Vanadium

Excretion, Toxicity, Lipid Effect in Man

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Vanadium was administered orally to human beings to establish (1) levels of tolerance, (2) relationship between oral dose and urinary excretion, (3) evidences of toxicity, and (4) the effect on circulating lipids.

METHOD

The product used was ammonium vanadyl tartrate,‡ in a concentration of 25 mg. per tablet. Subjects were maintained on normal diets and carried on normal activities. The drug was given orally with meals one to four times a day.

The amount of vanadium excreted in the urine was determined by the method of Talvitie;[1] urine specimens were also examined microscopically. Other parameters measured were serum glutamic oxaloacetic transaminase, blood urea nitrogen, white blood cell count, reticulocyte count and platelet count. Total lipids,[2] triglycerides, phospholipids[3] and total and free cholesterol[4] were measured in all patients; in three patients, 17-ketosteroids and 17-hydroxycorticosteroids also were measured. Venous arm blood was used.

Six patients received the medication for a minimum of six weeks. These patients were ambulatory and on normal diets. The total number of days of vanadium therapy per patient were forty-five, sixty-three, forty-seven, fifty-eight, forty-seven and sixty-eight; the total amount of vanadium salt administered per patient was 3,450, 4,325, 3,600, 3,875, 1,575 and 4,225 mg. One patient (who originally received 3,450 mg. vanadium) participated in a subsequent study for a forty-nine day period. During this second period 4,925 mg. of vanadium salt was given making the total dose in this one patient 8,375 mg. in ninety-four days. The age, sex, total number of days of therapy, total amount of drug administered and dosage of drug per day are indicated in Table I.

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‡ Prepared upon our request by Eli Lilly & Co., through the courtesy of Dr. William Martz.

RESULTS

Excretion

Table II illustrates the variation in the twenty-four hour urinary excretion of vanadium in four patients receiving varying doses orally. In subject D. T., there was a rough quantitative increase in the urinary excretion of vanadium when the dosage was changed from 50 to 75 mg. In subject M. R., greater amounts were excreted when the dosage was increased from 50 to 100 mg. In subject R. C., the urinary excretion was unpredictable relative to the oral dosage. In subject H. C., there was a rough quantitative relationship but there were wide fluctuations within dosages. In all patients, the wide fluctuations in urinary excretions suggested unpredictable absorption of the drug.

Toxicity

Laboratory alterations indicative of toxicity did not occur. Hematologic studies of white blood cell count, differential count, platelets and reticulocytes revealed no abnormalities. Urinalyses for albumin, hemoglobin and formed elements yielded negative results. Blood urea nitrogen and serum glutamic oxaloacetic transaminase levels were unchanged.

At the conclusion of the vanadium regimen the 17-ketosteroid[5] and 17-hydroxycorticosteroid[6] levels were measured in three female participants. These figures (in mg. per twenty-four hours) were 13.1, 11.8 and 18.2 for the 17-ketosteroids and 6.1, 8.3 and 9.5 for the 17-

TABLE I
Oral Ammonium Vanadyl Tartrate

Subject	Age (yr.) and Sex	Therapy (total no. of days)	Total Amount of Drug Administered (mg.)	Dosage per Day (no. of days given)			
				25 mg.	50 mg.	75 mg.	100 mg.
M. R.*	55, F	45	3,450	...	21	...	24
D. W.	54, F	63	4,325	5	12	40	6
H. C.	30, F	47	3,600	5	7	15	20
D. T.	35, F	58	3,875	9	25	24	...
G. D.	42, M	47	1,575	31	16	...	...
R. C.	40, F	68	4,225	...	35	33	...

* Participated in a second study for forty-nine days and received an additional 4,925 mg.

