Effect of Chelating Agent on Urinary Lead Excretion. Comparison of Oral and Intravenous Administration. (20073)

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The need of a more effective agent for the treatment of lead poisoning is evident. The methods of therapy currently available are either of questionable effectiveness or possess serious side-effects. Recently an organic chelating agent, disodium calcium ethylene diamine tetra-acetate (CaEDTA) has been suggested for the treatment of lead poisoning and shows promise of being superior to compounds previously used(1,2). CaEDTA is stable, odorless, water-soluble, and forms a stable complex with lead which is virtually non-ionized. CaEDTA is not concentrated in any particular organs or tissues of the body, is rapidly excreted in the urine, and apparently has little or no toxicity for man in the doses used(3,4).

A study was undertaken to determine the effectiveness of the drug administered by the oral and intravenous routes. There have been no reports on the use of oral CaEDTA in humans. If oral administration were effective, it would facilitate medical control of industrial exposures to lead and would thereby broaden the usefulness of the agent.

Methods and materials. Studies on 7 patients treated with CaEDTA† are reported here (5 adults and 2 children), who had either symptoms of lead poisoning or excessive amounts of lead in their blood and/or urine by chemical determination. The *dosage* schedule of CaEDTA was arbitrary. The intravenous dosage schedule used for adults was 1.0 g on the first day and 2.0 g a day thereafter; a total of 5 treatment-days was ordinarily employed. On the first day of treatment the dose was divided into 0.2 g and 0.8 g; subsequent doses were 1.0 g given twice daily. Each dose was diluted in 250 ml of 5% glucose in water and given slowly by intravenous infusion over a period of one hour, allowing at least 6 hours between doses. Children were given a test dose of 1 10 the calculated daily dose, as were adults; subsequent doses of 30 mg/kg in 5% glucose in water (infused slowly) were given twice daily. The *oral dose* used in both adults and children was 30 mg/kg administered twice a day. For study purposes the usual course of 5 days of continuous therapy was interrupted in patients J.S., W.B., and L.Q., for one or more days to demonstrate effectiveness of the agent or to begin an alternate route of therapy. Twenty-four hour urine collections and whole blood specimens were obtained before, during, and after the treatment period for lead analysis. (The dithizone method with buffer extraction was used(5)). Multiple hemograms and urinalyses were performed on specimens from all subjects. The serum levels of calcium, magnesium, inorganic phosphorus, chloride, sodium, potassium, total protein, urea nitrogen and thymol turbidity were followed.

Results. Intravenous administration produced a 10- to 40-fold increase in urinary lead excretion on the first day of therapy. Subsequent values were generally of a lower order of magnitude but were never less than 3 times the observed pretreatment level. In contrast to the adults, maximum urinary lead excretion of the 2 children occurred on the second day of intravenous therapy, *e.g.*, the value on the second day for J.S. rose to 60 times the control value.

Oral CaEDTA produced a different pattern of lead excretion from that obtained with intravenous administration. The rise in excretion tended to be more gradual, with maximal excretion occurring on the third or fourth day of therapy. When alternate routes of admin-

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† Supplied in ampules and as tablets by Riker Laboratories, Los Angeles, Calif.

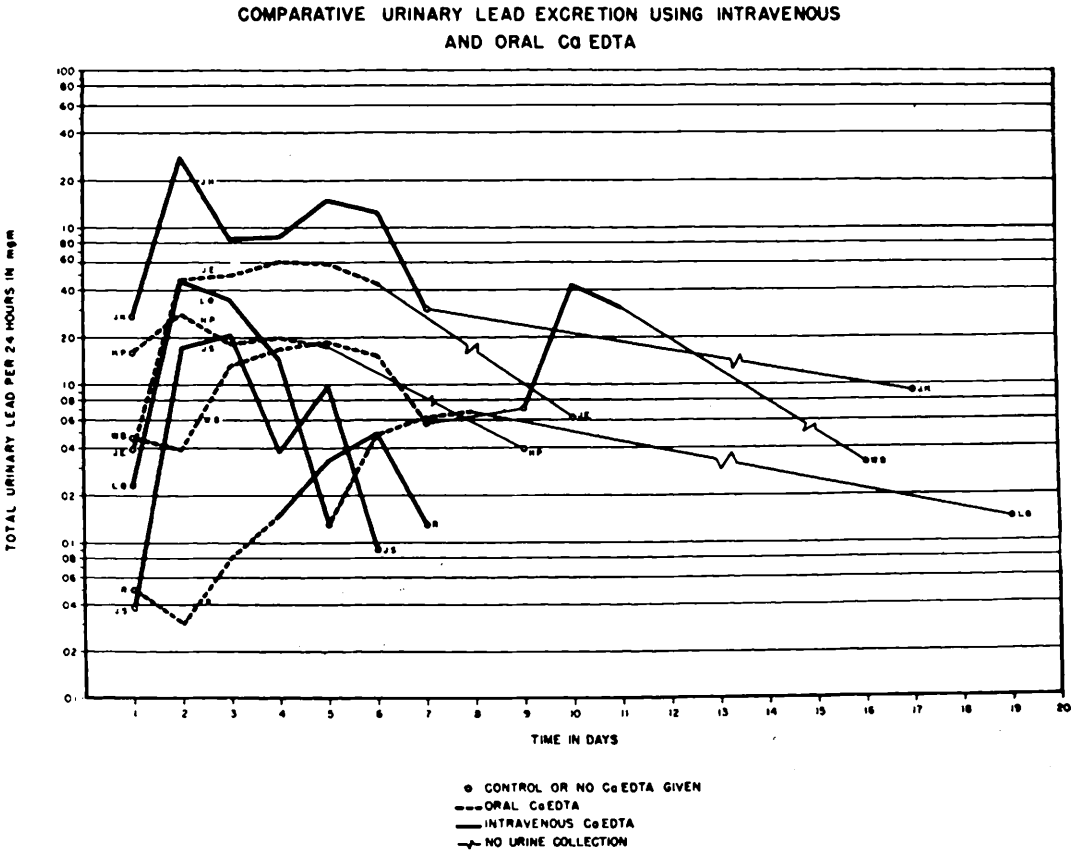

FIG. 1. The 24 hr urinary lead excretion in seven patients. A semilogarithmic scale is used for delineation of individual values. Treatment days are indicated by heavy or broken lines.

