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Chemical Corp Contract No. W-49-057-CWS-23
(Supplemental Agreement No. 6)

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STUDIES ON ZIRCONIUM, TANTALUM, COLUMBIUM, STRONTIUM AND LANTHANUM

I. ACUTE TOXICITY AND EFFECTS ON ENZYMATIC REACTIONS

Kenneth W. Cochran, Marcella Mazur, John Doull
and Kenneth P. DuBois

Several metals hitherto rather obscure have gained new importance due to their occurrence as fission products. A knowledge of the pharmacology of these elements, both in the stable and radioactive forms, would be of considerable use to personnel involved in research in this field. Information on the toxicity of these elements has gained added importance since the suggested use of zirconium for the treatment of plutonium poisoning by metal displacement (1) because of the possibility that other uncommon metals may find a similar usefulness in the future. For this reason and because it was necessary to establish the acute toxicity of the stable forms prior to toxicity studies on the radioactive forms we have examined the toxicity of salts of columbium, lanthanum, strontium, tantalum, and zirconium. For most of these elements adequate quantitative toxicity data are lacking. The present report describes the results obtained to date.

With the exception of strontium, relatively little work has been done on the pharmacodynamics of these compounds and even less on their biochemical effects. We have initiated studies on the effects of these metals on enzymatic reactions in an attempt to explain their toxic effects and to obtain information on their behavior in vivo because knowledge of the behavior of the stable form in biological systems should also apply to the radioactive isotopes. Our initial studies on the biochemical effects of these metals consisted of in vitro testing of their effects on succinic dehydrogenase and adenosine triphosphatase (ATP-ase) and are being extended to include other systems requiring metallic activators.

Materials and Methods

Adult male and female Sprague-Dawley rats whose weight ranged from 200 to 300 grams were used for the acute toxicity studies. The animals were kept caged in groups of four and food (Purina Chow) and water were offered ad lib. Aqueous solutions or suspensions of the various salts of the metals were administered in a single dose by intraperitoneal injection or orally by stomach tube. All animals were observed daily for a minimum of 10 days, but initial groups receiving a given compound were kept for periods up to 30 days to determine whether there would be any significant mortality occurring after the tenth day. Values for the LD-50 were determined by the log-probability method. All the LD-50 values given were derived from 10-day mortality data. No differences were noted in susceptibility of the male and female rats used.

Carworth Farms mice were employed for the studies of the in vitro action on enzymes and 5 per cent liver homogenates, made according to the technique of Potter and Elvehjem (2), were used. Succinic dehydrogenase activity was measured by the method of Schneider and Potter (3) and ATP-ase by the method of DuBois and Potter (4). In most cases the chloride salts of the metals were used to avoid the addition of another anion to the system.

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Acute Toxicity Studies

Rats acutely poisoned by these compounds exhibited symptoms characteristic of many metallic poisons. After lethal doses there was a progressive depression and decrease in activity until death occurred. The time of death varied from a few hours to a few days following the administration of the compounds. Few deaths occurred later than five days after poisoning except in the case of lanthanum where the survival time was somewhat more extended than with the other metals. The LD-50 values obtained by the intraperitoneal and oral administration of several salts of zirconium, lanthanum, columbium, strontium and tantalum are given in Table 1.

From these data it may be seen that the oral LD-50 for those zirconium compounds varies from 2500 to 10,000 mgm./kgm., which was equivalent to 853 to 2290 mgm./kgm. of zirconium. As is ordinarily the case the toxicity of the compounds was considerably greater when they were administered intraperitoneally with the LD-50 values ranging from 175 to 4100 mgm./kgm. of the salts or 63 to 939 mgm./kgm. of zirconium. The oral LD-50 values ranged from 2 to 20 times greater than the values obtained by intraperitoneal administration. The intraperitoneal LD-50 for zirconyl acetate was 7.3 per cent of the oral value while it was 11.4 per cent for zirconyl chloride, 50 per cent for zirconyl nitrate, 5 per cent for zirconium sulfate and 41 per cent for sodium zirconyl sulfate.

