THE USE OF Ca EDTA IN CASES OF LEAD INTOXICATION

In response to the considerable interest which has been expressed in calcium ethylenediaminetetracetate (Ca EDTA), a new drug which shows promise in the treatment of heavy metal poisoning, we are suggesting a protocol for the use of the drug in lead intoxication.

The purpose of suggesting a uniform mode of treating cases with this drug is to promote the use of case material as efficiently as possible in gathering information about the drug. It is hoped that during these initial stages the trial of the drug will be limited to experienced clinical investigators with adequate facilities for observation and follow up of the patients.

As an aid to such investigators, we have summarized the experience in the use of the drug in humans to date and are indicating a dosage schedule based on toxicity studies in animals. These studies were carried out by Dr. George Maison, Dept. of Pharmacology, Boston University School of Medicine.

Mr. Manfred Bowditch, Director of Health and Safety of the Lead Industries Association, has agreed to hold a registry of such protocols of Ca EDTA treated cases of lead poisoning in his office at 420 Lexington Avenue, New York 17, N. Y. It is planned by this means to make the information collected centrally available for study.

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PROTOCOL FOR THE USE OF Ca EDTA IN CASES OF LEAD INTOXICATION

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

NECESSARY CLINICAL DATA:

Name, sex and age,

Home Address,

Physician in charge,

Hospital,

Occupational History in the case of an adult,

Exposure History in the case of a child,

Medical History and Examination -

1. Character of onset; presenting signs and complaints,

2. Clinical course, including response to previous therapy,

3. Pretreatment physical examination, with particular attention to:

   a. Lead line of the gums,

   b. Involvement of the peripheral nerves by weakness or palsy of extensor muscles,

   c. Visible jaundice,

   d. Involvement of central nervous system, i.e. encephalopathy,

4. Pertinent laboratory findings: anemia, stippling, reticulocytes;

Medical Examination During Treatment -

Evidence of side or toxic actions in:

1. Cardiovascular system,

2. Gastrointestinal tract,

3. Genitourinary tract,

4. Central nervous system,

5. Blood,

Appraisal of effects, both objective and subjective;

Medical Examination After Treatment -

Careful observation for possible reactions for at least a month and at intervals thereafter, depending on the circumstances.

NECESSARY LABORATORY DATA:

1. If feasible, starting one week before the beginning of treatment, collect daily urine specimens and/or blood for lead assay. Continue daily assays for 2-3 days following cessation of treatment. When possible, coproporphyrin studies should be done on the urine.
2. Hematological tests to be done include Hgb, WBC and differential, hematocrit, bleeding and clotting time and bone marrow biopsy (or direct smears if biopsy is deemed impractical) - one set of values pretreatment.
3. Routine urine analysis and Addis count.
4. Further studies should include serum calcium and phosphorus if possible, total protein A/G ratio, N P N, prothrombin time, urine urobilinogen.

For close follow-up of the patient it is urged that certain laboratory tests should be run daily during treatment. These tests are listed below. Other tests should be done as frequently as practical or as circumstances indicate.

Hgb,

WBC and differential,

Serum calcium and phosphorus,

Prothrombin time,

Urine urobilinogen,

Blood lead and/or urinary lead,

Urinary coproporphyrin, if quantitative test is available.

This follow-up should continue for 3-7 days after the last administration of the drug and then at longer intervals as seems wise to the investigator.

SUGGESTED DOSAGE:

1. Route: intravenous drip only, not over 0.5 gm per 30 lbs. per hour.
2. Total dose limited to: 1 gm per 30 lbs. body weight per 24 hours.
3. Maximum total dose per week (7 days) of 5.0 gm per 30 lbs. body weight in divided doses.
4. Limit individual courses of treatment to 10 days, with one week rest period between; 7.5 gm maximum per 30 lbs. over 10 days.

