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Lithium Toxicity in Pregnant Swine[1,2] (40154)

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Lithium is an element that is used widely in human psychiatric research and treatment (1, 2). It is prescribed primarily to patients affected with recurrent manic-depressive illness. The lithium ion has also been used to reduce aggressive behavior in humans (3–5) and laboratory animals (6–8).

Data are conflicting regarding the effect of lithium on gestating females of several species. Weinstein and Goldfield (9) reviewed the literature of lithium teratology and cited studies in which teratogenic effects were reported in laboratory animals fed relatively high levels of lithium. They also reported that the incidence of fetal abnormalities was low in children of women fed lithium during pregnancy. The authors concluded that lithium administration during human pregnancy did not increase fetal abnormalities. However, they did list several precautions for pregnant women on lithium therapy. More recently, Rider and Hsu (10) reported that lithium increased preweaning mortality in rats and concluded that lithium treatment during gestation and lactation reduced reproductive performance in rats.

Most of the published research on the effect of lithium on reproductive function has used laboratory animals which have relatively short gestation periods. Yet, Weinstein and Goldfield (9) suggest that the effect of lithium on the gestating female and developing fetus may be related to the duration and mode of lithium ingestion. Swine have a gestation period that is over five times longer than rats. The gastrointestinal tract of swine is also similar to humans. Therefore, the objective of this experiment was to study effects of chronic lithium ingestion during gestation on the dam and offspring using the pig as an experimental model.

Materials and methods. Twenty-three females that had not displayed visual evidence of estrus for at least 30 days after breeding were randomized on the basis of weight and parity to one of two dietary treatments: (a) 2.3 kg day^{-1} of a barley-cull pea–soybean meal gestation ration containing 2818 kcal metabolizable energy kg^{-1} and individually fed to meet the National Research Council's (NRC) recommendation (11) of 6340 kcal metabolizable energy day^{-1} and (b) the same gestation ration supplemented with 3000 mg Li_2CO_3 (81 mEq Li) kg^{-1} offered *ad libitum* (Table I). Most females were in their second or third parity, with no first litter gilts being used.

Lithium is absorbed from the gastrointestinal track of humans within a few hours and around 50% is excreted in the urine within 24 hr (14, 15). Therefore, the lithium diet was fed *ad libitum* in an attempt to reduce high blood levels of lithium after a single feeding and maintain a more constant concentration in the systemic circulation. Data from preliminary experiments suggested that addition of 3000 mg Li_2CO_3 kg^{-1} would reduce caloric intake to near the NRC recommendation. Control swine were limit-fed once daily to prevent excessive gestation weight gain, which increases prenatal death loss (12, 13).

Females on both treatments were fed a 15% crude protein lactation ration (Table I) with no supplemental lithium at the rate of 2.3 kg day^{-1} during the last 5 days of gestation and *ad libitum* during lactation. Animals within each treatment were housed together. Feed consumption and body weight were measured at 60, 90 and 110 days of gestation. Body weight was also recorded after 21 days of lactation. Number of live and stillborn piglets and body weight were recorded at birth. Males in both treatments were castrated at 10 days of age. All piglets were weighed again at 21 days of age.

Six females on each of the two treatments were selected randomly and bled by anterior vena cava puncture at 30, 60, and 110 days of

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gestation. Serum was collected and stored at −20°. Females were fasted for 4 hr before each bleeding.

All serum samples were assayed in duplicate for lithium by atomic absorption spectrophotometry (16). A lithium reference solution of 1000 ppm was diluted in 6% dextran (w/v) to prepare standards.

Students' *t* test and analysis of variance were used to determine treatment effects (17). Either total number of piglets born or number of live piglets born was used as a covariate in the analysis of offspring data.

Results. Daily voluntary feed consumption of the ration in which 3000 ppm Li_2CO_3 was incorporated averaged 2.7, 3.0 and 2.8 kg for 30 to 60, 60 to 90, and 90 to 110 days postbreeding, respectively. Averaged over the last 80 days of gestation, lithium-fed females consumed 2.8 kg of feed daily. Their average energy intake was 7890 kcal day^{-1}, approximately 24% more than the NRC (11) recommendation.

