RADIOGRAPHIC USE OF LEAD E.D.T.A. IN MAN

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The water-soluble chelated compound lead ethylenediamine tetra-acetic acid (lead E.D.T.A. complex) has been shown experimentally to have value as a contrast medium for oral and parenteral administration (Sapeika, 1954, 1955a). The results from numerous studies in the laboratory indicated that the complex would very likely be of practical value for radiographic purposes in human subjects, since dense shadows could be obtained and intravenous injection produced no untoward pharmacological effects in doses satisfactory for pyelography; larger doses than those required for radiography produced a transitory fall of blood pressure. Lead calcium E.D.T.A. and bismuth E.D.T.A. are not so satisfactory (Sapeika, 1955b). The present report deals with investigations in man with the lead disodium E.D.T.A. complex ("sequestrol-lead NA2").

Lead E.D.T.A. is a white odourless powder which is very soluble in water, and, being un-ionized, does not give the usual chemical reactions of ionized lead. The metal is so firmly bound by the organic chelating agent that it cannot be precipitated by the common precipitating agents. The solution is clear, stable to light and heat, not unpleasant to taste, and not irritating in high concentration. The pH of a 50% solution is 8.0. *In vitro* it did not produce haemolysis of human or rabbit red blood cells, and on injection into rabbits it produced no change in coagulation time. The compound did not inhibit penicillin *in vitro*; it is not itself bacteriostatic.

Present Investigation

By Mouth

The lead complex was incorporated in a thick mucilage of starch (20%), 1 g. in each gramme of mucilage. Five grammes was swallowed on five occasions by three normal adults. No gastro-intestinal or other disturbances occurred. The stools, however, became black, and remained so for a few days before returning to normal colour.

Radiographs of the oesophagus of one subject are shown in Fig. 1 and demonstrate the satisfactory density of the contrast medium.

By Intravenous Injection

The lead complex was administered in 50% concentration in sterile (Seitz-filtered) aqueous solution, three to five minutes being taken for the injection. Radiographs of the urinary system were then taken at intervals of a few minutes in patients whose fluid intake had been previously restricted for the investigation.

Case 1.—A woman, aged 72, with carcinoma of the uterus with infiltration of the right ureter and metastases in the lungs was injected with 15 ml. of the solution. It produced no disturbance other than slight discomfort at the site of the injection. Shadows of the kidneys were evident at three minutes and still present at twenty-seven minutes. The left calices and ureter were well demonstrated. In Fig. 2 a radiograph taken at six minutes is shown.

Case 2.—A girl aged 9 with rheumatic heart disease and cardiac failure had 9 ml. of the solution injected; the only complaint was of temporary discomfort proximally along the line of the vein during the injection. The renal shadows

were evident at three minutes, at maximal density at fifteen minutes, and had disappeared at forty minutes. The results obtained with 18 ml. of injection of diodone (35%) intravenously five days later were not superior.

Case 3.—A woman aged 65 with carcinoma of the stomach and pyloric obstruction had 18 ml. of the solution injected. There was very slight temporary discomfort at the site of injection. Shadows of the kidneys were demonstrable in three minutes and were still present at the end of one hour. In Fig. 3 a radiograph taken at twenty minutes is shown.

Case 4.—A man aged 41, whose diagnosis was not clearly established, was admitted to hospital with signs of tetanus and treated on this basis, but he also had features compatible with a diagnosis of acute nephritis (oedema, raised blood urea, hypertension, oliguria, albuminuria, casts). In view of a tuberculous thoracic vertebra, sodium aminosalicylate and isoniazid were given and intravenous pyelography was performed to exclude renal tuberculosis. A large dose (27 ml. of solution) was injected intravenously. Shadows of the kidneys were demonstrable in three minutes and were still present at the end of three hours. The patient complained of abdominal discomfort about twenty minutes after the injection. Some hours later his temperature rose and he passed dark urine, but after a few hours the temperature and urine returned to normal. Examination of the blood and urine indicated an intravascular haemolysis; there was no porphyrin in the urine.

In the Nasal Sinuses

Lead E.D.T.A. in sterile 0.9% sodium chloride solution was used in adult subjects with no evidence of nasal disease. The concentrations studied were 5%, 7.5%, 17.5%, and 20%. After preliminary inspection of the nasal cavities a control erect occipito-mental radiograph was taken in each subject. The sinuses were then filled by displacement in Parkinson's lateral low head position, using 10 to 20 ml. of the solution. A radiograph was taken in the recumbent occipito-mental position; the subject was then brought upright, and erect occipito-mental and lateral views were taken.

Discussion

It has been demonstrated that lead E.D.T.A. complex can be used as a contrast medium for certain purposes in man.