Metabolic tracer studies (5,6) have indicated that the oral absorption of $Zr^{89}Cl_4$ with carrier was less than 0.01 per cent. With carrier-free $Zr^{89}OCl_2$ there was less than 20 per cent absorption from the abdominal cavity six days after intraperitoneal administration and less than 0.1 per cent of the administered dose was found in the tissues six days after oral administration (7).

It has been suggested (5,7) that intraperitoneally-administered zirconium is apparently deposited on the surfaces of intraperitoneal organs and it was believed that this may be due to the formation of insoluble zirconium phosphate at the site of administration.

The data presented here indicate that lanthanum injected intraperitoneally is about equally toxic as the chloride or as lanthanum ammonium nitrate. When administered orally, however, the LD-50 for lanthanum as the chloride was almost three times greater than the LD-50 value for lanthanum as the ammonium nitrate salt. This seems to indicate a greater absorption of lanthanum ammonium nitrate from the digestive tract rather than any inherent differences in the toxicity of the two compounds. The total retention four days after an orally-administered dose of $La^{140}Cl_3$ has been found to be approximately 0.3 per cent most of which was found in the liver (8). It has been stated (6,8) that some of the solution when given intraperitoneally may remain unabsorbed in the abdominal cavity on the surface of the organs and this has been estimated to be about 15 per cent of the administered dose four days after the solution was given.

Both of the subgroup V elements studied (tantalum and columbium) were relatively toxic as compared with the other metals included in this study.

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TABLE 1

ACUTE TOXICITY OF CERTAIN METALS TO RATS

(10-day observation period)

Compound	Oral LD-50			Intraperitoneal LD-50		
	Compound mgm./kgm.	Metal mgm./kgm.	No. of Animals	Compound mgm./kgm.	Metal mgm./kgm.	No. of Animals
Zirconyl acetate	4,100	1660	24	300	122	24
Zirconyl chloride	3,500	990	22	400	113	36
Zirconyl nitrate	2,500	853	24	1250	426	22
Zirconium sulphate	3,500	1253	22	175	63	40
Sodium zirconyl sulphate	10,000	2290	26	4100	939	22
Lantharum ammonium nitrate	3,400	830	23	625	153	24
Lantharum chloride	4,200	2370	24	350	197	32
Tantalum chloride	1,900	958	22	130	66	36
Potassium tantalum fluoride	2,500	1150	32	375	173	24
Potassium columbate	3,000	1140	22	225	86	26
Strontium chloride	5,000	1635	36	750	245	24

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However, experiments in progress with tantalum oxide indicate an extremely low toxicity for this substance probably due to poor absorption. Scott et al (6) state that the uptake and retention of Cb^{95} in the soft tissues, as well as the excretion of absorbed Cb^{95}, is greater than for most fission products.

The LD-50 for strontium administered intraperitoneally as strontium chloride was found to be 245 mgm. Sr per kgm. and for oral administration it was 1635 mgm. Sr per kgm. Tracer studies with carrier-free Sr^{89} (6) showed that 87.4 per cent was found in the feces, intestinal contents and urine four days after oral administration and 32.7 per cent four days after intraperitoneal administration.

The compounds which we studied were administered without regard to the pH of their aqueous solutions or suspensions since neutralization usually resulted in the formation of insoluble hydroxides. The question, therefore, arose as to whether the acidity contributed significantly to the toxicity. In this connection samples of the five zirconium salts and lanthanum ammonium nitrate were dissolved in water and the acid titrated with 0.1 N sodium hydroxide. In the case of the basic salt, potassium hexacolumbate, the base was titrated with 0.1 N hydrochloric acid. The acidity or alkalinity of these salts in milliequivalents of acid or base per kgm. injected with the administration of an intraperitoneal LD-50 was calculated and the data are presented in Table 2.

