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Embryotoxicity of 4-Deoxynivalenol (Vomitoxin) in Mice

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Several outbreaks of poisoning resulting from the consumption of moldy cereal grain have been reported since 1891 in different countries; most particularly the Soviet Union and Japan. These outbreaks effected not only animals that were fed the moldy grain but also humans who consumed bread made from mold-infected wheat or corn. A similar outbreak occurred among swine in 1963 in the U.S.A. with nausea, vomiting, abdominal pain and diarrhea as the predominant signs (CURTIN & TUITE 1966).

During a subsequent poisoning outbreak of swine in 1972, VESONDER et al. (1973) isolated a mycotoxin from moldy corn contaminated with Fusarium graminearum and named it vomitoxin since vomiting had been the salient sign of intoxication. The isolated toxin produced, upon feeding, similar signs in pigs (VESONDER et al. 1973). However, it was not certain whether this toxin which caused emesis in pigs was identical to the mycotoxin responsible for emesis in man. It was later found that feeds contaminated with vomitoxin or 4-deoxynivalenol was rejected by pigs (VESONDER et al. 1976).

The teratogenic potential of vomitoxin is at present unknown, therefore this study was conducted to assess the embryotoxic effects of vomitoxin in pregnant mice.

METHODS AND MATERIALS

Female Swiss-Webster mice weighing about 30 g, were paired overnight with proven males, and the morning that a vaginal plug was observed, was counted as day 1 of pregnancy. Fifteen to 19 mated females were assigned by random selection to each experimental group. Test doses of vomitoxin were 0, 5, 10 or 15 mg/kg b.w. in experiment I and 0.0, 0.5, 1.0 or 2.5 mg/kg b.w. in experiment II. Vomitoxin (purity 96%, containing 4% 4,7-dideoxynivalenol as impurity) was dissolved in dis tilled water and administered once daily by esophageal intubation for four consecutive days on days 8-11 of pregnancy. The volume of distilled water administered, in all groups was 1 ml/100 g body weight. The test and control females were weighed at frequent intervals during pregnancy and before (BC, Figure 1) and after cesarean section (AC, without uterine contents). On the 19th day of pregnancy, the dams were killed with CO_2, their uterine contents removed and necropsies performed. The number of early resorptions and fetuses dying late in their development were recorded and live fetuses were weighed and examined for external malformations. Two-thirds of the live fetuses from each litter were examined for skeleton development after alizarin staining. The remaining were fixed in Bouin's fluid and dissected to study visceral defects.

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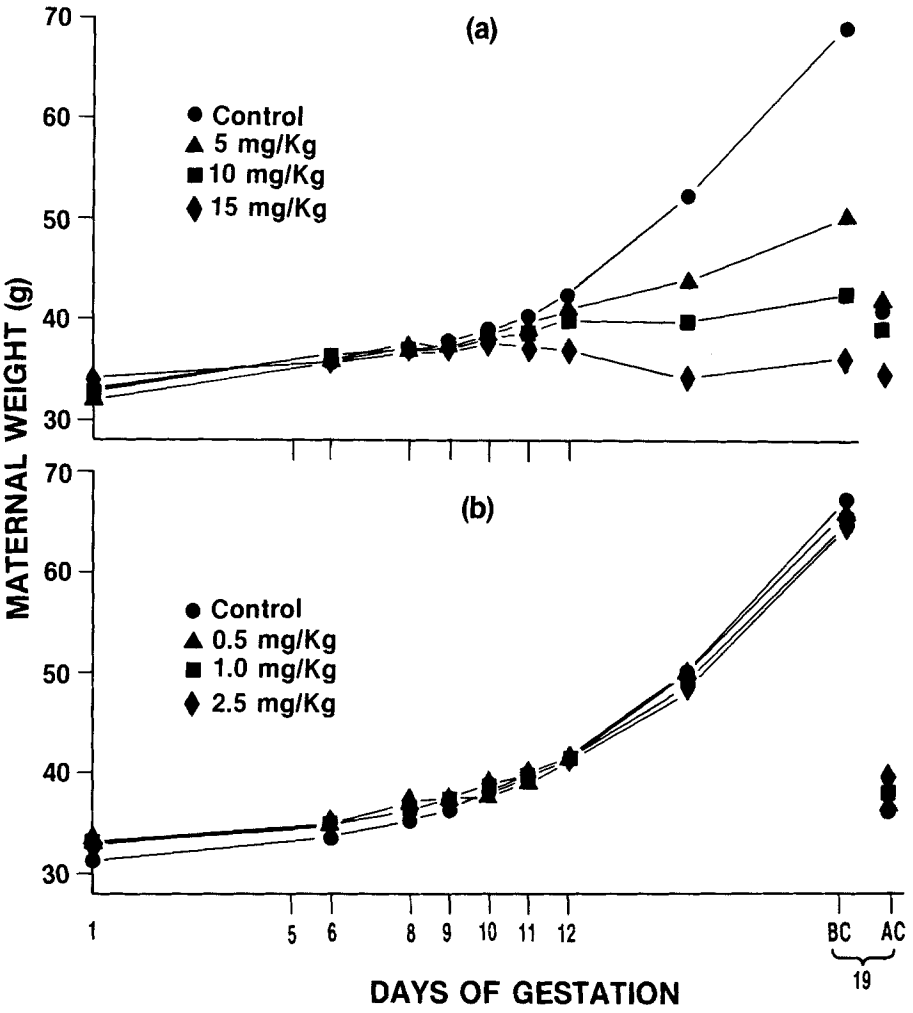

Figure 1. Maternal body weight on days 6, 8-12 and 19 (BC, before cesarean) of pregnancy and maternal carcass weight without uterus and its contents (AC). Dams were orally administered vomitoxin on days 8-11 of pregnancy.