TABLE II
Urinary Excretion of Vanadium Relative to Daily Oral Dose of Ammonium Vanadyl Tartrate

Subject	Date	Daily Dose (mg.)	Excretion of Vanadium in Urine	
			μg./ml.	μg./24 hr.
H. C.	4/11/61	25	0.028	43
	4/15/61	50	0.114	168
	4/18/61	50	0.073	182
	4/22/61	75	0.090	146
	5/2/61	75	0.088	136
	5/6/61	100	0.093	151
	5/13/61	100	0.146	285
	5/23/61	0*	0.049	105
	6/8/61	0	0	0
R. C.	5/2/61	50	0.014	28
	5/3/61	50	0.044	91
	5/4/61	50	0.049	98
	5/17/61	75	0.024	55
D. T.	5/2/61	50	0.017	25
	5/3/61	50	0.035	55
	5/4/61	50	0.038	44
	5/17/61	75	0.075	151
M. R. (first course)	5/16/61	50	0.140	273
	5/23/61	50	0.190	256
	5/29/61	50	0.146	259
	6/6/61	100	0.356	498
	6/20/61	100	0.354	488
	7/5/61	0	0.026	33
	7/18/61	0	0.010	14
	8/1/61	0	0	0
M. R. (second course)	8/1/61	0	0	0
	8/15/61	75	0.550	742
	8/22/61	100	0.975	1,365
	8/23/61	125	0.720	1,188
	8/30/61	125	1.300	1,514

* Stopped vanadium day before.

hydroxycorticosteroids (normal range for this laboratory: 17-ketosteroids 5 to 15 mg. per twenty-four hours volume excreted as dehydroisoandrosterene and 17-hydroxycorticosteroids 5 to 10 mg. per twenty-four hours volume).

All patients experienced gastrointestinal difficulties manifested by black, loosened stools and increased intestinal activity accompanied by cramps. In each subject, the oral dosage was limited by cramping and diarrhea.

Nausea, vomiting or pyrosis did not occur; neither did dysuria. On a daily dosage of 50 mg. or more, a purple-green tint developed on the tongue which occurred quickly and disappeared promptly. Discoloration of gums was not noted, and cheilosis did not occur. A distinct change in sensorium was not noted although two of the participants stated that they experienced greater fatigue and lethargy while taking vanadium than usual. Three participants noted increased dysmenorrhea.

A cholinergic-blocking drug,* given with each dose of vanadium, seemed to lessen the intestinal symptoms and permit therapy with a larger dose of vanadium.

Varying social consumption of alcohol did not alter the individual tolerance for vanadium.

Dosage of Vanadium

The total daily dose tolerated varied from 50 to 125 mg. The relationship of date, dosage

* Triglyclamol chloride, 50 mg., given four times daily, obtained through the courtesy of Dr. William Martz, Eli Lilly & Co.

TABLE III

Effect of Orally Administered Ammonium Vanadyl Tartrate on Cholesterol, Phospholipid (Phosphorus), and Triglycerides

