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EFFECTS OF VANADIUM ON REPRODUCTION, GESTATION, PARTURITION AND LACTATION IN RATS UPON ORAL ADMINISTRATION

J.L.Domingo[1], J.L.Paternain[1], J.M.Llobet[1] and J.Corbella[2]

[1]Department of Biochemistry, Faculty of Medicine, C/ San Llorenç 21, Reus and [2]Department of Toxicology, Faculty of Medicine, University of Barcelona, C/ Casanova 143, Barcelona, Spain.

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Summary

Sodium metavanadate was tested for its effects on fetal development, reproduction, gestation and lactation in Sprague Dawley rats. Male rats were administered $NaVO_3$ po at doses of 0, 5, 10 and 20 mg/kg/day for sixty days before mating with females which had received the same doses from 14 days previous to mating. These females received 0, 5, 10 and 20 mg $NaVO_3$/kg/day during the periods of gestation and lactation. No significant adverse effects could be observed on: number of corpora lutea, implantations, live and dead fetuses, and resorptions. Significant decreases were observed in the development of the pups in all the vanadium -treated groups. All the doses used produced toxic effects in the offspring.

Vanadium is a trace element which is widely distributed in nature. It has been extensively used in the hardening of the steel, the manufacture of pigments, in photography and insecticides. It has also been used as a catalyst in the production of various materials and has been found to be a health hazard to workers. Conjunctivitis, pharyngitis, rhinitis, chronic productive cough and tightness of the chest haven been reported (1,2). Also, medicinal uses of vanadium compounds can produce gastrointestinal disturbances. Oral ingestion of vanadium has been described as mainly toxic to the gastrointestinal tract, as less than 1% is absorbed from the gut (3,4).

On the other hand, vanadium compounds have gained increasing interest due to their possible role in cellular regulation, with profound effects on enzymes of plasma membranes (5). Orthovanadate has been found to be an inhibitor of (Na^+-K^+)ATPase from kidney, red blood cells, skeletal muscle and heart (6,7,8) as potent as cardiac glycosides giving 50% inhibitor at 40 nM (9).

However, the experimental data on the toxicological significance of vanadium is relatively limited (10,11,12,13,14). As usual exposure to vanadium is either oral or by inhalation, a short-term oral toxicity of vanadium in rats has been reported in a previous paper (15). This has been done in order to obtain an overall understanding of the toxicity of vanadium. Pursuing this line of research, the present study investigates the effects of vanadium on reproduction, gestation, parturition and lactation in rats.

Methods

Sodium metavanadate made by the Merck Company (Darmstadt, FRG) has been used for the experiments. Twenty female Sprague-Dawley albino rats (240-280 g) were administered po 0, 5, 10 or 20 mg/kg/day of sodium metavanadate

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9432

solutions for 14 days before mating with Sprague-Dawley males which had received sodium metavanadate po 0, 5, 10 or 20 mg/kg/day for 60 days. Oral doses were given intragastrically. Males and females were mated according to the respective dose levels. Daily vaginal smears were taken. Finding of sperm indicated copulation and designated day 0. Twenty males and females were used at each compound dose level. The animals were supplied by Biocentre (Barcelona, Spain) and had free access to a high protein rat diet (Panlab, Barcelona, Spain) and water. They were housed in a temperature controlled (22 + 2ºC) animal facility. About one half of the fertilized animals were sacrificed on day 14 of gestation and the following examination made: determination of the number of corpora lutea, total implantations, living and dead fetuses as well as the number of resorptions (16,17). The remaining females were allowed to deliver and to nurse their young to 21 days. During this period, the mothers continued receiving 0, 5, 10 or 20 mg/kg/day $NaVO_3$. The offspring were observed for mortality, normal body weight gain and general symptomatology after 1, 4 and 21 days of nursing. Also, body and tail lengths were measured on the same days. After 21 days, all the offspring were sacrificed. The heart, lungs, spleen, liver, kidneys and testicles (in males) were removed and weighed, and the relative organ weights were calculated.

The results were evaluated by means of the distribution-free ranking test according to Wilcoxon in the modified version of Mann and Whitney (18), and using the χ^2 test.

Results

Sodium metavanadate given orally to rats did not show recognizable adverse effects with respect to the fertility, which was not reduced. There were no signs of maternal toxicity during the study.