The good homogeneous gastro-intestinal shadows observed in the experimental animal after oral administration of the complex and the disadvantages of barium sulphate suspensions in man have previously been considered. In

FIG. 1.—Radiographs of normal oesophagus after ingestion of lead E.D.T.A.

FIG. 2

FIG. 3

FIG. 2.—Case 1. Radiograph showing the kidneys and the left calices and ureter, six minutes after intravenous injection of 15 ml. of lead complex 50% solution. FIG. 3.—Case 3. Radiograph showing both kidneys and renal pelvises twenty minutes after injection of 18 ml. of lead complex 50% solution.

the present investigation satisfactory shadows of the oesophagus have been obtained in man with small amounts of the complex (used as "lead swallows"). Caution will be necessary with the administration of large quantities of lead E.D.T.A. in view of the appearance of black discoloration of the stools, presumably from the formation of lead sulphide. The complex must undergo some enzymatic change in the gastro-intestinal tract, which may militate against its use in large amounts as a "lead meal"; this needs investigation. There is a possible use for the lead complex orally in infants, and as a lead enema. The dose taken orally did not cause irritation of the gastro-intestinal tract.

The use of lead E.D.T.A. to illustrate deglutition and the oesophagus has thus been demonstrated. With regard to the change undergone by the complex more distally in the alimentary canal, it is of interest that iron ethylenediamine tetra-acetic acid (ferric sodium versenate) also appears to be split in the gastro-intestinal tract, to release ionized iron, and that some iron is absorbed by the usual gastro-intestinal mechanism which maintains normal iron balance (Will and Vilter, 1954). The stools became greenish black in colour when large doses were taken, indicating the formation of an iron sulphide and also that at least some of the ferric sodium versenate is split, as the versene complex will not react with sulphides. Lead forms a more stable chelated complex than does iron, so that relatively less might be split off in the intestine and should absorption of lead ions occur control is possible: the patient could concurrently receive the chelating agent itself as calcium E.D.T.A., which is being used as an antidote in the treatment of acute and chronic lead-poisoning to bind the metal and cause its excretion as the non-ionizable complex. In animals large doses of lead E.D.T.A. orally did not cause untoward effects.

The intravascular injection of organic iodine preparations currently in use is apt to be followed by sensitivity reactions in a small percentage of patients. In animals the intravenous injection of the lead complex produced striking pictures of the urinary system without serious effects. In one patient (Case 4) with delayed renal excretion the intravenous injection of a large dose of lead E.D.T.A. (13.5 g. in 50% solution) caused temporary acute haemolysis, with apparent recovery. Since the metal is stated to be firmly bound (chelated) in the complex, the effect was presumed to be due to osmotic changes produced by the concentrated solution (Sollmann, 1948). It is of interest that in apparently healthy subjects haemolysis and

haemoglobinuria have been observed after the injection of 100 ml. of 25% saline (Heffter, 1927). This patient had been receiving isoniazid for a few days and sodium aminosalicylate for two days before the intravenous pyelography, and continued to receive these drugs subsequently; both these drugs can produce febrile and urinary disturbances. However, the appearance of an icteric tinge of the sclerotics eight days after the original episode led to the discovery of raised serum bilirubin and punctate basophilia, with albumin and urobilin in the urine but no porphyrins. Examination of Case 2, otherwise showing no untoward effects on the tenth day after her injection, then revealed the presence of punctate basophilia, which, however, was no longer present two days later. Case 1 showed no punctate basophilia during eight days

after the injection. Possibly some lead ions are set free in the blood, as it was accepted that there was no free lead in the preparation used.

The lead complex intravenously, perhaps with calcium E.D.T.A., provides some alternative to iodine compounds for urography. A practical point is that, unlike iodides, lead E.D.T.A. does not give a reaction with the orthotolidine test for blood. The lead complex did not produce a diuresis. This is interesting, since reports of patients treated with calcium E.D.T.A. for lead-poisoning—for example, Giles *et al.* (1955)—suggested that there was a diuresis associated with the elimination of lead. The intravenous studies show how rapidly the complex is carried through the circulation apparently unaltered, and excreted almost entirely by the kidneys. This is in keeping with the findings of Foreman and Trujillo (1954), who showed that, in human beings, labelled calcium E.D.T.A. is rapidly and almost entirely eliminated by glomerular filtration and tubular excretion. Subcutaneous injection in rats showed that absorption of the lead complex occurs rapidly enough for urography without ill effects in the doses used (Sapeika, 1954). It remains to be demonstrated whether this method of administration, possibly with the aid of hyaluronidase, is of value in infants.

In the nasal sinuses, shadows of good density have been obtained. The 20% solution used in the present investigation did not cause any immediate irritation or late reaction.

Many other uses for this contrast medium will require examination. The possibility of untoward effects occurring with large doses or in the presence of certain disease states, or when other drugs are being concurrently administered, should be borne in mind.