Subject	Date	Ammonium Vanadyl Tartrate (mg.)	Total Cholesterol (ml. %)	Phospholipid, Phosphorus (ml. %)	Triglycerides (ml. %)
R. C.	12/9/60	0	185	9.64	98
	1/23/61	0	158	7.89	130
	4/3/61	0	202	10.02	56
	4/25/61	50	232	9.65	...
	5/2/61	50	206	10.49	121
	5/3/61	50	200	9.70	...
	5/5/61	50	202	11.00	...
	5/9/61	75	215	10.47	50
	5/23/61	75	210	8.93	94
	6/6/61	0	212	9.66	81
	6/14/61	0	202	9.02	106
	6/21/61	0	183	8.40	143
H. C.	12/7/60	0	217	...	80
	4/5/61	0	218	10.30	30
	4/21/61	50	215	10.10	36
	5/5/61	100	191	9.91	29
	5/12/61	100	192	10.27	42
	5/19/61	100	182	9.26	31
	5/23/61	100	207	10.38	19
	5/26/61	0	207	10.68	69
	6/2/61	0	216	10.76	253
	6/9/61	0	203	9.75	123
	6/16/61	0	194	9.84	89
	6/23/61	0	187	8.65	84
	8/30/61	0	205		
G. D.	12/13/60	0	250	12.12	231
	1/20/60	0	241	...	...
	3/16/61	0	222	9.65	169
	4/20/61	25	255	9.50	56
	5/5/61	50	226	8.94	76
	5/8/61	0	204	8.70	108
	5/12/61	0	248	9.59	62
	5/24/61	0	222	9.12	90
	6/6/61	0	248	11.02	100
D. W.	4/10/61	0	343	14.10	150
	4/21/61	50	330	14.30	170
	5/5/61	75	327	14.06	198
	5/24/61	75	342	13.44	209
	6/6/61	100	308	14.07	273
	6/14/61	0	311	13.26	207
D. T.	12/6/60	0	188	...	...
	4/3/61	0	177	10.25	68
	4/25/61	50	222	11.00	94
	5/3/61	50	176	9.48	35
	5/5/61	50	166	8.72	69
	5/9/61	75	185	10.20	62
	5/23/61	75	174	9.60	71
	5/31/61	75	168	9.50	79
	6/6/61	0	192	10.12	98
	6/14/61	0	165	9.53	39
M. R.	5/1/61	0	442	17.30	97
	5/8/61	50	434	17.10	219
	5/23/61	50	385	16.12	101
	6/7/61	100	368	14.30	170
	6/21/61	100	393	14.73	111
	7/6/61	0	402	15.20	21
	7/18/61	0	398	15.60	91
	8/1/61	0	406	11.13	11
	8/16/61	100	418	15.25	41
	8/30/61	125	368	14.87	169
	9/6/61	125	380	15.22	259
	9/13/61	100	390	15.77	44

of vanadium and serum lipids is shown in Table III.

Subject R. C. was studied from December 9, 1960, to April 3, 1961, as a control or observation period. Vanadium therapy was begun on April 4, with 50 mg. of ammonium vanadyl tartrate being given daily, and continued to May 9, 1961, at which time the dosage was increased to 75 mg. and continued until June 6, 1961. Lipid studies were continued in the control period, after medication was discontinued, through June 21, 1961. Cholesterol, phospholipid and triglyceride levels are expressed in milligrams per cent. Similar data for the other five participants also are presented in Table III.

COMMENTS

Cholesterol biosynthesis both *in vitro*[7,8] and *in vivo*[9,10] has been reported to be inhibited by vanadium salts. In this limited series of cases treatment with vanadium (as ammonium vanadyl tartrate) did not lead to a marked decrease in the cholesterol concentration in the serum or to any appreciable changes in the triglyceride and phospholipid levels. A slight decrease in serum total cholesterol was observed in one subject (D. W., Table III) after two weeks of daily treatment with 100 mg. of the vanadium salt. This lower cholesterol level was maintained one week after treatment was discontinued. A similar response was observed in subject M. R. (Table III).

The serum phospholipids and triglycerides did not show a statistically significant trend after the administration of vanadium nor was there any apparent correlation between serum total cholesterol and the C:P ratio.

Vanadium has been reported to inhibit oxidative phosphorylation *in vitro*.[11] On this basis, it has been suggested that ATP levels of tissues *in vivo* may be altered by the administration of vanadium. The impairment of the synthesis of this vital compound conceivably could result in undesirable side effects; however, we found no overt evidences of toxicity from vanadium in any of the subjects studied. Except for the occurrence of cramps and diarrhea when large doses were given, there was no evidence of measurable toxic effect of vanadium on bone marrow, liver, kidney or adrenal gland during this study.

SUMMARY

Vanadium, as ammonium vanadyl tartrate, was given orally to six subjects. The total number of days of therapy were forty-five, sixty-three, forty-seven, fifty-eight, forty-seven and sixty-eight, and the total amount of vanadium salt administered was 3,450, 4,325, 3,600, 3,875, 1,575 and 4,225 mg. Except for cramps and diarrhea, which occurred when large doses were given, no toxic effects were noted. Varying amounts of vanadium excreted in the urine suggest unpredictable absorption. Statistical changes did not occur in blood lipids, phospholipids, triglycerides and cholesterol, and 17-ketosteroid and 17-hydroxycorticosteroid levels were unchanged.

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