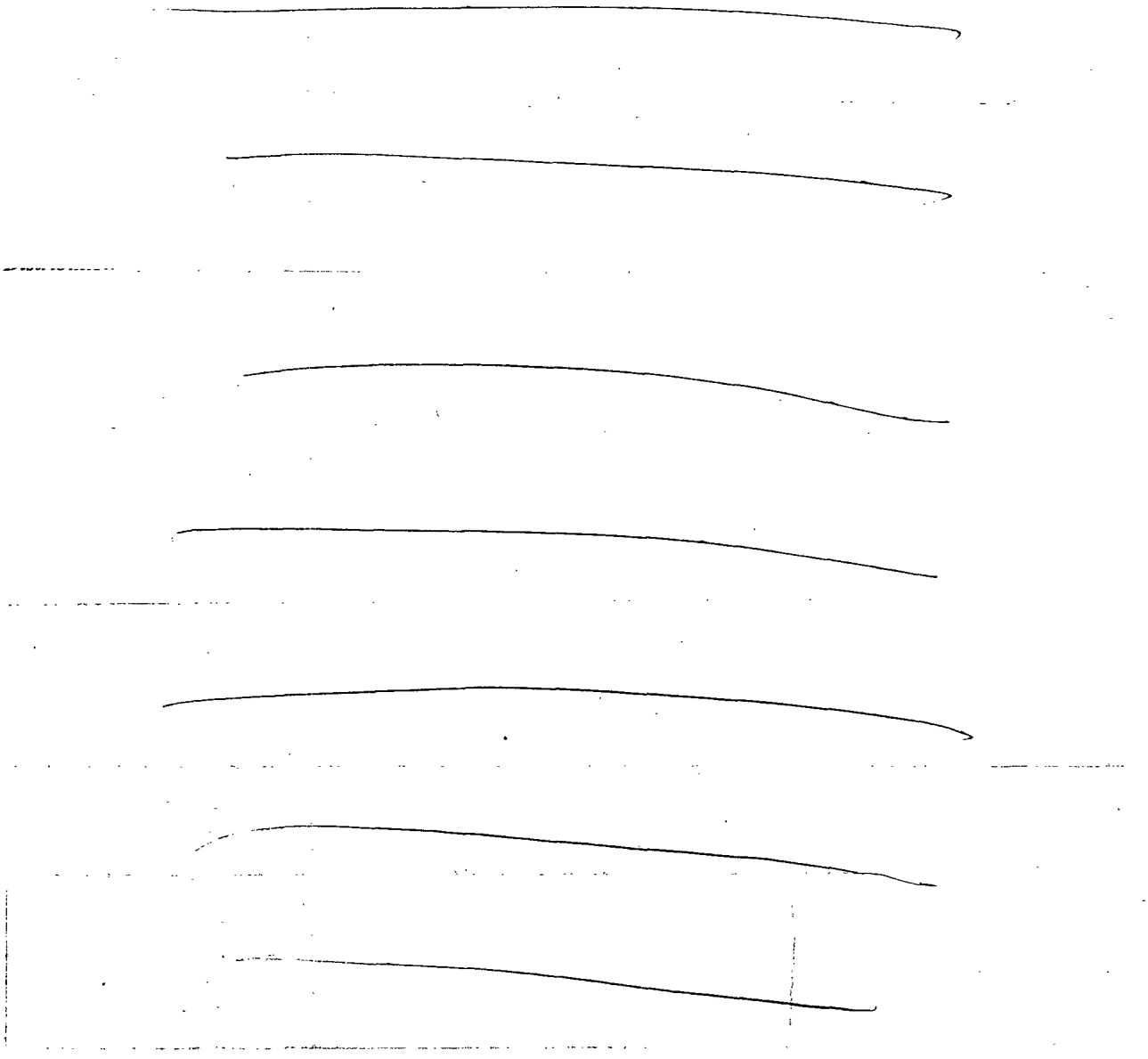

CONCLUSIONS

- The **effectiveness of Zn-DTPA in the treatment of transuranium radio-element contamination is established** in several peer reviewed published articles. [*Bruenger et. al., 1991; Breitenstein, 1983*]
- There is **no standardized pattern for treating patients** with Zn-DTPA. Therapy and treatment must be specifically tailored for individual patients under unique conditions.
- There are **no studies on overdose** of Zn-DTPA have been conducted in humans.
- There are **no well-controlled studies in children** were found in the reviewed literature.

- **No studies in pregnant women, or breast-feeding women** have been conducted. Based on results from a pregnant mice, rat, and dog models, Zn-DTPA is preferred over Ca-DTPA to treat a pregnant female with internal transuranic contamination due to that Ca-DTPA will lead to fetal death or malformations.
- **Pertaining to renally impaired and/or compromised liver function patients,** no data was available nor well controlled studies have been conducted. This may be of concern if Zn-DTPA is given intravenously, but less of a concern if given orally, due to the low absorption from the gut (~5%).
- **Co-administration of Zn-DTPA with other therapeutic agents for radio-element contamination is recommended to be the standard treatment.** This based on several animal models in which Zn-DTPA in addition to Calcium alginate, Prussian blue, and KI were used to treat multiple radio-element contamination or exposure.

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Concurrence:

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Cc: HFD-160 14,603 IND (1x); DIV.FILE (1x); STEWART (1X); SANCHO (1X); CHOI (1X)
HFD-870 JHUNT (1x); MALINOWSKI (1x)

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