Summary

Lead E.D.T.A. complex has been used in man for radiographic purposes. Dense shadows can be obtained with its local use, for example, in the oesophagus and the nasal sinuses; and for intravenous pyelography also it is a possible alternative contrast medium to organic iodine compounds. Certain disadvantages of large doses are discussed.

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PEPTIC ULCER IN GENERAL PRACTICE

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Peptic ulcer is very common in our present generation. Its incidence has increased rapidly and is still increasing (Alsted, 1953). It is a disorder, or more probably a group of disorders, with many problems. The causes are uncertain, the course is unpredictable, and the results of treatment are far from satisfactory. In addition its importance arises from the high morbidity rate and not inconsiderable mortality. This morbidity, because it affects primarily the working man between 30 and 60, is of economic importance in respect of loss of work-time.

Much has been written on this subject over the years, and most of the reports and papers have been based on hospital figures. Accurate and numerous as these figures are, it is possible that they may not present a correct picture of the disease because they include only cases referred for a consultant's advice and help. The referral rates of ulcer patients to hospital depend on a number of factors for which due allowance must be made and which vary in different parts of the country. Thus, where general practitioners have full facilities for radiological and pathological investigations the referral rates will be lower than in the "closed diagnostic" areas. Again, there is a natural tendency for more severe cases to find their way to hospital, the milder forms of the disease remaining under the sole care of the family doctor. In addition the rate will depend on the general practitioner himself; some practitioners may feel that all cases of ulcer should be seen by a consultant, whilst others refer only those they consider may require surgical treatment.

It is probable, therefore, that, as in other chronic diseases, we in general practice may observe a more accurate, if smaller, picture of the disorder as a whole. Because we live in the midst of our patients we are able to keep a close check on the course of the illness, including loss of work-time, personal suffering, and the effects on the whole family group. Another of our advantages is that if we have adequate records available we can easily carry out a lengthy follow-up of our ulcer

patients over many years and by this means try to elucidate more accurately the natural history of this group of conditions.

It has been felt, therefore, that some useful purpose may be served by noting the incidence, morbidity, and response to treatment of peptic ulcer in two general practices with almost 10,000 patients at risk.

Methods of Study

For the purposes of this work, records from two separate and adjacent practices in a South-east London residential suburb have been examined. These two practices are almost of identical size and pattern, and deal with the same type of population, of whom the majority belong to social classes II, III, and IV. Our patients' occupations are varied, but the majority are employed in clerical and industrial duties locally or in central London. There is no evidence of any real poverty or of any excess of prosperity.

The study is a retrospective one, and is based on records which have been kept in almost identical fashion over the period of the study. These records are able to show: (1) all the peptic ulcer cases in our practices; (2) all attendances over a period of two and a half years, and their purpose; and (3) periods of incapacity for work.

It is necessary to note our criteria for diagnosis of peptic ulcer. We have made the diagnosis only if there has been evidence of a positive radiological report plus a history of ulcer-dyspepsia. Most cases have been diagnosed by us personally, but in some we have relied on old medical reports, provided that these contained positive radiological records or confirmation at operation. We have tried to be particularly careful in excluding any doubtful cases.

Peptic ulcer is a chronic disorder, and a long period is necessary in order that an accurate picture may be obtained. We have therefore confined our main studies to cases which had been diagnosed five or more years previously, giving us a five-year-plus follow-up.

Incidence

To arrive at absolute figures is difficult, as one is bound to miss some cases of short duration and with minimal symptoms. It is possible that, relying as we have on strict criteria of diagnosis, our total incidence may be a little lower than is actually the case. Table I shows the incidence of peptic ulcer on July 1, 1954, and Table II that of cases with a history of five or more years.

TABLE I.—Incidence of Peptic Ulcer on July 1, 1954

	Male	Female	Total
Gastric ulcer	29	16	45
Duodenal ulcer	108	24	132
			177

TABLE II.—Incidence of Peptic Ulcer with a 5-Year-Plus History

	Male	Female	Total
Gastric ulcer	23	8	31
Duodenal ulcer	79	14	93
			124

There were 9,975 patients at risk on July 1, 1954, giving an incidence rate of 17.7 per 1,000. This compares with a London rate of 15.3 per 1,000 as reported by Stocks (1949). Doll *et al.* (1951), in a study of 6,000 London factory employees aged between 14 and 65, found an incidence of 56 per 1,000; our corresponding rate is 30 per 1,000.

Age at First Diagnosis

It is of little value to note simply the age incidence of these patients at the present time, for some have had a longer history than others. An attempt has therefore been made to ascertain the age at which the clinical diagnosis was first conclusively made. Table III shows this age at first diagnosis in all our peptic ulcer patients. This has