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IN REPLY REFER TO: H-4

March 11, 1952

Dr. Phillip A. Fuqua
Kadlec Hospital
Richland, Washington

Dear Phil:

I am sending the proposed protocol for your consideration and suggestions. I also am including all of the toxicity data that I could get together along with a record of the use of EDTA in humans to date, with references. When the information was obtained by personal communication I have included the original letter or manuscript whenever I could. These, of course, I would like to have returned for my file. I am sure there is no objection of your having copies made of things of special interest. I have marked thepapers I should like to have returned.

I looked up the citric acid data. Kety and Letonoff (Am. J. M. Sc. 205 406 (1943)) gave 20 grams of sodium citrate daily by mouth in the treatment of lead poisoning without any ill effects.

I wrote Dr. Fenn Poole of the Riker Laboratories in Los Angeles, and asked him to send you two dozen one gram ampules of Ca EDTA for human use and a liter of 25% Ca EDTA to Harry for animal experimentation.

As you can well surmise I am intensely interested in having Ca EDTA tried in a case and will be glad to cooperate in any way we can. Please keep me informed of developments and feel free to call on me at any time.

With best regards,

Sincerely yours,

Harry Foreman

Harry Foreman, M. D.

HF/m

US DOE ARCHIVES
RG 326 US ATOMIC ENERGY COMMISSION
DIVISION OF BIOLOGY & MEDICINE
Box 3353
Folder MH52 Toxicology

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CLINICAL LABORATORIES
GEORGETOWN UNIVERSITY HOSPITAL
WASHINGTON, D. C.

DIRECTOR
V. J. DAROINSKI, M. D.

26 May 1951

Harry Foreman, M. D.
University of California
Radiation Laboratory
Berkeley 4, California

Dear Harry:

I enjoyed very much hearing from you. I have the feeling that any discrepancy in our toxicity data on CaEDTA is accidental rather than real. The gal who keeps the books is currently out of town so allow me to check our records later for confirmation as to what I am about to tell you. I am writing you rather than delay you beyond the conference date of which you spoke.

As I recall our data on the toxicity of CaEDTA by vein in rabbits pointed to an M.L.D. 50 of about 2500 mg/Kg. Dosage I.P. in rats ran very much in the same order of of magnitude and I.V. in rats the values were slightly lower. We have conducted a good deal of high level chronic toxicity work in rats per os and again as nearly as I remember 2% concentration in the water has thus far (some months) been without effect.

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The human data I can give you with closer assurance because I compiled the story myself. In one case of chronic Berylliosis a man has been given a total of 98 g. of CaEDTA by vein over a period of 22 days. The dosage was gradually upped daily from 100 mg. to finally 10 grams at a single I.V. injection. There was no indication of toxicity either acutely or cumulatively over the period of treatment or afterwards. Interestingly enough even the usual indications of calcium ion introduction by the I.V. route -- namely, the warm sensation used for ~~in~~ inculation time determination, was absent. The work was done at another institution and Be analysis in the urine have not yet been completed.

I have my own doubts as to the potential effectiveness in chronic Be poisoning. I feel that the ~~dosage~~ damage may have been irreparably done beyond reversible change even if the Be could be cleaned out of the system.

I do not know what your data are on the toxicity of CaEDTA. There are three points bearing comment. The first refers to the necessity that free Versene be absent from the preparation under study. The second

problem bears on the equal requirement that excess calcium ion be absent in the solution and finally, in this situation, one should also guard against an excess of salt that may inadvertently creep in the solution in adjustment of ph by acid or base. These points having been cared for I have the feeling that our results will be the same. I am wondering if I can get Dr. Singer at Bersworth Chemical Company to prepare a batch of CaEDTA for both of us, so that we can make a direct comparison.

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In this connection we have completed a rather extensive determination of the M.L.D. 50's of Pb Acetate and Pb Versene I.P. in rats that may have some bearing on the subject. Although the rat is resistant to lead poisoning, as is known from other work, we have been able to establish that for Pb Acetate the I.P. M.L.D. 50 runs about 650 mg/Kg. calculated as Pb^{++}. For Pb Versene the value for the M.L.D. 50 is about 2500 mg/Kg. of Pb^{++}. For this work the acute toxicity was defined as death having occurred within a period of one week.

I'd like to hear from you on your own work. How is Kopp's old group getting along on the Ca45 problem? Anything new? Are they still in business?

Very best regards,

Martin

Martin Rubin

MR:m

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PROTOCOL FOR THE USE OF Ca EDTA IN HUMANS

AIMS: 1. To test the efficacy of Ca EDTA in accelerating the excretion of Plutonium in humans.

2. To determine toxic effects, if any.

3. To obtain data for establishing an optimum dosage.

4. To determine the best mode of administration of the drug.

GENERAL PROCEDURE: 1. Starting one week before administration of the drug, 24 hour urine and feces specimens are to be collected.

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2. On day of test - (a) physical examination with special emphasis on skin condition and neurological status, (b) 20 cc blood for laboratory tests to be drawn. The tests to be run include RBC, WBC, HGB, Hematocrit, serum Ca, P, total protein A/G ratio, NPN, Addis count, PSP urine urobiligen and blood and urine EDTA levels.

