Title

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Berkeley, California

THE DEPOSITION OF CARRIER-FREE RADIO-VANADIUM IN THE RAT FOLLOWING INTRAVENOUS ADMINISTRATION*

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The various compounds of vanadium have been of interest from the point of view of their possible chemical action and toxicity upon biological systems as well as an interest in the role which vanadium may play in cellular metabolism.

According to the work of Franke and Moxan (1), $NaVO_3$ was toxic to rats when fed in the diet at 25 parts per million and the minimum fatal dose being 4.0 to 5.0 milligrams per kilogram body weight. Similar studies conducted by Daniel et al (2) showed that 92 parts per million of Na_3VO_4 in a diet fed to rats resulted in the death of the animals (3). They were able to tolerate 23 parts per million and showed no demonstrable accumulation effect. The administration of 4 milligrams of Na_3VO_4 to rats daily by stomach tube resulted in profound vanadium poisoning. This was associated with lung hemorrhages, diarrhea, and hind leg paralysis. Damage to the gastro-intestinal tract was observed with inflammation and ulceration (3).

The excretion pattern of vanadium in man after intravenous administration has been studied by Kent (4) who has shown that 81 percent of it could be recovered from the urine and 9 percent in the feces. If vanadium is present in biological material, it exists in trace amounts of less than 1 to 5 parts per million according to the investigations of Daniel (5) using spectrographic methods of analysis. The materials analyzed were eggs, milk, and tissues from the rat including muscle, blood, and viscera. Similar studies were conducted earlier by Boyd (6) who demonstrated vanadium to be present in human pancreas,

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kidney and liver, but not in brain.

Vanadium is considered by Rygh (7) to be a trace element of biological importance in aiding the deposition of calcium in bone.

In the studies cited above, relatively large amounts of vanadium were used as compared to the distribution of carrier-free radioactive vanadium. Although the vanadium administered becomes part of the vanadium pool of the body, which according to the above studies may be extremely small, it represented less than 3×10^{-4} micrograms of elemental vanadium at the time it was injected into each animal. The minimum amount detectable spectrographically is 2×10^{-3} micrograms according to Boyd (6). Because of the small amount of vanadium used as a tracer, the distribution data obtained should represent the normal metabolism of vanadium more exactly than when larger amounts of this element are used.

Method

The radio-vanadium used in these studies was produced by bombarding a titanium target in the cyclotron with deuterons. This results in the formation of V^{48} by the following reactions: $Ti^{47}(d,n)V^{48}$ and $Ti^{48}(d,2n)V^{48}$. The V^{48} thus formed has a half-life of 16 days. It decays by K capture, 42 percent, and positron emission, 58 percent to stable $titanium^{48}$. The maximum energy of the electrons produced is 0.72 Mev and the decay is associated with 0.98 and 1.33 Mev gamma rays (8)(9).

The radio-vanadium was chemically separated from the target using procedures reported by Haymond et al (10) and prepared for administration to the rats as an isotonic saline solution of radio-vanadium in the plus five state at a pH of 5.5. The titanium used contained less than 1 microgram of vanadium per gram of titanium and reagents of laboratory grade were employed. The maximum amount of vanadium for the entire preparation was estimated to be less than 10 micrograms and no animal received more than 5 percent of the preparation. This was administered to four groups of rats, containing three animals in each group, and the amount given is indicated in Table I. One of

TABLE I

THE DEPOSITION OF CARRIER-FREE RADIO-VANADIUM IN THE RAT 1, 4, 15, AND 64 DAYS AFTER INTRAMUSCULAR INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND ARE EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT IN THE 1, 4, AND 15 DAY GROUPS RECEIVED 4 MICROCURIES OF RADIO-VANADIUM. EACH RAT IN THE 64 DAY GROUP RECEIVED 8 MICROCURIES OF RADIO-VANADIUM