Five of the 12 pregnant females assigned to the lithium diet did not give birth (Tables II and III), apparently aborting or resorbing the fetuses. Body weights of the females on each treatment did not differ ($P > 0.05$) at initiation of the experiment or 30 or 60 days later (Table III). However, lithium-fed females weighed less ($P < 0.05$) than control animals at 110 days postbreeding. The five females that were fed lithium and did not give birth weighed 30 kg less at 110 days postbreeding than at 30 days postbreeding, whereas the seven females that completed pregnancy lost 22 kg during this same period. Control females gained 26 kg during the last 80 days of gestation.

The lowest detectable concentration of lithium by atomic absorption spectrophotometry in this study was 0.0043 mEq l^{-1}. The intraassay coefficient of variation was 2.5%. Serum lithium levels of control females remained in the nondetectable range throughout the entire study (Table III). Females consuming the lithium diet had serum lithium concentrations (mean ± SE) of 1.4 ± 0.2 and 2.3 ± 0.3 mEq l^{-1} at 60 and 110 days of gestation. Three of the 6 females selected for blood sampling remained pregnant. Serum lithium concentration of these three females averaged (± SE) 1.3 ± 0.2 and 1.8 ± 0.2 mEq l^{-1} and the three females that did not complete pregnancy averaged 1.5 ± 0.3 and 2.8 ± 0.2 mEq l^{-1} at 60 and 110 days postbreeding, respectively.

Average offspring born per litter and birth weight did not differ ($P > 0.05$) between treatment groups (Table II). However, lithium-treated females gave birth to fewer ($P < 0.05$) live piglets, more mummies and stillbirths ($P < 0.01$), lighter ($P < 0.01$) litters and had fewer ($P < 0.01$) offspring alive at 21 days of age. Mortality from birth to 21 days of age (mean ± SE) was 23% ± 3 and 45% ± 12 on the control and lithium diets, respectively. Growth rate of piglets born to females fed lithium during gestation did not differ ($P > 0.05$) from control piglets.

Discussion. Females in this experiment would likely consume at least 5 kg day^{-1} of this high energy ration if fed *ad libitum* (18). This would provide more than 14,000 kcal day^{-1} of metabolizable energy, which is over twice the NRC recommendation (11) for gestating swine. The NRC recommends limit-feeding pregnant swine to prevent excessive gestation weight gain. Therefore, the control animals were restricted to a single feeding of 2.3 kg day^{-1} to prevent exceeding the NRC

TABLE I. PERCENT COMPOSITION OF GESTATION AND LACTATION RATIONS.

Ingredient	Gestation ration	Lactation ration
Barley	74.75	40.0
Corn	—	30.0
Soybean meal (47.5% crude protein)	5.0	10.0
Peas, seeds, cull grade	10.0	10.0
Alfalfa meal, sun-cured	6.0	5.0
Animal fat	1.0	1.0
Dicalcium phosphate	1.4	1.4
Limestone	1.0	1.0
Salt, iodized	0.25	0.5
Trace mineral premix[a]	0.10	0.2
Vitamin premix[b]	0.50	0.5
Magnesium sulfate	—	0.15
Antibiotic premix[c]	—	0.25

[a] Trace mineral premix contained: 10.0% manganese, 10.0% iron, 10.0% zinc, 1.0% copper, 0.3% iodine and 0.1% cobalt.

[b] Vitamin premix contained the following per kg of premix: 880,000 IU vitamin A, 132,000 IU vitamin D_2, 440 mg riboflavin, 2.2 g D-calcium pantothenate, 7.04 g niacin, 176 g choline chloride, 4.4 mg vitamin B_{12}, 550 mg menodione sodium bisulfite.

[c] Supplied per kg of feed: 100 mg chlortetracycline, 110 mg sulfamethazine and 55 mg penicillin.

TABLE II. EFFECT OF LITHIUM CARBONATE INGESTION ON PREGNANT SWINE AND OFFSPRING.

