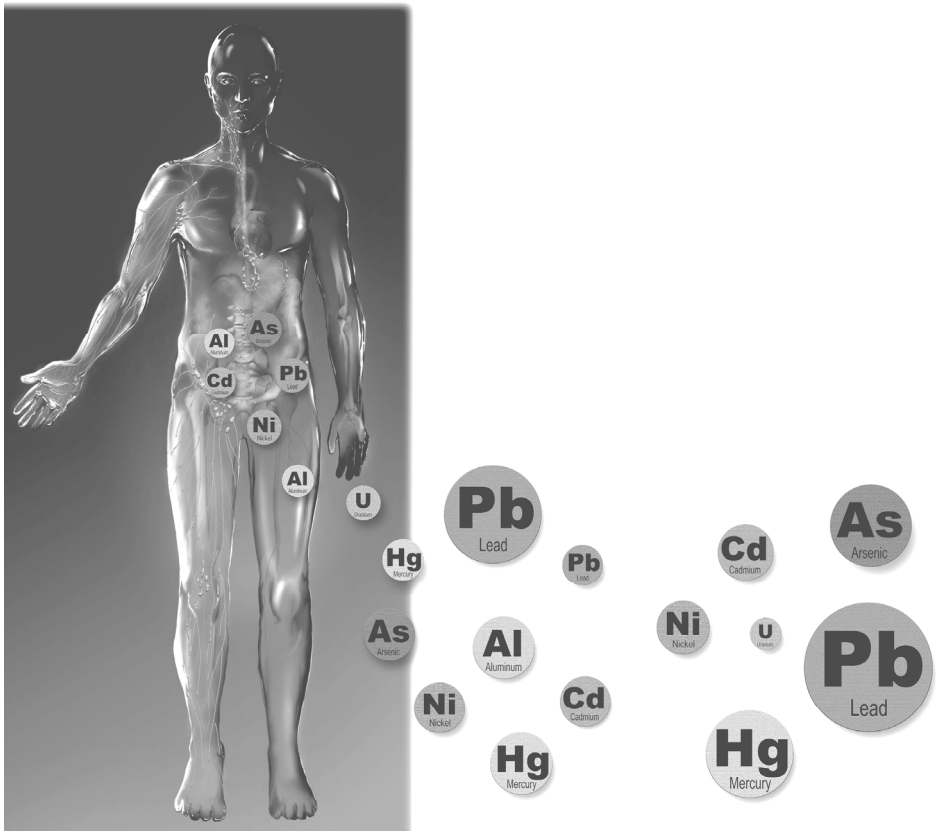

Compendium

Clinical Publications and Scientific Validation for $CaNa_2$ EDTA Chelation Suppositories (Detoxamin®)

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Compendium of Scientific and Clinical Studies on $CaNa_2$ EDTA Chelation Suppositories (Detoxamin©)

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Compendium of Scientific and Clinical Studies on $CaNa_2$ EDTA Chelation Suppositories (Detoxamin©)

Introduction

The following is a compilation of research documents and publications on pharmacokinetics, safety and efficacy of Detoxamin chelation suppositories. These studies were conducted by the following teams of researchers and physicians:

Rita Ellithorpe, MD…….. Tustin Longevity Center, Tustin, CA
Brett Jacques, ND…….. " " "

Tony Jimenez, MD…… Hope4Cancer Institute, Baja California, MX

Theodore Rosema, MD……. ACAM President Elect, Landrum, South Carolina

Garth Nicolson, PhD……. Inst. for Molecular Medicine, Laguna Beach, CA

Robert Settineri, MS…….. Sierra Research, Irvine, CA

Larry Clapp, PhD, JD…….Prostate Health Resources, Santa Monica, CA

M Pelletier, MD, CCN, FACOG…... Living Longer Inst., Cincinnati, Ohio
James Lavelle, ND, RPh, CCN……. " " "
Michael Schmidt, PhD, CCN ……... " " "
Ross Pelton, RPh, PhD, CCN …….. " " "

Harold Ravins, DDS…… Center for Holistic Dentistry, Los Angeles, CA

Paul Mazur, PhD……Biological Test Center (BTC), Irvine, CA
Glenwood Gum, PhD…… " " "
Ernest. H. Pfadenhauer, MS…….. " " "
Gerry Button, BS……... " " "
Julian Le, BS……. " " "

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ORIGINAL RESEARCH

Comparison of the Absorption, Brain and Prostate Distribution, and Elimination of $CaNa_2$ EDTA of Rectal Chelation Suppositories to Intravenous Administration

Rita Ellithorpe, MD,[1] Paul Mazur, PhD, Glenwood Gum, PhD,[2] Gerry Button, BS,[2] Julian Le, BS,[2] Ernest H. Pfadenhauer, MS,[3] Robert A. Settineri, MS,[3] Garth Nicolson, PhD[4]

1. Tustin Longevity Center, Tustin, California
2. Biological Test Center, Irvine, California
3. Research Consultant, Sierra Research, Irvine, California
4. The Institute for Molecular Medicine, Laguna Beach, California

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Julian Le, BS,[2] Ernest H. Pfadenhauer, MS,[3] Robert A. Settineri, MS,[3] Garth Nicolson, PhD[4]

1. Tustin Longevity Center, Tustin, California
2. Biological Test Center, Irvine, California
3. Research Consultant, Sierra Research, Irvine, California
4. The Institute for Molecular Medicine, Laguna Beach, California

ABSTRACT

Rectal suppositories were compared to IV administration of C14-labeled calcium disodium ethylenediaminetetraacetate (CaNa2EDTA) to evaluate the absorption, brain and prostate tissue distribution, and excretion in rats. The absolute bioavailability of CaNa2EDTA in blood following rectal dosing was 36.3% of the IV dose route, which confirmed that rectal dosing is an efficient method for delivering ethylenediaminetetraacetic acid (EDTA) to tissues. The ratio of radioactive residues of EDTA in tissues compared to blood, following IV or rectal dosing of C14 labeled CaNa2EDTA, showed negligible brain localization. However, prostate tissues were found to have a mean ratio of 3.69 via the IV route and 13.6 rectally. The total recovery of C14 EDTA expressed as percent of administered dosed IV was a mean of 47.3% and 30.3% rectally at eight hours when the test was concluded. The suppository formulation of CaNa2 appears to be well absorbed, delivering high levels of EDTA to prostate tissue.

* *Correspondence:*
Rita Ellithorpe, MD
Tustin Longevity Center
13422 Newport Avenue # L
Tustin, CA 92780
Phone: 714-544-1521 Fax: 714-544-1904
E-mail: edaly@ tlcmd.net

INTRODUCTION

Heavy metal exposures in the twenty-first century are an established global health concern. The FDA has approved EDTA as a chelation agent for the removal of heavy metals. It has been placed on the FDA "Generally Recognized as Safe" (GRAS) list for the past sixty years. Extensive national and international clinical experiences demonstrate that acute and chronic human exposure to a wide range of heavy metals can be treated with considerable efficacy using EDTA. It is widely administered, with considerable cost to the patient, as an intravenous (IV) solution, which entails 15 to 30 sessions in a physician's office, taking two to five hours per visit. The transrectal delivery of several pharmacological agents is well established. Therefore, using a rat animal model, we set out to determine if the rectal administration of EDTA is absorbed, resulting in significant blood and tissue levels.

The pharmacodynamic effects of therapeutic agents differ widely in their route of administration, penetration, absorption, and distribution in body tissues. For medicinal agents to act, they must be absorbed and transported to the appropriate tissue or organ, penetrate to the responding cell surface or sub-cellular and interstitial space, and elicit a response or alter ongoing processes.[1] The parenteral and intramuscular forms of EDTA are well absorbed, but not very practical for routine usage.[2] Oral forms of EDTA have been shown to be poorly absorbed (2% to 5%), and topical and subcutaneous forms have been reported as not being

absorbed at all.[3,4,5,6,7,8,9,10] A relatively new alternative and more convenient route of administration is rectal suppository delivery of a proprietary suppository formula of EDTA ($CaNa_2$ EDTA, Detoxamin,® World Health Products, Draper, Utah), which is the basis of this pharmacokinetic (PK) study. Although IV EDTA dosing is well characterized and has been used for decades, little is known about the absorption of rectal suppositories.

In an effort to elucidate the absorption characteristics of $CaNa_2$ EDTA in a suppository form, a rat model was chosen. ^{14}C-labeled EDTA Calcium Disodium salt was administered as a tracer in the suppository and in intravenous forms; blood, urine, and selected tissue levels were evaluated over eight hours.

MATERIALS AND METHODS

^{14}C-labeled EDTA free acid (11.7 mCi/mmol, Lot No. 63151012, purity greater than 98%) was obtained from MP Biomedicals (Irvine, CA). For the IV dosing solution, ^{14}C-labeled EDTA was added to normal saline to achieve concentrations needed to deliver a final dose of 7.53 µCi in approximately 1 gram. The rectal suppository (a proprietary suppository formula of EDTA, $CaNa_2$ EDTA, Detoxamin® Health Products, East Draper, Utah, Lot No. 228-190-0117) was prepared by adding ^{14}C-labeled EDTA solution from Moravek to molten suppository. For the animal dose, approximately 100 µL of the mixture (containing 23.7 µCi per dose) was taken up in a cylindrical glass pipette equipped with a plunger and allowed to cool to room temperature, where it re-solidified.

The radioactive concentration of the IV dosing solution was calculated by Liquid Scintillation Counting (LSC). The prepared dosing solutions were stored and refrigerated.

Ten male Sprague Dawley rats were obtained from Taconic, Oxnard, CA. Animals were 6 to 7 weeks old and weighed 157 to 187 grams on Day 1. The animal experiments were performed at the Biological Test Center (BTC), in Irvine, CA. Quarantine and care of animals were performed per BTC Standard Operating Procedures.

Prior to dosing, 10 animals were weighed. Cannulated animals (six animals to undergo IV dosing) were randomized for placement into Group A or B. Uncannulated animals (four animals to undergo rectal dosing) were not randomized and were placed into Group C. Treatment groups are presented below.

Animals were fasted (food withheld) for 16.5 to 19.5 hours before ^{14}C-EDTA administration. Prior to dosing, rats were anesthetized with an intramuscular combination injection of ketamine hydrochloride (40-90 mg/kg) and xylazine (5-10 mg/kg). Water and feed were withheld from animals for four hours after ^{14}C-EDTA administration, and then food and water were given *ad libitum*.

For Group C, the contents of the colon were removed before dosing by flushing with normal saline heated to 37°C. Rectal doses were administered via a 100 µL glass cylindrical tube, gently heated to allow partial liquefaction of the suppository material. Blood samples of approximately 100 µL were taken. Each sample was placed in combustion cones and stored frozen prior to combustion and LSC analysis. The time of blood collection was recorded.

A terminal blood sample was collected from all animals via heart puncture (1 hour ± 5 minutes after dosing for Group A animals; 8 hours ± 15 minutes after dosing for Group B and C animals). Each animal was anesthetized with an intramuscular combination injection of ketamine hydrochloride (40-90 mg/kg) and xylazine (5-10 mg/kg), and euthanized by exsanguination following heart puncture. As much blood as possible was collected from each rat into heparinized tubes. The time of blood collection was recorded. Four 100-µL aliquots of whole blood were transferred to combustion cones. Two of the aliquots were combusted for determination of radioactivity by LSC, and two were kept frozen as reserve samples.

Absorbent paper was placed in the restrainers to collect urine 0 to 4 hours after dosing. Urine was collected from the individual metabolism cages 4 to 8 hours after dosing. For urine samples collected in absorbent paper, water was added to the paper and urine extracted. For urine samples collected from metabolism cages, the urine was freeze-trapped to avoid atmospheric oxidation, evaporation, and bacterial degradation, and the urine collection pan was rinsed with water.

Following euthanasia by exsanguination, the brain and prostate were collected from each animal. Prior to collec-

Group	No.	Treatment	^{14}C-EDTA Dose (µCi)	Route	Blood Collection Time points (Time After Dosing)[1]
A	2	^{14}C-EDTA	10	IV	1 hour
B	4	^{14}C-EDTA	10	IV	5, 15, 30 minutes; 1, 2, 4, 8 hours
C	3[2]	^{14}C-EDTA	20	Rectal	5, 15, 30 minutes; 1, 2, 4, 8 hours

1. Blood collection times were ± 1 minute for the 5-minute time point; ± 3 minutes for the 15- and 30-minute time points; ± 5 minutes for the 1-hour time point; and ± 15 minutes for the 2-, 4-, and 8-hour time points.

2. The fourth animal in group C, animal, No. 55905, was dead (attributed to anesthesia) 15 minutes after dosing.

tion, the brain was perfused with approximately 5 mL of saline via the carotid artery. Both organs were stored at -20º C. Following completion of blood kinetics analysis, brains and prostates were combusted for determination of radioactivity by LSC. Brains were homogenized prior to combustion, while prostates were directly combusted.

Duplicate aliquots of each urine sample (0.1 mL) and cage rinse sample (1 mL) were transferred to liquid scintillation counting vials and the amount of radioactivity determined by LSC; Insta-Gel was used as the scintillation fluid. Each of the rectal dosing solution samples, tail vein blood samples, and heart puncture blood samples in combustion cones were combusted. Brain and prostate samples were combusted. Combusted samples were trapped in Carbon-14 Cocktail (R.J. Harvey, Hillsdale, NJ) present in liquid scintillation counting vials, and the amount of radioactivity was determined by LSC.

Sample combustion was performed using a Harvey Sample Oxidizer, Model OX300 (Harvey Instrument, Hillsdale, NJ). All radioactivity measurements were performed using a Beckman Liquid Scintillation Spectrometer. Any radioactivity measurement of less than 100 dpm was considered close to background and was not repeated.

When applicable, summary statistics (mean and standard deviation) were prepared to characterize the data (i.e., radioactivity measurement and percent dose). PK parameters, including Area under the Curve (AUC), half-life, Maximum Concentration in blood (C_{max}), Time to Maximum Concentration (T_{max}), and bioavailability, were calculated using WinNonlin (Pharsight Corporation, Mountain View, CA).

RESULTS

Individual and mean (± SD) body weights and administered ^{14}C-EDTA doses are presented in Table 1. Radioactivity recovered from blood at different time intervals is presented in Figures 1 and 2. As shown in Figure 2, the absorption phase occurring within the first two hours after dosing for all three rectally-dosed animals was maximal, and the apparent biphasic absorption may have been related to additional material being released from the rectal suppository; the blood levels from the IV doses did not show a biphasic response.

Mean AUC, half-life, C_{max}, T_{max}, and bioavailability of derived radioactivity in blood are presented in Table 2. The T_{max} of EDTA following intravenous dosing occurred at 0.083 hours. The T_{max} of EDTA following rectal dosing occurred at 0.417 hours. The half-life of EDTA following intravenous dosing was 1.50 hours, and the half-life of EDTA following rectal dosing could not be calculated since a terminal elimination phase could not be determined. The absolute bioavailability of EDTA in blood following rectal dosing was 36.3 compared to the IV bolus of 100%. Radioactivity recovered from urine at different time intervals is presented in Table 3. Following intravenous dosing, the amount of radioactivity excreted in urine decreased over the 8-hour study period (46.3% of dosed radioactivity excreted at the 0 to 4 hour interval, and 0.935% of dosed radioactivity excreted at the 4 to 8 hour interval). Following rectal dosing, the amount of radioactivity excreted in urine remained relatively constant over the 8-hour study period (15.8% of dosed radioactivity excreted at the 0 to 4 hour interval, and 14.4% of dosed radioactivity excreted at the 4 to 8 hour interval).

Radioactivity recovered from tissues (brain and prostate) expressed as a ratio of the radioactivity in blood is

Figure 1. EDTA levels in blood over time following intravenous administration of ^{14}C-EDTA.

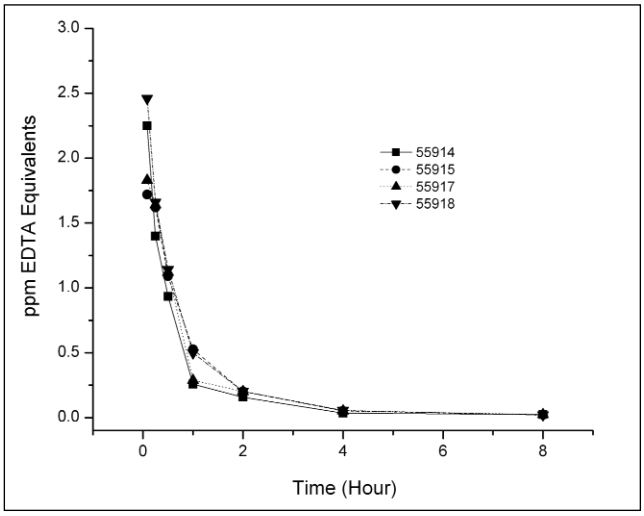


Figure 2. EDTA levels in blood over time following rectal administration of ^{14}C-EDTA

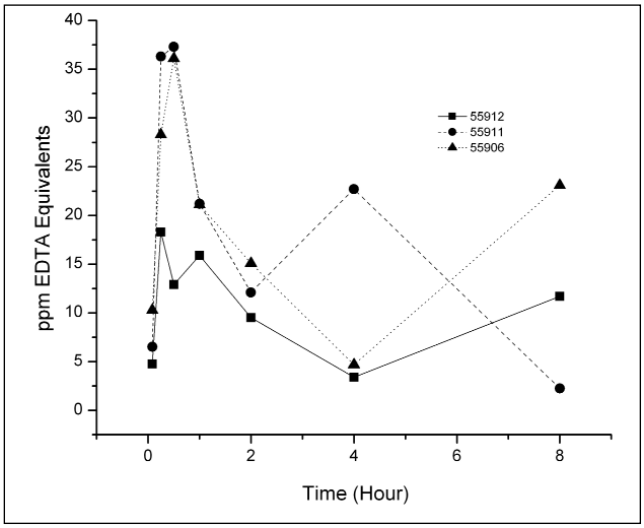


Table 1. Body Weights and Administered ^{14}C-EDTA Doses

Group	Animal Number	Body Weight (kg)	Dosage Weight (g)	Dose (mg/kg)	Total Dose (µCi)	Total Dose (dpm)
A	55921	0.187	1.0019	1.31	7.64	16,954,958
A	55920	0.184	0.9906	1.31	7.55	16,763,730
	Mean:	0.186		1.31	7.59	16,859,344
	± SD:	0.002		0.00	0.06	135,218
B	55918	0.166	0.9899	1.45	7.55	16,751,884
B	55915	0.175	0.9776	1.36	7.45	16,543,734
B	55917	0.177	0.9718	1.34	7.41	16,445,582
B	55914	0.183	0.9804	1.31	7.47	16,591,118
	Mean:	0.175		1.37	7.47	16,583,079
	± SD:	0.007		0.06	0.06	127,819
C	55912	0.167	0.1100	214.4	24.6	54,534,057
C	55911	0.157	0.0970	201.1	21.7	48,089,123
C	55906	0.162	0.1120	225.0	25.0	55,525,585
	Mean:	0.162		213.5	23.7	52,716,255
	± SD:	0.005		12.0	1.8	4,037,765

Table 2. Mean AUC, half-life, C_{max}, T_{max}, and bioavailability of EDTA in blood following intravenous or rectal administration of ^{14}C-EDTA

Group	Route	Stat.	Dose (mg/kg)	AUC (µg x Hr/mL)	AUC Inf (µg x Hr/mL)	Half-life (Hour)	Cmax (µg/mL)	Tmax (Hour)	Absolute Bioavailability (%)
B	Intravenous	MEAN	1.37	1.86	1.91	1.50	2.07	0.083	N/A
		SD	0.06	0.20	0.19	0.34	0.35	0.000	
		N	4	4	4	4	4	4	
C	Rectal	MEAN	213.5	105.8	307.3	N/A[1]	30.6	0.417	36.3
		SD	12.0	32.2	225.6	N/A[1]	10.6	0.144	
		N	3	3	3	3	3	3	

N/A = not applicable

Absolute bioavailability (%) = $\dfrac{(AUC_{test} \times Dose_{ref})}{(AUC_{ref} \times Dose_{test})} \times 100$

Where "test" data is the rectal data, and "ref" (reference) data is the intravenous data.