	1 day		4 days		15 days		64 days	
Organ	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.21	.16	.10	.10	.05	.07	.03	.03
Lung	.46	.26	.29	.18	.15	.08	.04	.02
Spleen	.68	.53	.63	.65	.45	.38	.15	.17
Blood	4.60	.30	1.52	.11	.20	.01	.01	<.01
Liver	8.69	.78	6.23	.64	2.37	.22	.89	.08
Kidney	6.41	2.65	4.35	1.82	1.57	.76	.26	.09
Adrenal	.02	-	.01	-	.02	-	<.01	-
Thyroid	.02	-	.01	-	<.01	-	<.01	-
Lym. Gl.	-	.43	-	.47	-	.35	-	-
Pancreas	.21	.20	.19	.15	.10	.10	.10	.02
Brain	.05	.03	.03	.01	.02	.01	.01	<.01
Fat	-	.28	-	.06	-	.08	-	<.01
Stomach	.99	.33	.24	.13	.10	.01	.02	<.01
Sm. Int.	3.66	.43	.96	.13	.54	.04	.22	.02
Lg. Int.	6.12	.66	1.40	.21	.41	.04	.13	.01
Skeleton	14.1	.68	9.94	.53	8.98	.47	4.58	.23
Muscle	7.65	.07	4.96	.04	4.15	.04	2.19	.02
Skin	5.14	.18	4.46	.18	2.73	.11	.98	.03
Pituitary	.02	-	<.01	-	<.01	-	-	-
Eyes	.02	.07	<.01	.03	.01	.02	<.01	.01
Testes	.36	.12	.57	.17	.38	.13	.29	.09
Urine	32.3	-	39.6	-	44.0	-	54.7	-
Feces	7.82	-	24.3	-	33.7	-	35.4	-

the above groups was sacrificed at 1, 4, 15, and 64 days after intramuscular administration. The rats used in this study were males averaging 246 grams total body weight. Tissue samples were taken for radioactive assay and were ashed and prepared for counting with a G.M. counter as described in an earlier paper (11). The actual recoveries were 86, 97, 101, and 112 percent of the radio-vanadium administered for the 1, 4, 15, and 64 day groups of animals, respectively.

Results

The major portion of the radio-vanadium administered by intramuscular injection to the left hind leg was absorbed from the injection site there remaining 23.7, 22.4, 9.0, and 5.6 percent of the dose in the left leg at 1, 4, 15, and 64 days, respectively.

Of the radio-vanadium absorbed initially, rapid excretion occurred in the urine (32.3 percent) during the first 24 hours after injection and continued at a diminishing rate during the course of the experiment. At 64 days after administration, over one-half of the radio-vanadium absorbed was excreted in the urine, and most of the remainder was in the feces. For the first 15 days after radio-vanadium administration, the fecal excretion is considerable and represented 35.4 percent of all of the radio-vanadium excreted by the 64th day.

It may be noted from Table I that the carrier-free radio-vanadium is eliminated rather rapidly from the soft tissues with the exception of muscle. For example, the deposition in the liver and kidney fell approximately to 10 percent and 3.5 percent, respectively, of the maximum uptake, between the first and 64th day. Retention by the skeleton may be considered significant both on the basis of the per organ and per gram accumulation. At the 64-day interval the highest concentrations on a per gram basis were noted in skeleton, spleen, kidney, liver, and testes. These concentrations are quite significantly greater than organs and tissues such as heart, lungs, mucle, and digestive tract. The overall retention in the rat over the 64-day period is approximately 10 percent of the radio-vanadium absorbed from the intramuscular site of injection.

In addition to the intramuscular injection series described above, one group of animals was given 2 microcuries of radio-vanadium intragastrically and sacrificed 8 days later. Over 99 percent of the radio-vanadium administered was recovered in the excreta and this was primarily in the feces. There were measurable amounts retained by liver, kidney, small intestine, bone, and muscle and amounted to .06, .03, .02, .17, and .14 percent of the dose per organ, respectively. The radioactivity accountable to vanadium in the skin could have come from outside contamination. On a per gram wet weight basis, less than .01 percent of the radio-vanadium administered was found in any tissue. (See Table II).

