EXPERIMENTAL ADMINISTRATION OF EDTA

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Harry Foreman, M. D.

Ca EDTA was administered experimentally to two individuals bearing a small body burden of plutonium. In the first case, where the exposure had occurred seven years previously, there was a ten-fold increase in Pu urinary excretion over the period of the weeks trial of treatment. In the second case representing the situation of acute exposure, approximately 50% of the body burden was removed in the 16 days of treatment.

C^{14} labeled EDTA was administered to humans in a study of the metabolism of the compound. It was found that the material passes through the body unchanged. It is excreted via the kidney by both glomerular filtration and tubular excretion. The turnover time after intravenous administration is approximately one hour. The material passes into all the tissue spaces except the red cells. It is poorly absorbed when given orally and absorbed not at all through the skin.

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3-22-54

For The Atomic Energy Commission

William A. Colson

Chief, Declassification Branch

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Ladc 1629 (Complete Paper)

AECU-2923

EXPERIMENTAL ADMINISTRATION OF ETHYLENEDIAMINETETRAACETIC ACID IN
PLUTONIUM POISONING

Harry Foreman, M. D., Los Alamos, N. M., Philip A. Fuqua, M. D.,
Richland, Washington and William D. Norwood, Richland, Washington

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By way of introduction I should like to say a few words about the propriety of presenting a talk on such an obscure subject as "Plutonium Poisoning," to a group of practical physicians as this. First of all, historically speaking (if one can speak of events of 4 or 5 years ago as history), interest in EDTA as a means for removing heavy metals from the body first arose in conjunction with studies on radioactive materials, such as plutonium, etc. At that time, stimulated by the increasingly widespread use of radioactive materials, an intensive research program was undertaken to find means to alleviate the harmful effects of internally deposited radioelements. EDTA, as an agent for internal decontamination, was developed as part of that program. Since then, as you have heard this afternoon, EDTA has found application in other types of heavy metal poisoning. A presentation of the application of the drug in radioactive poisoning is therefore well included in any program on EDTA. Secondly, it is highly probable that radioactive materials such as plutonium will find increasing use in industry as time goes by and therefore it well behooves industrial physicians to start to become acquainted with the potential health hazards associated with these materials and the possible means for coping with these hazards.

Of the 600 odd radioactive isotopes (or more properly, radionuclides) that are known there are only about a dozen or so that are produced and used in sufficiently large quantities and have sufficiently long half-lives to constitute serious potential health hazards. Of this group, there are a few that are particularly dangerous and insidious and to which research efforts for a therapeutic regimen are especially directed. These are the so-called "bone seekers;" radium, plutonium and the radioactive isotopes of strontium, calcium and barium and some

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of the rare earths. On entry into the body, these materials rapidly become fixed in the skeleton and are eliminated at very slow rates. When long-lived isotopes such as Pu^{239} and Ra^{226} are involved the body is subject to uninterrupted irradiation for the remainder of its lifetime. Because the irradiation persists for such long periods and is selectively directed at a particularly radiosensitive area, i.e., the region of the bone marrow, it takes only exceedingly small amounts, microgram quantities, in the body to produce injury. The type of injury resulting, as we have learned from animal studies and from well-documented case records on individuals bearing body burdens of radium and mesothorium, is particularly disabling and discomfiting, i.e., osteitis, bone necrosis, pathological fractures, osteogenic sarcoma as well as hematopoietic damage (1).

Of the radioactive "bone-seekers" which may find use in industry in large quantities in the future, Pu is a most likely one because of its value as a prime fuel in nuclear energy power plants. Fortunately, due to well-conceived medical and industrial hygiene practices and perhaps fortuitous circumstances, there have never been any serious plutonium cases in the United States, as far as we know, so that almost all of our information on internally deposited plutonium has been obtained from animals (2).

The metabolic fate of plutonium depends upon a number of factors; the route of entry (oral, parenteral or inhalation) chemical and physical state at the time it is introduced into the body and to a certain extent the animal species involved. However, without going into details a few general statements can be made to give a brief orientation about the behavior of the material in the body.

Plutonium is very poorly absorbed from the G. I. tract; only from .005 to 0.01 per cent of an orally administered dose enters the systemic circulation.

