LEAD EDTA COMPLEX

A WATER-SOLUBLE CONTRAST MEDIUM

N. Sapeika, B.A., M.D., Ph.D., F.R.S.S.A.F.

Department of Physiology and Pharmacology, University of Cape Town

Ethylenediamine tetraacetic acid (EDTA) (‘sequestrol’, ‘versene’, ‘tetrine’, ‘trilon’, etc.) is a white crystalline amino acid. It is a synthetic organic non-colloidal chelating agent. With sodium it forms di-, tri-, and tetra-sodium salts; these all act as chelating compounds. The term chelation refers to a chemical reaction in which the chelating agent forms a ring structure with a metal, binding it so tightly that it is unionized and thus unable to take part in the usual reactions. The chelating compounds here considered form unusually stable, soluble, unhydrolysed complexes with the alkaline-earth metals and heavy metals; these complexes resist the action of most of the agents which precipitate these metals. The metal is bound in the complex in a form which is inactive and which shows none of its usual chemical properties. Each EDTA molecule bonds a molecule of the metal so that the product is quantitatively more effective against the heavier metals than the lighter ones.8 In the case of the lead complex, 1 mol (292 g. EDTA) combines with more than two-thirds of its own weight of lead (atomic weight 207).

When injected intravenously into animals and man EDTA itself given in large doses over short periods lowers the systemic calcium levels, and can produce hypocalcaemic tetany.9 Injection of preformed calcium EDTA does not, however, affect calcium homeostasis and is non-toxic. The absence of toxicity of this compound is attributed to its physiological inertness since 99% of the material tagged in the methylene position with radioactive carbon could be recovered from the urine after intravenous administration to rats.10 Calcium EDTA given by injection greatly accelerates the excretion of lead, particularly from soft tissues, since the calcium in this complex is displaced by lead, as by certain other metals. It induces an excess excretion of lead deposited in bone. No free ions are liberated in the mobilization of the lead. Because of this detoxicating and antidotal action the complex has been used in acute and chronic lead poisoning in human beings, causing marked enhancement of the excretion of the metal as lead EDTA medium was the injection by Weil (1902-03) of mixtures of lead sulphate into the maxillary and frontal sinuses.10 Ordinary lead compounds have, however, not been used as contrast media for many years because of their toxicity.

The availability of lead EDTA complex which is water-soluble and apparently non-toxic suggested its use to the author as a contrast medium in diagnostic radiology. This forms the subject of the present report.

METHODS

Lead EDTA dissolved in water (25% and 50% concentrations) was administered to animals by various routes. The pH value of the solutions was 8.0.

Tests for Toxicity

A 25% solution was applied to rabbit conjunctiva and to the mouth and skin (human). In rabbits 100 mg. per kg. was injected intravenously, and in rats 1 ml. 25% solution (1 g. per kg.) given subcutaneously and intraperitoneally. The 25% and 50% solutions were also administered to numerous animals by mouth (through a stomach tube) or by other routes for the radiographic studies mentioned below.

Radiography

(a) Oral Administration. Lead EDTA complex in 25% and 50% solution was administered through a stomach tube in doses of 2 ml. to rats weighing 160 to 200 g. Emulsion of barium sulphate (8 oz. in 16 fl. oz. water) which is used in man was administered to other rats in 2 ml. doses for comparison. All animals had been deprived of food for 12-18 hours beforehand. They were lightly anaesthetized after administration of the contrast medium (with pentobarbitone sodium given by injection) to enable radiographs to be taken. A series of films showed the radiographic appearances of the alimentary canal at different periods after the administration of the radiopaque medium.

(b) Parenteral Administration. In order to determine the possibility of retardation of absorption of the contrast medium 0.5 ml. of solution of lead EDTA 25% (1) in water, and (2) in polyvidone (PVP; polyvinyl-pyrrolidone) 3.5% solution, was injected in rats in two places in the subcutaneous tissue on each side of the
middle line of the anterior abdominal wall. The fate of the compound after absorption might also be demonstrated by radiographs taken at intervals after the injection.

Intravascular injection of a 50% solution was made in rabbits' ears to determine its value in angiography.

(c) Microradiography. A warmed solution of lead EDTA 50% in 10% gelatin solution was injected into the renal arteries of a rabbit killed by a blow on the head and bled from the jugular vessels. The renal vessels were then tied and the organs excised and fixed in formalin. Sections of the kidneys about ½ mm. thick were subsequently prepared for radiography.

RESULTS

Lead EDTA solutions administered by mouth or by injection in the various experiments in rats did not produce ill effects or death in the doses used; autopsies on animals which received large doses by injection showed the kidneys to be paler than normal. No signs of irritation followed applications of the solutions to the conjunctiva and the peritoneal membrane, or to human mouth and skin.

Radiography

(a) After administration by mouth the contrast medium was demonstrable in the stomach and intestines (Figs. 1 and 2). The 50% concentration produced as dense shadows as the suspension of barium sulphate but good radiographs were also obtained with the 25% concentration. The lead complex gave a more homogeneous and persistent shadow of the gastro-intestinal tract and indication of being well mixed with the gastro-intestinal contents. All evidence of the medium had practically disappeared in 24 hours.
(b) Injection of the solution subcutaneously in rats showed that the complex is removed almost completely in 1 hour and is not delayed beyond this period by administration in polyvidone (PVP) solution. However, within ½ hour following the subcutaneous injection the kidneys and bladder (urine) were demonstrable on the radiograph, and at the end of 1 hour not only were these more clearly shown, but the renal pelves, the ureters (in one instance particularly), and the urethrae were clearly visible (Fig. 3). The animals showed no ill effects.

