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Embryotoxic Effects of Sodium Metavanadate Administered to Rats During Organogenesis

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J. L. PARTERNAIN, J. L. DOMINGO, J. M. LLOBET and J. CORBELLA. *Embryotoxic Effects of Sodium Metavanadate Administered to Rats During Organogenesis.* Rev. esp. Fisiol., 43 (2), 223-228, 1987.

Pregnant Sprague-Dawley rats were given orally a daily dose of 0, 5, 10 or 20 mg $NaVO_3$/kg from the sixth through the fourteenth day of pregnancy. Fetal examinations were performed on day 20 of gestation. Sodium metavanadate was neither embryolethal nor teratogenic in rats when administered orally at 20 mg/kg/day or lower. Nevertheless, this dose was embryotoxic.

Key words: Vanadium, Pregnant rats, Oral administration, Embryotoxicity.

The interest concerning the role played by metals in certain congenital malformations has been increasing. Mercury, lead and cadmium have been known to be teratogenic for many years (6, 7, 11).

Also, nickel, thallium, selenium and arsenic among other elements have been reported as teratogenic (9, 12, 14, 19).

It is a well known fact that vanadium posses grave risks to health. Inhalation exposure to vanadium can cause conjunctivitis, pharyngitis, rhinitis, chronic productive cough and tightness of the chest (17, 20). Vanadium salts have been used medicinally as antiseptic, spirochetocide, antituberculotic and antianemia agents, and general tonic. However, the medicinal use may result in gastrointestinal disorders and mild renal and nervous system effects (8). Moreover, vanadium compounds have attracted the investigators' interest due to their possible role in cellular regulation, with profound effects on enzymes of plasma membranes (10, 15). Orthovanadate has been found to be a potent inhibitor of (Na^+-K^+)ATPase in the kidney, red blood cells, skeletal muscle and heart (1, 2, 4), yielding 50% inhibition at 40 nM (3).

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However, there is relatively little information on the experimental toxicity of vanadium compounds. In previous works both the acute and the short-term toxicity of sodium metavanadate given orally to rats were studied (5, 13).

Ir order to obtain an overall understanding of vanadium toxicity the present study was undertaken to further examine the adverse effects of sodium metavanadate in rats when given throughout most of organogenesis.

Materials and Methods

Sodium metavanadate ($NaVO_3$) of analytical grade was purchased from E. Merck (Darmstadt, FRG).

Adult female and male Sprague-Dawley rats (weighing not less than 250 g) were obtained from Interfauna (Barcelona, Spain). The female were caged with males overnight and examined the following morning for the copulating plug or for spermatozoa by vaginal lavage. The day of vaginal plugs or spermatozoa detection was defined as day one of pregnancy. The animals were kept individually in Makrolon cages under standardized conditions with 12 hours of fluorescent light per day, 20-23°C room temperature, and 40-60% relative humidity. All animals were allowed free access to water and food (Panlab diet, Barcelona).

Groups of 20 pregnant rats were given intragastrically a daily dose of 5, 10 or 20 mg $NaVO_3$/kg dissolved in distilled water on days 6-14 of gestation. The control group was given distilled water. The sodium metavanadate solutions were prepared to give any dose in a volume of 1 ml/250 g body weight. Cesarean sections were performed on the 20th day of gestation and the following examination made and compared with the control values: number of corpora lutea; total implantations; number of live and dead fetuses; number of resorptions; the average fetus body weight; placental weights; fetal body length and fetal tail length. All fetuses were examined for abnormalities and sexed. One half of the fetuses from each litter were fixed in Bouin's solution and subsequently examined for visceral anomalies by razor-blade sectioning (18). The remaining fetuses from each litter were stained with alizarin red S and examined for skeletal anomalies.

The magnitude of the differences between the groups was calculated either by Student's t-test or Mann-Whitney U test. The litter was the treatment unit on which statistical analyses were based.

Results

The number of apparently non-pregnant animals increased in the group receiving the highest dose of $NaVO_3$.

The results of the effects of $NaVO_3$

Table I. *Effects of sodium metavanadate given orally on days 6-14 of gestation in rats.* Results are presented as arithmetic mean per litter ± SD. In brackets, the percentages of normal and abnormal fetuses. M = males; F = females.

Dosage (mg/kg day)	Litters	Corpora lutea	Implantations	Resorptions	Fetuses		Liver fetuses			
					Liver	Dead	M	F	Normal	Abnormal
0	14	14.9±0.91	13.7±0,81	0.1±0.04	13.4±1.10	0.1±0.04	104	92	192(97.9)	4(2.1)
5	14	16.0±0.80	13.3±3.50	0.3±0.05	12.6±1.89	0.3±0.08	110	80	156(82.1)	34(17.9)
10	12	14.8±1.23	13.3±2.19	1.8±0.25	11.3±0.70	0.2±0.04	80	56	126(92.6)	10(7.4)
20	8	15.3±1.23	13.5±1.88	1.0±0.12	11.9±1.47	0.5±0.16	46	52	64(63.3)	34(34.7)