1. The terminal elimination phase was not observed, therefore, the half-life could not be calculated.

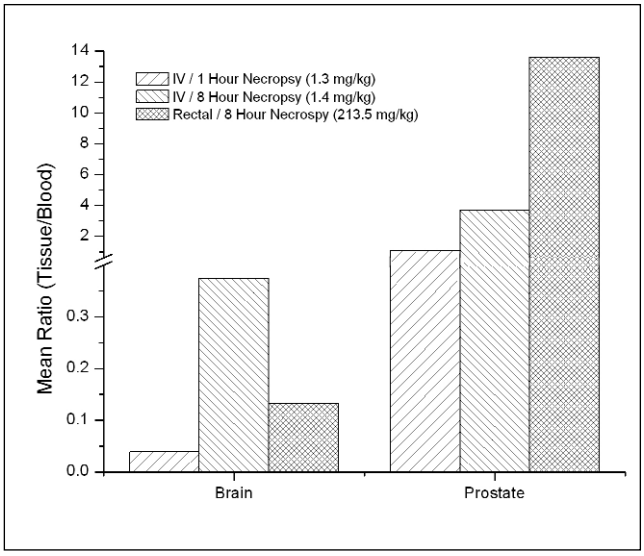
References for the above formula are as follows:

1) Kwon Y. *Handbook of Essential Pharmacokinetics, Pharmacodynamics, and Drug Metabolism for Industrial Scientists*. New York: Kluwer Academic/Plenum Publishers, 2001.

2) Shargel L, Yu A. *Applied Biopharmaceutics and Pharmacokinetics, 4th ed.* Norwalk, Connecticut: Appleton & Lange, 1999

presented in Table 4 and Figure 3. The prostate retained higher levels of radioactivity than the brain following both intravenous and rectal dosing, with the highest level of radioactivity found in the prostate following rectal dosing. The total recovery of radioactivity from urine and tis- sues expressed as percent of dose is presented in Tables 5 and 6. Total recovery represents the combined total percent of dose in urine and tissues. Following intravenous dosing, 41.4% and 47.3% of the radioactive dose was recovered 1 hour and 8 hours after dosing, respectively; of which virtually all was in urine. Following rectal dosing, 30.3% of the radioactive dose was recovered 8 hours after dosing, of which virtually all was also in urine.

Figure 3. Ratio of tissue and blood radioactive residues (ppm) following intravenous or rectal administration of ^{14}C-EDTA.



DISCUSSION

This study has shown that the proprietary formula of Ca Na_2 EDTA has been effectively absorbed from the lower enteral route in rats, through the anal portal into the rectum or lower intestine to reach blood and tissue levels via rectal sup-

Table 3. ^{14}C-EDTA-derived radioactivity excreted in urine expressed as percent of administered dose following intravenous or rectal administration of ^{14}C-EDTA

Group A: IV (1 hour) Time Interval (Hour)	Animal No. 55921		Animal No. 55920		% Dose		Cum. % Dose	
	% Dose	Cum. % Dose	% Dose	Cum. % Dose	Mean Values	± S.D.	Mean Values	± S.D.
0-1	38.1	38.1	44.7	44.7	41.4	4.7	41.4	4.67
Total	38.1		44.7				41.4	4.67

Group B: IV (8 Hour) Time Interval (Hour)	Animal No. 55918		Animal No. 55915		Animal No. 55917		Animal No. 55914		% Dose		Cum. % Dose	
	% Dose	Cum. % Dose	% Dose	Cum. % Dose	% Dose	Cum. % Dose	% Dose	Cum. % Dose	Mean Values	± S.D.	Mean Values	± S.D.
0 - 4	58.5	58.5	53.4	53.4	38.2	38.2	35.2	35.2	46.3	11.4	46.3	11.4
4 - 8	1.20	59.7	0.78	54.1	0.97	39.2	0.79	36.0	0.935	0.197	47.3	11.5
Total	59.7		54.1		39.2		36.0				47.3	11.5

Group C: Rectal (8 Hour) Time Interval (Hour)	Animal No. 55912		Animal No. 55911		Animal No. 55906		% Dose		Cum. % Dose	
	% Dose	Cum. % Dose	% Dose	Cum. % Dose	% Dose	Cum. % Dose	Mean Values	± S.D.	Mean Values	± S.D.
0 - 4	20.0	20.0	16.7	16.7	10.8	10.8	15.8	4.67	15.8	4.67
4 - 8	2.53	22.5	19.7	36.4	21.1	31.9	14.4	10.3	30.3	7.08
Total	22.5		36.4		31.9				30.3	7.08

positories. Bioavailability has now been established for this mode of administration in an animal model and is strong evidence that EDTA suppositories are an adequate and medically acceptable approach to providing the benefits of chelation.

Intravenous dosing resulted in greater elimination of radioactivity in urine at the 0 to 4 hour time point, but the percent of dose recovered drastically decreased by the 4 to 8 hour time point, while the level of recovery was relatively steady at both time points following rectal dosing. The slow and consistent movement of $CaNa_2$ EDTA via rectal administration may have lesser toxicity since there are significant blood and tissue levels to chelate metals without a high dose EDTA IV drip over many hours. These data point to the ability of rectal suppositories to deliver a continuous lower dose concentration of EDTA for longer periods of time compared with IV administration, allowing EDTA to bind metals efficiently and effectively.

In tissues, significant amounts of radioactivity were recovered from the prostate following intravenous or rectal dosing, with the highest level of dosed radioactivity (179.6 ppm) recovered 8 hours following rectal dosing. This observation of rectal administration, revealing higher amounts of EDTA in prostate tissue as compared to IV, can have far-reaching implications of a more complete distribution of EDTA into interstitial and intracellular spaces, further leading to more efficient chelation of compartmentalized heavy metal content with $CaNa_2$ suppositories.

EDTA is not bio-transformed in the body. It is excreted in hair, urine, feces, saliva, and perspiration. This study shows that animals excreted 47.3% and 30.3% of dosed radioactivity in urine during the 8 hours following intravenous and rectal dosing, respectively. The 30.3% excretion of EDTA in the urine corresponds closely to the rectal dose bioavailability calculated from the blood levels (36.3%).

Blood samples were taken over an 8-hour period, and during this time, the rectal administration showed high levels of absorbed ETDA with no apparent elimination phase observed. If further blood samples had been taken, the bioavailability calculated for rectally administered EDTA would have undoubtedly been much higher, since the bioavailability calculation presented here only used up to 8-hour blood level data. No extrapolation of the AUC could be done since the levels at 8 hours were actually increasing in two out of three animals. Further research is indicated over a longer time span to quantify the actual half life of the suppository form of administration.

CONCLUSIONS

This proprietary suppository formulation appears to be a viable dosing mechanism for delivery of $CaNa_2$ EDTA to the bloodstream in this rat model, showing substantial circulating levels of EDTA for least 8 hours after administra-

Table 4. Ratio of radioactive residues of EDTA in tissues (µg/g) to blood (µg/g) following intravenous or rectal administration of ^{14}C-EDTA

Group A: IV (1 Hour)	Ratio of Radioactive Residues of EDTA			
Sample	Animal No: 55921	Animal No: 55920	Mean Values	± SD
Brain	0.039	0.039	0.039	0.000
Prostate	1.80	0.357	1.08	1.02

Group B: IV (8 Hour)	Ratio of Radioactive Residues of EDTA					
Sample	Animal No: 55918	Animal No: 55917	Animal No: 55915	Animal No: 55914	Mean Values	± SD
Brain	0.345	0.318	0.487	0.351	0.375	0.076
Prostate	6.70	2.01	3.07	2.98	3.69	2.06

Group C: Rectal (8 Hour)	Ratio of Radioactive Residues of EDTA				
Sample	Animal No: 55912	Animal No: 55911	Animal No: 55906	Mean Values	± SD
Brain	0.050	0.288	0.056	0.132	0.135
Prostate	8.90	14.4	17.4	13.6	4.31
Note: Brain was perfused with normal saline prior to collection.					

Table 5. Total recovery of radioactivity expressed as percent of administered dose following intravenous or rectal administration of ^{14}C-EDTA.

Group	Animal No.	% Administered Dose		
		Urine	Tissue	Total
A	55921	38.1	0.05	38.2
	55920	44.7	0.02	44.7
	Mean:	41.4	0.04	41.4
	± SD:	4.67	0.02	4.65
B	55918	59.7	0.02	59.8
	55915	54.1	0.01	54.2
	55917	39.2	0.01	39.2
	55914	36.0	0.02	36.0
	Mean:	47.3	0.02	47.3
	± SD:	11.5	0.01	11.5
C	55912	22.5	0.01	22.5
	55911	36.4	0.01	36.4
	55906	31.9	0.10	32.0
	Mean:	30.3	0.04	30.3
	± SD:	7.08	0.05	7.09

Table 6. Total recovery of radioactivity expressed as percent of administered dose following intravenous or rectal administration of ^{14}C- EDTA.

	% Administered Dose		
Sample	Group A	Group B	Group C
Urine	41.4	47.3	30.3
Tissue	0.04	0.02	0.04
Total	41.4	47.3	30.3

tion. EDTA appears to be favorably distributed to the prostate, but not the brain, following both IV and rectal dosing. The excretion of rectal $CaNa_2$ EDTA administration in urine corresponds well with the rectal dose bioavailability of blood levels. The absolute bioavailability of EDTA in blood following rectal dosing was 36.3% within the 8-hour period. Additional testing is required to confirm and duplicate these results in humans.

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The other authors at The Biological Test Center are independent contract researchers paid for their research services by World Health Products.

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Draft Submittal for Publication in the World Journal of Urology

Anti-Microbial plus $CaNa_2EDTA$ Chelation Suppository Therapy for Chronic Prostatitis/Pelvic Pain Syndrome with or without Prostatic Hyperplasia: Preliminary Study

Rita Ellithorpe[1], MD, Larry Clapp[2], JD, Tony Jimenez[3], MD, Brett Jacques[4], ND, Robert Settineri[5], MS, PhD, and Garth L. Nicolson[6], PhD

Tustin Longevity Center, Tustin, CA, [2]Prostate Health Resources, Santa Monica, CA, [3]Hope 4 Cancer Institute, Baja California, Mexico, [4]Tustin Longevity Center, Tustin, CA, [5]Sierra Research, Irvine, CA, and [6]Institute for Molecular Medicine, Laguna Beach, CA

Abstract

Patients with chronic prostatitis/pelvic pain syndrome are characterized by treatment failures, a high incidence of prostate calcium deposits and poor quality of life. We used proprietary suppositories containing calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$) to remove metal and calcium cations. Participants (N=31) with chronic prostatitis, with or without prostate hyperplasia, and prostate calculi (mean age=61) were treated with tetracycline (500 mg/day) and $CaNa_2EDTA$ suppositories (750 mg 4X/week) for 90 days. Using the NIH Chronic Prostatitis Symptom Index significant post-treatment mean reductions in symptoms ($p<0.0106$) and pain ($p<0.0122$) were found along with a significant improvement in mean quality of life ($p<0.0022$). Overall, the mean total scores showed significant post-treatment reduction ($p<0.0006$). In addition, use of the International Prostate Symptom Score indicated significant reductions in 5/7 symptom categories and significant reduction of mean overall scores ($p<0.0001$). Analysis of blood and stool post-treatment indicated significant changes in mobilized, secreted cations (cadmium, copper, boron, lead, molybdenum, magnesium and calcium). In addition, the blood cholesterol/high density lipoprotein ratio was significantly decreased ($p<0.0005$). However, using the Erectile Function Index Questionnaire there was significant mean improvement in only 7/15 questions, resulting in non-significant overall mean improvement, and there were non-significant reductions in prostate calcifications at this suppository dose level. The data suggest that combining $CaNa_2EDTA$ suppositories with tetracycline can significantly reduce symptoms and pain in refractory chronic prostatitis with or without prostate hyperplasia.

Keywords: Prostatitis symptoms, antibiotic, EDTA suppository, bacterial biofilm, prostate calcifications

Corresponding Author: Prof. Garth Nicolson, Dept. of Molecular Pathology, The Institute for Molecular Medicine, P.O. Box 9355, Laguna Beach, CA 92652; Email: gnicolson@immed.org

Introduction

Prostatitis is a common urological condition, and it has been estimated that up to one-half of men will suffer from symptoms of this disease at some time during their lives [1]. At any one time 2-10% of men suffer from prostatitis [2]. Prostatitis is classified within a complex series of syndromes (NIH category I-IV prostatitis) that vary widely in clinical presentation and response to treatment. Acute bacterial prostatitis (category I) and chronic bacterial prostatitis (category II) are characterized by uropathogenic infections of the prostate gland that respond well to antimicrobial treatment, whereas chronic prostatitis/chronic pelvic pain syndrome (category III, accounting for 90%-95% of prostatitis cases) is marked by a mixture of pain, urinary and ejaculatory symptoms and presence of prostate calculi with no uniformly effective therapy [3].

Several different classes of bacterial infections have been found in acute and chronic prostatitis, including Gram-positive and –negative bacteria [1, 2, 4, 5], cell wall-deficient forms (Mycoplasma, Ureaplasma, Chlamydia) [4, 6, 7] and biofilm-forming bacteria [8-10]. The latter forms are likely to be important in chronic prostatitis and have proven to be particularly difficult to effectively treat [10, 11]. Biofilms contain bacterial glycosaminoglycans, salts (especially calcium and other cations) and other molecules [12, 13]. According to Parsek and Singh [14] biofilms support bacterial: (a) adhesion, (b) clustering, (c) localized infection, and (d) increased resistance to antibiotic treatment in the host. They do this by providing a protective structure for bacterial colonies so that they can evade mechanical stresses, host responses and antimicrobial agents.

Calcium and other cations are thought to play a structural role in biofilms as well as in cellular and tissue deposits, such as calculi, a calcium apatite-containing mineral deposit that is often associated with category III chronic prostatitis/chronic pelvic pain syndrome [15]. In some studies the presence of calculi is a feature that is associated with antimicrobial resistance and treatment failure [16, 17]. Although the presence of calculi in chronic prostatitis/chronic pelvic pain syndrome and its association with disease symptoms are controversial [17], Geramoutsos et al. [18] found that larger deposits of calculi were associated with chronic prostatitis symptoms.

Patients with NIH Category III chronic prostatitis/chronic pelvic pain syndrome have a high incidence of calculi, antibiotic treatment failures and poor quality of life [16, 17]. They also show evidence of biofilm-forming bacterial infections [17]. Therefore, Shoskes et al. [17] initiated a preliminary complex treatment study with 16 patients using an antibiotic (500 mg tetracycline per day) plus a calcium chelator (1500 mg ethylenediaminetetraacetic acid, EDTA) and a proprietary vitamin-mineral nutraceutical and found significant decreases in the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) in most patients and decreases in prostatic calcium-containing stones (calculi) in one-half of the patients examined.

Toxic heavy metals, such as mercury, lead, cadmium, nickel and others [19,20], can also be chelated with EDTA, and in some cases these heavy metals are carcinogenic to prostate tissue [21, 22]. Their removal from prostate tissue along with excess calcium can be accomplished with long-term EDTA administration. Thus we initiated a study based on the work of Shoskes et al. [17] to test the hypothesis that combinations of oral tetracycline and a patented, proprietary suppository (Detoxamin®) containing $CaNa_2EDTA$ that is known to produce a long tissue half-life of EDTA in rats [23] would decrease chronic prostatitis symptoms along with cation deposits and increase quality of life.

Patients and methods

Patients

Criteria for inclusion in the study included: men aged 40 years or older (N=31, mean age= 61, range 41-73) with a diagnosis of chronic prostatitis and the presence of prostate calcifications on ultrasound, absence of painful pelvic side wall spasm on rectal palpation, and the absence of allergy to tetracycline. Exclusionary criteria included: chronic debilitating condition other than prostatitis, such as chronic inflammatory or irritable bowel disease, chronic diarrhea or constipation, tetracycline allergy, cognitive decline (unable to comprehend instructions and answer questions), renal or hepatic dysfunction, inability to tolerate anal suppositories and absence of prostate calcifications. Of the participants, all but 7 showed evidence of prostate hyperplasia, varying from mild (48%) to moderate or severe (29%) as assessed by prostate sonogram. Participants were entered into an open label treatment trial where laboratory and clinical data were collected before and after treatment. Prior to entry all patients had a complete medical history and urological examination.