Table 1. Effects of $NaVO_3$ given orally to rats killed on day 14 of gestation[a]

	Doses $NaVO_3$ (mg/kg/day)			
	0	5	10	20
No. of pregnant rats	6	8	7	6
Corpora lutea	15.5 ± 3.0	16.0 ± 2.6	16.0 ± 1.8	13.8 ± 1.7
Total implants	12.7 ± 2.7	13.6 ± 1.9	14.0 ± 2.6	12.7 ± 1.0
Live fetuses	11.7 ± 1.8	12.5 ± 1.9	12.3 ± 2.9	9.8 ± 1.3
Dead fetuses	0.3 ± 0.2	0.4 ± 0.2	0.7 ± 0.3	0.8 ± 0.4
Resorptions	0.7 ± 0.3	0.7 ± 0.3	1.0 ± 0.4	2.1 ± 0.8

[a]The results are expressed as mean values ± SE

The effect of $NaVO_3$ on reproduction parameters in the rats killed on day 14 of gestation are given in Table 1. The oral administration of vanadium had no significant adverse effects on the following parameters: number of corpora lutea, number of implantations, number of live and dead fetuses and number of resorptions. Although the administration of 10 and 20 mg/kg/day $NaVO_3$ resulted in an increase in the number of dead fetuses as in the number of resorptions when compared to the control group, these increases were not significant ($P > 0.05$).

Table 2 summarizes data from rats pups nursed by vanadium-treated mothers during lactation. Results are presented 1, 4 and 21 days after birth. The number of litters, living and dead young per litter in the treated rats, as well as the average body weight per litter did not show any significant

differences with the control group on days 1 and 4 of nursing, except for a decrease in the average body weight per litter for the highest dose tested. Some significant decreases in these parameters could be observed on day 21 of nursing. However, no effect dose-response may be induced.

Table 2. Summary of data rat pups nursed by vanadium-treated mothers during a period of 21-days

		Doses $NaVO_3$ (mg/kg/day)			
	Day	0	5	10	20
No. of litters	1	11	10	12	9
	4	11	10	11	8
	21	11	10	9	7
No. of living young	1	117	115	139	95
	4	116	115	111	79
	21	108	109	55	76
No. of dead young	1	0	8	5	5
	4	1	0	28	16
	21	8	6	56	3
Dead/living ratio (x100)	1	0.0	6.9	3.6	5.2
	4	0.8	0.0	20.1	16.8
	21	6.8	5.2	50.4	3.7
Male/female ratio	1	1.16	0.98	1.24	1.02
	4	1.18	0.98	1.31	1.02
	21	1.11	1.05	1.75	1.00
Living young/ litter ($\bar{X} \pm SE$)	1	12.2 ± 2.2	11.5 ± 3.5	11.5 ± 2.8	10.2 ± 3.3
	4	12.0 ± 2.9	11.5 ± 3.3	9.3 ± 4.1	8.8 ± 4.0
	21	11.0 ± 1.9	10.9 ± 3.4	4.6 ± 2.6[b]	8.6 ± 4.5
Dead young/ litter ($\bar{X} \pm SE$)	1	0.1 ± 0.0	0.9 ± 0.4	0.7 ± 0.3	1.3 ± 0.7
	4	0.2 ± 0.1	0.0 ± 0.0	2.2 ± 1.0	1.4 ± 0.8
	21	1.0 ± 0.6	0.6 ± 0.3	4.7 ± 2.1[b]	0.2 ± 0.1
Average body weight/litter (g ± SE)	1	94.1 ± 18.1	78.2 ± 24.2	91.1 ± 44.5	64.8 ± 21.2
	4	138.8 ± 23.8	119.5 ± 53.3	106.5 ± 32.6	87.5 ± 33.7[a]
	21	466.9 ± 95.2	365.6 ± 85.4	252.7 ± 150.9[b]	312.5 ± 110.8[a]

[a,b]Significantly different to the control group, $P < 0.05$ or $P < 0.01$, respectively

Table 3 shows the data on rat pups nursed by vanadium-treated mothers. Body weight, body length and tail length of animals in the treated groups showed significant decreases during all the period of lactation in both males and females, when compared with the control values.

Lastly, the relative organ weights of rat pups killed after 21 days of lactation are summarized in Table 4. There were significant decreases in the relative organ weights of spleen, liver and kidneys. As can be seen, slight effect dose-response may be induced.

Table 3. Average body weight, body length and tail length of rat pups nursed by vanadium-treated mothers