Item	Dietary Li_2CO_3 (mg kg^{-1}) 0: Mean	0: Adjusted mean[b, c]	3000: Mean	3000: Adjusted mean[b, c]
Number of pregnant females allotted	11		12	
Number of females remaining pregnant	11		7	
Total piglets born per litter	12.3 ± .6[a]		10.6 ± .9	
Number of live piglets born per litter[b]	12.1	11.3 ± 0.4	8.3	9.6 ± 0.4*
Number of mummies and stillbirths per litter[b]	.6	.6 ± 0.4	2.1	2.1 ± 0.5**
Birth weight, kg[b]	1.3	1.3 ± 0.1	1.00	1.1 ± 0.1
Litter birth weight, kg[b]	16.6	15.4 ± 1.0	9.4	11.1 ± 1.2**
Number alive at 21 days of age[c]	9.1	8.0 ± 0.4	4.9	6.5 ± 0.5**
Pig weight at 21 days of age, kg[c]	4.6	4.0 ± 0.4	3.8	4.8 ± 0.5
Litter weight at 21 days of age, kg[c]	42.7	36.3 ± 3.6	25.6	35.6 ± 4.6

[a] Mean ± SE.
[b] Adjusted for total piglets born per litter by analysis of covariance.
[c] Adjusted for number of live piglets born per litter by analysis of covariance.
* $P < 0.05$.
** $P < 0.01$.

TABLE III. EFFECT OF LITHIUM CARBONATE INGESTION ON WEIGHT GAIN AND SERUM LITHIUM CONCENTRATION OF GESTATING SWINE.

Item	Time (days)	Dietary Li_2CO_3 (mg kg^{-1}) 0	3000
Weight, kg			
Post-breeding	30	197.9 ± 14.4[a] (11)[b]	200.7 ± 13.8 (12)
Post-breeding	60	202.9 ± 14.4 (11)	188.8 ± 13.8 (12)
Post-breeding	90	203.1 ± 14.2 (11)	180.2 ± 13.5 (12)
Post-breeding	110	224.3 ± 14.1 (11)	173.3 ± 13.5 (12)*
Post-farrowing	21	203.7 ± 11.5 (11)	198.1 ± 17.0 (5)
Serum Lithium, mEq l^{-1}			
Post-breeding	30	ND[c] (6)	ND (6)
Post-breeding	60	ND (6)	1.4 ± 0.17 (6)
Post-breeding	110	ND (6)	2.3 ± 0.26 (6)

[a] Mean ± SE.
[b] Number of females.
[c] Nondetectable; less than 0.0043 mEq l^{-1}.
* $P < 0.05$.

recommendation of 6340 kcal metabolizable energy day^{-1}.

Females assigned to the lithium diet were fed *ad libitum* in an attempt to reduce excessively high blood levels of lithium that might occur after consumption of the daily ration at one meal. They consumed 2.8 kg day^{-1}, or nearly 8000 kcal metabolizable energy day^{-1}. It is possible that the slightly additional energy intake of lithium-fed females caused the reduction in number of live piglets born $litter^{-1}$. However, it is more likely that lithium caused these toxic side effects because: (A) Lithium-treated females consumed 24% more metabolizable energy. Instead of becoming obese, they lost 27 kg of body weight. (B) Piglets born to lithium-fed females were lighter, whereas swine that consume additional energy during gestation generally give birth to larger piglets (12, 13). (C) A slightly greater consumption of energy during gestation has not been reported to cause the high percentage of abortions that occurred in the lithium-fed females and (D) Excess energy consumption during gestation does not increase piglet death rate before 21 days of age (12, 13). Yet, fewer piglets from the lithium-fed females survived.

Females fed the lithium diet consumed 1.6 g of lithium daily, or 1.2 mEq kg^{-1} day^{-1}.