Laboratory/Clinical Tests

The following laboratory/clinical tests were performed pre- and post-treatment: non-fasting comprehensive blood chemistry and lipid panel (Southern California Reference Laboratory), Tustin, CA), blood analysis for heavy metals and essential minerals, fecal metals analysis (Doctors Data, Inc., St. Charles, IL), digital rectal exam and prostate sonogram using a Fukuda Denshi Model FF sonic UF-750XT Power Color Doppler (PCD) with 3D imaging capability. Analysis of elements was performed by ICP-Mass Spectroscopy following digestion of the specimen in a closed microwave system. For a given mineral element, these procedures measure the sum of the amounts of surface-adhering and intracellular content, regardless of chemical form. Participants also took the NIH-CPSI [24], International Prostate Symptom Score (IPSS) [25] and Erectile Function Index (EFI) [26] surveys.

Study Design

The study received Institutional Review Board (IRB) approval, and before admission each patient signed an informed consent document. Participants in the study were examined and tested (as above) before and after three months administration of tetracycline (HPN Pharmaceuticals, Torrance, CA; 500 mg PO daily) and use of Detoxamin® (World Health Products, Draper, Utah) time-release suppositories (4-times per week) each containing 750 mg disodium calcium EDTA ($CaNa_2EDTA$). Each day during the trial participants took two tabs of a multi-vitamin, mineral and trace mineral supplement (Health Genesis, World Health Products) to replace essential minerals and one capsule of a probiotic mixture in an oil matrix capsule (stored refrigerated; Healthy Trinity, Natren, Westlake Village, CA) to replace depleted gut flora [27,28]. At the end of therapy laboratory and clinical tests and clinical surveys were completed as described above and compared to pre-treatment tests and surveys.

Statistical analyses

Post-pre measurements were analyzed by paired t-test comparisons with Bonferroni corrections. Reliability was evaluated by Cronbach's alpha coefficient. In some cases parametric statistical results were checked by nonparametric Wilcoxon tests.

Results

Blood and fecal elements

A panel of mineral element tests were performed on packed red blood cells pre/post treatment and compared among participants. Post-treatment analyses indicated that were significant increases in mean red blood cell copper, boron, molybdenum and magnesium levels and a borderline significant increase in calcium and decreases in arsenic, cadmium and lead, suggesting that the $CaNa_2EDTA$ was mobilizing some tissue elements during the trial (Table 1). Analysis of fecal metals indicated that mean copper, tungsten and to a lesser degree beryllium levels were significantly increased post-treatment, whereas cadmium was significantly decreased (Table 2).

Blood Serum Chemistries

The non-fasting comprehensive blood chemistry panel showed the cholesterol/HDL ratio was significantly decreased ($p<0.0005$) post-treatment, but no significant changes in creatinine, BUN/creatinine ratio or calcium levels were observed (Table 3).

Chronic prostatitis symptom index (NIH-CPSI)

Examination of the NIH-CPSI domains indicated that there were significant decreases in mean Urinary Symptom Score, mean Pain Symptom Score and mean Quality of Life Score post-treatment (Table 4). The mean Urinary Symptom Score post-treatment decreased from a pre-treatment mean of 3.709±2.08 to a mean of 2.84±2.25, a mean decrease of 0.87±1.99 post-treatment ($p<0.0106$), whereas the pain symptom mean score decreased from 4.35±4.54 to 3.10±3.67, a mean decrease of 1.25±2.95 ($p<0.0122$). The mean quality of life index score decreased from 4.68±2.81 to a mean of 3.45±2.53, a mean decrease of 1.23±2.22 post-treatment ($p<0.0022$). Overall the NIH-CPSI mean total scores decreased from 12.74±8.31 to 9.39±6.16, a mean decrease of 3.35±0.93 ($p<0.0006$).

International prostate symptom score (IPSS)

Using the International Prostate Symptom Score (IPSS) survey form indicated significant reductions in 5 out of 7 categories and significant reduction of overall symptoms post-compared to pre-treatment (Table 5). Significant reductions were found in incomplete

emptying of bladder ($p<0.0082$), frequency of urination ($P<0.0044$), urgency of urination ($p<0.00001$), and intermittency of urination ($P<0.0741$), weak stream ($p<0.0003$), quality of life score ($p<0.0191$) and overall score ($p<0.0001$) (Table 5). Non-significant reductions were found in urination straining and nocturia (Table 5).

Erectile function index (EFI)

Using the EFI survey scores on 7 of 15 questions showed positive changes, indicating improvement in self-evaluated conditions, whereas 8 of 15 showed negative changes (Table 6). Thus overall there was not a significant overall change in EFI scores. The lack of significant improvement was confirmed by use of nonparametric Wilcoxon tests.

PCD sonography

Transrectal Power Color Doppler (PCD) sonography showed that there were no significant decreases in prostatic calcifications at the treatment levels used in this study (data not shown).

Discussion

Similar to Shoskes et al. [17] we found that patients with NIH Category III chronic prostatitis could be successfully treated in an open label trial with tetracycline (500 mg/day) and Detoxamin® suppositories containing 750 mg of $CaNa_2EDTA$ used 4-times per week for 90 days. In the present study the dose of $CaNa_2EDTA$ was half of the amount used by Shoskes et al. [17]. Using the NIH-CPSI and IPSS survey forms significant post-treatment reductions in mean index of prostatitis symptoms and pain were found along with significant improvements in mean quality of life and mean overall scores. The IPSS is also used as a validated instrument for benign prostatic hyperplasia [29], suggesting the positive influence of symptom reduction for this condition as well as prostatitis. Approximately 77% of the patients in our study had benign prostatic hyperplasia or cancerous prostate lesions.

We did not see a significant increase in mean overall Erectile Function Index post-treatment; however, in 7 of 15 questions there were significant improvements. Since this patient group is generally unresponsive to multiple courses of antibiotics alone and other therapies, we agree with Shoskes et al. [17] that this approach represents a significant improvement in therapy of Category III chronic prostatitis. As in Shoskes et al. [17], this open label study is

limited in terms of the number of patients entered and lack of blinded control arms, and thus no conclusions can be drawn as to mechanism of action and durability of the effect.

In our study, Detoxamin® $CaNa_2EDTA$ suppositories were used to loosen and remove calcium and heavy metals from patients with established prostatic calcifications and chronic prostatitis while on tetracycline. That some metals and calcium were being mobilized by the $CaNa_2EDTA$ suppositories was shown in blood and fecal tests. In particular, the mean levels of copper, boron, molybdenum, magnesium and calcium were significantly increased in packed red blood cells as well as significant decreases in arsenic, cadmium and lead in fecal matter in the post-treatment tests, suggesting that tissue stores of these elements were being affected. The presence of heavy metals and cations like calcium varies widely in different patients, and we found differences among patients in the amounts of these elements present in blood and stool when $CaNa_2EDTA$ suppositories were used. Since approximately 77% of the patients in our study had a diagnosis of benign or cancerous prostate lesions, the removal of potentially carcinogenic heavy metals was a desirable effect of the therapy. Certain heavy metals, such as arsenic, cadmium, chromium and lead, among others, are known have carcinogenic potential, and their long-term exposure is associated with an increased incidence of prostate and other cancers [30,31]. However, the potential role of heavy metals in the pathogenesis and progression of already established cancers and in affecting the symptoms of chronic prostatitis remain uncertain.

We previously studied the pharmacokinetics and tissue concentrations (bioavailability) of Detoxamin® $CaNa_2EDTA$ and compared it to IV administration of $CaNa_2EDTA$ [23]. We found that there were substantially higher tissue-to-blood concentration ratios of EDTA via the suppository route compared to IV administration. Prostate tissues were found to have 8 hr mean tissue-to-blood ratios of 13.6 (rectal suppository) and 3.69 (IV), respectively [23]. This finding supports the mechanism of action of $CaNa_2EDTA$ chelation suppositories on the target tissue in question (prostate) and was an initial justification for this clinical trail.

Another aspect of the use of $CaNa_2EDTA$ suppositories is that bacterial biofilms contain high amounts of divalent cations like calcium that are important in maintaining their structures [32]. The presence of biofilm-producing bacteria has been associated with chronic prostatitis [14,17,32], and the use of calcium supplements is associated with increased risk of urinary

tract infections [33]. Calcium is also important in bacterial adhesion element in the urinary tract either as an adhesion promoting cation or inhibitor of secreted host glycoproteins that prevent bacterial adhesion to the urinary tract [34]. Thus removal of excess calcium ion and calcium complexed to extracellular bacterial proteoglycans and glycosylaminoglycans could be important in reducing bacterial adherence and chronic prostatitis symptoms.

There is a rather long history of the use of EDTA in clinical studies [35-39]. Animal experiments have shown that EDTA is extremely safe and relatively high doses are well tolerated without noticeable side effects [40,41]. However, in a few reports a few subjects receiving IV EDTA had reversible renal damage [42,43], and temporary numbness and tingling in IV administered EDTA are relatively common [44]. None of these adverse effects were found in the current study using Detoxamin® $CaNa_2EDTA$ suppositories. The Detoxamin® $CaNa_2EDTA$ suppositories were found to be well tolerated and safe. Interestingly, although not the focus of this study, we found that mean HDL and LDL lipid blood panel determinations showed significant improvements post-treatment. We and others [17] have concluded that the addition of EDTA suppositories to antibiotic therapy of chronic prostatitis significantly reduced symptoms and improved outcome.

Table 1. Red Blood Cell Elements Pre-Post Treatment Comparisons*

Element	Pre Treatment	SD	Post Treatment	SD	Mean Change	SD	Min	Max	Test Statistic	p > |t|	p > t	p < t
Lead	0.0286	0.0122	0.0214	0.0091	-0.0073	0.0056	-0.023	0.004	-7.23	0.0000	1.0000	0.0000
Copper	0.5667	0.0457	0.6035	0.0504	0.0358	0.0387	-0.05	0.1	5.15	0.0000	0.0000	1.0000
Boron	0.0534	0.0282	0.0676	0.0354	0.0142	0.0223	-0.03	0.064	3.56	0.0013	0.0006	0.9994
Molybdenum	0.0009	0.0002	0.0012	0.0003	0.0003	0.0004	-0.0007	0.0011	3.53	0.0014	0.0007	0.9993
Magnesium	43.9677	3.7281	45.7097	3.6805	1.7419	2.8162	-3	7	3.44	0.0017	0.0009	0.9991
Cadmium	0.0011	0.0002	0.0010	0.0001	-0.0001	0.0003	-0.001	0	-2.42	0.0217	0.9892	0.0108
Arsenic	0.0051	0.0041	0.0044	0.0029	-0.0007	0.0019	-0.006	0.003	-2.12	0.0425	0.9787	0.0213
Zinc	11.6903	0.8931	11.4742	0.9518	-0.2161	0.5734	-1.6	1.2	-2.10	0.0444	0.9778	0.0222
Calcium	12.2258	1.9615	13.1613	1.6752	0.9355	2.5682	-7	6	2.03	0.0515	0.0258	0.9742
Potassium†	78.3871	2.5518	79.1290	2.7418	0.7419	2.6073	-4	5	1.58	0.1236	0.0618	0.9382
Mercury	0.0051	0.0052	0.0043	0.0040	-0.0007	0.0027	-0.009	0.005	-1.53	0.1358	0.9321	0.0679
Iron	934.838	38.827	943.483	32.289	8.6452	32.701	-58	67	1.47	0.1515	0.0757	0.9243
Manganese	0.0152	0.0049	0.0148	0.0044	-0.0003	0.0019	-0.006	0.002	-0.96	0.3442	0.8279	0.1721
Vanadium	0.0002	0.0000	0.0002	0.0001	0.0000	0.0001	-0.0002	0.0003	0.57	0.5722	0.2861	0.7139
Selenium	0.3632	0.2145	0.3571	0.1650	-0.0061	0.0838	-0.34	0.09	-0.41	0.6868	0.6566	0.3434
Phosphorus	567.903	31.442	569.096	23.873	1.1935	22.983	-48	61	0.29	0.7745	0.3872	0.6128
Chromium	0.0008	0.0004	0.0008	0.0007	0.0000	0.0008	-0.0017	0.0035	0.24	0.8107	0.4053	0.5947
Thallium	0.0001	0.0000	0.0001	0.0000	0.0000	0.0000	0	0	1.00	1.0000	1.0000	1.0000

*Results reported as mg/g or ppm
†Results reported as mEq/g

Table 2. Fecal Elements Pre-Post Treatment Comparisons*												
Element	Pre Treatment	SD	Post Treatment	SD	Mean Change	SD	Min	Max	Test Statistic	p > |t|	p > t	p < t
Copper	43.710	14.272	59.000	17.920	15.290	20.980	-25	67	4.06	0.0003	0.0002	0.9998
Cadmium	0.557	0.354	0.371	0.179	-0.186	0.301	-1.03	0.19	-3.45	0.0017	0.9992	0.0008
Tungston	0.093	0.060	0.151	0.092	0.058	0.109	-0.261	0.228	2.99	0.0055	0.0028	0.9972
Beryllium	0.006	0.005	0.008	0.007	0.003	0.008	-0.022	0.025	1.82	0.0791	0.0395	0.9605
Antimony	0.062	0.037	0.047	0.033	-0.015	0.048	-0.112	0.104	-1.72	0.0956	0.9522	0.0478
Nickel	5.771	2.774	6.803	2.803	1.032	3.554	-6.9	10.1	1.62	0.1164	0.0582	0.9418
Thallium	0.018	0.014	0.015	0.005	-0.003	0.011	-0.049	0.013	-1.61	0.1189	0.9405	0.0595
Arsenic	0.219	0.139	0.189	0.104	-0.030	0.105	-0.41	0.11	-1.59	0.1234	0.9383	0.0617
Bismuth	0.070	0.197	0.207	0.676	0.137	0.708	-0.988	3.537	1.08	0.2900	0.1450	0.8550
Platinum	0.001	0.001	0.032	0.167	0.031	0.167	0	0.93	1.03	0.3092	0.1546	0.8454
Mercury	0.180	0.288	0.210	0.377	0.031	0.167	-0.3	0.796	1.02	0.3167	0.1583	0.8417
Lead	0.247	0.145	0.270	0.136	0.023	0.170	-0.54	0.41	0.75	0.4586	0.2293	0.7707
Uranium	0.115	0.091	0.110	0.101	-0.005	0.102	-0.204	0.372	-0.27	0.7861	0.6069	0.3931

*Results reported as mg/Kg dry weight of feces

Table 3. Comprehensive Blood Chemistry Panels Pre-Post Treatment Comparisons								
Parameter	Mean Change	SD	Min	Max	Test Statistic	p > |t|	p > t	p < t
SCRL SGOT	4.226	4.287	-8	13	5.49	0.0000	0.0000	1.0000
SCRL HDL CHOL	5.903	6.764	-3	20	4.86	0.0000	0.0000	1.0000
SCRL SGPT	3.097	4.077	-10	10	4.23	0.0002	0.0001	0.9999
SCRL URIC ACID	-0.477	0.644	-1.9	1.4	-4.13	0.0003	0.9999	0.0001
SCRL CO2	1.645	2.259	-3	6	4.05	0.0003	0.0002	0.9998
SCRL CHOL/HDL	-0.455	0.653	-3.1	0.9	-3.88	0.0005	0.9997	0.0003
SCRL BILIRUBIN	0.129	0.218	-0.2	0.7	3.30	0.0025	0.0013	0.9987
SCRL POTASSIUM	-0.410	0.734	-1.6	1.3	-3.11	0.0041	0.9979	0.0021
SCRL LDL CHOL	-14.290	26.768	-78	56	-2.97	0.0058	0.9971	0.0029
SCRL CHLORIDE	-1.290	2.636	-7	3	-2.73	0.0106	0.9947	0.0053
SCRL ALK PHOSPHATE	4.032	9.318	-16	32	2.41	0.0223	0.0112	0.9888
SCRL A/G RATIO	-0.058	0.139	-0.3	0.2	-2.33	0.0265	0.9868	0.0132
SCRL SODIUM	-1.065	2.756	-7	5	-2.15	0.0397	0.9802	0.0198
SCRL GLOBULIN	0.081	0.227	-0.5	0.5	1.98	0.0574	0.0287	0.9713
SCRL LPPLA2	-10.774	30.737	-71	60	-1.95	0.0604	0.9698	0.0302
SCRL CREATININE	0.029	0.086	-0.1	0.2	1.87	0.0711	0.0355	0.9645
SCRL PSA TOTAL	7.079	21.103	-4.34	107.22	1.87	0.0716	0.0358	0.9642
SCRL BUN/CREAT RATIO	0.855	3.870	-5.6	13.3	1.81	0.0803	0.0402	0.9598
SCRL GLUCOSE	8.000	24.596	-25	64	1.78	0.0853	0.0427	0.9573
SCRL CHOL	-8.097	32.232	-99	65	-1.40	0.1722	0.9139	0.0861
SCRL GGPT	0.581	2.391	-4	9	1.35	0.1865	0.0932	0.9068
SCRL BUN	1.355	4.168	-6	16	1.23	0.2283	0.1141	0.8859
SCRL HS CRP	-1.074	5.007	-27.7	0.7	-1.19	0.2416	0.8792	0.1208
SCRL CALCIUM	0.065	0.316	-0.6	1	1.14	0.2643	0.1321	0.8679
SCRL VIT D 25	-2.226	15.836	-31	52	-0.78	0.4400	0.7800	0.2200
SCRL TOTAL PROTEIN	-0.161	1.310	-7	0.7	-0.69	0.4982	0.7509	0.2491
SCRL SCORE ALBUMIN	-0.016	0.163	-0.3	0.4	-0.55	0.5869	0.7066	0.2934
SCRL VLDL CHOL	1.258	14.799	-32	53	0.47	0.6394	0.3197	0.6803
SCRL TRIGLYCERIDES	5.581	74.359	-163	269	0.42	0.6790	0.3395	0.6605

