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A Study of the Effect of 2,3-Dimercaptopropanol (Bal) Upon The Metabolism of Plutonium



## Authors

Kawin, Bergene
Copp, D Harold

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Bergene Kawin and D. Harold Copp

January 23, 1950





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# A STUDY OF THE EFFECT OF 2,3-DIMERCAPTOPROPANOL (BAL) UPON THE METABOLISM OF PLUTONIUM*

Bergene Kawin and D. Harold Copp.

Division of Physiology, University of California Medical School, and the Crocker Radiation Laboratory; University of California, Berkeley, Calif.

The transuranic element, plutonium, presents a major health hazard. Its acute radiation toxicity, high degree of retention by the skeleton, and extremely low rate of elimination from the body accentuate its lethal nature. The number of workers engaged in the industrial production of this element in connection with the atomic energy program, as well as the investigative use of plutonium in the laboratory, intensifies this danger. For this reason considerable effort has been devoted to the search for possible methods of therapeutic treatment for plutonium poisoning.

The compound, 2,3-dimercaptopropanol (BAL), has been shown to be effective in the treatment of systemic poisoning produced by a number of metals. These include arsenic(1-4) mercury (5,6) cadmium (7) and antimony (8). More recently(9) BAL has been shown to increase the excretion, and lengthen the survival time, of animals injected with polonium. The efficacy of BAL in these cases is dependent upon its dithiol groups. The production of biochemical lesions by these metals is attributable to the inactivation of essential enzymes or tissue protein systems by combination of the metal with their prosthetic sulfhydryl groups. The addition of BAL results in the formation of a comparatively undissociable and stable BAL-metal complex. The removal of the metal through the formation of this complex effectively reactivates the enzyme system. The metal is excreted from the animal as the BAL-metal complex. By this general mechanism BAL removes the metal cation from the body.

*This document is based on work performed under Contract No. W-7405-eng-48-A for the Atomic Energy Commission.

The possible value of BAL in treatment of plutonium poisoning was investigated in the following experiment by studying its effect on experimentally injected plutonium.



Methods

Seventeen young adult female rats ranging in weight from 200 to 240 grams were each injected intramuscularly with 15 micrograms of hexavalent plutonium as the chloride (half-life $2.4 \times 10^4$ years) into the right front leg. The total volume of the injection in each case was 0.25 milliliters. The plutonium, in acid solution, was diluted with physiological saline. The final pH was about 3.0. Standards were prepared in duplicate.

The animals were separated into three groups. Group 1, consisting of seven animals, received no treatment. These animals served as controls. Groups 2 and 3, consisting of five animals each, received several injections of 10 milligrams of BAL in 0.1 milliliters of oil into the muscles of the hind legs. The animals of Group 2 received a single injection of BAL five hours prior to the plutonium injection, and nine injections of BAL spaced at four-hour intervals thereafter. The animals in the third group received only the nine injections following plutonium administration.

All animals were placed in separate metabolism cages to permit separate collections of excreta. The animals were fed ad libitum upon a stock diet. They lost 5 to 6 grams weight during the period of the experiment. The urine and feces collections were pooled for the individual animals for the periods 0-2 days and 3-8 days following the injection of plutonium.

At the end of the eighth day the animals were sacrificed and the liver, kidneys, right femur, right front leg, and the left front leg were removed separately. The residual portions of the animal were assayed together as 'carcass'. Assay of the plutonium in the tissues and excreta was done by the method described

by Scott et al (10). The difference between right and left front legs gave a measure of the plutonium remaining unabsorbed at the site of injection.

Results and Discussion

The results of the experiment are shown in Tables I and II, and Figure 1. Table I shows the distribution of the injected plutonium, expressed as percent of the administered dose. Values for the left front leg are not listed, since they were used to correct for the amount of plutonium remaining unabsorbed at the site of injection in the right front leg. It can be seen that about half of the plutonium was unabsorbed in all three groups. The figures obtained for the various tissues and the excreta showed no significant effects of the BAL treatment.

In Table II the distribution is expressed as a percentage of the plutonium absorbed from the injection site. Here, as in Table I, the distribution of plutonium in all three groups does not vary significantly. Following an initially high urinary elimination, the excretion of plutonium falls to a very low level. The fecal excretion remains consistently low. There appears to be a slightly greater uptake in the soft tissues (liver and kidneys) of the animals treated with BAL. In Group 3 the deposition of plutonium in the femur is somewhat lowered. However, when examined statistically, these differences appear to be of very slight significance.

In Figure 1 the data of Table II are presented graphically. Here the similarity of plutonium metabolism in both treated and untreated animals is demonstrated.