These data indicate that the compounds varied considerably in their acidity but it does not appear that the amounts of acid injected could account for the wide differences in the LD-50 values of the various compounds. Although zirconium sulfate, which is the most acidic of the group, is also the most toxic administration of an LD-50 entails the injection of the least amount of acid. This finding as well as other evidence of a lack of correlation between acidity and toxicity indicates that the toxicity of these compounds is not due primarily to their acidic nature.

Effect of lanthanum, zirconium, cesium and strontium on succinic dehydrogenase

In initiating studies on the actions of these metals on enzymatic reactions we selected enzyme systems which require metallic activators such as calcium for maximal activity. Succinic dehydrogenase was the first enzyme studied because for maximum activity the test system requires calcium (9) and aluminum (9). Furthermore, it has been shown (10) that the activity of this enzyme is increased by the presence of chromium and certain rare earths as well as aluminum.

In addition to testing the action of the metals on the intact succinic dehydrogenase system tests were made to observe whether they could replace calcium or aluminum in the system. Data on the effect of lanthanum (as the ammonium nitrate salt) on the succinic dehydrogenase activity of mouse liver is given in Table 3, where it may be seen that in the absence of any metallic ion the succinic dehydrogenase activity is less than one-half the control value which is obtained in the presence of 4×10^{-4} M calcium and aluminum. Calcium and aluminum separately, but at the control concentrations mentioned above, showed 85 per cent and 56 per cent, respectively, of the control activity. With 1×10^{-5} M lanthanum, the activity was 78 per cent of the control and with 4×10^{-4} M calcium plus 1×10^{-5} M lanthanum the activity was 103

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TABLE 2

RELATION OF ACIDITY TO TOXICITY

Compound	m.equiv. acid/gm.	IP LD-50 mgm./kgm.	m.equiv. acid inj'd, mgm./kgm.
Zirconyl acetate	9.3	300	2.8
Zirconyl chloride	5.8	400	2.3
Zirconyl nitrate	6.0	1250	7.5
Zirconium sulphate	10.6	175	1.8
Sodium zirconyl sulphate	3.0	4100	12.3
Lanthanum ammonium nitrate	0.1	625	0.06
Potassium columbate	1.0 (base)	225	0.22 (base)

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TABLE 3

EFFECT OF LANTHANUM ON MOUSE LIVER
SUCCINIC DEHYDROGENASE

Metal	Concentration of Metal, Molar	Per Cent of Control Activity
Control (Ca + Al)	(4×10^{-4})	(100)
None	-	48
Ca	4×10^{-4}	85
Al	4×10^{-4}	56
La	1×10^{-3}	33
	4×10^{-4}	50
	1×10^{-4}	64
	1×10^{-5}	78
	1×10^{-6}	52
	1×10^{-7}	38
La + 4×10^{-4} M Ca	1×10^{-3}	80
	4×10^{-4}	99
	1×10^{-4}	96
	1×10^{-5}	103

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per cent of the control. Thus, lanthanum effectively replaced aluminum in the test system indicating that these two metals belonging to the same group possess similar biological effects.

Zirconium in concentrations ranging from 1×10^{-3} to 1×10^{-8} M as both zirconyl chloride and zirconium sulfate had no significant effect on succinic dehydrogenase and similar results were obtained with potassium tantalum fluoride (10^{-4} to 10^{-7} M). Barium and magnesium chloride (4×10^{-4} M) had no effect when tested for their ability to replace calcium nor did any of the other salts (4×10^{-4} M) except strontium. A system with strontium chloride (4×10^{-4} M) as the only salt added showed 67 per cent as much activity as did the calcium plus aluminum control, and with strontium plus aluminum (each 4×10^{-4} M) 78 per cent of the control activity resulted whereas the activity without any metal was 57 per cent and with aluminum alone 55 per cent of the control activity. This indicated that strontium is at least partially able to replace calcium in activating succinic dehydrogenase.

Columbium as potassium hexacolumbate was found to inhibit mouse succinic dehydrogenase, with 1×10^{-3} M causing 65 per cent inhibition and 5×10^{-4} M producing 51 per cent inhibition. Yttrium chloride also caused 25 per cent inhibition at a final concentration of 1×10^{-3} M. The pH of the reaction mixture was checked in the presence of the highest concentration of each salt used and it was found to be no different from that of the control system. The inhibitory effect of columbium was interesting in view of the toxicity of this metal suggesting that the acute toxicity may be explained on the basis of interference with metallic activated enzymatic reactions.