3. Complete laboratory tests to be run every day. P. E. to be done before each time the drug is administered with careful observation for eruptions, jaundice, neurological changes, headaches, anorexia, diarrhea and oliguria.

4. Administration of the drug - 5 gms in 1000 cc saline given by I.V. drip over a period of 2 hours.

5. Laboratory work and collection of specimens to continue until 3 days after the last administration of the drug.

DISCUSSION

The use of EDTA in humans is still so recent that very few reports have reached the stage of publication. Most of the information contained in this table was obtained by personal communication with the people presently engaged in the work. Because of the current nature of the work the compilation necessarily is not complete. It covers, however, most of the cases up to January, 1952.

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It is quite surprising that in view of the recent application of this agent to biological problems (approximately 1½ years), there are already between 60 to 70 applications in humans in which the drug or its chelates were administered intravenously and 2 cases in which it was applied topically. It is being used extensively in a ureteral and vesical irrigating solution for the dissolution of stones. One series of 20 to 30 cases is already on report. Recently the drug has been used in processing of human plasma and a number of cases have received the drug in this manner.

The doses range from 100 mgm to as high as 10 gm administered intravenously in a single dose. One individual received a total of 95 gm over a period of 22 days.

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Patients receiving the drug were carefully followed clinically and by laboratory tests. When the Ca chelate was used there were no alterations in the serum Ca, Na, K, P and protein levels. The only possible toxic effect which bears further investigation is the aberration in the Addis Test results reported in the case which received 95 gm of Ca EDTA. No clinical evidence of renal impairment was apparent at the time. When the Ni chelate was used the serum values were apparently unaltered. The use of the Mg chelate resulted in noticeable depression of the serum Ca and P levels. This is to be expected in view of the fact that Ca will displace Mg from combination with EDTA and will be removed from the body as the chelate of the EDTA. Phosphorus serum level depressions were secondary to the Ca changes. The application of unchelated EDTA is not recommended for humans in view of its property for lowering serum Ca. Even when the material is applied percutaneously in a 5% ointment there was a marked drop in serum Ca from 11 mgm to 8 mgm per 100 cc in 2 days.

It should be noted that extensive toxicity experiments were carried out in animals both at Berkeley and by Dr. Rubin and his group at Georgetown University before any of this work with humans was done. Less than 400 mgm per kilo of body weight of the EDTA will result in death with hypocalcemic tetany in 20 minutes in the rat. Similar levels apply for rabbits. With the Ca chelate, however, the LD_{30}^{50} days was found to be 3 gm per kilo of body weight when administered intraperitoneally to the rat. Death occurred with marked ascites resulting from the injection of a highly hypertonic solution into the intraperitoneal cavity.

In chronic toxicity studies, animals have been fed a stock diet containing 3% Ca EDTA for 5 months. This represents a daily intake of approximately 1.5 gm per kilo of bodyweight. There were no apparent ill effects. The animals had a daily food intake similar to the control animals and over the period of time they had the same weight gain. At autopsy no unusual findings were noted on gross examination. Some of the tissues are being prepared for histological examination. Animals fed a diet containing 5% Ca EDTA developed a diarrhea which persisted through the course of the experiment. These animals exhibited about two-thirds of the weight gain of the control animals. Animals fed on a 10% diet all died within a week. They had a very marked diarrhea.

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THE MEDICAL USE OF ETHYLENEDIAMINETETRAACETIC ACID (EDTA)

A Compilation of Cases

No.	Compound Used	Dosage	Reason for Use	Therapeutic or Physiological Effect	Toxic Effects	Comments	Ref.
1. ♂, 37	Ca EDTA	Range from 100 mgm to 10 gm I.V. up to a total amount of 94.9 gm.	Rx of beryllliosis	None observable; no change in serum Ca, Na and K values	Questionable Addis count changes	Received ACTH concurrently	1
2. Several terminal cancer cases	Ni EDTA	1 gm I.V.[a]	Research	None observable	None observable	88% normal in 2 hours. 100% in 36 hours.	2
3. 2 cases	Mg EDTA	120 mg I.V.[a] followed by 180 mg I.V.	Rx of hypertension	Lowering of systolic pressure as much as 30 mm Hg for 3-4 days. Lowering of diastolic pressure as much as 40 mm.	Depression of Ca and P serum levels. Ca down to 8 mg/100 cc and P to 2mg/100cc		3
4. 2 cases	EDTA	Percutaneous administration of ointment containing 5% EDTA	Research		Lowering of serum Ca down to 8 mg/100cc		4
5. 20-30 cases	EDTA	5% solution in water as an irrigating medium	Rx of ureteral lithiasis	Dissolution of stones	Bladder irritation		5,6, 7
6. 30 cases	EDTA	1.5 gm combined with one unit plasma.	Inclusion results from processing of plasma.				8
7. 3 year, ♂	Ca EDTA	Range from 150 mg to 750 mg I.V. daily up to a total of 65 gm.	Rx of lead encephalopathy	Alleviation of lethargy and twitchings. Increase in blood Pb levels.	Rise in NPN up to upper limits of normal.		9
8. ? ♂	EDTA	2 to 5 gm daily I.V. up to 12 gm in 5 days.	"Controlled bone lysis"	Elevated Urinary calcium output. Serum calcium levels maintained. Bone was apparently decalcified.		Use of calcium chelate would avoid this.	10

[a] Estimated or calculated value.

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