While the amount of carrier-free radio-vanadium found in the organs and tissues was small after intragastric administration, there was a significant quantity present in liver, kidney, bone, and muscle. That present in the skin may have resulted at least in part from external contamination from the excreta. That which was observed to be present in the small intestine and large intestine could be accounted for on the basis of traces of unabsorbed radio-vanadium. It may be noted that there is a rough correlation between the relative content in liver, kidney, bone, and muscle of carrier-free radio-vanadium following the two routes of administration. From this and the data presented in Table II, it would appear that absorption from the digestive tract of the rat of carrier-free Na_3VO_4 lies in the range of 0.5 percent.

From these data, it would appear probable that in man small amounts of vanadium are present in the body, though probably too minute to be detected by any of the classical procedures of chemistry and physics.

Discussion

The studies reported above indicate that radio-vanadium is stored to some extent in the tissues of the body after parenteral administration. These tissues are primarily skeleton, gonads, kidney, liver, and spleen. Since the total radio-vanadium administered per rat was less than 3×10^{-4} microgram, the

TABLE II

FATE OF CARRIER-FREE RADIO-VANADIUM IN THE RAT 8 DAYS AFTER INTRAGASTRIC ADMINISTRATION. THE DOSE OF CARRIER-FREE RADIO-VANADIUM WAS 2 MICROCURIES AND LESS THAN 3×10^{-5} MICROGRAMS OF RADIO-VANADIUM. VALUES EXPRESSED ARE AS PERCENT OF DOSE CORRECTED FOR RECOVERY.

Organ	% per organ	% per gram
Heart	<.01	<.01
Lungs	<.01	<.01
Spleen	<.01	<.01
Blood	.01	<.01
Liver	.06	<.01
Kidney	.03	.01
Adrenal	<.01	<.01
Thyroid	<.01	-
Lymph Gland	<.01	<.01
Pancreas	<.01	<.01
Brain	<.01	<.01
Fat	<.01	<.01
Stomach	<.01	<.01
Sm. Int.	.02	<.01
Lg. Int.	.06	<.01
Bone	.17	<.01
Muscle	.14	<.01
Balance	.02	-
Skin	.08	<.01
Pituitary	<.01	-
Eyes	<.01	.01
Testes	<.01	<.01
Urine	1.56	-
Feces	97.9	-

actual amount retained by these organs was relatively small and this neglects the factor of radioactive decay. For example, 64 days after radio-vanadium administration, 90 percent was excreted thus leaving less than 3×10^{-5} micrograms of the radio-vanadium administered in the body in the vanadium pool of the body or far less than one part per billion. These studies corroborate the findings of Daniel (5) who showed that the vanadium content of rat tissues was lower than 5 to 1 parts per million, this being the limit of the sensitivity of their analytical method. Our studies suggest, however, that vanadium in small amounts may be a normal constituent in the body and not just a trace which has not been excreted because of deposition in the reticulo-endothelial elements of the body. This does not imply that it is an essential trace element.

For example, studies with carrier-free silver in which similar submicrogram dosages were employed (11) demonstrated that the silver was so completely and rapidly excreted that the residual concentration remaining after 64 days was less than 1/1000 of that observed with radio-vanadium at the same time interval.

An estimated maximum of stable vanadium given to each rat was less than 0.5 microgram. Thus is it not improbable that only a small fraction of all vanadium atoms administered were radio-vanadium. However, the small total given probably is not sufficient to alter the results as compared to using a preparation containing no stable vanadium. In practice, very minute contamination is unavoidable.

Summary

Tracer studies in the rat have been conducted employing carrier-free radio-vanadium (V^{48}). There is an initial relatively rapid excretion by way of the kidneys and digestive tract, following intramuscular administration of carrier-free pentavalent radio-vanadium in isotonic saline at pH 5-6. Four groups of three rats each were employed and the groups sacrificed at 1, 4, 15,

and 64 days.

At the 64-day interval approximately 10 percent is retained in the body. Principal organs of retention at this interval are the skeleton, muscle, liver, testes, and kidney. The highest concentration per gram of wet tissue was observed in the skeleton, testes, kidney, and liver.

Intragastric adminstration was performed on one group of three rats and it would appear that approximately 0.5 percent was absorbed from the digestive tract.

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