Table 4. NIH-CPSI (Chronic Pain Symptom Index) Scores Pre-Post Treatment Comparison

Parameter	Pre Treatment	SD	Post Treatment	SD	Mean Change	SD	Test Statistic	p > |t|	p > 1	p < 1
Urinary Symptom Score	3.7097	2.085	2.839	2.225	-0.871	1.9957	-2.43	0.0213	0.9894	0.0106
Pain Symptom Score	4.355	4.542	3.097	3.673	-1.258	2.9549	-2.37	0.0244	0.9878	0.0122
QOL Score	4.677	2.809	3.452	2.253	-1.226	2.2167	-3.08	0.0044	0.9978	0.0022
Total Score	12.742	8.306	9.387	6.157	-3.355	0.9312	-3.60	0.0011	0.9994	0.0006

Table 5. International Prostate Symptom Scores (IPSS)
Matched pair t-tests for each question, quality of life and total score

Parameter	Pre Mean	Post Mean	Mean Change	Test Statistic	p > |t|	p > t	p < t
Incomplete Emptying	1.677	0.968	-0.710	-2.832	0.0082	0.9959	0.0041
Frequency	2.581	1.839	-0.742	-3.081	0.0044	0.9978	0.0022
Intermittency	1.645	1.065	-0.581	-1.851	0.0741	0.9630	0.0370
Urgency	2.290	0.968	-1.323	-5.261	0.0000	1.0000	0.0000
Weak Stream	2.387	1.419	-0.968	-4.055	0.0003	0.9998	0.0002
Straining	0.774	0.516	-0.258	-1.092	0.2835	0.8582	0.1418
Nocturia	1.871	1.597	-0.274	-1.516	0.1400	0.9300	0.0700
QOL Score	2.774	2.129	-0.645	-2.477	0.0191	0.9904	0.0096
Total Score	13.226	8.371	-4.855	-4.526	0.0001	1.0000	0.0000

Table 6. Erectile Function Index (EFI) Scores Matched pair t-tests for each question and EFI total score							
Question	**Pre Mean**	**Post Mean**	**Mean Change**	**Test Statistic**	**p > |t|**	**p > t**	**p < t**
EF1	4.35	3.85	-0.50	-2.125	0.042	0.979	0.021
EF2	4.23	3.97	-0.26	-1.393	0.174	0.913	0.087
EF3	3.84	3.63	-0.21	-0.806	0.426	0.787	0.213
EF4	3.56	3.47	-0.10	-0.390	0.699	0.650	0.350
EF5	3.48	3.65	0.16	0.579	0.567	0.283	0.717
EF6	2.19	3.13	0.94	2.799	0.009	0.004	0.996
EF7	3.55	3.52	-0.03	-0.133	0.895	0.552	0.448
EF8	3.48	3.48	0.00	0.000	1.000	0.500	0.500
EF9	4.05	3.77	-0.27	-0.902	0.374	0.813	0.187
EF10	4.31	3.87	-0.44	-1.510	0.142	0.929	0.071
EF11	4.29	4.10	-0.19	-0.828	0.414	0.793	0.207
EF12	3.53	3.68	0.15	1.055	0.300	0.150	0.850
EF13	3.65	3.94	0.29	1.103	0.279	0.139	0.861
EF14	3.60	4.00	0.40	1.388	0.175	0.088	0.912
EF15	3.69	3.87	0.18	1.232	0.227	0.114	0.886
EF Total Score	55.69	55.79	0.10	0.037	0.971	0.485	0.515

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Effects of $CaNa_2$ EDTA (Detoxamin®) Suppositories on Excretion of Heavy Metals

Living Longer Institute, Cincinnati, Ohio

Pelletier, M., MD, CCN, FACOG, Lavalle, J., ND, RPh, CCN, Ellithorpe, R., MD*, Schmidt, M., PhD, CCN, Pelton, R., RPh, PhD, CCN, Settineri, R., MS

Abstract

A formidable amount of data exists that clearly indicate the insidious toxicity of non-physiological metals such as mercury, lead, nickel, cadmium, arsenic and aluminum where specific mechanisms for the neurotoxic, nephrotoxic and immune-dysregulatory effects of these metals are identified. A major portion of the population is at risk for chronic, low-level exposure to toxic heavy metals from environmental and occupational sources, as well as dental materials. This clinical interim clinical pilot trial has evaluated the safety and efficacy of a recently developed suppository delivery of $CaNa_2$ EDTA. Suppositories provide direct access to the systemic circulation, efficiently bypassing portal circulation and liver metabolism via the hemorrhoidal veins on the first pass. The study examined the ability of $CaNa_2$ EDTA suppositories to remove a variety of the most prevalent toxic heavy metals as determined by excretion in urine and feces. Twelve healthy adult subjects, ranging from 25 to 65 years of age, were administered $CaNa_2$ EDTA suppositories over a course of 90 days. Excretory specimens were evaluated on 0 (pre-treatment), 3 and 90 days post-treatment. An initial provocation with DMSA was given orally several days before the Day 0 samples were taken and again on Day 90 post-treatment. Results showed significant excretion ($P< 0.05$) with cumulative $CaNa_2$ EDTA therapy of Day 3 and Day 90 compared to Day 0 with arsenic, lead, cadmium and nickel in feces samples as well as significant excretions ($P< 0.05$) with arsenic, lead, mercury, cadmium and nickel in urine samples. There were no differences in the safety profile comparisons within comprehensive metabolic chemistry panels between pre- and post-treatment blood values. Only minor transient complaints of loose stools and gas were reported in several subjects. Calcium disodium EDTA suppositories appear to be a safe and effective means to slowly and consistently remove a variety of toxic heavy metals as evidenced by urine and fecal analysis. There is increased need and demand for more consumer friendly, less invasive, less time-consuming broad specificity metal chelation protocols consistent with the time constraints and health goals of many members of our society today.

*** Presenter**

Introduction

A plethora of published biomedical studies clearly indicate the insidious toxicity of non-physiological metals such as mercury, lead, cadmium and aluminum, and the specific mechanisms for the neurotoxic, nephrotoxic and immune-dysregulary effects of the metals have been well elucidated. To date, DMPS (iv and po) DMSA (po) and slow-drip Na_2-EDTA have been appropriately evaluated for efficacy in both acute and chronic metal toxicity. The USEPA, FDA, CDC and State Health departments recognize the growing global problem of chronic low level exposure to toxic metals; however the prevailing criteria for initiation of treatment fall short of the more rigorous standards of those who practice preventative/comprehensive medicine versus crisis management. Na_2-EDTA is FDA approved for lead detoxification (also chelates other metals), but the most common method of administration (slow drip intravenous method) is very expensive, invasive and far too time-consuming for most adults in our fast-paced society.

Adults are at risk for chronic, low-level exposure to toxic metals from environmental and occupational sources, as well as dental materials. Furthermore, aging is associated with increased risk for chronic, low-level *re-exposure* to lead because the vast majority of lead is sequestered in bone and dissolution of the bone matrix is a common problem with aging. Lead, released from the bone, where it is relatively inert, has a far greater adverse effects when it is subsequently taken up by extremely vulnerable cells in the central and peripheral nervous system, heart and kidneys. The bottom line: there is increased need and demand for more consumer friendly, less invasive, less time-consuming broad specificity metal chelation protocols that are consistent with the time constraints and health goals of many members of our society today.

Detoxamin $CaNa_2$-EDTA Suppositories provide a safe and effective alternative to the expensive and invasive traditional slow drip EDTA protocol for metal detoxification. The fact that $CaNa_2$-EDTA administered rectally might be an effective means for Hg detoxification is in sharp contrast to the relative inefficiency of traditional EDTA chelation, which is based upon *urinary excretion.*

Within the era of cost-containment and the risk of AIDS and other communicable blood-borne diseases, time constraints and affordability issues, suppository drug delivery is becoming a more viable option for doctors and patients. Suppositories provide direct access to the systemic circulation, efficiently bypassing the portal circulation and the liver metabolism on the first pass. It is a little known fact that the lower and middle hemorrhoidal veins bypass the liver and do not undergo first-pass metabolism. Therefore, suppositories can deliver the drug rapidly to the lower and middle hemorrhoidal veins for absorption. The rectum is an interesting area for drug absorption because it is not buffered and has a *neutral pH.* It also has very little enzymatic activity, thus enzymatic degradation does not occur. The rectal mucosa is more capable than the gastric mucosa of tolerating various drug-related irritations. This is especially important in patients with gastric disease. The anorectal physiology provides a

large surface area for drug absorption. Another factor that is important in drug delivery is drug solubility. The osmosis process allows the drug to transfer from the vehicle in the suppository, across the membrane of the rectum, and into the hemorrhoidal veins. As we become more aware of the potential complications of infection associated with the use of IVs, suppository administration provides a preferable alternative.

The body sequesters Hg in the liver by binding it to cholesterol and converting it into bile that then flows into the intestines. As bile is used to breakdown dietary lipids, some of the Hg becomes unbound in the intestinal tract. Detoxamin CaNa2-EDTA Suppositories deliver the chelation ability just where the maximum Hg excretion is taking place.

With traditional EDTA chelation, patients are limited to no more than two IV treatments a week because of the renal and hepatic toxicity of EDTA. Detoxamin $CaNa_2$-EDTA Suppositories provide a much slower administering rate, which allows:

- The EDTA has more opportunities to bind to heavy metals. Through galvanic series of metals & alloys, the EDTA has greater opportunities to bind with heavy metals closer to the cathodic end of the series.

- The maximum amount of recommended EDTA in one week to be spaced out into nightly treatment, *greatly enhancing the chelation efficacy of Detoxamin $CaNa_2$-EDTA.*

With traditional IV EDTA chelation, physicians and nursing staff need to be constantly vigilant for blood serum calcium deficiency.

- Traditional EDTA IV lowers ionized plasma calcium during infusion. The body attempts to maintain homeostasis by producing an increase in circulating parathormone. The intermittent infusion period increases of parathormone caused by traditional EDTA IV infusion and have a profound negative effect on bone metabolism.

- Hypocalcaemic tetany is an inherent risk of traditional EDTA IV chelation. Medical staff need to be ever vigilant for warning signs of neuromuscular irritability and fasciculation that requires the administration of intravenous calcium, such as calcium gluconate or similar products, to reverse the potentially life threatening symptoms of hypocalcaemia.

- *There have been no reported hypocalcaemia episodes with Detoxamin $CaNa_2$-EDTA*

Rectal administration of Detoxamin $CaNa_2$-EDTA suppositories has proven to be a safe and effective alternative to the traditional slow drip EDTA protocol, but currently there is no published data yet to address the efficacy of Hg chelation with Detoxamin $CaNa_2$-EDTA Suppositories.

Objectives

***Primary*:**

- To assess the effect of Detoxamin on mobilization of Pb, Hg, Cd, As, Fe, and other metals in humans as determined by blood, urine, feces, and hair.

***Secondary*:**

- To assess the safety of Detoxamin as measured by symptom inventory, serum chemistry, blood lipids, and selected inflammatory markers in humans.

- To determine whether Detoxamin therapy is associated with alteration in markers of oxidative stress.

- To assess the variability in urinary excretion of selected metals from baseline to 90-day endpoint, following DMPS IV push, in non-treated human controls.

Experimental Design

1) *Subjects.*

Healthy adult (25-65 y.o.) human subjects will be identified at the Living Longer Institute. Subjects will be excluded from the study if they (a) have undergone placement or removal of amalgams within the past 3 months, (b) have undergone chelation therapy, (c) are exposed through occupation or hobbies to Hg, Pb, Cd, As, or other toxic metals, (d) have been diagnosed with diabetes, cancer, renal disease/insufficiency, biliary obstruction or liver disease (eg. hepatitis), or any other significant medical condition, (e) do not have regular bowel habits, (f) have chronic inflammatory bowel disease, diarrhea or constipation, (g) are pregnant, lactating or use diuretics, (h) are allergic to EDTA. The numbers of small, medium and large mercury amalgams should be recorded for each subject upon initial evaluation and, if possible, the number of mercury-filled root canals.

2) Study Population

The study will be conducted in up to 50 adult male and female subjects in generally good health. A single clinical investigational center will participate.

Subjects will be non-randomly assigned to one of two groups as designated below:

A_0	n=10	Non-Treatment Control
A_1	n=40	Detoxamin Suppository

(2) *Crucial Dietary Restrictions*

After identifying subjects (n=50), informed consent forms will be signed and the subjects will adhere to the following dietary restrictions. The following are to be STRICTLY AVOIDED FOR AT LEAST 7 DAYS PRIOR TO THE BASELINE URINE AND FECAL SPECIMEN COLLECTIONS AND THROUGHOUT THE DURATION OF THE STUDY: any type of fish or seafood (including shellfish, seaweed), bentonite clay, Na-alginate, keratin, aluminum containing antacids, colonics, barium enemas, mineral or castor oil, colloidal minerals, activated charcoal, "chitosan-type" products, chlorella, cilantro, porphra-zyme or other chlorophyll-rich supplements/phytonutrients, products that contain EDTA or any other potential metal mobilization agent. Due to the potential lead contamination of some calcium supplements, Ca supplementation should be withheld unless absolutely necessary.

(3) *Experimental Protocol*

Before the administration of Detoxamin $CaNa_2$-EDTA Suppositories, and after 7 days of adherence to dietary restrictions, the subjects will collect a 24-hr. urine specimen, a bowel movement, blood sample, and hair sample. The urine and fecal and hair samples will serve as the baseline to unprovoked toxic metal data. After completing the tests described above, the Detoxamin $CaNa_2$-EDTA Suppositories will be administered. Continued adherence to dietary restrictions is imperative throughout the remainder of the sample collection period. Detoxamin $CaNa_2$-750mg EDTA Suppositories will be taken at night by each subject, prior to bedtime for 90 days (total 90 suppositories). Subjects should eat at least 3 hours prior to bedtime to prevent potential discomfort. Patients should be encouraged to consume 2-3 liters of purified water per day. Patients are also taking a multi-vitamin, mineral and trace mineral supplement (Health-Genesis) to replace the essentials that are removed during therapy.

(4) *Specimen Collections*
All specimens must be submitted to The Living Longer Institute in the provided containers, as they are ascertained to be trace element free.

Summary of testing / specimen requirements

Pre- Detoxamin $CaNa_2$-EDTA Suppositories

a) Hair Analysis
b) Comprehensive stool analysis with fecal metals analysis.
c) 24-hr urine collection for baseline urine elements
d) Blood sample

Post- Detoxamin $CaNa_2$-EDTA Suppositories

a) Hair Analysis
b) Comprehensive Stool Analysis with Fecal Metals analysis after the 3rd suppository, and one after the 90th suppository.

c) 24-hr urine collection (toxic & essential) after the 3rd suppository, and one after the 90th suppository.

d) Blood sample after the 90th suppository.

Hematology (whole blood)	**Chemistry (serum)**	**Pregnancy (urine)**
Hemoglobin Hematocrit Total diff. and leukocyte count Red blood cell count Platelet count Platelet aggregation	24 fasting sample Glucose Total protein Albumin Total bilirubin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase LDH Calcium Sodium Potassium BUN Uric acid Creatinine VAP Cholesterol test* (see below) Serum Iron Serum Ferritin Transferrin Saturation Total Iron Binding Capacity PTT (activated partial thromboplastin time) Thrombin time Prothrombin time Hfe Genotype**	Females

Schematic Outline of Study Procedures

Assessment Description	**Prescreening**	**Baseline**	**Follow-up Post-CaEDTA Provocation**	**Follow-up**	**Follow-up**
Study timepoint Clinic visit #	**Day -14 to -1 Telephone**	**Day 0 Visit 1**	**Day 3 Visit 2**	**Day 90 Visit 3**	**Day 100 Visit 4**
Informed consent	VERBAL	WRITTEN			
Review of entry criteria	X	X			
Medical history		X			
Dietary questionnaire	X				
Vital signs and weight		X		X	
BMI		X		X	
Diagnostic exam		X		X	
Oral DMSA screen for study inclusion/exclusion	X				
IV DMPS provocation w/12-hour urine		X			X
CBC with differential		X		X	
Clinical chemistry panel		X		X	
Phlebotomy for retained specimens		X		X	
Urine pregnancy test		X			X
Dispense study medication		X			
Administration of study medication		X		X	
Drug accountability		X		X	
Subject global assessment of disease (VAS)-Diary card	X				
Inv. global assessment of disease		X			
Mini mental status examination		X			
Hamilton Rating Scale for Depression		X			
Adverse events		X		X	X
Concomitant medications	X	X		X	X

Corporate Sponsorship

This trial was conducted by Living Longer Health in collaboration with World Health Products, LLC, for-profit corporations operating in Cincinnati, OH and Irvine, CA respectively.

Results

Significant excretion was observed ($P < 0.05$) with cumulative $CaNa_2$ EDTA therapy of Day 3 and Day 90 compared to Day 0 with lead, arsenic, cadmium (Figure 1) and nickel (Figure 2) in fecal samples. In addition, statistically significant cumulative excretions ($P < 0.05$) in arsenic, lead, mercury, cadmium and nickel in urine samples (Figure 3) were found. There were no differences in the safety profile comparisons within comprehensive metabolic chemistry panels between pre- and post-treatment blood values. Only minor transient complaints of loose stools and gas were reported in several subjects. Calcium disodium EDTA suppositories (Detoxamin) appear to be a safe and effective means to slowly and consistently remove a variety of toxic heavy metals, as evidenced by urine and fecal analysis.