It has been shown previously (10) that, following the intramuscular injection of plutonium, 60 to 70 percent of the metal is accumulated in the skeleton. There is a very low rate of elimination. The results of this experiment would indicate that the distribution and excretion of plutonium is not significantly altered by the administration of BAL. The unreactivity of plutonium towards BAL is in contradistinction to the behavior of such heavy metals as arsenic, mercury and

polonium, which react with the sulfhydryl groups of BAL. It suggests that the mechanisms of the distribution and excretion of plutonium may be largely independent of the activity of sulfhydryl groups.

Summary

1. The effects of 2,3-dimercaptopropanol (BAL) upon the metabolism of intramuscularly injected Pu(VI) have been investigated.

2. The use of BAL produced no significant alterations in the distribution and excretion of plutonium as compared to the pattern shown by control animals.

3. The metabolism of plutonium does not appear to be related to sulfhydryl groups.

4. On the basis of its ineffectiveness in changing the metabolism of plutonium, BAL does not appear to be an effective therapeutic treatment for plutonium poisoning.

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TABLE I

THE EFFECTS OF BAL TREATMENT UPON THE DEPOSITION AND EXCRETION OF INTRAMUSCULARLY INJECTED PLUTONIUM

| Part | Percent of Dosage* | | | | | |
|---|---|---|---|---|---|---|
| | Controls | | Pretreated | | Post-Treated | |
| Liver | | 7.1±0.8** | | 8.0±1.3 | | 8.1±1.3 |
| Kidneys | | 0.7±0.1 | | 1.3±0.6 | | 0.8±0.1 |
| Femur | | 1.8±0.1 | | 1.5±0.1 | | 1.1±0.3 |
| Carcass | | 35.6±3.0 | | 27.8±2.5 | | 31.8±6.5 |
| Unabsorbed in Injected Leg | | 43.5±2.6 | | 53.0±5.0 | | 48.4±5.9 |
| Urine (0-2 day) | 5.5±0.8 | | 3.6±0.8 | | 4.7±1.1 | |
| (3-8 day) | 0.9±0.2 | | 1.0±0.2 | | 0.6±0.1 | |
| Total | | 6.4±0.8 | | 4.6±0.8 | | 5.3±1.3 |
| Feces (0-2 day) | 1.3±0.3 | | 0.7±0.2 | | 0.7±0.3 | |
| (3-8 day) | 3.6±0.6 | | 3.1±0.4 | | 3.8±0.8 | |
| Total | | 4.9±0.4 | | 3.8±0.6 | | 4.5±1.1 |

*Values in this table have been adjusted to 100% recovery. The actual total recoveries approximated 89-90%± 6.0% in all groups. Carcass values have been corrected for the plutonium present in the right front leg bone as separate from the amount retained in the injected muscle of that leg.

**Standard error of the mean: $S.E. = \sqrt{\frac{\Sigma(x-\bar{x})^2}{n(n-1)}}$

TABLE II

THE EFFECTS OF BAL TREATMENT UPON THE DEPOSITION AND EXCRETION OF INTRAMUSCULARLY INJECTED PLUTONIUM CORRECTED FOR AMOUNT RETAINED AT INJECTION SITE

| Part | Percent of Dosage* | | |
|---|---|---|---|
| | Controls | Pre-Treated | Post-Treated |
| Liver | 12.6±1.4 | 17.0±2.8 | 15.7±2.5 |
| Kidneys | 1.2±0.2 | 2.8±1.3 | 1.5±0.2 |
| Femur | 3.2±0.2 | 3.2±0.2 | 2.1±0.6 |
| Carcass | 63.0±5.3 | 59.1±5.3 | 61.7±12.6 |
| Urine (0-2 day) | 9.7±1.4 | 7.7±1.7 | 9.1±2.1 |
| (3-8 day) | 1.6±0.4 | 2.1±0.4 | 1.2±0.2 |
| Total | 11.3±1.4 | 9.8±1.7 | 10.3±2.5 |
| Feces (0-2 day) | 2.3±0.5 | 1.5±0.4 | 1.3±0.6 |
| (3-8 day) | 6.4±1.1 | 6.6±0.8 | 7.4±1.5 |
| Total | 8.7±0.7 | 8.1±1.3 | 8.7±2.1 |

*Values in this table are computed upon the amount of plutonium actually absorbed from the site of the injection.

FIGURE 1. THE EFFECTS OF INTENSIVE BAL TREATMENT ON THE DEPOSITION AND EXCRETION OF PLUTONIUM IN RATS