This is as compared to 20-25% of a radium dose administered similarly. On the other hand once Pu is in the body it is by far and large retained indefinitely, i.e., 85-90% of an intravenously injected dose is retained. Only 20-40% of an injected radium dose remains in the body for any length of time (3). The hazard from Pu then is not so much from material taken by mouth, that is unless relatively large amounts are swallowed, but from inhalation of Pu-laden dust or spray and from Pu-contaminated puncture wounds. Experiments in rats have indicated that over 90% of an intramuscularly injected dose of Pu citrate (a relatively soluble form) is still present at the injection site by 24 hours and 60% by the end of 10 days (4). If this obtains in humans, it would indicate that debridement would be fruitful even at late time periods. Brues has pointed out that 1 μ g of plutonium left in the subcutaneous tissues of a rat was sufficient to result in fibrosarcoma (5).

About 60% of a dose of Pu that finds its way into the body ends up in the skeleton. Plutonium in the skeleton lays down in the trabecular endosteal and periosteal regions (4). Radium distributes largely throughout the cortex. Nevertheless, as indicated above, pathological changes produced by each are essentially the same, qualitatively. From the consideration of radiant energy delivered per unit weight, one might expect plutonium to be 1/50 as toxic as radium. Plutonium is an alpha emitter with a half life of 24,000 years as compared to Ra with a half life of 1600 years and which in equilibrium with its daughter products has mixed alpha, beta and gamma radiation. However, experimental findings indicate Pu is more toxic than one might predict and the tolerance dose set for Pu is only 5 times instead of 50 times greater than radium, on a weight basis, i.e., 0.5 μ g for Pu and 0.1 μ g for radium. The tolerance dose is considered the best estimate (with a considerable safety factor) for dose which will produce no harm during the lifetime of the affected individual.

The problem of therapy of plutonium poisoning, aside from debridement of

soft tissue deposits and palliative measures for relief symptoms is one of hastening the elimination of Pu from the body. In a few days Pu becomes well fixed in the skeleton. Except for this early time period, therapy must be directed at removing Pu from bone. At present there are two methods which show promise; Shubert's(6), zirconium citrate procedure and the EDTA procedure, the subject of this talk.

The principle involved in the EDTA procedure has been indicated by the previous speakers. EDTA mobilizes heavy metals from the body by virtue of its ability to form stable water-soluble chelates with these metals which then are rapidly excreted via the kidney. EDTA combines with many metals including ones essential to the body, in particular calcium. Injected quickly intravenously it can lower serum calcium so rapidly as to produce death in hypocalcemic tetany. In order to prevent depletion of body calcium, EDTA is introduced into the body fully combined with calcium, namely as the calcium chelate. The material still functions in mobilizing such metals as Pb and Pu because of its preferential avidity towards these metals as compared to calcium. Calcium is displaced from combination with EDTA by Pb and Pu and the material excreted as Pb or Pu chelate. Ca^{++} is excreted independently.

Ca EDTA is a relatively non-toxic drug. Metabolic studies using C^{14} labeled material indicates that it passes through the body unchanged (7). It is excreted via the kidney by both glomerular filtration and tubular excretion. The turnover time from the blood is approximately one hour after intravenous administration and one and one-half hours after intramuscular injection. It quickly mixed with almost all of the body water except that it does not pass into the red cells and passes relatively slowly into the spinal fluid compartment. It is poorly absorbed from the gastrointestinal tract.

Our experience with the drug for removal of Pu from humans has been limited to two cases. Neither case had a large enough body burden to produce injury,

but each excreted sufficient Pu in his urine to serve as a subject for testing the efficacy of the drug in removing the material from the body.