Effect of zirconium, columbium, lanthanum, strontium and yttrium on ATP-ase

Adenosine triphosphatase (ATP-ase) requires the presence of calcium for maximal activity. It was, therefore, of interest to test the effect of the metals employed in our studies on the activity of this enzyme in the presence and absence of calcium to note whether any of the metals could replace calcium as the activator and to observe whether any of them inhibited the activity of this enzyme. In vitro tests were, therefore, carried out using mouse liver homogenates as the source of the enzyme. All of the salts, with the exception of cesium chloride, caused some inhibition in the range of concentrations tested. The results of these tests are given in Table 4.

By plotting the logarithm of the inhibitor concentrations employed against the percentage of the control activity the molar concentration of each inhibitor necessary to produce 50 per cent inhibition of the system was estimated as follows: columbium chloride, 4.2×10^{-4} M; potassium columbate, 5.8×10^{-4} M; lanthanum chloride, 4.4×10^{-3} M; strontium chloride, 8.3×10^{-2} M; yttrium chloride, 4.5×10^{-3} M; and zirconium chloride, 1.05×10^{-3} M. In the case of ATP-ase in vivo studies must be conducted before significance is attached to these effects although it is interesting to note that the most effective inhibitor tested (columbium) is also one of the most toxic of the compounds which we examined during this study.

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TABLE 4

EFFECT OF COLUMBIUM, LANTHANUM, STRONTIUM, YTTRIUM, AND ZIRCONIUM ON ATP-ase ACTIVITY OF MOUSE LIVER

Metal	Concentration, Molar	Per Cent Inhibition
Columbium chloride	1.5×10^{-3}	87
	7.5×10^{-4}	60
	7.5×10^{-5}	9
Potassium columbate	1.5×10^{-3}	74
	7.5×10^{-4}	20
	7.5×10^{-5}	3
Lanthanum chloride	6×10^{-3}	53
	3×10^{-3}	44
	7×10^{-4}	10
Strontium chloride	6×10^{-3}	28
	3×10^{-3}	17
	7×10^{-4}	2
Yttrium chloride	6×10^{-3}	78
	3×10^{-3}	56
	7×10^{-4}	20
Zirconium chloride	6×10^{-3}	100
	3×10^{-3}	98
	7×10^{-4}	32

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DISCUSSION

The metabolism of the radioactive forms of the metals included in this study has been studied rather extensively (5,6,7,8) and the results of these studies have been summarized by Hamilton (11), but relatively little toxicological or pharmacological information concerning them is available. The pharmacodynamics of zirconium compounds have been studied by Marui (12) and van Kiekerk (13). Harding (14) comments on the inert character of injected zirconium silicate in sublethal doses and mentions the use of zirconium oxide as a radiographic contrast medium as suggested by Kaestle (15), who found no toxic effects from 0.4 gm./kgm. of a soluble zirconium salt injected subcutaneously into rabbits or from zirconium oxide eight months after its intragluteal injection into rats. Other similar findings have been reported (1,16, 17) including the absence of toxic effects from injecting 300 mgm. of zirconium silicate intraperitoneally into guinea pigs (14). McClinton and Schubert (18) found the LD-50 of zirconyl ion injected intraperitoneally as zirconyl citrate to be 1710 mgm./kgm. and the gluconate to be 247 mgm./kgm., and suggest that the greater toxicity of the gluconate may be due to its being excreted slower than the citrate. The approximate intraperitoneal LD-50 of zirconyl nitrate for mice has been reported as 450 mgm./kgm. (19) and for rats 1185 mgm./kgm.