Table II. *The effect of sodium metavanadate on fetuses.*
Results are presented as arithmetic means per fetus ± SD

Dosage (mg/kg/day)	Fetuses	Body weight (g)	Placenta weight (g)	Body length (cm)	Tail length (cm)
0	196	2.31 ± 0.43	0.99 ± 0.31	3.11 ± 0.23	1.12 ± 0.10
5	190	2.46 ± 0.21	0.85 ± 0.23**	3.35 ± 0.28	1.07 ± 0.12*
10	136	2.24 ± 0.37	0.99 ± 0.31	3.20 ± 0.20	1.15 ± 0.10
20	98	2.12 ± 0.17	0.94 ± 0.19	2.91 ± 0.23	1.06 ± 0.10*

* $p < 0.01$; ** $p < 0.001$.

following daily oral doses to pregnant rats on days 6 through 14 of gestation are summarized in table I. The number of litters decreased when 20 mg/kg/day $NaVO_3$ were administered. The administration of vanadium had no significant adverse effects on the number of corpora lutea and number of implantations. The doses of 10 and 20 mg/kg/day $NaVO_3$ caused an increase of the number of resorptions and number of dead fetuses, although no significant effect on the resorption rate could be demonstrated. The incidence of abnormalities in fetuses from treated dams was remarkably higher than the incidence in the control group, especially in the group given 20 mg/kg/day $NaVO_3$. Lastly, the differences between the number of male and female fetuses were not significant.

Slight differences in body weight, body length and tail length were observed between fetuses from treated dams and controls. The average weights of placentas were also similar (table II).

Visceral and skeletal examinations of fetuses did not reveal significant abnormalities in any group. However, the incidence of hemorrhages in facial area (18.4%) in fetuses from dams given 20 mg/kg/day $NaVO_3$ was significantly higher than the incidence in the controls (0.0%). Moreover, in some fetuses of the same group, additional abnormalities were observed (hydrocephaly, 1.0%). In the 5 and 10 mg/kg/day groups, a greater number of abnormal fetuses than in the control group were also obsrved (tacelble III).

Discussion

When $NaVO_3$ was administered to pregnant rats on the 6th to 14th days of gestation at sublethal doses (13), the dif-

Table III. *Summary of abnormalities in rats treated with sodium metavanadate (mg/kg/day), during organogenesis.*
In parentheses, the percent affected fetuses.

Dosage	0	5	10	20
Fetuses observed	196	190	136	98
Hemorrhage in facial area (%)	2 (1.0)	9 (4.8)	2 (1.5)	18 (18.4)
Hemorrhage in abdominal cavity (%)	0 (0.0)	5 (2.6)	2 (1.5)	0 (0.0)
Hemorrhage in dorsal area (%)	2 (1.0)	10 (5.3)	0 (0.0)	10 (10.2)
Hemorrhage in thorax (%)	0 (0.0)	3 (1.6)	2 (1.5)	2 (2.0)
Hemorrhage in extremities (%)	0 (0.0)	7 (3.7)	4 (3.0)	2 (2.0)
Hydrocephalia (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)

ferences between the treated and the control animals in the values of resorption rates and dead fetuses were not significant. Consequently, embryolethality can not be suggested by the figures for percent of dead and resorbed fetuses. On the other hand, $NaVO_3$ had no effects on fetuses. Fetal body weight and body length were indicative of a normal growth of the fetuses.

The most conspicuous results may be the relatively high incidence of abnormalities of hemorrhagic character in the treated groups. The abnormalities in the 20 mg/kg/day are unusual in type and frequency, and must be attributed to the treatment. The hemorrhages did not occur spontaneously in the same frequency in the fetuses of untreated dams. Nevertheless, due to the absence of significant visceral and skeletal malformations, it cannot be conclude that $NaVO_3$ was teratogenic.

Relationships can be established between the so called «no toxic-effect» and any vanadium residue, e.g., in food, water, etc., thus permitting the calculation of safety factor for the human intake of vanadium. Taking the value of a safe intake of vanadium of 2.5 mg/person per day as basis (16), the calculation for a person of 70 kg of weight would be 0.036 mg V/kg/day. Compared to the possible no observed effect level for embryonic development (10 mg $NaVO_3$/kg/day or 4.18 mg V/kg/day), a safety factor of more than 100 can be calculated. Moreover, it must be remarked that these $NaVO_3$ administrations have not produced toxic effects in the mother rats, which is in agreement with our previous report, when rats were orally administered $NaVO_3$ for 3 months (5).

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Resumen

Se estudia el efecto del metavanadato sódico administrado por vía oral a ratas gestantes, cepa Sprague-Dawley, desde los días sexto al decimocuarto de gestación, a dosis de 0, 5, 10 y 20 mg/kg/día. Se realizan exámenes fetales el día 20 de gestación. El metavanadato sódico a dosis de 20 mg/kg/día o inferiores no resulta ni embrioletal ni teratogénico, aunque esta dosis es embriotóxica.

Palabras clave: Vanadio, Embriotoxicidad, Organogenesis en ratas.

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