The first case involved a 40 year old female technician who does routine chemical operations with low level Pu solutions at Los Alamos. During the course of her work a flask containing $\text{Pu}(\text{NO}_3)_4$ in 1 M HNO_3 broke and she received a 2 cm laceration across the base of her left thumb from a jagged piece of contaminated glass. First aid treatment consisted of cleansing the wound area with soap and water and stopping the profuse bleeding with a couple of sutures and a small pressure dressing. Counts over the surface of her hand varied from 500 to 1000 c/m of alpha contamination. From that time on urine samples were saved for Pu assay. Figure 1 shows the results of urine assays. After repeated sampling had ruled out the possibility that urine counts were not coming from her hands or clothing and that Pu had really entered the body as a result of the accident, she was started on a trial of the drug. The wound area was first debrided to eliminate the possibility of a dangerously large subcutaneous or intramuscular deposit slowing feeding Pu into the system. Actually the debrided material yielded only 1700 c/m, a miniscule quantity. She was given 2.5 gm Ca EDTA in 250 cc saline slowly by I.V. drip twice daily at the times indicated in Fig. 1. She was hospitalized the first day but thereafter received her treatment in the first aid room on a come-and-go basis.

As can be seen from Fig. 1, the treatment produced a striking increase in Pu excretion, particularly on the first day, a rise from a pretreatment level of 12 dpm to 1300 dpm. The treatment apparently is less effective as time goes on although it is difficult to judge the extent of this because the normal excretion rate (excretion without treatment) as indicated by the continuous curve outlined on the lower portion of the figure is also dropping with time. It is interesting to note the striking initial drop in excretion when the treatment is stopped and then a slower leveling off to the base line. It is estimated

from the excretion curve that she had a body burden of 25,000 to 30,000 dpm originally and 20-25% of this was removed in the sixteen days of treatment. Had drug been started within a few hours after the accident, when the Pu was still largely in the blood stream or soft tissues, it is likely that the amount removed would have been considerably more.

Case 2 represents the situation where the Pu was firmly fixed in the body. It involves a male chemist who was 25 years old at the time of his exposure, namely 7 years before the trial of the drug. It is presumed that his exposure came about from inhalation of vapor spray during neutralization and oxidation of Pu-containing solutions. It is estimated from his urinary excretion that his body burden is 1.2 μg . He has never had any signs or symptoms indicative of injury from the Pu. The trial was carried out purely as a test for the efficacy of the drug in chronic Pu poisoning. He was given the material intravenously in saline by slow I.V. drip. The dosage schedule and results are indicated in Fig. 2. Here, as might be expected, the increases in excretion are not nearly as spectacular as in the early treatment case. There was an overall average increase of about tenfold over pretreatment levels during the 5 days of trial. It would be interesting to see if the drug continued to be effective when given daily over a prolonged period since it is apparent from the results that in chronic Pu poisoning it will require months, if not years of treatment to deplete the body of its Pu store. This is not a particularly desirable situation but it is a preferable alternative to damaging Pu poisoning just as prolonged insulin injections are preferable to serious diabetes. Fortunately there have never been any serious cases of chronic Pu poisoning in the United States as far as we know, and if acute exposures are treated as soon after the accident as possible it is likely we may never have to face the chronic problem.

In animal experiments where it is possible to analyze tissues it was found that the skeleton as well as the soft tissues are depleted of Pu by the treatment.

The data present in Fig. 3 represent the situation similar to Case 2, namely when treatment was started after Pu was long fixed in the skeleton. In the animal experiment treatment was started one month after the Pu had been injected intravenously. The test animals were injected intravenously daily for one month. At the end of that time their skeletons had one third less Pu than the control animals.

It is well to point out here that from a consideration of stability constants it can be seen that EDTA will not affect the Sr or Ra content of the body. The avidity of EDTA is greater for Ca than it is for Ra and Sr and hence when injected into the body the drug will deplete the Ca content before it noticeably affects the Ra or Sr content.

In summary one can say that Ca EDTA accelerates the excretion of Pu by humans, particularly when given shortly after the metal has entered the body. It offers promise in a situation which previously had been considered hopeless with respect to therapy.

ACKNOWLEDGMENTS

The authors wish to express their thanks to Mr. W. Moss of H-5 group at Los Alamos and to Mr. R. L. Watters of the Radiological Sciences Department at Richland for their skillful performance of the many and complicated urine Pu assays.

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FOOTNOTES

This work was done under the auspices of the Atomic Energy Commission at the Los Alamos Scientific Laboratory of the University of California, Los Alamos, New Mexico, and at the Kadlec Hospital, General Electric Company, Hanford Atomic Products Operation, Richland, Washington.

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DISINTEGRATIONS Pu PER MINUTE
PER 24 HOUR URINE SAMPLE