Figure 1

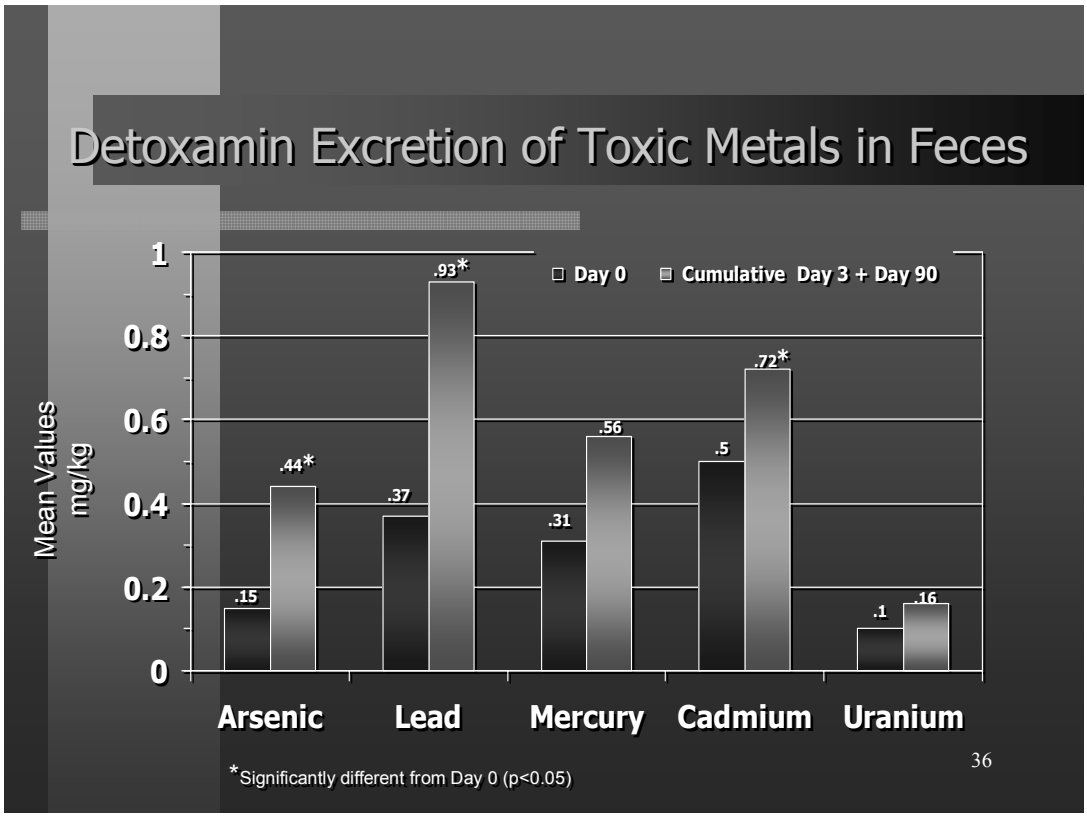


Figure 2

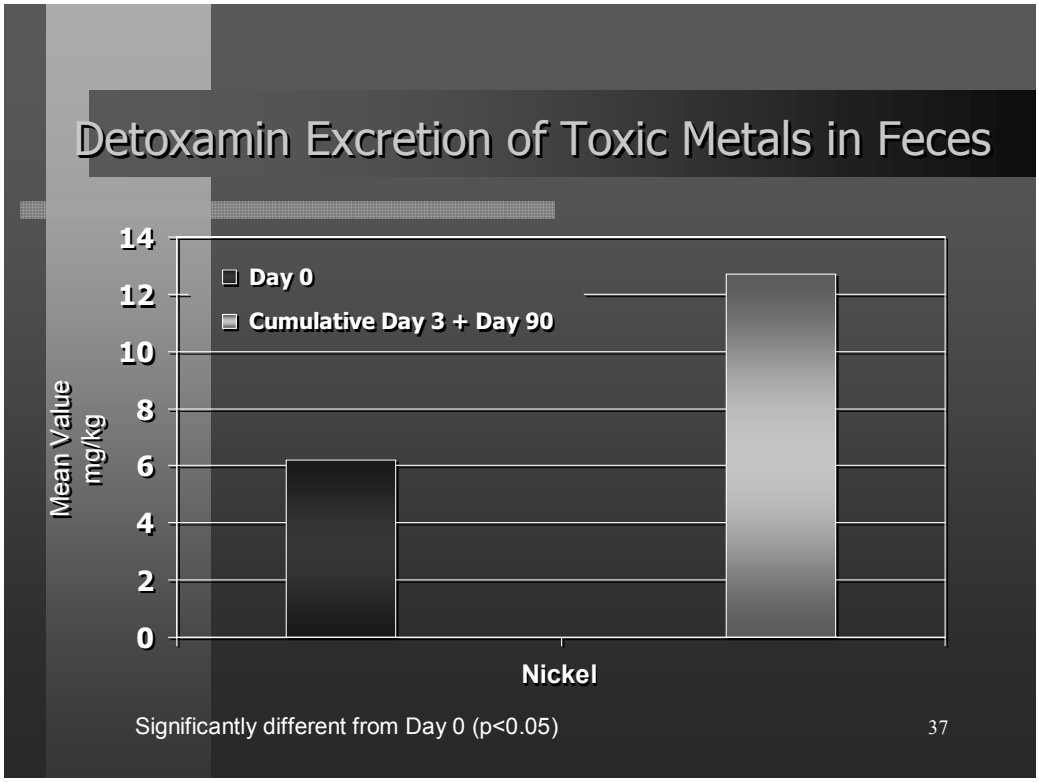
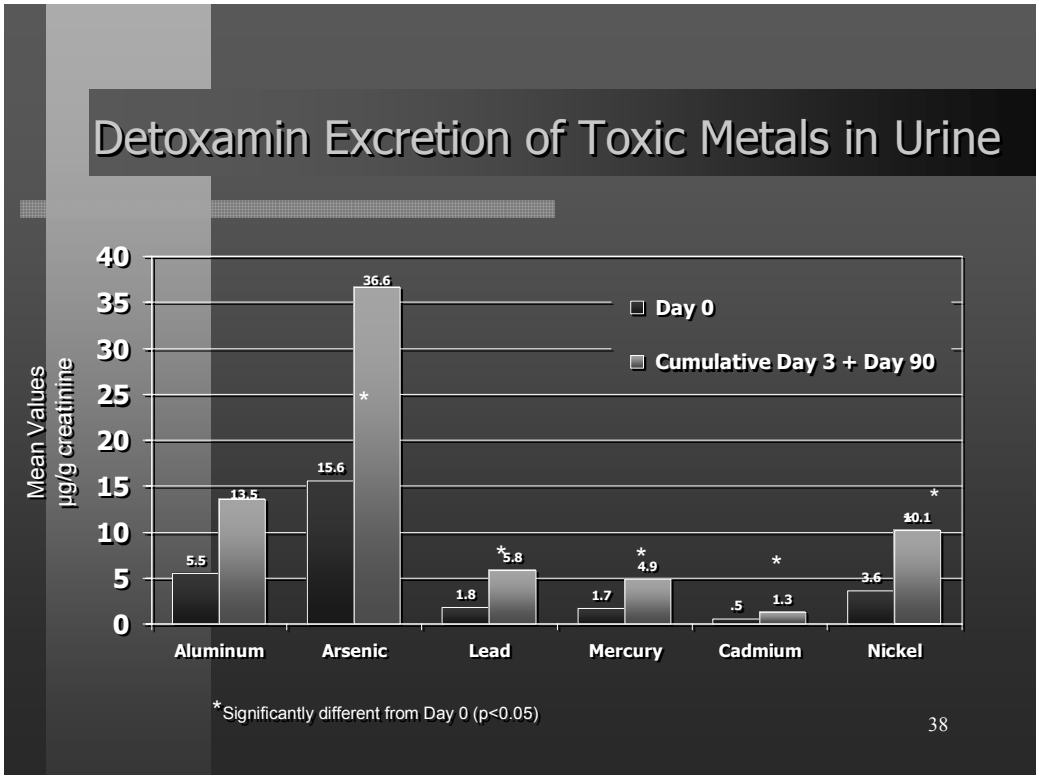


Figure 3



The Effects of Detoxamin $CaNa_2$ EDTA Suppositories on Elevated Blood Lead Levels in Children

IRB Approved Study in the Dominican Republic

A Clinical Report in Association with Columbia University and Fordham University

Ted Rozema, MD

Abstract: The effect of lead poisoning on high percentages of the pediatric population is cause for concern and it is one of the most common and preventable pediatric health problems today. Currently, the primary form of medical intervention consists of an expensive and painful $CaNa_2$ EDTA intramuscular injection. The availability of an easily administered effective medical treatment is an important component in controlling worldwide lead poisoning. This study utilizes a new form and route of administration of $CaNa_2$ EDTA, Detoxamin® suppositories. Rectal $CaNa_2$ EDTA suppositories (2000mg) were administered once per evening to 20 children for 10 consecutive days, no treatment after the following 10 consecutive days and re-administration of the initial suppository dose for another 10 consecutive days. Lead blood showed continual excretion from the pre-treatment concentration of 66.64µg/dL to 83.67µg/dL post treatment at the end of the 30 trial period. Lead urine levels rose from a baseline of 4.23µg/g creatinine to 325.55µg/g creatinine after only one suppository administration. The lead urine levels then dropped to 61.45µg/g creatinine within the first 10 days of treatment, and decreased to 9.94µg/g creatinine after the next 10 consecutive days of no treatment and rose to 22.71µg/g creatinine after the last 10 days of suppository administration. These data indicate significant and consistent excretion of lead in both blood and urine with the use of $CaNa_2$ EDTA suppositories in children exposed to high levels of lead. $CaNa_2$ EDTA suppositories offer a simple, convenient, non-invasive and cost- effective means of effective chelation for lead poisoning.

Introduction: Childhood lead poisoning is one of the most common pediatric health problems in the world today, and it is entirely preventable and reversible. Enough is now known about the sources and pathways of lead exposure, about ways of preventing this exposure, and about ways of reducing the lead content of the body to eradicate this disease permanently. The persistence of lead poisoning, in light of all that is known, presents a singular and direct challenge to public health authorities, clinicians, regulatory agencies, and society.

Lead is ubiquitous in the human environment as a result of industrialization. It has no known physiological value. Children are particularly susceptible to lead's toxic effects. Lead poisoning, for the most part, is silent: most poisoned children have no symptoms. The vast majority of cases, therefore, go undiagnosed and untreated. Lead poisoning is widespread. It is not solely a problem of inner city or minority children. No socioeconomic group, geographic area, or racial or ethnic population is spared.

Previous lead statements issued by the Centers for Disease Control (CDC) have acknowledged the adverse effects of lead at lower and lower levels. In the most recent previous CDC lead statement, published in 1985, the threshold for action was set at a blood lead level of 25 µg/dL, although it was acknowledged that adverse effects occur below that level. In the past several years, however, the scientific evidence showing that some adverse effects occur below levels at least as low as 10 µg/dL in children has become so overwhelming and compelling that it must be a major force in determining how we approach childhood lead exposure.

It is not possible to select a single number to define lead poisoning. Epidemiological studies have identified harmful effects of lead in children at blood lead levels at least as low as 10 µg/dL. Some studies have suggested harmful effects at even lower levels, but the body of information accumulated so far is not adequate for effects below about 10 µg/dL to be evaluated definitively. As yet, no threshold has been identified for the harmful effects of lead.

Because 10 µg/dL is the lower level of range at which effects are now identified, primary prevention activities are typically directed at reducing children's blood lead levels below 10 µg/dL or 14 µg/dL. While the overall goal should be to reduce children's blood lead levels below 10 µg/dL, there are entrenched reasons for not attempting to do interventions directed at individual children to lower blood lead levels of 10-14 µg/dL. First, practical medical interventions for children with blood lead levels in this range have previously

been unavailable. Second, the sheer numbers of children in this range would preclude effective case management in established intravenous therapy. Clearly, a simply and effective therapy such as suppository is needed.

The single, all-purpose definition of childhood lead poisoning has been replaced with a multi-tiered approach, described in the following table:

CLASS	Blood lead concentration (µg/dL)	COMMENT
I	<10	A child in Class I is not considered to be lead poisoned.
IIA	10-14	Many children (or a large proportion of children) with blood lead levels in this range should trigger community-wide childhood lead poisoning prevention activities. Children in this range may need to be rescreened more frequently. A decrease in blood lead levels would be beneficial.
IIB	15-19	Child should receive nutritional and educational interventions and more frequent screening. If the blood lead level persists in this range, environmental investigation and intervention should be done. Non-invasive medical intervention should be done.
III	20-44	Environmental evaluation, remediation and a medical examination should take place. Such a child needs pharmacological treatment of lead poisoning.
IV	45-69	A child in Class IV will need both medical and environmental interventions, including even I.M. chelation therapy.
V	69>	A child with Class V lead poisoning is a medical emergency. Medical and environmental management must begin immediately.

Lead is a poison that affects virtually every system in the body. The risks of lead exposure are not based on theoretical calculations. They are well known from studies of children themselves and are not extrapolated from data on laboratory animals or high-dose occupational exposure. Since 1970, our understanding of childhood lead poisoning has changed substantially. As investigators have used more sensitive measures and better study designs, the generally recognized level for lead toxicity has progressively shifted downward. Before the mid-1960s, a level above 60 µg/dL was considered toxic (Chisholm and Harrison, 1956). By 1978, the defined level of toxicity had declined 50% to 30 µg/dL.

Lower blood lead levels cause adverse effects on the central nervous system, kidney and hematopoietic system. Blood lead levels as low as 10 µg/dL, which do not cause distinctive symptoms, are associated with decreased intelligence and impaired neurobehavioral development (Davis and Svendsgaard, 1987; Mushak et al, 1989).

The concern about adverse effects on central nervous system functioning at blood lead levels as low as 10 µg/dL is based on a large number of rigorous epidemiological and experimental studies. Several well-designed and carefully conducted cross-sectional and retrospective cohort studies in many different countries have been conducted (Lansdown et al., 1986; Fulton et al., 1987; Fergusson et al., 1988; Silva et al., 1988; Bergomi et al., 1989; Hansen et al., 1989; Hatzakis et al., 1989; Winneke et al., 1990; Lyngbye et al., 1990; Needleman et al., 1990; Yule et al., 1981; Hawk et al., 1986; Schroeder et al., 1985). Some inconsistencies can be found in the results of these studies, but the weight of the evidence clearly supports the hypothesis that decrements in children's cognition are evident at blood lead levels well below 25 µg/dL. No threshold for the lead-IQ relationship is discernable from these data. Recent evaluation of 24 major cross-sectional studies provides strong support for the hypothesis that children's IQ scores are inversely related to lead burden (Needleman and Gatsonis, 1990).

According to the Natural Resources Defense Council, blood lead levels as low as 10 µg/dL, which do not cause distinctive symptoms, are associated with reading and learning disabilities, reduced attention span and behavioral problems. The ramifications of the proliferation of lead pollution from industrialization, combined with the devastating effects of health, are sobering. A simple and effective therapy, such as EDTA chelation via suppository, is urgently needed.

Materials and Methods: A cluster of previously untreated children with high blood lead levels was desired for the purpose of testing the efficacy of Calcium disodium EDTA rectal suppositories to remove toxic metals from the human body.

1.) Determinization of study area: Friends of Lead Free Children, a non-profit organization connected to Columbia University and Fordham University, assisted in the search. A residential neighborhood in Haina, Dominican Republic was selected. The residential neighborhood was located adjacent to a battery recycling plant. All preliminary testing indicated 100% of residents as markedly toxic with lead.

2.) The selection of subjects into the study: Children who had been identified with blood lead levels over 10 mcg/dL were determined in a twenty-four hour urine collection by Ion Coupled Plasma Emission Spectroscopy. Hg. Analysis was determined by cold vapor mercury analysis.

3.) Individual treatment of lead overload: Cautious removal of lead from body depots was achieved through the use of Calcium disodium EDTA rectal suppositories. The use of suppositories provided for the prevention of local corrosive action of toxic metals on mucous membranes.

4.) Compensation: Compensation was not paid to subjects; however, no charges were incurred by participants for the drug and laboratory testing.

5.) Safety: By determining the concentration of heavy metals in the urine following provocative stimulation, the therapy with EDTA was scientifically determined, providing a safe treatment program. The study simultaneously provided diagnostic information regarding heavy metal burden as well as a defined treatment protocol for lead toxicity in a pediatric population. EDTA is a substance with low systemic and local toxicity and is generally well tolerated. The drug, per se, has been classified GRAS by the FDA, no cases of anaphylaxis have been reported through the oral administration of EDTA or through its use as a food additive.

6.) Alternative therapies: Alternative therapies were available for the treatment of metal intoxications, including (R,S)-2,3-dimercapto propane-1-sulfonic acid (DMPS,) as well as its close standing analog, DMSA. A significant advantage of using EDTA suppositories in a pediatric population include:

—a) Cooperative binding constant for lead.

—b) The suppository route of administration at bedtime was (is) an easy and acceptable delivery system.

—c) The antioxidant/free radical quenching role of EDTA made it superior over the other agents available due to the fact that neurological dysfunction was (is) recognized as a result of free radical mediated damage.

—d) EDTA was already approved for oral administration by the FDA and is on the GRAS list.

—e) EDTA is an ANTIDOTE to counteract the TOXIC action of lead from the environment.

7.) Medical care: Medical care was provided by Universidad de Autonomia de Santa Domingo. In the event of a medical emergency connected with the study, subjects were to contact the appropriate center, but this was never necessary. In addition, all participants could receive product and clinical information by calling: Ted Rozema, M.D., the principal investigator.

8.) Data coordination: Data was coordinated and maintained by the principal investigator, all data was statistically analyzed. Information was made available to all appropriate authorities, including IRB of the GLCCM and the FDA.

9.) Clinical laboratory: Clinical laboratory facilities and medical support was provided by AmScot Medical Laboratories, Inc. To ensure the safety and integrity of the study, the following analyses were assessed:

a) Baseline:
— Smac 18 with CBC - manual differential Blood lead determination
— Urine (24-hour collection) —heavy metals to include: Pb, Cd, Hg, As, Ni, Al
— B2 - micro globulin (serum) Anti - TPO Total Ca/Ca2+ Mg/Mg2+ Pt/APTT PTH

b) Provocative EDTA challenge:
— Blood lead determination
— Urine (9-hour) - heavy metals - Pb, Cd, Hg, As, Ni, Al
— B2 - micro globulin (serum) Total Ca/Ca2+ Mg/Mg2+ Pt/APTT PTH

c) Mid-study laboratory evaluation:

— Blood lead determination
— CBC - manual differential Urine (9-hour) - heavy metals - Pb, Cd, Hg, As, Ni, Al
— B2 - micro globulin (serum)
— Total Ca/Ca2+ Mg/Mg2+
— Pt/APTT PTH

d) Post study (6 weeks):
— Blood lead determination
— SMAC 18 with CBC - manual differential
— Urine (9-hour) - heavy metals - Pb, Cd, Hg, As, Ni, Al
— B2 - micro globulin (serum)
— Total Ca/Ca2+ Mg/Mg2+
— Anti-TPO
— PTH

Research Protocol: A study to determine the efficacy of Calcium disodium EDTA (Detoxamin, supplied from World Health Products, Draper, Utah) used as a rectal suppository in removing toxic metals from the human body. Subjects: children with proven lead toxicity (blood lead levels >10µg/dL). Study design:

1.) Enrollment.

