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NEW METHODS OF DELEADING HEAVY LEAD ABSORPTION USING CALCIUM MONO SODIUM ETHYLENE DIAMINE TETRA ACETATE (EDTA)*

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After dealing with this subject for thirty years, I still find new and unexpected types of lead exposure, non-industrial as well as industrial. In all cases the dosage, that is, concentration and duration of exposure, is important. For my own understanding and for that of others, each case should be analyzed from the point of view of lead absorption as distinct from lead intoxication. Evidence of lead absorption is shown by the demonstration of lead line, a few stippled cells 5 to 10 per fifty fields, coproporphyrin in the urine, and, when medical-legal need demands it, quantitative study of lead in the urine. These findings do not, however, necessarily spell lead poisoning.

Lead poisoning or lead intoxication occurs only when, in addition to the above mentioned findings of lead absorption, we have symptoms or signs of actual disability. These symptoms may be merely weakness due to a secondary anemia usually preceded by a rapidly rising stippled cell curve. Lead intoxication occurring in 90 per cent of the cases is that of typical abdominal lead colic associated with ever-increasing constipation. As a positive therapeutic test and in contrast to the acute surgical belly, such a lead colic is relieved rapidly by intravenous calcium gluconate. Lead palsy which occurs only one-tenth as often as lead colic is the second commonest type of lead intoxication. Treatment for this in the past has been rest of the affected part for several months.

The rarest type of lead intoxication in adults is lead encephalopathy. In children, however, it is the most common type and seems to be increasing. In the past, treatment has not been specific for lead encephalopathy in the child. In the majority of cases, the outlook has been poor, frequently resulting in death or a serious residual in the form of mental deterioration. However, with increased use of Calcium EDTA the outlook has apparently improved.

In the treatment of the commonest type of lead intoxication in the adult, namely, the lead colic, there are two aims (1) the immediate relieve of symptoms, and (2) ridding the system of absorbed lead by some type of deleading therapy after the acute symptoms have subsided. If we were merely scientific we would simply remove the individual from lead exposure, knowing that within a week or two the lead colic symptoms would subside spontaneously. However, such a strictly scientific form of therapy is inadequate.

Since introduced by Joseph Aub in 1926 calcium salts have been efficacious when given intravenously for the relief of lead colic. However, such relief by calcium gluconate seems to be due to the non-specific effect of calcium in relaxing smooth muscle, rather than an immediate clearing away of the lead by the calcium.

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For actually ridding the system of absorbed lead by deleading there have been many different types of therapy suggested in the past 25 to 30 years. Clinicians have advocated shift of the acid-base metabolism, low calcium intake, high phosphorous diet with magnesium sulphate sodium citrate, and the long used potassium iodine type of therapy. However, no single method has been completely satisfactory. All have been questioned by a number of workers in the field. Certainly no such general agreement upon treatment for deleading exists as does for the relief of smooth muscle colic by calcium gluconate. Calcium Mono Sodium Ethylene Diamine Tetra Acetate, also called Calcium EDTA, Versene or Sequestrine, recently introduced, may be the deleading agent when given intravenously. Certainly it increases the urinary lead excretion markedly. To show how effective this new drug is in stimulating urinary lead excretion, we need only to note the previous levels in acute lead intoxication of about .3 to .8 mgs. lead per liter of urine lead, now raised 10 to 20 times this old excretory figure.

Let me emphasize that we are discussing the use of Calcium EDTA, not Sodium EDTA. Calcium EDTA seems to be harmless, though the sodium salt in much heavier dosage than I have used may produce a lower nephron nephrosis. Detailed blood chemistry and bone marrow studies of my hospital series showed no toxic effects from the Calcium EDTA except a slight transient bone marrow depression in 2 of 7 cases. In California, experimental work is being done as to possible toxicity of Calcium EDTA.

Publications on this subject began to appear about 1950. Reports on the subject from individuals and medical centers throughout the country have been increasing especially since 1952 and number about 80.

The theory of action of this new drug, Calcium EDTA, is that it chelates or binds a metal-ion like lead by complexing the metal in a ring structure so tightly that it is un-ionized. This apparently renders the metal harmless for safe excretion. Whether, however, such complexing will cause immediate relief of symptoms such as actual lead colic is still an open question. We do know that it is the most effective from of deleading that has yet been discovered either in the acute type of lead intoxication or the chronic type of lead absorption.