Table 1

Prenatal values from mice orally dosed with 4-deoxynivalenol on days 8-11 of pregnancy

	Experiment I				Experiment II			
mg/kg/day	0	5	10	15	0	0.5	1.0	2.5
Number of females pregnant/number initiated on test	15/15	14/15	12/15	13/15	15/18	16/19	19/19	17/19
Implants per pregnancy Mean ± SE	16.9±0.4	15.6±0.5	14.5±1.0	12.5±1.3	14.6±0.6	15.7±0.6	13.8±0.8	15.0±0.6
Number of females showing no live fetuses	0	6	12	13	0	0	0	0
Number of resorptions ÷ total implants x 100	4	80*	100*	100*	5	4	3	9*
Number of dead fetuses	4	3	-	-	3	4	1	2
Live fetuses per dam mean ± SE	15.9±0.9	5.1±1.4*	0	0	13.8±0.6	14.8±0.6	13.4±0.8	13.5±0.9
Fetal weight (g.), mean	1.2	1.0*	-	-	1.3	1.3	1.3	1.2

* significantly different from control, $p < .05$

Table 2

Incidence of anomalies and aberrations in fetuses from mice treated orally on days 8-11 of pregnancy with 4-deoxynivalenol (data compiled from Experiments I and II)

	Experiment I		Experiment II			
	Control	5.0 mg/kg	Control	0.5 mg/kg	1.0 mg/kg	2.5 mg/kg
Total number of anomalous fetuses/number examined	11/239	34/41	8/207	9/236	22/254	148/229
Number of litters with anomalous fetuses/number examined	7/15	8/8	7/15	6/16	13/19	17/17
Effects in external and visceral morphology, %						
cleft palate	3	0	0	0.4	1	3
exencephaly	0	7	0	0	0	0
postural change in hindlimb uni- and bilateral syndactyly	0	0	0	0	3	4
polyphalangy	0	5	0	0	0	0
hypoplastic cerebellum	0	0	0	0	0	0.4
Number of fetuses examined for skeletal development	164	25	145	164	171	156
Effects on Skeleton, %						
a) Cervical vertebrae atlas fused with occipital or axis	0	11	0	0	0	8
b) Lumbar vertebrae:						
Body divided or partly absent; fused arches	0	33	0	0	0	16
Dysgenesis	0	7	0	0	0	3
c) Sternebrae:						
one sternebra missing	0	48	0	0	0	25
fused, divided or scrambled	4	19	1	3	8	26
d) Ribs:						
One or two ribs missing	0	93	0	0	1	72
13th rib rudimentary	1	4	3	2	2	7
Fused ribs	1	52	0	0	0	13
Extra rib	1	4	1	0	1	1
e) Ulna, tibia or fibula: short or missing	0	0	0	0	0	3

RESULTS

Vomitoxin caused vaginal bleeding and diarrhea in the 15 mg/kg and only diarrhea in the 10 mg/kg group. None of the test dams died although a progressive decrease in mean body weight gain was observed at the 5, 10 and 15 mg/kg doses (Figure 1). The decrease in body weight gain in the 5, 10 and 15 mg/kg groups apparently resulted from the resorption of embryos (see below) rather than from any obvious toxic effects on the dams per se. This was concluded since test and control group comparisons showed no statistically significant differences in the maternal weights adjusted for weight of conceptuses or in carcass weights of dams without uterus or its contents at term (AC, in Figure 1). No adverse effects were apparent in dams treated with doses of up to 2.5 mg/kg in experiment II.

The incidence of resorptions was 100% at the 10 and 15 mg/kg doses and 80% in the 5 mg/kg (Table 1). The latter dose, in addition, caused reductions in the number of live fetuses and average fetal weight. The increase in the rate of resorptions at the 2.5 mg/kg dose was less marked, yet statistically significant. However, the mean number of live fetuses per litter at this dose showed no statistically significant decrease although resorptions were increased. All prenatal values at the 0.5 and 1.0 mg/kg doses were within the control range.

The external and visceral anatomy presented low incidences of several anomalies at the 5 mg/kg (Experiment I), 2.5 and 1.0 mg/kg (Experiment II). A dose-response relationship was difficult to ascertain (Table 2), since these anomalies occurred either at the highest dose or at a low incidence in one or two dose groups. A number of skeleton malformations were present in the 1, 2.5 and 5 mg/kg groups in a dose-related manner. Important among these were: lumbar vertebrae with fused arches or partly absent centra; ribs, absent or fused; sternebrae, missing, fused or scrambled. The histologic examination revealed no treatment-related pathologic changes in the fetal tissues at any dose.

DISCUSSION

In this study vomitoxin manifested a specific lethal effect on the mouse embryo associated with or without maternal vaginal bleeding but with no apparent maternal toxicity at the 2.5, 5, 10 and 15 mg/kg doses. Multiple teratogenic effects occurred at the 2.5 and 5 mg/kg doses but no adverse effects were observed at the 0.5 mg/kg dose.

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