2.) Blood lead levels drawn to enter into study with simultaneous determination of urine lead excretion (total urine minerals - if possible with parental assistance).

3.) Treatment phase.

	PRE	AFTER 10 DAYS	AFTER 10 DAYS	AFTER 10 DAYS
BLOOD	XX — Supp	XX — No supp	XX — Supp	XX
URINE	XX — Supp	XX — No supp	XX — Supp	XX

4.) Placement of a rectal suppository containing 2 grams of Calcium Disodium EDTA nightly for 10 days, then 10 days without EDTA, then placement of the EDTA suppository for 10 days, continue this program for two courses of treatment.

5.) Laboratory determinations:

Purpose is to demonstrate gradual reduction of both blood and urine lead levels over time with a simple and cost-effective method. It was anticipated that

methods to reduce lead intake would be in place during and after this study. Unfortunately, no environmental mitigation was ever enacted.

Specimen Collection Regimen: Pre-study:
1.) Collection of 3 to 5 ml of whole blood in heparinized, lead-free curettes.

2.) Collection of 9 hours of urine. This was measured from the time the child went to bed until 9 hours later. It was anticipated that the children were not getting up at night to urinate and mother would need to watch to catch the first morning specimen, then determine the 9-hour point and collect the additional urine to make the complete collection This provided a base line for both blood levels and excretion on a daily basis.

Just before the first suppository:
1.) Collection of 1 to 5 ml of whole blood in heparinized, lead-free curettes.

2.) Insertion of the first suppository in the child's rectum, high as possible, just before the child goes to sleep, preferable with the child already in the bed.

The morning after the first suppository:
1.) Collection of 9 hours of urine. This was measured from the time the child went to bed until 9 hours later. It was anticipated that the children were not getting up at night to urinate and mother would need to watch to catch the first morning specimen, then determine the 9 hour point and collect the additional urine to make the complete collection.

The morning before the 10th suppository:
1.) Collection of 3 to 5 ml of whole blood in heparinized, lead-free curettes.

The morning after the 10th suppository:
1.) Collection of 9 hours of urine. This was measured from the time the child went to bed until 9 hours later. It was anticipated that the children were not getting up at night to urinate and mother would need to watch to catch the first morning specimen then determine when is the 9 hour point and collect the additional urine to make the complete collection.

The morning of the 19th day: This is the last day without a suppository before the next ten days of suppository administration.
1.) Collection of 3 to 5 ml of whole blood in heparinized, lead-free curettes.

2.) Collection of 9 hours of urine. This was measured from the time the child went to bed until 9 hours later. It was anticipated that the children were not getting up at night to urinate and mother would need to watch to catch the first morning specimen, then determine the 9 hour point and collect the additional urine to make the complete collection. This gave us a determination of equilibration after no treatment for 10 days.

The morning of the 30th day:
1.) Collection of 3 to 5 ml of whole blood in heparinized, lead-free curettes.

The morning after the 30th suppository:
1.) Collection of 9 hours of urine. This was measured from the time the child went to bed until 9 hours later. It was anticipated that the children were not getting up at night to urinate and mother would need to watch to catch the first morning specimen, then determine the 9 hour point and collect the additional urine to make the complete collection. All specimens were taken to the laboratory of Dr. Conrado Depratt at the Instituto De Quimica of the Universidad Autonoma de Santo Domingo.

Results: Average 20 children test data:

BLOOD LEAD LEVELS		
Pre-study	66.64	µd/gL
After 10 days of suppositories	39.09	µd/gL
After 10 days without suppositories	61.45	µd/gL
After 10 more days on suppositories	83.67	µd/gL

URINE LEAD EXCRETION LEVELS		
Pre-study	004.23	µd/g creat
After 1st suppository	325.55	µd/g creat
After 10 days of suppositories	061.445	µd/g creat
After 10 days without suppositories	009.04	µd/g creat
After 10 more days on suppositories	022.71	µd/g creat

The data clearly demonstrates that Detoxamin, (EDTA delivered in rectal suppository form), effectively removes lead from children with lead poisoning. The continued high excretion level, after 10 days without Detoxamin is of special interest. Also of special interest is the rebound effect in the blood lead levels. Its degree reflects the high amount of stored lead in the tissue and bones and the attendant mobilization effect. Each time the blood lead level was diminished, additional lead was mobilized from the tissues and bones.

It was anticipated that methods to reduce lead intake would be in place during and after this study. Unfortunately, no environmental mitigation was ever enacted. Ideally, environmental intervention would have been enforced and the Detoxamin Calcium disodium EDTA rectal suppository therapy would have continued for a 6-month duration. This circumstance was not possible.

Clinical Case Studies of Patients on $CaNa_2$ EDTA (Detoxamin©)

Rita Ellithorpe, MD

Tustin Longevity Center, Tustin California

Summary

Dr. Rita Ellithorpe performed random packed red blood toxic heavy metal analysis to approximately 279 patients. She found a 98% presence of multiple toxic metals in the test sampling. Dr. Ellithorpe has over seven years experience with practical clinical use of Detoxamin and has administered the supplement to over 1800 patients totaling over 100,000 doses. The overall clinical outcomes, in general, with patients on Detoxamin are improved mental clarity, increased energy, increased endurance with physical activity, reduced blood pressure, improved lipid profiles, enhanced cardiovascular performance, improved libido, improvement in symptoms of prostatitis and prostate conditions and an overall improvement in quality of life.

Figures 1, 2 and 3 are summaries three clinical case studies of patients on Detoxamin.

Figure 1

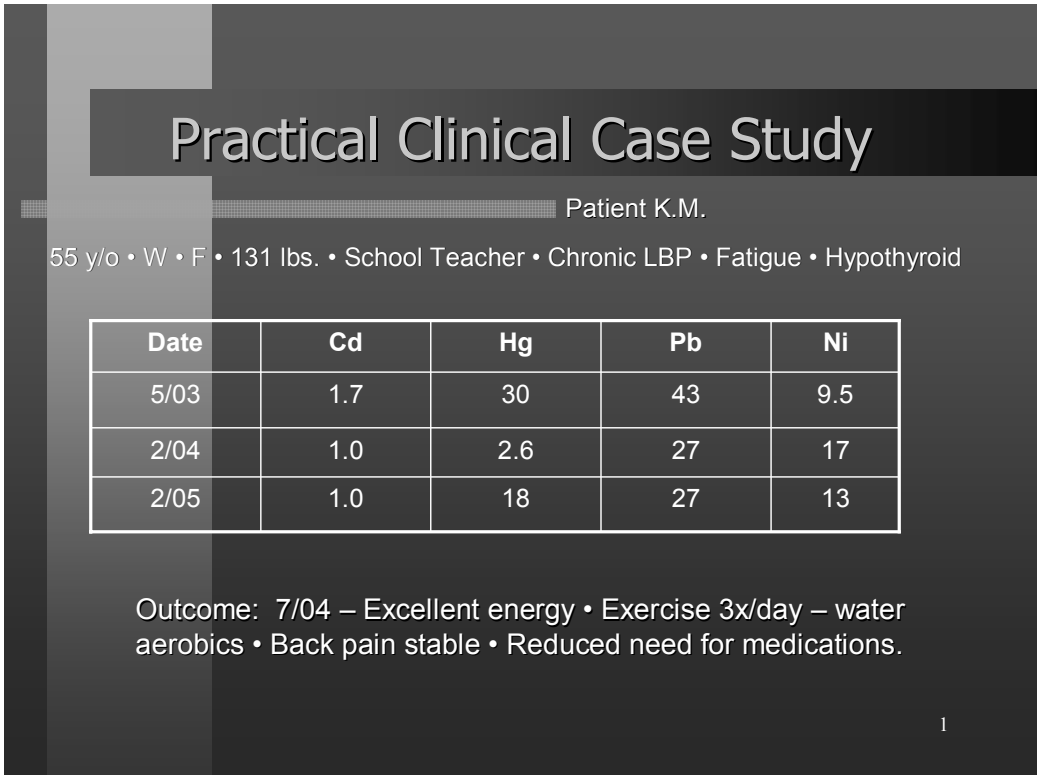


Figure 2

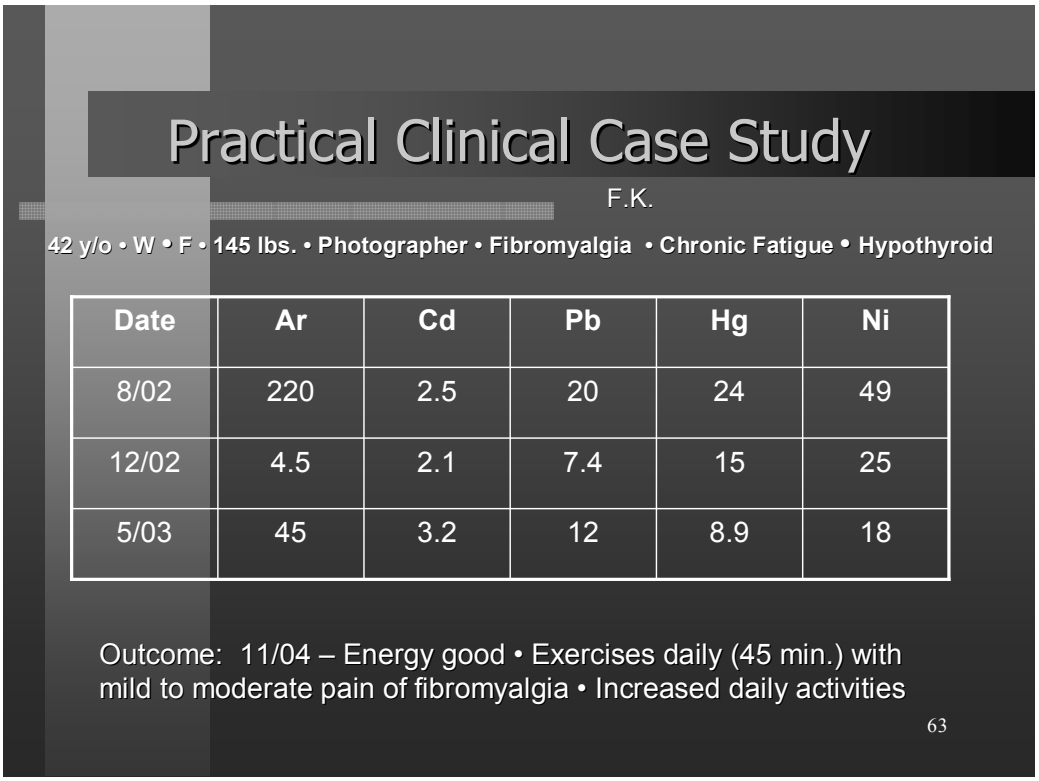
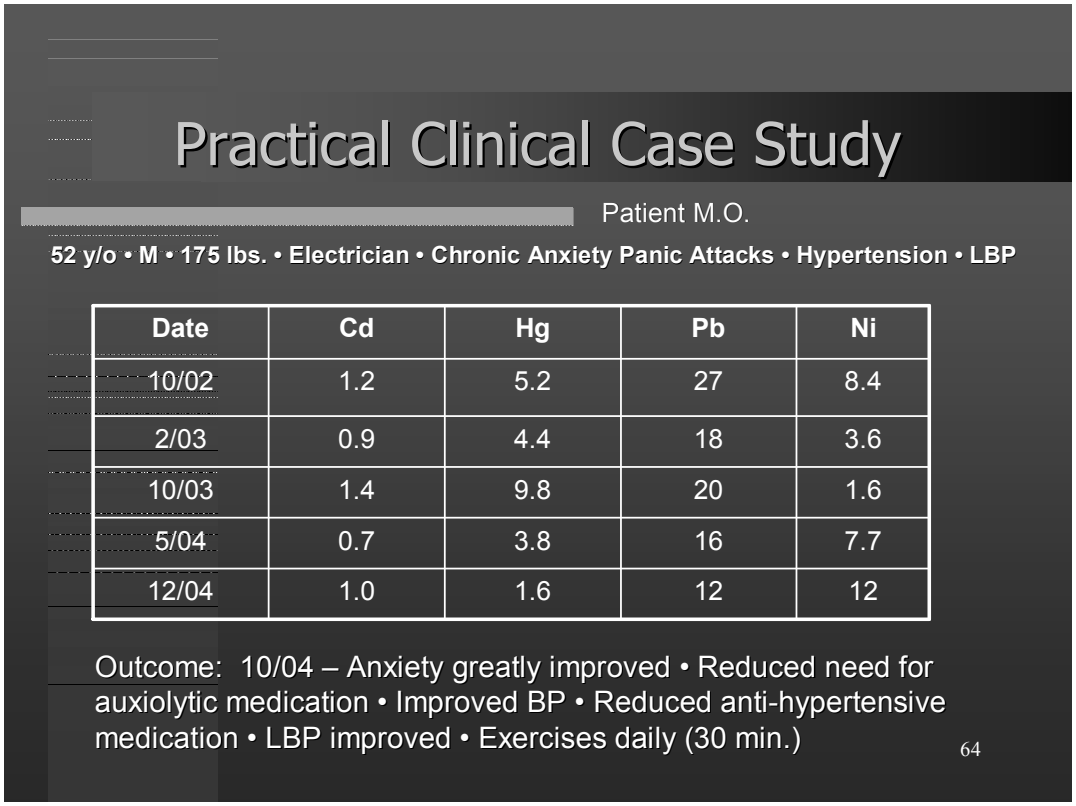
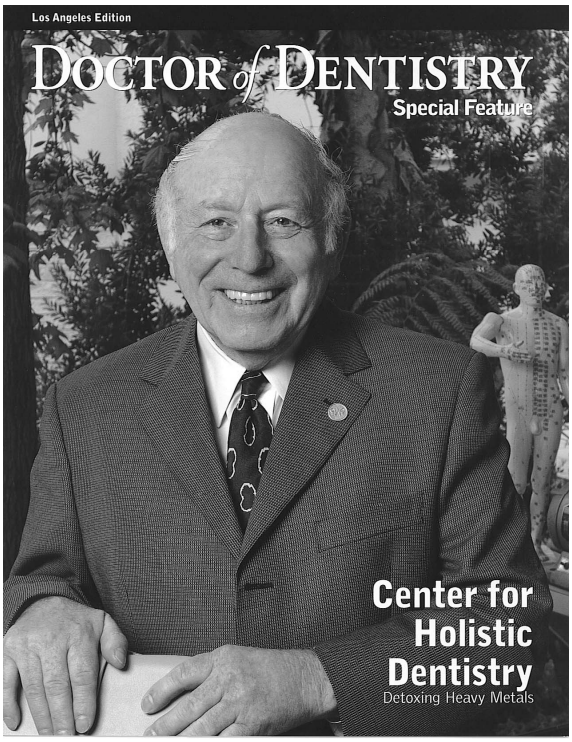


Figure 3


Practical Clinical Case Study
Patient M.O.
52 y/o • M • 175 lbs. • Electrician • Chronic Anxiety Panic Attacks • Hypertension • LBP
Date | Cd | Hg | Pb | Ni
10/02 | 1.2 | 5.2 | 27 | 8.4
2/03 | 0.9 | 4.4 | 18 | 3.6
10/03 | 1.4 | 9.8 | 20 | 1.6
5/04 | 0.7 | 3.8 | 16 | 7.7
12/04 | 1.0 | 1.6 | 12 | 12
Outcome: 10/04 – Anxiety greatly improved • Reduced need for auxiolytic medication • Improved BP • Reduced anti-hypertensive medication • LBP improved • Exercises daily (30 min.)
64



Dr. Harold Ravins

Detoxing Heavy Metals

By Debbie L. Sklar

There are a lot of exciting new discoveries in dental medicine to provide better outcomes for patients. One of the emerging fields is what has been called complementary, integrative or holistic medicine, combining traditional folk remedies from cultures worldwide with the most cutting-edge technologies and techniques of the mainstream.

Harold Ravins, D.D.S., a general dentist and the founder of Raveco Holistic Dental Center in Beverly Hills, has been in private practice since 1963. "I've always thought that the mouth is a mirror into the overall body," said Dr. Ravins. He said he hopes that in the near future holistic dentistry will become the norm.

"As heavy metal toxicity and acupuncture were eventually accepted by mainstream medicine, dentists should keep an open mind about other elements of alternative medicine," he commented.

With his drive and determination, Dr. Ravins continues to break new ground in the area of holistic dentistry by offering patients what he believes to be a healthier way to take care of their teeth - as part of their whole body.

THE PATH TO INTEGRATIVE DENTISTRY


Harold Ravins, D.D.S., practices a high level of conventional dentistry within the context of a holistic approach to health.

Born and raised in Buffalo, NY, Dr. Ravins is the son of third-generation kosher meat packers. He said he knew early on that he wanted to become a dentist and was always intrigued by biology.

"I learned how to stitch the chickens as a kid, and this helped me become an excellent surgeon, "he laughed, "I was interested in dentistry at the age of 9 or 10, as well as nature because my own dentist took a lot of time explaining dentistry to me."

After graduating from Fairleigh Dickenson School of Dentistry in New Jersey in 1960, he attended a graduate program in oral bacteriology at Ohio State University. He went back to his native Buffalo for a year to work with his mentor, but quickly tired of shoveling snow, Instead, he longed for the sunny weather of California and found himself on the road headed west.