This may be near the maximal voluntary intake of lithium for swine. This level, which appears to be toxic to pregnant swine, is much less than that given to mice (19, 20) and rats (21–23) where no toxicity symptoms were reported. Since the gestation length of swine is 114 days, this study permitted observations on pregnant females that were maintained on lithium for at least 80 days. Therefore, pigs in this study consumed lithium over a much longer time period than other studies that used animal species with shorter gestation lengths. Lithium ingestion over this long period of time could account for the toxic side effects.

Humans on lithium therapy consume 0.46 mEq kg^{-1} day^{-1}, which generally maintains serum lithium concentrations ranging from 0.5 to 1.2 mEq l^{-1} (9). Serum concentrations of lithium in the female pigs remaining pregnant averaged 1.5 mEq l^{-1}, which is similar to the highest levels recommended for humans. Females that did not complete pregnancy had serum lithium values of 2.8 mEq l^{-1} during late gestation, which suggests these levels are toxic to pregnant swine. Even though the lithium-fed animals were provided feed *ad libitum*, it is possible that there were fluctuations in serum lithium levels resulting from variation in the amount of food ingested. Fluctuations in feed intake could have exposed the fetuses to irregular pulses of lithium, resulting in the toxicity symptoms observed (9).

The biochemical mechanism by which lithium caused these toxic side effects is unclear. Perhaps lithium directly affected some reproductive hormone or organ. However, because of the body weight loss at an adequate level of nutrient intake, we speculate that lithium caused the abortions and other toxic side effects by interfering with the absorption or metabolism of dietary nutrients, causing weight loss and a concommitant mobilization of body stores. Eventually, maternal stores of energy or protein may have been reduced, and the fetus or placenta developed inadequately.

There is some support for this theory at the cellular level. Glucose and amino acid absorption in the small intestine are known to be sodium-dependent (24). It is probable that there are specific carriers for glucose and amino acids that require activation by sodium before transport into the intestinal villus can occur. Bosackova and Crane (25) reported that intestinal absorption of glucose *in vitro* was reduced when lithium was used to replace sodium. These authors speculated that lithium displaced sodium on the carrier molecule, resulting in a reduction in the amount of glucose and amino acids absorbed.

This theory agrees with the slightly fewer and lighter piglets born to swine fed lithium during gestation as well as the higher ($P < 0.01$) number of malformed and stillborn piglets (Table II). Furthermore, females assigned to the lithium diet appeared to be extremely emaciated at termination of the experiment. When lithium-fed females were returned to the control diet and fed *ad libitum* during lactation, milk yield was ostensibly adequate to support growth rate of offspring at a level comparable to control females.

Trautner *et al.* (21) reported that the main effect of chronic lithium ingestion in rats was a reduction in ovulation rate. Weinstein and Goldfield (9) recommended that women on lithium therapy should be removed from treatment during the first one-third of pregnancy. Results from this experiment show that lithium ingestion over the last 80 days of gestation can adversely affect reproductive performance in swine, even after ovulation and implantation have occurred.

Summary. Twenty-three pregnant swine were fed either 2.3 kg of a ration containing 2818 kcal metabolizable energy kg^{-1} once daily or fed the same ration supplemented with 3000 mg Li_2CO_3 kg^{-1} and fed *ad libitum* during the final 80 days of gestation. Lithium was not fed during lactation. Lithium-fed females voluntarily consumed 2.8 kg day^{-1}. Swine that consumed lithium lost 27 kg of body weight during gestation and weighed less ($P < 0.05$) than control females at 110 days of gestation. All of the control females gave birth to piglets but only 58% of the lithium-fed females completed pregnancy. Females consuming lithium gave birth to fewer ($P < 0.05$) live piglets, more ($P < 0.01$) mummies and stillbirths and lighter ($P < 0.01$) litters. Fewer ($P < 0.01$) of the liveborn piglets born to lithium-treated females survived to 21 days of age. It is suggested that lithium caused these toxic effects by interfer-

ing with absorption or metabolism of dietary nutrients. This resulted in mobilization of maternal body stores and caused inadequate development of the fetus or placenta. These data also demonstrate that short-term gestation studies with rats and mice may not be applicable to humans.

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