The toxicity of the rare earths has received more attention. When injected intravenously they prevent blood clotting through an antiprothrombin action (21), but they are too toxic for such use in man (22). The subcutaneous LD-50 of lanthanum chloride for mice has been reported as 3500 mgm./kgm. (23, 24). No information on the toxicity of tantalum or columbium was found in the literature and Fairhall (25) states that to his knowledge none is available, although the tolerance of tantalum metal by tissues is known (26,27). Tantalum foil and tantalum oxide are sufficiently non-toxic to have been suggested for covering serious burns (28,29). One would expect columbium and tantalum to be rather toxic in view of the toxicity of the other member of subgroup V, vanadium (25). Although much work has been done on the action and metabolism of strontium in various animals, relatively little data on its acute toxicity has been published. The minimum lethal dose for rats has been reported to be 123 mgm./kgm. when injected intravenously as strontium chloride (30).

Our studies have indicated that there is a considerable difference in the toxicity of various salts of a given metal. This difference is undoubtedly due in part to differences in absorption. Most of the metals tested are relatively non-toxic when compared with substances like arsenic, selenium, mercury and lead. However, certain of them, such as columbium, might well give rise to acute poisoning if administered in large doses or perhaps if continued ingestion of their salts occurred.

The stimulation of succinic dehydrogenase by lanthanum has been reported previously (10) and our finding that it was able to replace aluminum in this system was not surprising in view of the chemical similarities of the two metals. This finding indicates that aluminium and lanthanum behave similarly in biological systems. Vincke and Oelkers (24) found that rare earths inhibit serum lipase of man and rabbits and the esterase of pig liver, pancreas and rabbit muscle. It has also been reported that the dehydrogenase activity of yeast cells and yeast extract is inhibited by lanthanum (31). Zirconium and yttrium were reported to have practically no effect while

lanthanum had an inhibiting effect on the oxidative processes of organisms (32). The inhibition of ATP-ase by strontium may well be due to its competition with calcium since the two metals belong to the same group and have a number of chemical similarities. The extent to which these effects contribute to the mechanism of action of these metals awaits further in vivo studies. Both additional toxicity studies and further enzyme tests are in progress at the present time and will be presented in a subsequent report.

SUMMARY

1. The acute 10-day LD-50 of zirconium with various anions was found to range from 990 to 2290 mgm./kgm. of Zr when the compounds were administered orally, and from 63 to 959 mgm./kgm. of Zr when they were given intraperitoneally in rats. For lanthanum (as the ammonium nitrate and chloride salts respectively) the LD-50 values were 830 and 2370 mgm./kgm. of La when given orally and 153 to 197 mgm./kgm. of La when they were given intraperitoneally. The LD-50 for columbium as potassium hexacolumbate given orally was found to be 1140 mgm./kgm. of Cb as compared with 86 mgm./kgm. Cb when the salt was given intraperitoneally. The LD-50 values for tantalum as the chloride and as potassium tantalum fluoride, respectively, were 958 and 150 mgm./kgm. Ta by oral administration and 66 and 173 mgm./kgm. Ta when administered by the intraperitoneal route. The oral LD-50 for strontium chloride was 1635 mgm./kgm. while the intraperitoneal LD-50 was 245 mgm./kgm. Sr.

2. Lanthanum chloride (1×10^{-5} M) was found to be able to replace aluminum as an activator for the succinic dehydrogenase system. Strontium chloride (4×10^{-4} M) was partially effective in replacing calcium in this system.

3. Columbium (5×10^{-4} M potassium hexacolumbate) caused approximately a 50 per cent inhibition and 1×10^{-3} M yttrium chloride produced a 23 per cent inhibition of the succinic dehydrogenase activity of mouse liver in vitro.

4. Cesium chloride failed to inhibit the ATP-ase activity of mouse liver in vitro while salts of other metals caused 50 per cent inhibition at the following molar concentrations: columbium chloride, 4.2×10^{-4}; potassium columbate, 5.8×10^{-4}; lanthanum chloride, 4.4×10^{-3}; strontium chloride, 8.3×10^{-2}; yttrium chloride, 4.5×10^{-3}; and zirconium chloride, 1.05×10^{-3}.

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