My hospital cases were treated with 5 cc. intravenously or one gram of Calcium EDTA diluted in 250 cc. of 5% glucose in distilled water over a period of 20 minutes twice a day for five days followed by a rest period of two days with a resumption of the five day course. This was followed by an additional period of rest for two days and finally a course of four days as before. Uniformly lead excretion went up and porphyrinuria went down. Some feel that this latter finding is most important because it may be an index of improved liver function slides.

My own experience covers about twenty cases in whom I used Calcium EDTA intravenously. Seven of these were under hospital control and showed no lasting residual. Thirteen outpatients who were workers having heavy lead absorption but no evidence of any disabling lead intoxication, were also studied. They were treated on a purely prophylactic and preventive basis supplemented by the reduction of lead exposure by increased engineering protective techniques installed by plant management. These 13 cases of extremely heavy lead absorption followed intense lead exposure due

to their work in smelting scrap battery plates. It was a small plant where engineering protection had, at that time, been entirely inadequate. It then seemed that the men would either have to be laid-off or hospitalized. Inasmuch as they had no symptoms, and management promised marked improvement in engineering protection, I felt it advisable to treat them intravenously with Calcium EDTA. All were given one to four courses of Calcium EDTA intravenously on the following modified schedule while at work and without symptoms. The men were sent to the company doctor's office one hour each day for five days a week. During the first part of the hour each man was given intravenously 5 cc. of Calcium EDTA in 250 cc. of 5% glucose in normal saline over a period of 20 minutes. He rested one-half to three-quarters of an hour and then returned to work. At no time did any man show untoward symptoms, and all insisted they felt better. The lead lines of the gums disappeared, and the stipped cells dropped markedly. Because these cases were studied while at work and were not under hospital control, it was impossible to study their 24 hour urine excretion. However, their urine porphyrin dropped rapidly and continued low just as in the 7 cases studied under hospital control.

In summary, these clinical cases seem to show that Calcium EDTA given intravenously is an excellent method of ridding the organism of lead by deleading, though in my experience it does not relieve lead colic promptly. My studies as well as other reports in the literature prove it to be superior to any previous deleading treatment and entirely safe.

One recent and detailed report of three cases treated with Calcium EDTA at the Massachusetts General Hospital, is that by Hardy[1]. All of Dr. Hardy's cases were subsiding lead intoxication, lead colic type cases, whereas two of mine were actually having acute lead colic. My experience in these two cases, moreover, tends to suggest that the intravenous Calcium EDTA will not relieve lead colic at once, though it certainly increases the urinary lead excretion. Immediate relief of symptoms can, therefore, be best obtained by supplementary calcium gluconate given intravenously in alternate doses with the Calcium EDTA.

Whether or not Calcium EDTA may be used prophylactically in the form of tablets for oral use in the cases of heavy lead absorption remains to be studied further. Such oral therapy is certainly not as effective as the intravenous form.

Experience in these 7 cases of heavy lead absorption treated under hospital control and the 13 cases treated in the doctor's office while at work, indicates that the intravenous Calcium EDTA is both effective and safe as a deleading agent. However, this is to be considered an emergency measure. Proper engineering protective devices which prevent lead exposure and resultant lead absorption are still the best treatment.

ADDENDUM September 10, 1956.

A detailed report of the 7 hospital cases referred to in this paper was presented before the American Medical Association June 22, 1954 and published in December 1954[2].

Since this time a number of other individuals have reported cases treated with Calcium EDTA with prompt and effective elimination of lead. However, Foreman[3] has

recently reported a case of a patient heavily loaded with plutonium whom he had treated with Calcium EDTA. He sounds a note of warning regarding nephrotoxic hazard from uncontrolled Edathamil Calcium-Disodium therapy. After a preliminary 5 gm. treatment of 4 days followed by two days rest, the drug was administered for another 12 consecutive days. This is definitely a more concentrated type of therapy than I have recommended. However, because plutonium is apparently more difficult to remove from the body than is lead, this therapy seemed necessary. His patient then showed evidence of apparent damage to the renal tubules though this was fortunately reversible.

Foreman then did further experimental work on rats treated daily for 16 days which led him to believe that 2.5% of patients given 9 grams of the drug a day for 16 days would be expected to develop nephrosis. However, he recommends the therapeutic dosage level of 5 grams a day given not more than 5 days in succession and followed by a two-day rest period as well within the desirable safety limits. The dose of 2 grams a day that I have used and found successful seems safe in the individual who does not already have evidence of acute or chronic renal disease.

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