THE HUMAN USE OF ETHYLENEDIAMINETETRACETIC ACID (EDTA)

A Compilation of Cases

No.	Compound Used	Dosage	Reason for Use	Therapeutic or Physiological Effect	Toxic Effects	Comments	Ref.
1. 3 cases, children	Ca EDTA	.5 gm in divided doses to total of 8 gm	Rx of acute Pb poisoning	Alleviation of lethargy in 2-3 hrs. Marked increase in alertness	No change in hematological findings. No change in blood chemistry		1
2. 1 child	Ca EDTA	1 gm dose daily for 5 days	Chronic Pb poisoning		No toxic manifestations		2
3. 3 cases	Ca EDTA	2 gm doses daily up to a total of 30 gm in 3 weeks	Rx of subacute Pb poisoning	Subjective improvement Decrease in Pb line Increase in red count from 3.9 to 5.2 m. in one month	Reported bone marrow depression Later refuted		3
4. 1 case age 3	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		1
5. 1 case age 37	Ca EDTA	Range from 100 mgm to 10 gm I.V. up to a total amount of 94.9 gm	Rx of beryllosis	None observable; no change in serum Ca, Na and K values	Questionable Addis count changes	Received ACTH concurrently	4
6. 60 cases	EDTA	1.5 gm combined with one unit blood	Anticoagulant		None	Blood elements well preserved	5
7. 11 cases	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 prevents this	6
8. 1 case	EDTA	Doses up to a single dose 20 gm I.V. in 20 min	To lower serum calcium in patient with Ca of breast; with osteolytic lesions	Lowering of serum calcium from 25 mg/100 cc to 8.8 mg/100 cc in 1 hr	Apprehension, headaches, restlessness		7
9. 5 cases	EDTA	.01 M solution as eye wash	Dissolution of calcified plaques in cornea	Favorable results	No evidence of toxicity		8
10. 20-30 cases	EDTA	5% solution in water as an irrigating medium	Rx of ureteral lithiasis	Dissolution of stones	Bladder irritation		9, 10, 11
11. 11 cases	EDTA	Percutaneous administration of ointment containing 5% EDTA	Research		Lowering of serum Ca down to 8 mg/100 cc		12
12. 12 cases	Mg EDTA	120 mg I.V. followed by 180 mg I.V.	Rx of hypertension	Lowering of systolic pressure as much as 80 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 2 mg/100 cc		13
13. 2 terminal cancer cases	Ni EDTA	1 gm I.V.	Research	None observable	None observable	88% excreted in 2 hrs. 100% in 36 hrs.	14

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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 July, 1952. It is surprising that, in view of the recent application of this agent to biological problems, there are already over a hundred applications in humans in which the drug or its chelates were administered.

There have been eight cases of Pb poisoning treated with Ca EDTA; 5 in children and 3 in adults. In the 4 acute cases in children there was marked alleviation of symptoms within several hours of treatment. In every case where urinary Pb assays were determined, there was considerable enhancement of Pb excretion following treatment, up as high as a factor of 20 in one case. There was no evidence of toxicity from the use of the drug, nor were there symptoms associated with the mobilization of the Pb. The highest single dose of Ca EDTA that was administered was 10 gm, given to a patient with berylliosis. This patient received a total of 98 grams over a period of 22 days. In a very large series the uncomplexed acid was used as an anticoagulant for transfusions into patients. Even in the individuals receiving multiple transfusions there was no evidence of ill effect. In other cases the EDTA was given experimentally to study Ca metabolism. In one striking instance, a terminal carcinoma case with osteolytic lesions, where the serum Ca levels were as high as 25 mg/100 cc, a single dose of 20 grams EDTA was administered intravenously in 20 minutes. The serum Ca level was brought down to 8.8 mg/100 cc in one hour. In other experimental studies the Ni and Mg chelates were administered. The use of the Mg chelate resulted in appreciable 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. Other human applications included such uses as ureteral irrigation to dissolve calculi and eye washes to remove calcific deposits. Topical applications in the form of water-soluble ointments indicate that EDTA is readily carried through the skin.

The low toxicity of Ca EDTA is explained by the findings in studies using the C^{14} labeled material. The material is excreted unchanged. All of the drug can be accounted for in the excreta. Sixty to 90 per cent of the administered drug is present in the urine after 6 hours; 95-99 per cent in 25 hours. The remainder is in the feces. Distribution studies reveal no unusual localization of the drug in any organ during the time the material is in the body.