istration were used in the same individual, the maximal value of lead excretion attained with the use of intravenous infusion of CaEDTA always exceeded the maximal value obtained when oral medication was employed. Nonetheless, on the day of maximal excretion, a 5- to 10-fold rise of the 24-hour urinary lead excretion above the observed control values was attained with oral medication in all cases except J.P.

The blood lead values, stipple and reticulocyte counts showed a definite tendency to decrease. No consequential alterations were found in the chemical analyses on the serum.

There were no significant untoward effects observed when the dosage schedule given was followed. (Observations included 19 patients given CaEDTA: 4 patients followed by blood lead determinations only, 2 cases too recently treated for complete evaluation at this time; 2 "normals" given an infusion of CaEDTA, and 4 patients with other heavy metal poisonings.) Patients L.Q. and J.P. complained of malaise and light-headedness, and L.Q. also noted mild arthralgia on the first day of therapy. These symptoms, however, cleared entirely on the second day of therapy and did not recur. J.P. received 30 mg/kg of CaEDTA orally 3 times a day for the first 2 days of his 5-day course of treatment. He developed loose stools and abdominal pain after 48 hours on CaEDTA, which persisted until the medication was discontinued. This attempt to give a priming dose was undertaken when it was noted that two other patients receiving oral medication had little rise in urinary lead excretion in the first 24 hours of therapy. The desired effect was not obtained.

Discussion. The calcium chelate is used in the treatment of lead poisoning because chela-

tion by EDTA is not specific for lead. There is a definite order of chelation which varies for a given di- or tri-valent ion with the pH of the solution(3). Popovici *et al.*(6), have shown that the rapid intravenous injection of the non-chelated EDTA in rabbits produced tetany and death from hypocalcemia. By administering the compound as the calcium chelate, this danger is eliminated and toxicity is minimal.

The cases presented demonstrate that CaEDTA was well tolerated and effective in producing significant increases in the excretion of lead by the kidney. Those patients manifesting symptoms due to lead ingestion noted a prompt alleviation of symptoms. The increase in urinary lead excretion consequent to oral administration of CaEDTA was quantitatively less and maximal excretion was attained more slowly than when CaEDTA was given intravenously. Gastro-intestinal absorption of CaEDTA was suggested by the increase in urinary lead excretion following oral administration; however, the formation of the lead EDTA complex in the gastro-intestinal tract with subsequent absorption cannot be ruled out. Mosey and coworkers have shown that the lead EDTA complex when taken by mouth was rapidly absorbed from the upper gastro-intestinal tract(7). Further study is needed to clarify this point.

Summary. Seven patients with abnormally elevated blood lead and/or urinary lead excretion values are presented who received CaEDTA orally, intravenously, or by both routes. This organic chelating agent effected a marked increase in urinary lead excretion by both routes. Intravenous administration was more effective than oral therapy. Preliminary results indicate that CaEDTA is the most effective agent proposed for the treatment of plumbism. Side-reactions were minimal with the dosage schedule employed.

1. Bessman, S. P., Reid, H., Reinousky, A., and Rubin, M., *Med. Ann. Dist. Columbia,* 1952, v21, 312.

2. Belknap, E. L., *Indust. Med. and Surg.,* 1952, v21, 305.

3. *Tech. Bull. No. 2* (1950), Bersworth Chemical Co., Framingham, Mass.

4. Lead Industries Assn. Bull., July, 1952.

5. Bambach, J., and Burkey, R. E., *Ind. Eng. Chem.,* Analytical Ed., 1942, v14, 904.

6. Popovici, A., Geschickter, C. F., and Rubin, M., PROC. SOC. EXP. BIOL. AND MED., 1950, v74, 415.

7. Mosey, L., *et al.,* unpublished data.

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Comparison of Effects of Various Phosphate Compounds and Aluminum Silicate on Isolated Frog Heart. (20074)

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Various investigators, Linder and Rigler(1), Sheikhon(2), Lichtneckert(3), Loewi(4), have noted the restorative effects of adenosine triphosphate on the hypodynamic frog heart. A great variety of surface active substances such as sodium oleate, animal charcoal, camphor and serum are also known to increase the amplitude of contraction of the hypodynamic frog heart, Wieland(5), Clark(6). The present experiments were undertaken to study the effects of various phosphate compounds, ATP, ADP and sodium tripolyphosphate(TPP) on the hypodynamic frog heart and to compare them with a surface active substance, aluminum silicate (bentonite).

Methods. The heart of a frog, *Rana pipiens,* was removed, suspended in oxygenated Ringer solution† in a glass muscle cham-

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† NaCl 0.65 g %, KCl 0.014 g%, $CaCl_2$ 0.012 g %, adjusted to pH 7.3 with phosphate buffer.