"I always had the aspiration of becoming a successful dentist in California," he recalled. "Dentistry there, as now, was the gold standard for the country and I was very into cosmetic work that was being done in Beverly Hills. I came, got a job here, but always wanted to have my own practice."

However, the formative years were not always smooth sailing for Dr. Ravins.

"It was about 1968 when I was diagnosed with incurable sciatica by my orthopedist," he said. "It was a long weekend in Vegas and after walking the strip with my cane and wife, a taxi cab pulled up to us and it turned out to be a classmate of my wife's who was going for his chiropractic boards."

The classmate invited Dr. Ravins and his wife up to his apartment where he treated the dentist, who suddenly felt much better.

"On Monday, I went back to the tennis courts, and when my orthopedist, also a tennis player, heard my story he said a few unpublishable words and I realized most other doctors would refuse to give evidence of the efficacy of alternative modalities a fair hearing," he said. "I later studied with chiropractors, and introduced cranial therapy to several of my study groups at that time and I published an article called 'Car Crash, Jaw Lash.'"

Dr. Ravins, who still attends many seminars and conferences to keep abreast of the fields, always seems to be in the right place at the right time. He has been fortunate to study with some of his most prominent dental colleagues, among them Dr. Harry Tepper, an orthodontist and innovator in his own right. He taught Dr. Ravins to use removable braces to prevent and correct crooked jaws and teeth for children and adults - a revolutionary idea then. Dr. Ravins did orthodontics for the first 25 years of his career.

"I was learning about more treatment procedures that most dentists did not accept," he said. "But there was always a minority of us who were more open-minded. I was always interested in nutrition and, amazingly, our dental school in New Jersey had the first organic cafeteria in the country in 1956. I joined the International Academy of Applied Nutrition in the 1960s."

Taking a leap of faith, Dr. Ravins decided to create the Raveco Holistic Dental Center after three years of building up his general practice in Beverly Hills.

"I became concerned about the harmful effects of the mercury in amalgam fillings, which are 50% mercury, around this time," he explained. "I haven't done an amalgam filling in 20 years, and I use porcelain or white composites instead. I used to use gold, but not anymore because of the new CAD-CAM system and I have been following the European dentists by staying metal free. I had my own amalgams removed 38 years ago."

He was intrigued by the broader field of holistic dentistry, he said. Holistic, Dr. Ravins explains, indicates that what is going on in the mouth affects the entire body.

"Back in the early 1900s, a very famous Canadian physician, Sir William Osler, wrote that the mouth is a mirror of the body. He was celebrated as the 'Father' of modern clinical medical practice, I, too, take the position that whatever dentistry is performed in the mouth affects the general health of the patient. It's no surprise that holistic dentistry is becoming more popular in the public's eye and it is going to become a much bigger part of general dentistry in the coming decade."

Dr. Ravins tests his patients' cellular health using a device NASA uses to determine the health of astronauts.

A FIRST VISIT

When a patient first visits Dr. Ravin's office, they receive a standard dental examination, including checking for periodontal infection.

But the holistic objective is to also find hidden infections in the mouth that are not considered the usual dental problems. In many situations, pain is not the primary indicator of a health problem. Detection is accomplished with good quality X-rays and a comprehensive clinical examination, which includes various levels of dental acupuncture energistic testing (James Oschman, Ph.D., correlates traditional Asian medicine's concept of the body's energy with Western science in Energy medicine: The Scientific Basis).

Another part of this first visit includes a bite analysis involving the T-scan test. The patient bites down on paper with a computer chip that transmits a picture of how the teeth contact each other and how well the jaw is functioning.

Included in this comprehensive examination, according to the principles of whole body dentistry, is the BIA, or bioelectrical impedance analysis, which was developed for NASA in the 1970s to measure body mass and detects cellular health in astronauts. It is a painless way to measure the electrical activity of the cell membranes on the foot to determine whether cells are absorbing nutrients and resisting toxins. It is a good indicator as to whether the immune system is functioning normally and provides an excellent marker for overall wellness.

The safest and easiest way to diagnose the presence of heavy metals in the body is a fecal test, which Dr. Ravins stated provides incontrovertible scientific evidence that many patients suffer from poisoning. The metals measured are mercury (with amalgams and without), lead, nickel, uranium, antimony, tungsten, thallium, platinum, beryllium, arsenic, bismuth, cadmium and copper. The fee is $185; the total evaluation including a written report is under $1,000.

"The center has been looking for years for an accurate, safe way to determine mercury toxicity," he said. "We discovered the heavy metal fecal test that was used in pediatric medicine for years, but that was not very popular with the U.S. medical community." The center also found the best lab in the U.S. for processing the test accurately.

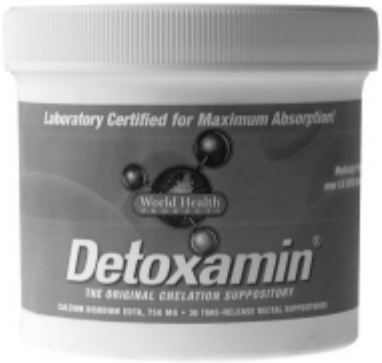
At present, Dr. Ravins has more that 200 patients who have been tested for heavy metals in their system before they had amalgam removal. (The center also found a lab that met its standards.) The result was that 99% showed toxic levels of mercury. He invites other dentists to take the test for themselves and to let him know if they might have an interest in attending a workshop about detoxification he plans to conduct.

"I don't provoke or tell my patients that they should have their amalgams taken out because of the mercury," he said. "I give them literature that talks about the harmful effects of mercury. They are asking me to remove them, and I, in turn, ask them to take the fecal test; most come back with high levels. Yet, according to the American Dental Association, there is no scientific proof that the mercury in amalgam is leaking into the body."

It's an illogical position, argues Dr. Ravins. "The government's own scientists agree that mercury is very toxic, we now have tests that show a large number of people have height levels of mercury, so are we going to say that putting mercury in the mouth for a lifetime is not related?" In fact, although amalgam fillings saved millions of teeth in the past, they have been banned in some European countries for many years and we now have healthier materials to use instead of amalgam, he points out.

The ADA does say it is okay to remove amalgams at the patient's request and most dentists will do so cynically, Dr. Ravins commented. But his colleagues are starting to come around. The State Dental Licensing Board no longer requires using mercury amalgams to practice and is the first dental board in the U.S. to take that pioneering position. "Ten years ago, I would have been considered nuts with all of this, but now
the evidence is hard to deny."

DETOXIFYING MERCURY



Once the levels of mercury have been uncovered, it is not as easy as just going in and chiseling out the old amalgams.

"It requires a great deal of experience and understanding, because each patient is so different," he said. "The periodontal evaluation is extremely important because if you have an infection in the mouth, it can contribute to other infections in the body. But if we do a BIA and the cells aren't working right, it means that something is wrong with the overall cellular health."

Dr. Ravins is so adamant about the dangers of mercury that he even has negative ion machines in his operatories to take out mercury vapors in his office.

"The mercury vapors are most horrendous to our health. Since the vapors are positive(ly) charged, they attach to the negative ions generated in the room and are collected on a positive cathode reservoir on the wall," he said. "I have to clean the reservoirs every three weeks. Most other toxic gases are also positively electrically charged."

So, why not just simply open a window? Because he would be fined $2,500, since mercury is recognized as so poisonous by the Environmental Protection Agency.

Dr. Ravins said that recently, a young woman contemplating pregnancy came in for a dental examination regarding the mercury issue.

"She said she wanted to be toxic-free on conception and then referred her husband to me for the same reason," he recalled.

One of the ways of ridding the body of mercury toxins is by using a new detoxification product called Detoxamin, a CaN2 or calcium disodium EDTA time-released suppository, manufactured by World Health Products in Irvine, CA.

(EDTA is certified by the FDA for doctors to remove excess lead from the body and the FDA recently approved research of CaN2 EDTA indicating this was effective for removing mercury, as well, and a safer chemical to use.)

"Through all our studies, we've discovered that it could take months, or even years, to rid the body of such toxins. This suppository is a convenient way to do it and I'm so impressed by this product that I decided to start using the product on myself," Dr. Ravins said.

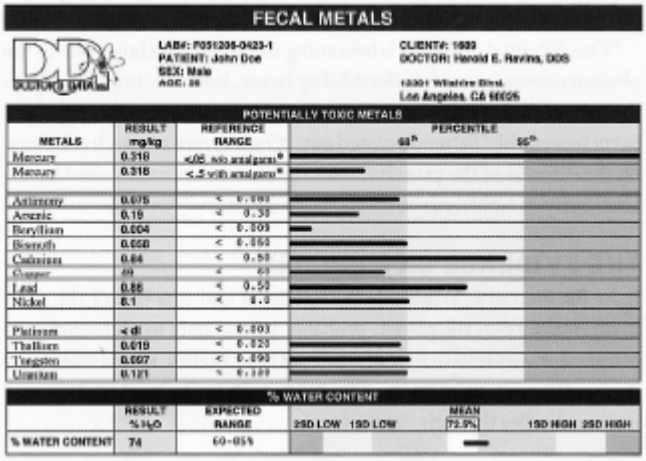
World Health Products is the originator and developer of the patented formula and "Detoxamin is the only product of its kind that actually has the proof to back up its claims," Dr. Ravins noted, "Many companies promote better price and make product claims that have absolutely no scientific or clinical reference of any kinds."

"Scientific evidence is important because all EDTA suppositories are not alike. Formulas, ingredients, consistency, time-release and other important aspects that create high absorption of EDTA are all different. If you have used IV EDTA chelation before, you know absorption and bioavailability are the keys to performance. Detoxamin is the only viable alternative to IV EDTA chelation in the world." according to CEO Edward Salmon.

IV EDTA chelation although very efficacious, is very expensive, invasive, time-consuming and inconvenient, he points out, putting this needed therapy out of reach for most people. Oral EDTA chelation products are poorly absorbed and Detoxamin fits today's lifestyle with its simple, convenient, gently and efficient toxin removal with proven pharmacokinetic absorption and clinical efficiency, he added.

"Our patented chelation is becoming the preferred choice due to the obvious convenience and affordability factor, but more importantly, to the extraordinary efficacy, safety and scientific validation through third party (research) "Salmon pointed out. "Our current research is focused on the diseases of the prostate, with significant success assessed by the University of California at Irvine biostatisticians."

A typical fecal test shows a patient's heavy metal toxicity.



FECAL METALS

LAB#: F051208-0423-1
PATIENT: John Doe
SEX: Male
AGE: 58

CLIENT#: 1693
DOCTOR: Harold E. Ravins, DDS
12301 Wilshire Blvd.
Los Angeles, CA 90025

POTENTIALLY TOXIC METALS

METALS	RESULT mg/kg	REFERENCE RANGE	PERCENTILE 68th	PERCENTILE 95th
Mercury	0.318	<.05 w/o amalgams*		
Mercury	0.318	<.5 with amalgams*		
Antimony	0.075	< 0.080		
Arsenic	0.19	< 0.30		
Beryllium	0.004	< 0.009		
Bismuth	0.050	< 0.060		
Cadmium	0.84	< 0.50		
Copper	49	< 60		
Lead	0.86	< 0.50		
Nickel	8.1	< 8.0		
Platinum	< dl	< 0.003		
Thallium	0.019	< 0.020		
Tungsten	0.007	< 0.090		
Uranium	0.121	< 0.100		

% WATER CONTENT

	RESULT % H_2O	EXPECTED RANGE	2SD LOW	1SD LOW	MEAN 72.9%	1SD HIGH	2SD HIGH
% WATER CONTENT	74	60-85%					

THE EVIDENCE ON MERCURY

As for mercury, World Health Products said it is one of the most toxic elements on the planet, probably second only to plutonium, yet people worldwide have it in all tissues of their bodies. It continues to be dumped into our waterways and soil, placed into our teeth and injected into our bodies through vaccinations.

Toxicity cause by excessive mercury exposure is now becoming recognized as a widespread environmental problem and is continuing to attract a great deal of public attention. A Nationals Academy of Science study published in July 2001 estimates that up to 60,000 children born in the U.S. each year may be affected by mercury toxicity. In March of 2002, an environmental group had charged the FDA of failing to warn the public of the dangers of mercury contamination from eating tuna, which contains high levels of mercury. Texas researchers have found a possible link between autism and mercury in the air and water. In fact, the incidence of autism has grown in the past 20 years, from one in every 2,000 children to as high as one in every 166. Researchers have been hard pressed to explain the increase, but many believe mercury to be the culprit, World Health Products points out.

The United Nations' World Health Organization also reports that the amount of mercury absorbed daily by the average human body is 0.3 micrograms (mcg) from water and air, 2.61 mcg from fish and 17 mcg from dental amalgams. Research points out that 80% of mercury vapor is absorbed into the blood, going directly from the nose to the brain, following nasal nerve pathways. Dentists have four times as much of a body burden of mercury than

average non-dentist people. Dental workers show 50 to 300% more mercury in hair and fingernails than the average population. Before public awareness campaigns started, it is a notable fact that the preservative thimerosal (usually added to vaccines) contained mercury. In 1999, the Centers for Disease Control called for the removal of mercury from vaccines. Paradoxically, the CDC still continues to recommend the measles, mumps and rubella vaccine, World Health said.

According to World Health's website: "If you are one of the millions of Americans who has received silver dental fillings, take notice. Mercury makes up about 50% of every amalgam dental filling, also known as 'silver' fillings, Amalgam fillings can release mercury for up to 70 years. Someone with eight amalgams, for example, could have 120 mcg released into the saliva per day. The maximum allowable by the EPA is less than 0.1 mcg per kilogram of body weight per day to be absorbed into the human body. We now know that the dental mercury/silver amalgam filling is 'chemically and electrically active.' Science has proven that every time we eat, drink or breathe, we may be absorbing disturbing releases of decomposing, toxic particles - mercury included. This chronic, toxic accumulation is being shown to have serious, long-term consequences on our immune system, resulting in a variety of diseases and conditions. Consider that while 78% of Americans have dental fillings, 95% of people with disorders of the central nervous system such as MS, epilepsy, paralysis and migraines also have silver dental fillings. This begs the question, 'Would you want mercury - one of the most powerful neurotoxins on the planet - embedded in your mouth, only inches from your brain?' The answer is obvious. This is the same reason why you can no longer buy an oral or rectal mercury thermometer.

Salmon challenges dentists to take the heavy metal toxicity fecal test, which World Health can also supply, as a starting point. It is simple, using a prepaid package, with results in a week.

ACUPUNCTURE AND INTERCONNECTION

Raveco Holistic Dental Center staff (left to right): Elisa Geller (front office), Sandy Urbino-Mallette (office manager), Nicole Murillo (front office), Jolla Navarro (dental assistant), Yesenia Reneria (dental assistant), Leanh Ly, RDH, Martha Moreno (dental assistant), Harold Ravins, D.D.S., CDA, Giri Palani, D.D.S.

"Every medical problem is interconnected throughout the body, which is why, in acupuncture, teeth are tied to different organs," Dr. Ravins said. "Since the science is there regarding acupuncture, the insurance industry has recognized this several years ago. As a certified dental acupuncturist, I use it on almost every patient. This is part of the new dentistry involving quantum mechanics and energy, which (Raveco Holistic Dental Center) has documented over the years. By crossing the midline of the mouth - the conception meridian - with a metal wire or bridge, this blocks the energy flow. The symptoms that are cleared include headaches and neck aches' advantages then include improved vision, equilibrium restored, and behavior modifications in children with orthodontic wires. Many prostate patients have been able to reverse their prostate disease diagnosis by addressing the mouth as part of the overall cause of the problem." Heavy metals have been shown to inflame the prostate, too.

But everything Dr. Ravins does is not "alternative." He tries to stay abreast of the latest dental technology and is an avid user of the CEREC system for making dental crowns. He is fully equipped with digital X-rays, which reduce radiation by 90% compared to film. He also used Diagnodent, a laser instrument which measure decay where the X-ray cannot.

"The center as also been using laser dentistry for more than 10 years in the treating of gum disease, and more recently, we are able to treat teeth for decay, nerve infection and tooth sensitivity without using injections, as well as for bleaching," he said. "It's excellent for children - no more needles for drilling."

Dr. Ravins is hoping to add an associate to the Raveco Holistic Dental Center to help him expand the practice to meet demand as the public becomes more interested in these things.

"I plan to take my 45 years of study and teaching of holistic dentistry to the forefront of the dental profession," he said. "The plan is to share all of this with a new partner who can continue the importance of this work and possibly buy the practice at some point. In five years, I see myself doing clinical research to show how the mouth can help keep a person healthier and prevent disease."

At 73, Dr. Rains is just getting started with what may be the most ambitious project in the history of dentistry.

Harold Ravins, D.D.S.
12381 Wilshire Blvd. #103
Los Angeles, CA 90025
(310)207-4617

hravins@earthlink.net
www.ravecoholistic.com

Edward Salmon, CEO
World Health Products
1582 Deere Ave #B
Irvine, CA 92606
(949) 474-0309
jsalmon@detoxamin.com
www.detoxamin.com
(can provide doctors with both the heavy metal toxicity fecal test and Detoxamin)

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877-656-4553

Safety Profile

Detoxamin Safety Overview

DETOXAMIN®

U.S. Patent 5,602,180
Calcium Disodium EDTA
Calcium Disodium EDTA Time-Release Suppositories
For the removal of toxic heavy metals.

Description

Detoxamin (CaNa2EDTA) is a rectal, time-release suppository that binds and removes or decreases toxic heavy metal contamination in the body and comes in four strengths 375mg, 750mg and 1000mg and 1500mg. Detoxamin uses calcium disodium EDTA, a synthetic amino acid, in a suppository form as a chelating agent in a cocoa-butter base with methocel E4M premium USP for a time-release effect. The suppositories are a soft solid, bullet-shaped preparation designed for easy self insertion into the rectum through the anus. Each suppository dissolves at body temperature and gradually spreads over the lining of the lower rectum where it is absorbed into the bloodstream.