		Day	Doses $NaVO_3$ (mg/kg/day) 0	5	10	20
Body weight (g ± SE)	M	1	7.9 ± 0.9(63)	7.0 ± 1.1(57)[c]	6.5 ± 0.9(77)[c]	6.7 ± 0.6(48)[c]
		4	11.7 ± 1.3(63)	9.6 ± 1.8(57)[c]	9.7 ± 1.2(63)[c]	8.9 ± 0.8(40)[c]
		21	42.0 ± 8.3(57)	34.3 ± 7.9(56)[c]	33.7 ± 10.8(35)[c]	33.6 ± 7.6(38)[c]
	F	1	7.6 ± 0.9(54)	6.8 ± 1.0(58)[c]	6.4 ± 0.9(62)[c]	6.5 ± 0.6(43)[c]
		4	11.2 ± 1.9(53)	9.5 ± 1.6(58)[c]	9.3 ± 1.4(48)[c]	8.8 ± 1.1(39)[c]
		21	41.0 ± 6.7(51)	32.5 ± 6.3(53)[c]	29.7 ± 7.2(20)[c]	32.1 ± 8.8(38)[c]
Body length (mm ± SE)	M	1	56.8 ± 3.5	54.2 ± 3.6[a]	53.4 ± 3.4[b]	53.1 ± 3.0[b]
		4	67.1 ± 3.4	62.0 ± 4.4[c]	64.7 ± 3.6[c]	62.2 ± 2.5[c]
		21	119.1 ± 6.1	108.0 ± 10.0[c]	102.8 ± 16.2[c]	104.8 ± 10.8[c]
	F	1	55.5 ± 3.4	53.6 ± 3.7[b]	52.4 ± 3.9[c]	52.0 ± 2.6[c]
		4	65.5 ± 3.0	61.4 ± 3.8[c]	63.0 ± 3.7[c]	61.5 ± 3.3[c]
		21	119.7 ± 6.9	105.5 ± 11.3[c]	100.9 ± 11.7[c]	104.4 ± 11.3[c]
Tail length (mm ± SE)	M	1	19.2 ± 2.2	18.7 ± 2.3	18.5 ± 2.6	19.2 ± 1.7
		4	30.4 ± 2.4	23.9 ± 3.4[c],	25.8 ± 3.8[c]	23.6 ± 2.3[c]
		21	66.6 ± 7.0	65.8 ± 7.0	70.7 ± 12.0	62.4 ± 8.6
	F	1	19.6 ± 2.7	19.1 ± 2.0	18.3 ± 2.5[b]	19.6 ± 1.6
		4	30.7 ± 2.4	25.1 ± 3.1[c]	26.2 ± 3.8[c]	24.3 ± 2.5[c]
		21	70.4 ± 8.0	66.3 ± 7.0[b]	68.9 ± 9.5	61.0 ± 6.0[c]

M = males; F = females

In parentheses the number of animals studied

[a,b,c]Significantly different from the control group, $P < 0.05$, $P < 0.01$ or $P < 0.001$ respectively

Discussion

The doses of $NaVO_3$ administered in this study, which correspond approximately with 1/5, 1/10 and 1/20 of the po LD_{50} of mother rats (14) did not produce significant adverse effects on the fertility, reproduction and parturition in the vanadium-treated rats. Nevertheless, the development of the offspring always significantly decreased from birth and during all the lactation period. These decreases were observed for all the tested doses and must be imputed to the treatment. Also, the significant decreases in the weights of liver, spleen and kidneys of the pups whose mothers received $NaVO_3$ during the lactation, are due to a reduction in the growth of these animals according to the criterion "organ weight/body weight" (19).

The results of this experiment demonstrate that a dose of at least 5 mg/kg/day $NaVO_3$ in mother rats (corresponding to roughly 2.1 mg vanadium/kg body wt/day) may result in toxicity for the offspring. In a previous study, this dose did not have toxic results for adult rats (15).

Taking account that a safe intake of vanadium in food, water, etc., of 2.5 mg/person/day has been reported (20), the calculation for a person of 70 kg weight would be 0.036 mg V/kg/day or 0.086 mg $NaVO_3$/kg/day. This last value is about sixty times lower than 5 mg $NaVO_3$/kg/day, dose which has been

found to be toxic for the pups whose mothers received $NaVO_3$.

Table 4. Relative organ weights of rat pups nursed by vanadium treated mothers (g per 100g body weight ± SE)

	Doses $NaVO_3$ (mg/kg/day)			
	0	5	10	20
Heart	M 0.79 ± 0.21 F 0.80 ± 0.23	0.71 ± 0.12 0.72 ± 0.17	0.72 ± 0.16 0.92 ± 0.27	0.64 ± 0.13[a] 0.71 ± 0.10
Lungs	M 1.34 ± 0.36 F 1.38 ± 0.34	1.42 ± 0.26 1.32 ± 0.37	1.60 ± 0.55 1.76 ± 0.67	1.53 ± 0.26 1.49 ± 0.13
Spleen	M 0.51 ± 0.18 F 0.56 ± 0.25	0.40 ± 0.17 0.39 ± 0.23[a]	0.54 ± 0.14 0.53 ± 0.14	0.38 ± 0.17[a] 0.35 ± 0.11[b]
Liver	M 5.12 ± 0.58 F 5.53 ± 0.45	4.72 ± 0.56[a] 5.04 ± 0.80[a]	4.63 ± 0.40[a] 5.01 ± 0.75[a]	4.57 ± 0.54[a] 4.72 ± 0.63[b]
Kidneys	M 1.48 ± 0.26 F 1.56 ± 0.17	1.30 ± 0.19[a] 1.38 ± 0.22[a]	1.41 ± 0.19 1.45 ± 0.20[a]	1.39 ± 0.18 1.32 ± 0.16[b]
Testicles	M 0.68 ± 0.16	0.62 ± 0.09	0.68 ± 0.08	0.63 ± 0.13

M = males; F = females; [a,b]Significantly different to the control group, $P < 0.05$ or $P < 0.01$ respectively

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