Injection into the rabbit's ear demonstrated the vessels (Fig. 4).

(c) Sections of kidney injected into the renal artery with lead complex in gelatin solution indicated that the medium could be used in microradiography.

**DISCUSSION**

The investigation of the lead EDTA complex as a radiopaque medium shows it to have many useful features which may make it of value in radiographic diagnosis. It would appear to have advantages over many of the agents at present in use. It is very soluble in water, stable and inexpensive. It may be given orally and parenterally. With different concentrations varying degrees of contrast can be obtained in radiography. The lead is firmly bound by EDTA; for absolute safety those who consider the possibility of lead being set free in tissues may prepare the lead EDTA complex in a solution of EDTA.

Contrast media are being extensively used by a variety of techniques, and introduced into all parts of the body. Many agents have been tried, but only a few are in practical use, and ideal agents for various purposes have still to be discovered.

Barium sulphate suspended in water tends to flocculate and precipitate, and therefore attempts have been made to prepare stable colloidal suspensions. Although barium sulphate is insoluble in water it has nevertheless been demonstrated in rats that the metal is definitely absorbed. The lead complex in aqueous solution used in the present investigation gives good contrast, and may prove even more useful in other vehicles.

The iodine-containing compounds are not altogether satisfactory. They are irritating when injected outside blood vessels. Because severe reactions (local and general) and deaths have followed intravascular injection of these compounds, patients have to be tested for hypersensitivity to iodine before injections are made. In cerebral angiography, for example, diodone (diodrast)
has been shown to have a direct toxic action on nerve cells and to produce vasoconstriction. Latent vascular injury in the brain may be aggravated by this type of preparation. In angiocardiacography iodine compounds are reasonably safe but produce unpleasant subjective reactions. Thrombosis of the injected vein is liable to occur. The cause of this may be the forcing of large amounts of contrast medium rapidly into the vein. Whether lead EDTA complex is more satisfactory for intravascular injection in man remains to be shown. Large amounts and high concentration, especially when given under pressure, may also produce changes in endothelial linings and other tissues.

In bronchography stable water-soluble contrast media are being widely used with the advantage that, as rapid removal occurs, no material is left behind to obscure radiographs of the lungs in readings of later films. Lead EDTA may prove useful in this regard, and there may not be the objection to its use in tuberculosis when iodiine preparations are contra-indicated.

Thorium dioxide (thorotrast) has limited uses, and carries the risk of radioactivity that may produce serious effects long after its deposition in the tissues.

Studies on human beings will determine whether lead EDTA can replace compounds such as those considered in this discussion. The fate of the complex after its administration in single doses, and in repeated amounts, will have to be determined. The available literature contains little reference to such studies. In one report it is stated that certain workers have shown that the complex taken by mouth is rapidly absorbed from the upper gastro-intestinal tract, but that further study is needed to clarify this point. In the present investigation it has been shown that, after injection of the medium in rats, the liver, kidneys and urinary tract are visualized; intravenous injection in rabbits also demonstrated the liver and kidneys. More work will have to be done with different doses to determine the possible use of the lead complex for visualization of the alimentary canal, sinuses and fistulae and such purposes as, for example, angiography, hepato-renography, descending pyelography and portal venography, and as a test for renal function. Large doses may need to be used, which may be dangerous when given intravenously. The distribution of the material suggests that the complex tagged with radioactive carbon may prove useful in smaller quantities for diagnosis and radiation therapy.

SUMMARY

Lead EDTA complex is a water-soluble contrast medium. It can be given orally or parenterally. After injection in rats and rabbits the liver and kidneys, and in rats also the rest of the urinary tract, were demonstrable by radiographs.

The complex may prove useful in radiological diagnosis for visualization of the alimentary canal, and in hepatorenography, pyelography, portal venography, microangiography and other techniques; also for example as a test for renal function, but further work needs to be done to determine the largest effective doses that can be given by injection. Tagged with radioactive carbon the complex may be of value for these and other purposes.

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REFERENCES


STERILIZATION OF MILK*

J. A. RICHTER, B.Sc., L.R.C.P., L.R.C.S., D.P.H., T.D.D.
Tuberculosis Officer, Port Elizabeth

In sterilized milk we have a powerful weapon against malnutrition. It is well known on the continent of Europe, but until recently was almost unknown in South Africa. During the past year, however, it has been available to consumers in Port Elizabeth and has established itself as an item of undoubted interest to Public Health.

In this discussion there are two main factors to be considered: (1) the value of milk as a food for infants, children and adults, and (2) methods of conservation of this valuable food under unfavourable climatic conditions. Other factors to be considered are: the quantity of milk available, the consumption of milk per head of population, the standard of living of the people, their stabilized food habits, the general state of nutrition including deficiency conditions, the climate, and, last but not least, the price to the consumer.

THE FOOD VALUE OF MILK

One cannot determine the food value of milk by a single coefficient any more than one can decide on the fertility of the soil by a single measure. One can, however,