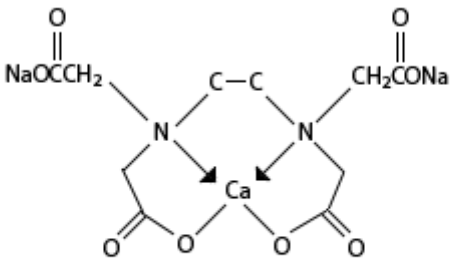
Recent Pharmacokinetic Data

Pre-clinical animal studies suggest that Detoxamin's absolute bioavailability following rectal administration is 36.3 % of the IV dose; this was ascertained by C14 labeled radio-labeled calcium disodium EDTA (Detoxamin). The ratio of radioactive residues of EDTA in prostate tissues showed a mean value of 13.6 via the rectal route compared to 3.69 via the IV route. The total recovery of C14 EDTA expressed as percent of administered dose was 30.3 % rectally and 47.3% IV after eight hours. The study reflected a standard pharmacokinetic model for IV dosing, whereas a unique bi-phasic curve was observed in rectal administration over the same eight hour period. The suppository Detoxamin formulation appears to be well absorbed delivering high levels of EDTA in prostate tissue and is efficiently excreted.

Structural Formula

Edetate Calcium Disodium, USP, CAS 23411-34-9;
Calcium Disodium Ethylenediaminetetraacetate; Calcium Disodium (Ethylenedinitrilo) Tetraacetate; Calcium Disodium Edetate; Ethylenediaminetetraacetic Acid, Calcium Disodium Salt) USP

C10H12CaN2Na2O8 2H2O



Clinical Pharmacology

The pharmacologic effects of CaNa2EDTA are due to the formation of chelates that bind with any metal that has the ability to displace calcium from the molecule, a feature shared by lead, zinc, cadmium, manganese, iron and mercury another metals. Intravenous studies have shown that EDTA is distributed primarily in the extracellular fluid with only about 5% of the plasma concentration found in spinal fluid. Almost none of the compound is metabolized. The primary source of lead chelated by EDTA is from bone, subsequently, soft-tissue lead is redistributed to the bone when chelation is stopped. (3, 4) It has been shown in animals that following a single dose EDTA, urinary lead output increases and the blood lead concentration decreases with subsequent decreases in internal redistribution of lead. (5)

Detoxamin, CaNa2EDTA may have an altered pharmacological profile from IV EDTA due to the rectal route of administration.

Pre-Clinical Toxicology Studies

The acute oral LD_{50} of calcium EDTA for the rat was found to be 10,000 ± 740 mg per kilogram body weight and for the rabbit and dog, approximately 7 and 11 g. respectively. The acute toxicity in rats was not altered by prior feeding of a diet suboptimal in respect to calcium, iron, copper and manganese.

In 2-year feeding studies with rats receiving diets containing calcium EDTA at levels to provide 50, 125 or 250 mg per kilogram body weight no adverse effects on growth or food efficiency were observed. Hematological examinations conducted periodically and determination of prothrombin time, blood sugar, NPN and serum calcium were likewise normal throughout the test period. Responses similar to those seen in the parent generation were observed in the rats of the three succeeding generations maintained on the same diet. Under the stresses of repeated pregnancies and lactation, no adverse effect of calcium EDTA was observed as measured by any of the usual indexes of reproduction or lactation efficiency. At autopsy neither gross examination nor the weights of the major organs disclosed any significant differences between the test and control groups. The histopathologic findings likewise revealed no consistent or dose-related effects.

Observations on the incidence and severity of dental caries, and the “line tests” of the tibias failed to suggest any evidence of an adverse effect on the calcification processes. Determinations of the xanthine oxidase content in liver tissue at autopsy, and on carbonic

anhydrase content of the blood, revealed no significant changes resulting from chronic ingestion of calcium EDTA. The normal physiologic responses and behavior of the rats, even under the stresses of reproduction thought successive generations, are consistent with the lack of effect of the chelating agent on these or other important metallo-enzyme systems.

Groups of dogs were fed diets furnishing 0, 50, 100 and 250 mg of calcium EDTA per kilogram body weight for 1 year. Every dog gained weight during the test period, regardless of dietary treatment. The hematologic findings suggest that the dogs at all dosage levels were in an even better state of health after 1 year of test feeding than they were initially. No significant deviations from normal or control values were noted throughout the test period in urine or in blood chemistry, including the values for prothrombin time. Roentgenographic examinations of the rib cages and leg bones of the dogs in the highest dosage group and of the femurs of all dogs at or near the termination of the test period showed no evidence of osseous change.

All dogs survived the 1-year test period. No gross aberrations were seen at autopsy, and the weights of the liver, kidneys, spleen, heart, adrenals and gonads were all within normal limits. Histopathologic findings of the liver, kidneys, pituitary, adrenals and 12 additional organs in the dogs of the highest dosage group were negative (6)

Ca-disodium EDTA LD_{50}

Animal	Route	(mg/kg bw)	References
Rat	oral	10,000 ± 740	Oser et al., 1963
Rabbit	oral	7,000 approx.	Oser et al., 1963
Rabbit	i.p.	500 approx.	Bauer et al., 1952
Dog	oral	12,000 approx.	Oser et al., 1963

$CaNa_2EDTA$ produced minimal focal hydropic kidney changes in 58% of animals, disappearing almost two weeks after stopping the injections (7).

Short-term studies

Rat

Groups of five male rats received 250 or 500 mg/kg bw $CaNa_2EDTA$ i.p. daily for three to 21 days and some were observed for an additional two weeks. Weight gain was satisfactory and histology of lung, thymus, kidney, liver, spleen, adrenal, small gut and heart was normal except for mild to moderate renal hydropic change with focal subcapsular swelling and proliferation in glomerular loops at the 500 mg level. There was very slight involvement with complete recovery at the 250 mg level. Lesions were not more severe with simultaneous cortisone administration (7).

Groups of three male and three female rats were fed for four months on a low mineral diet containing one-half the usual portion of

salt mixture (i.e. 1.25% instead of 2.50%) with the addition of 0% and 1.5% $CaNa_2EDTA$. The test group showed a reduced weight gain, but there was no distinct difference in general condition of the animals (8).

In another experiment three groups of eight to 13 male and female rats were fed a low-mineral diet containing 0, 0.5 and 1% of $CaNa_2EDTA$ for 205 days. No significant differences from the controls were shown regarding weight gain, mortality, gross pathology of the organs and histopathology of liver, kidney and spleen except a very slight dilatation of hepatic sinusoids. Blood coagulation time, total bone ash and blood calcium level were unaffected. No significant erosion of molars was noted. Basal metabolism was in the normal range (9).

Dog

Four groups of one male and three female mongrels were fed diets containing 0, 50, 100 and 250 mg/kg bw $CaNa_2EDTA$ daily for 12 months. All appeared in good health, without significant change in blood cells, hemoglobin and urine (pH, albumin, sugar, sediment). Blood sugar, non-protein nitrogen and prothrombin time remained normal. Radiographs of ribs and of long bones showed no adverse changes at the 250 mg level. All dogs survived for one year.Gross and microscopic findings were normal (6).

Long-term studies

Rat

Four groups of 25 male and 25 female rats were fed diets containing 0, 50, 125 and 250 mg/kg bw $CaNa_2EDTA$ for two years. Feeding was carried on through four successive generations. Rats were mated after 12 weeks' feeding and allowed to lactate for three weeks with one week's rest before producing a second litter. Ten male and 10 female rats of each group (F_1 generation) and similar F_2 and F_3 generation groups were allowed to produce two litters. Of the second litters of the F_1, F_2 and F_3 generations only the control and the 250 mg/kg bw groups were kept until the end of two-years' study on the F_0 generation. This scheme permitted terminal observation to be made on rats receiving test diets for 0, 0.5, 1, 1.5 or 2 years in the F_3, F_2, F_1 and F_0 generations, respectively. No significant abnormalities in appearance and behavior were noted during the 12 weeks of the post weaning period in all generations. The feeding experiment showed no statistically significant differences in weight gain, food efficiency, haemopoiesis, blood sugar, non-protein nitrogen, serum calcium, urine, organ weights and histopathology of liver, kidney, spleen, heart, adrenals, thyroid and gonads. Fertility, lactation and weaning were not adversely affected for each mating. Mortality and tumor incidence were unrelated to dosage level. The prothrombin time was normal. There was no evidence of any chelate effect on calcification of bone and teeth. Liver xanthine oxidase and

blood carbonic anhydrase activities were unchanged (6).

Comments:

$CaNa_2EDTA$ is metabolically inert and no accumulation in the body has been found. A vast clinical experience in its use in the treatment of metal poisoning has demonstrated its safety in man. Long-term feeding studies in rats and dogs gave no evidence of interference with mineral metabolism in either species. Adverse effects on mineral metabolism and nephrotoxicity were only seen after parenteral administration of high doses.

Clinical Safety

Two carefully monitored clinical trials revealed no significant adverse effects, either patient reported or within blood chemistry panels of those on the studies. The researchers at the Living Longer Institute, Cincinnati, OH state that the dosage form is gentle and appears to create little biological burden and is well tolerated. Only minor transient complaints of loose stools, rectal gas, headache, lethargy and minor joint pain were reported.

Within the Living Longer clinical the following lab parameters were compared between pre and post treatment with Detoxamin in all subjects:

Comprehensive Metabolic Panel

- Albumin
- Total Bilirubin
- Calcium
- Chloride
- Creatinine, Serum
- Glucose
- Alkaline Phosphatase
- Potassium
- Total Protein
- Sodium
- AST (SGOT)
- Urea Nitrogen (BUN)
- Bicarbonate (CO2)
- ALT (SGPT)
- C-Reactive Protein

No statistical difference in above lab parameters between pre and post treatment were observed with Detoxamin.

Dr. Ted Rozema performed a study with 20 children with high lead blood levels utilizing 1000 mg Detoxamin suppositories over a thirty-day period. No adverse effects were reported.

Safety in Clinical Practice

Dr. Rita Ellithorpe, MD has treated over 1800 patients with Detoxamin and administered over 100,000 doses of the product over a six-year period; other than minor discomfort complaints that were dismissed due to other meds or lifestyle events occurring within a very small percentage of those on the product. Dr. Ellithorpe observed no significant adverse effects and no aberrant blood chemistry values in her practice with the use of Detoxamin.

Post Marketing Safety

There have been over 2,500,000 doses of Detoxamin administered to over 50,000 patients worldwide, with over 2500 health care professionals recommending Detoxamin to their patients within the last eight years. The most common minor complaints were loose stools and gas experienced in the first few applications. Detoxamin is safe for children.

Side Effects

Detoxamin in the suppository form appears to have few minor side effects. Renal excretory function should be within normal limits prior to treatment. Daily urinalysis is not required when using Detoxamin suppositories. With Detoxamin the following side effects may occur rarely: loose stools, headache, rectal discomfort, nausea, and loss of appetite. These symptoms are usually rare and transient. The most common complaints are loose stools and gas experienced in the first few applications.

Usage in Pregnancy

Safe use of CaNa2EDTA suppositories has not been established with respect to adverse effects on human fetal development. However, animal studies on fetal development utilizing high doses of EDTA have shown no ill effects for several generations. It is recommended that Detoxamin should not be used in women of childbearing potential and particularly during pregnancy only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Precautions

Treatment with Detoxamin has been shown to cause a lowering of blood sugar and insulin requirements in patients with diabetes who are treated with insulin. Diabetic patients should check their insulin and glucose levels. Adverse side effects are extremely rare. Detoxamin exhibits no known adverse renal, hepatic, cardiovascular, gastrointestinal or central nervous system effects.

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Tustin
Longevity
Center

Rita Ellithorpe, M.D.
13422 Newport Avenue Suite L
Tustin, **CA** 92780
(714) 544-1521 ph www.tlcmd.net
(714) 544-1904 fax **rellithotpe@tlcmd.net**

STATEMENT OF CLINCAL EXPERIENCE WITH
DETOXAMIN ($CaNa_2$ EDTA)

Rita R. Ellithorpe, M.D.

I have been familiar with E.D.T.A. chelation therapy for the treatment of potentially toxic heavy metals for most of my life, having received this therapy myself as early as the age of sixteen. I have seen several of my own family members receive this therapy on multiple occasions for primarily its cardiovascular enhancing effects. Each of these personal experiences was positive and was completed without any adverse side effect. Having now reached the age of fifty and obtaining some distance from the completion of Medical School (North Chicago Medical School/1978-82) and an internship in family practice (Womack Army Medical Center, Fort Bragg, NC/1982-83), I have now administered this FDA approved chelating agent to countless patients of mine as well as to myself and to my family members. Most of this therapy was made available through the intravenous form of chelation until the convenience and vastly more affordable form of suppositories (Detoxamin - $CaNa_2$ EDTA) which has become available to me approximately five years ago. I am truly pleased with the effectiveness in this form for the reduction of potentially toxic heavy metals in appropriately screened, eligible patients. I can state without reservation the safety and health-enhancing potential of this product for this industrialized, toxic environment we live in is enormous. I have treated over 1800 patients with Detoxamin and administered over 100,000 doses of the product and observed no significant adverse effects and no aberrant blood chemistry values. Our results at my clinic indicate this has been a great help in restoring and preserving patient health.

Toxic Heavy Metal Diagnosis

Fecal Metal Analysis

We recommend an initial stool analysis to detect the presence and quantity of toxic heavy metals in your patients. This is a simple, relatively easy procedure that is done at home and mailed to the diagnostic laboratory. Our clinical trials have shown significant excretions of heavy metals with Detoxamin treatment over time.

It is suggested to perform a fecal test before Detoxamin is administered and follow up after month of treatment (one suppository 4 evenings per week for six months).

The fecal metal analysis offers the following advantages to health practitioners:

1. Assessment of exposure to, and excretion of, toxic metals and elements
2. Monitor natural route of metal detoxification
3. Convenient specimen collection procedure
4. Analysis by ICP-MS
5. Result specific commentary provided
6. Correlates to significant findings increased of metal excretion with Detoxamin

Description

Analysis of elements in feces provides important information about the potential for toxic metal burden. For many toxic metals, fecal (biliary) excretion is the primary natural route of elimination from the body. Fecal elemental analysis also provides a direct indication of dietary exposure to toxic metals. Specimen collection is convenient for the patient and only requires a single-step procedure.

Analysis of elements in feces provides a comprehensive evaluation of environmental exposure, potential for accumulation in the body, and possibly endogenous detoxification of potentially toxic metals. For many toxic elements such as mercury, cadmium, lead, antimony and uranium, biliary excretion into the feces is the primary natural route of elimination from the body. The primary process by which the body eliminates the insidious sulfhydryl reactive metals is through the formation of metal-glutathione complexes, of which greater than 90% are excreted into the bile. Evidence for the extent of exposure to mercury from dental amalgams is provided by the fact that fecal mercury levels are highly correlated with the number of amalgams in the mouth.* It also clear that fecal mercury levels for people with dental amalgams are remarkably similar from day to day, and approximately ten times higher than in people who do not have mercury amalgams.

Administration of pharmaceutical metal binding agents results in excretion of toxic metals primarily through the kidneys into the urine. In contrast, support of natural detoxification processes enhances the rate of excretion of toxic metals into the feces. Elemental analysis of fecal specimens can provide a valuable tool to monitor the

efficacy of natural detoxification of metals in infants or patients who are on very limited and defined diets that do not contain contaminated solid foods. A preliminary study performed at Doctor's Data indicates that biliary/fecal excretion of mercury and lead may be markedly enhanced following high dose intravenous administration of ascorbic acid. Other orthomolecular or nutraceutical protocols may also enhance the fecal excretion of metals and hence potentially decrease burden on the kidneys. Further research to identify and validate such therapies is warranted.

A primary objective of preventive medicine is avoidance or removal of exposure to toxic substances. The rate of oral absorption of toxic metals varies considerably among elements, and among subspecies of a particular element. Fecal elemental analysis can provide a direct indication of dietary exposure. Orally, the percent absorption of nickel, cadmium and lead is usually quite low, but varies significantly in part due to the relative abundance of antagonistic essential elements in the diet. That is particularly evident for lead and calcium, and cadmium and zinc. Chronic, low-level assimilation of the toxic metals can result in significant accumulation in the body. The results of fecal elemental analysis can help identify and eliminate dietary exposure to toxic metals.

The fecal metals test was not developed to replace the pre and post urinary toxic metals provocation test, but rather provides an alternative for infants, children or adults for whom urine collection is problematic, or for individuals who do not tolerate the available pharmaceutical metal detoxification agents. Elements are measured by ICP-MS and expressed on a dry weight basis to eliminate variability related to water content of the specimen.

Fecal metal tests can be ordered directly from Doctor's Data, Inc:

Doctor's Data, Inc.
3755 Illinois Avenue
St. Charles, IL 60174-2420
800.323.2784

Optional Heavy Metal Analysis

Red Blood Cell Elements

1. Measurement of toxic and functional intracellular elements
2. Analysis by ICP-MS
3. Result specific commentary provided
4. Requires unwashed packed red blood cells

Analysis of red blood cells provides the best diagnostic tool for assessing the status of elements that have important functions inside cells or on blood cell membranes. Blood cell element levels are useful for assessing cardiac influences, anti-inflammatory processes, anemia, immunological function, glucose tolerance and other disorders that are associated specifically with zinc deficiency.

Urine Toxic Metals

1. Assessment of toxic element burden and essential element wasting
2. Monitors detoxification therapy
3. Analysis by ICP-MS
4. Interpretive report provided
5. Variable urine collection periods

Analysis of elements in urine provides diagnostic information on potentially toxic elements such as lead, mercury, cadmium, nickel, beryllium, arsenic and aluminum, and assessment of the efficiency of renal resorption of essential elements such as magnesium, calcium, sodium and potassium.

Hair Toxic Element Exposure Profile

1. Measurement of toxic and essential elements
2. Inexpensive, noninvasive
3. Analysis by ICP-MS
4. Result specific commentary provided
5. Requires 0.25 g hair

Extensive research established that scalp hair element levels are related to human systemic levels. The strength of this relationship varies for specific elements, and many researchers consider hair as the tissue of choice for toxic and several nutrient elements. Unlike blood, hair element levels are not regulated by homeostatic mechanisms. Thus, deviations in hair element levels often appear prior to overt symptoms and can thereby be a valuable preliminary tool for predicting the development of physiological abnormalities.

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